

Efficacy and Safety of the Selective Aldosterone Synthase Inhibitor Lorundrostat in Moderate-to-Severe Apnea and Hypertension: Explore-OSA

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American
Heart
Association.

Disclosures

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Explore-OSA Randomized Cross Trial

FINANCIAL DISCLOSURE:

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Background



- OSA is estimated to affect ~30-80 million people in the US and ~1 billion people worldwide¹⁻³
- The prevalence of OSA in patients with treatment-resistant or uncontrolled HTN is ~70-80%⁴⁻⁷
- Autonomous aldosterone production is maintained by multiple factors associated with obesity and OSA, with increased adrenergic tone being particularly important in males^{8,9}
- Several small trials of MRA in patients with OSA demonstrated reduced AHI; the hypothesized mechanism is reduction of rostrocaudal fluid shift⁸
- However, RCTs of CPAP have reported only modest reductions in systolic BP (2-3 mmHg) and no consistent reduction in adverse cardiovascular outcomes¹⁰⁻¹²
- The introduction of lorundrostat and other ASIs that directly reduce aldosterone production provide a novel approach to directly test the effects of aldosterone on AHI and BP in individuals with OSA^{13,14}

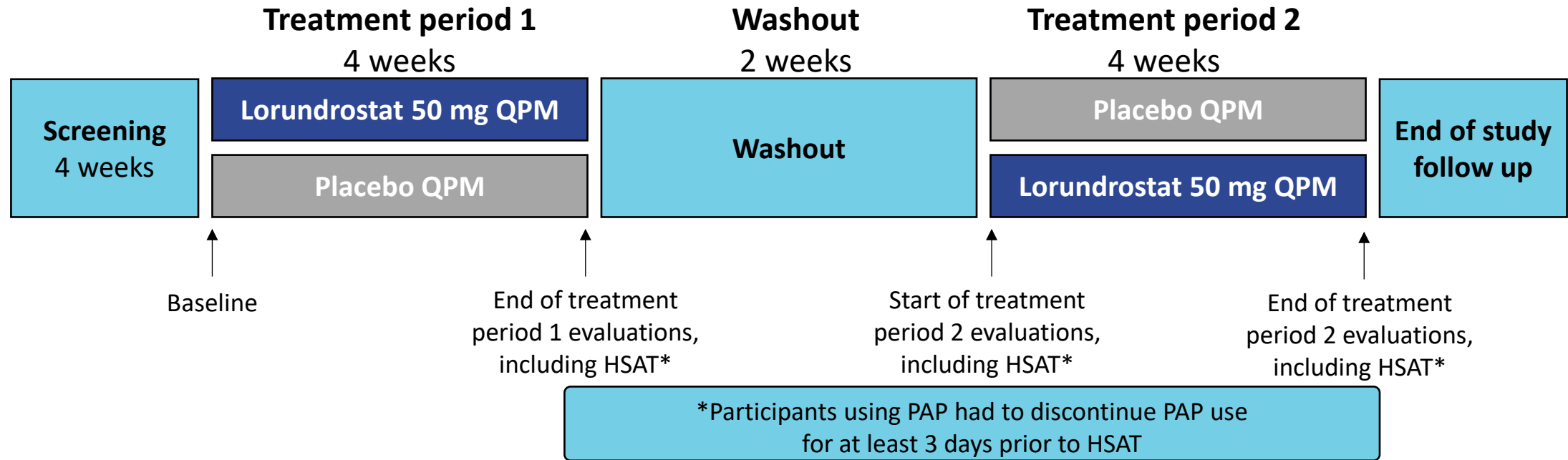
Trial Objectives

In individuals with moderate or severe OSA and uncontrolled or resistant hypertension:

1. Test the hypothesis that reduction in aldosterone production for 4 weeks reduces upper airway obstruction assessed by AHI
2. Test the hypothesis that reduction in aldosterone production for 4 weeks leads to a clinically meaningful reduction in BP
3. Characterize the safety profile of lorundrostat
4. Explore the effect of lorundrostat on mechanistic and clinical biomarkers

Explore-OSA Trial Design

Phase 2, randomized, double-blind, placebo-controlled, crossover trial across 19 sites in the US



Primary endpoint

Placebo-adjusted change from baseline in AHI at Treatment Week 4

Secondary endpoints

Placebo-adjusted change from baseline at Treatment Week 4 in AOBP SBP, nighttime average SBP, FOSQ-10, Epworth Sleepiness Scale, PROMIS-Sleep Disturbance, PROMIS-Sleep-Related Impairment

Key Eligibility Criteria

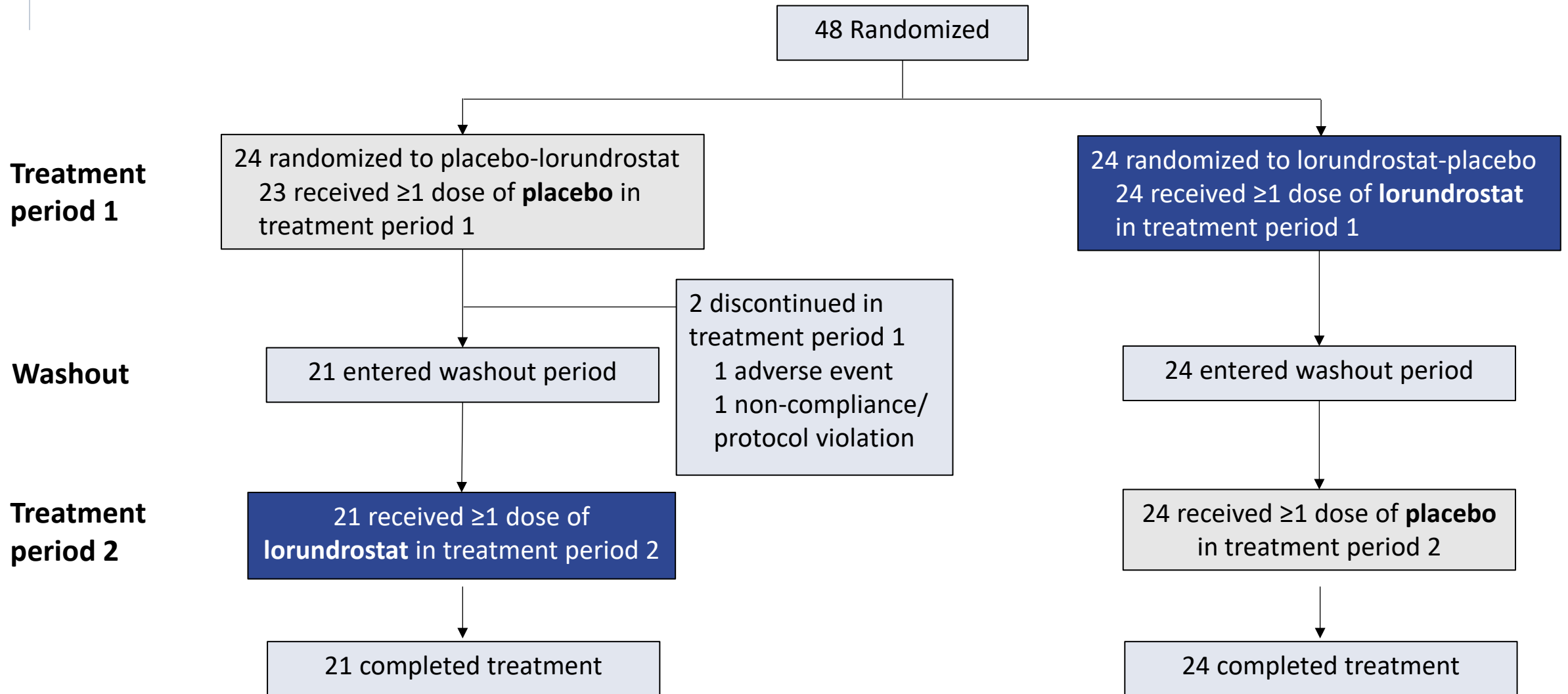
Inclusion Criteria

- Age 18-75 years old
- BMI ≥ 27 kg/m²
- AHI ≥ 15 events/h
- AOBP SBP 130-180 mmHg and DBP 60-110 mmHg at screening and randomization
- If CPAP/APAP, >4 /night compliance for at least 3 months prior to study

Exclusion Criteria

- GLP-1 utilization within 8 weeks of randomization
- Any surgical intervention for sleep apnea or major ENT within 3 months of screening
- History of Obesity Hypoventilation Syndrome, daytime hypercapnia, or central or mixed sleep apnea (with $\geq 50\%$ mixed or central apneas/hypopneas)
- BiPAP
- K⁺ >5.0 mmol/L at screening
- eGFR <45 mL/min/1.73 m²
- OTC or prescription medications that could affect sleep or cause somnolence

Explore-OSA CONSORT Diagram



Baseline Demographics & Characteristics

Participants were all obese, non-sleepy with a severe degree of OSA; 35% were Black; and ~one-third on PAP therapy



Characteristic	n=48 ^a
Age, mean (SD), years	58.8 (8.4)
Female, n (%)	19 (39.6)
Black or African American, n (%)	17 (35.4)
Hispanic or Latino, n (%)	12 (25.0)
BMI	
Mean (SD)	37.4 (7.2)
≥30 kg/m ² , n (%)	42 (87.5)
Neck circumference, mean (SD), cm	44.1 (5.4)
Type 2 diabetes mellitus, n (%)	14 (29.2)

Characteristic	n=48 ^a
eGFR (creatinine), mean (SD), mL/min/1.73 m ²	89.2 (14.9)
Seated AOBP SBP , mean (SD), mmHg	142.3 (8.7)
PAP use^c , n (%)	18 (37.5)
Baseline AHI (/h)	
Mean (SD)	48.5 (26.7)
Moderate (15-29), n (%)	16 (33.3)
Severe (≥30), n (%)	32 (66.7)

Characteristic	n=47 ^b
AHT class, n (%)	
ACE inhibitor or ARB	24 (51.1)
Diuretic	14 (29.8)
CCB	12 (25.5)
Epworth Sleepiness Scale, mean (SD)	9.8 (4.6)

Mean duration of exposure was 32.1 days during lorundrostat treatment and 32.0 days during placebo treatment, consistent with the planned 4-week (28-day) treatment periods^d

^aOf 48 randomized participants, 47 received ≥1 dose of study drug (lorundrostat or placebo). ^bReported in participants who received ≥1 dose of study drug. ^cParticipants who were medically prescribed and deemed compliant with PAP therapy for ≥4 hours per night (CPAP or autoPAP) and for at least 3 months prior to the study enrollment were eligible for the study. Participants on PAP therapy were instructed to comply with PAP therapy for the duration of the study. Participants who were using PAP suspended their PAP use for at least 3 days prior to the protocol-defined HSAT, including the HSAT at screening. ^dA medication adherence platform was provided on a smartphone application, which provided built-in reminders and a communication system to allow real-time intervention for missed doses, to reinforce the proper dosing schedule, and improve data integrity.

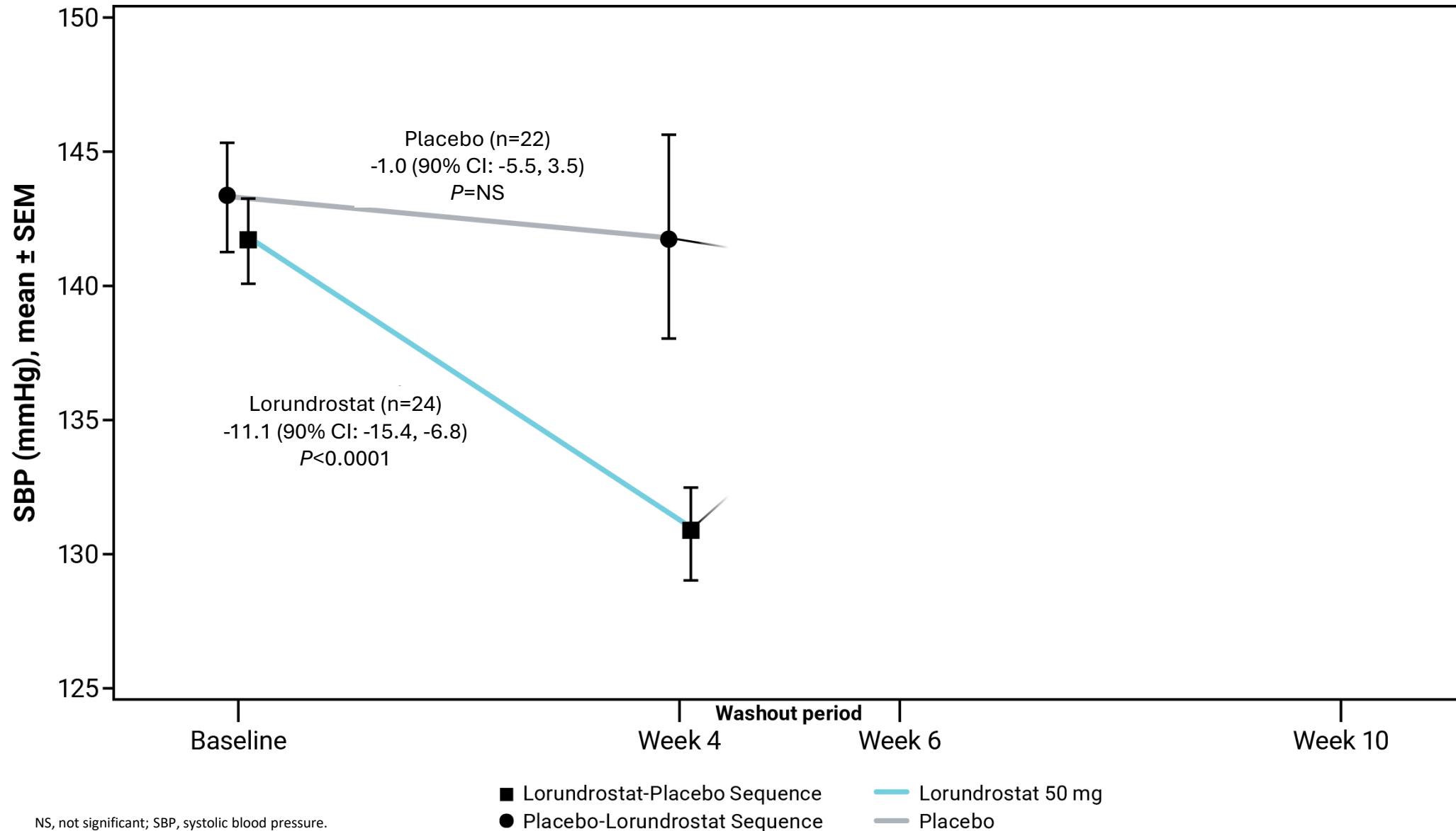
ACE, angiotensin-converting enzyme; AHI, apnea-hypopnea index; AHT, antihypertensive therapy; AOBP, automated office blood pressure; ARB, Angiotensin II receptor blocker; autoPAP, automatic positive airway pressure; BMI, body mass index; CCB, calcium channel blocker; CPAP, continuous positive airway pressure; eGFR, estimated glomerular filtration rate; HSAT, home sleep apnea test; OSA, obstructive sleep apnea; PAP, positive airway pressure; SBP, systolic blood pressure.

Results: AHI and Other Sleep-Specific Outcome Measures Were Unaffected

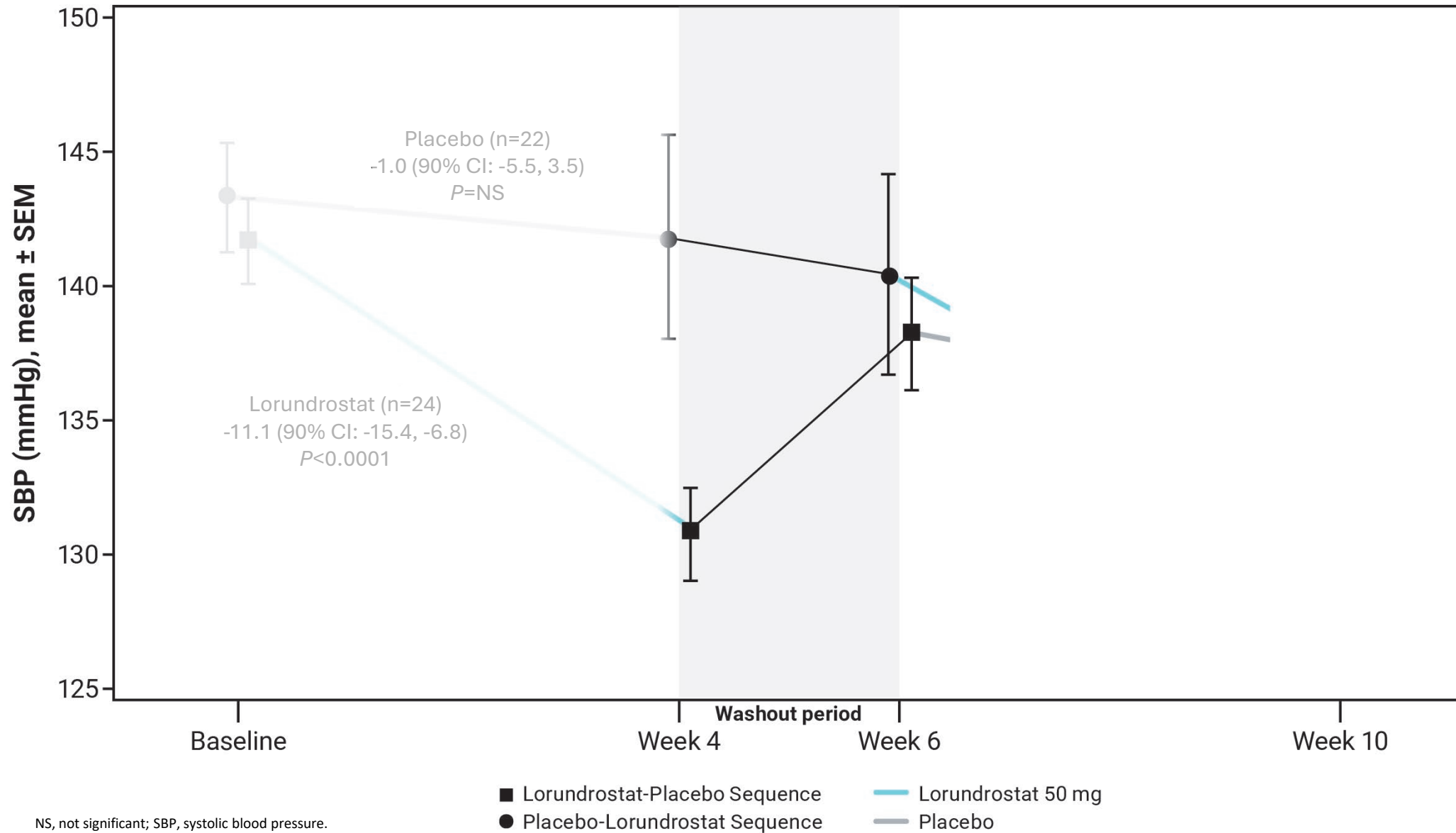
Endpoint	n		LS Mean Difference (90% CI) Lorundrostat vs Placebo	P-value
	PBO	LOR		
Change from baseline in AHI at Week 4, events/h	47	47	-1.416 (-5.143, 2.311)	NS
Change from baseline in Sleep Specific Hypoxic Burden at Week 4, % min/h	47	47	-3.166 (-20.170, 17.459)	NS
Change from baseline in FOSQ-10 at Week 4	47	47	-0.035 (-0.411, 0.340)	NS

No statistically significant change in exploratory patient-reported outcomes at Week 4: Epworth Sleepiness Scale, PROMIS Sleep Disturbance, and PROMIS Sleep-Related Impairment

Clinically Meaningful Reduction in Morning SBP

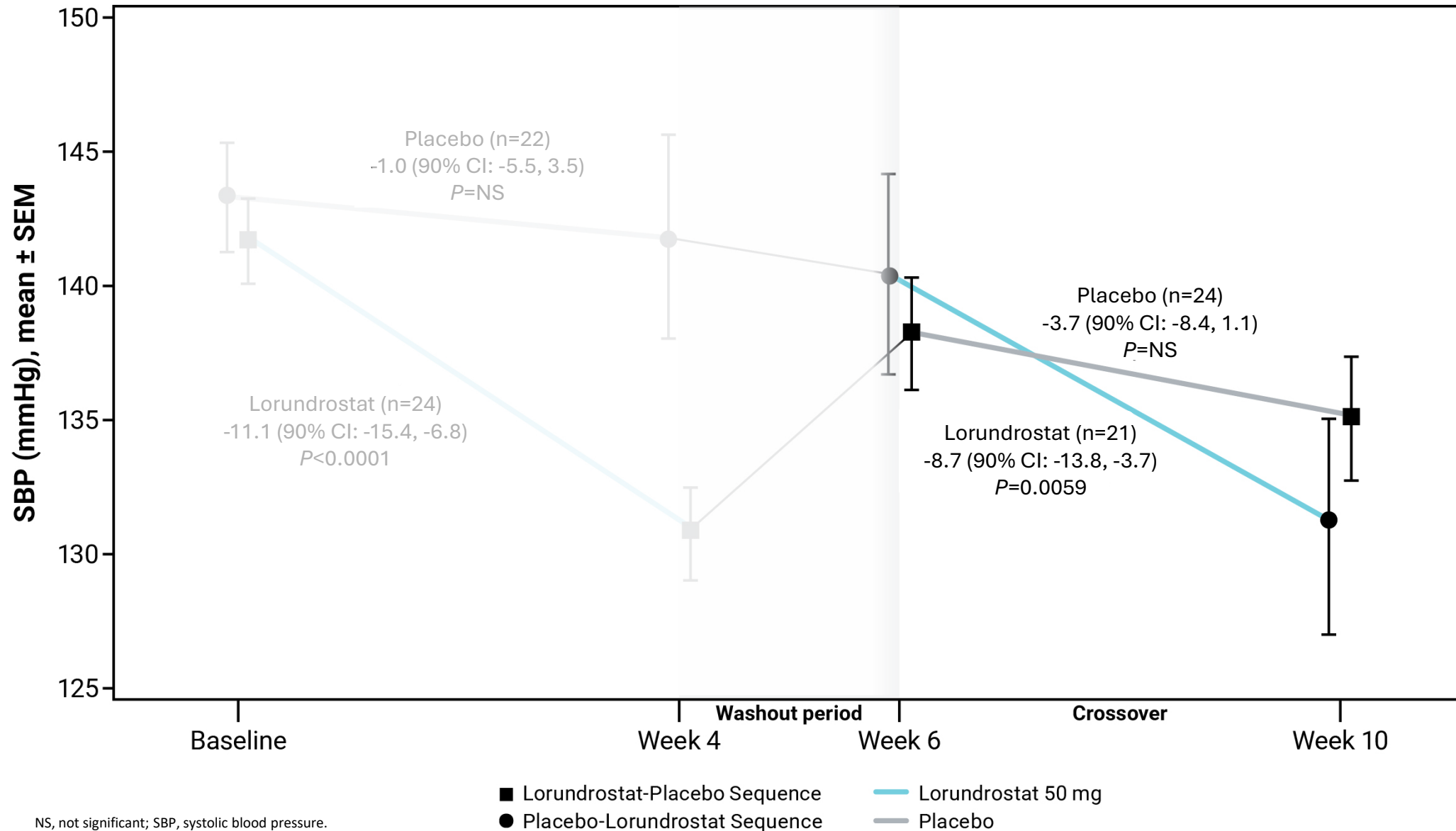


Clinically Meaningful Reduction in Morning SBP



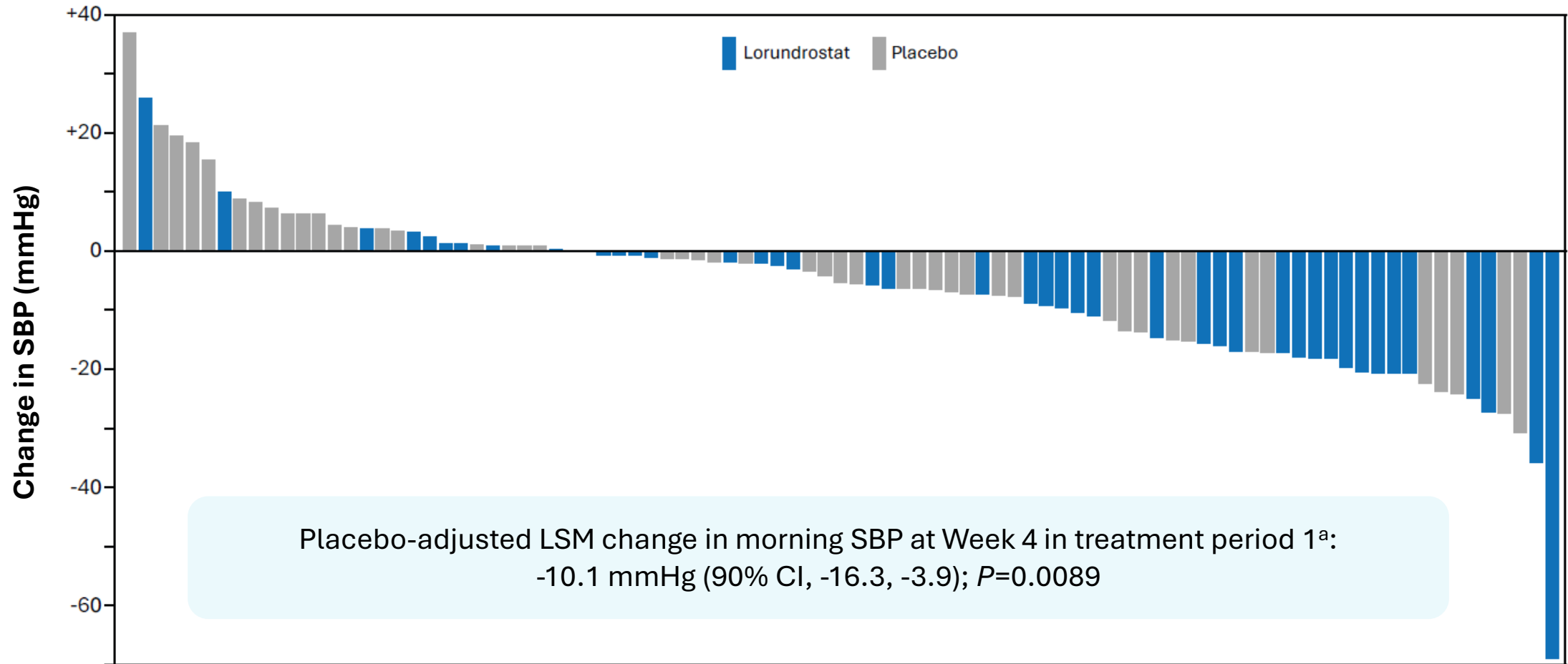
NS, not significant; SBP, systolic blood pressure.

Clinically Meaningful Reduction in Morning SBP



NS, not significant; SBP, systolic blood pressure.

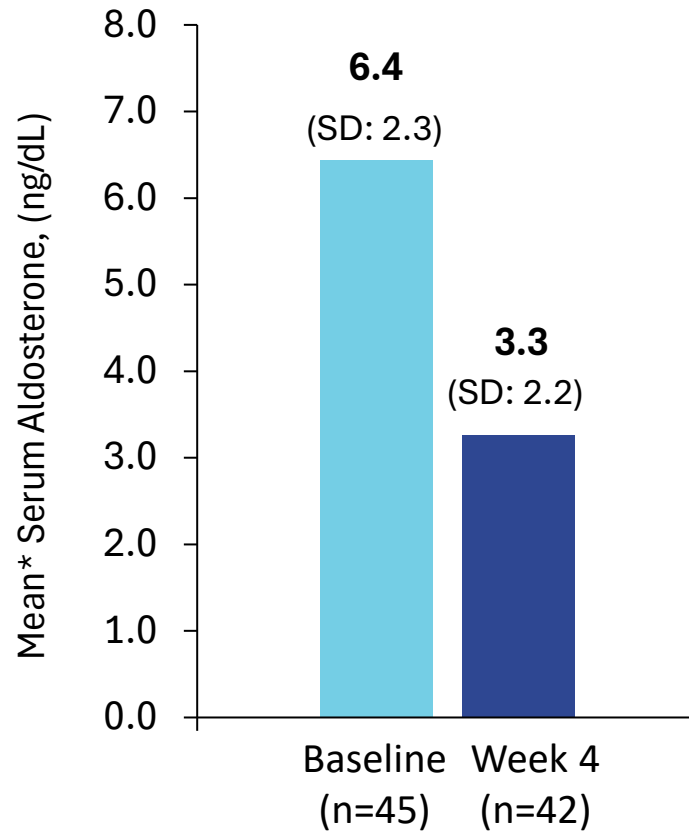
Clinically Meaningful Reduction in Morning SBP Observed in the Majority of Trial Participants



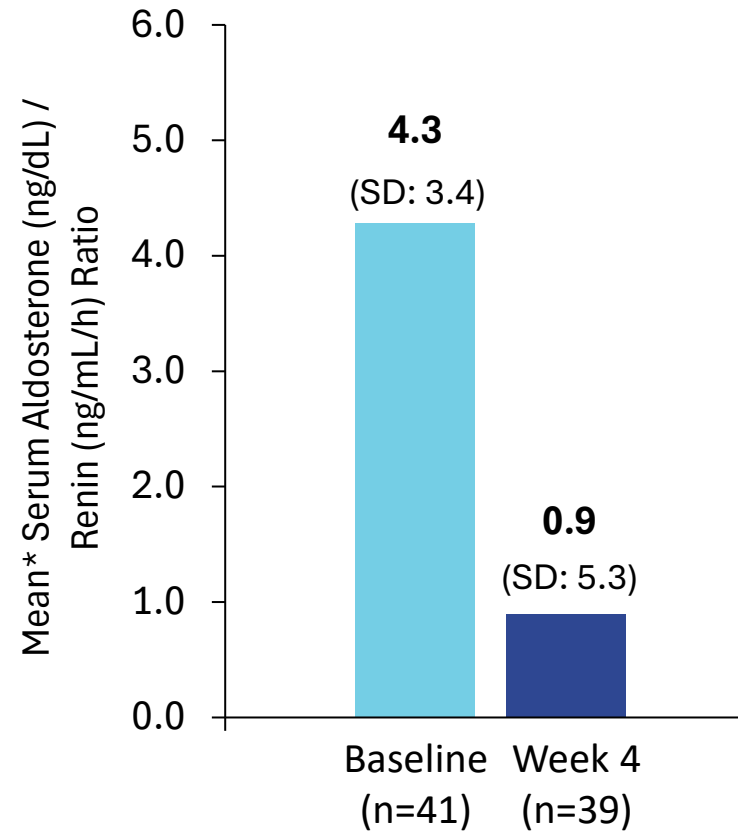
^aBP measured 24h after last dose of study medication.
LSM, least squares mean; SBP, systolic blood pressure.

Changes in RAAS Biomarkers During Lorundrostat Treatment at Week 4

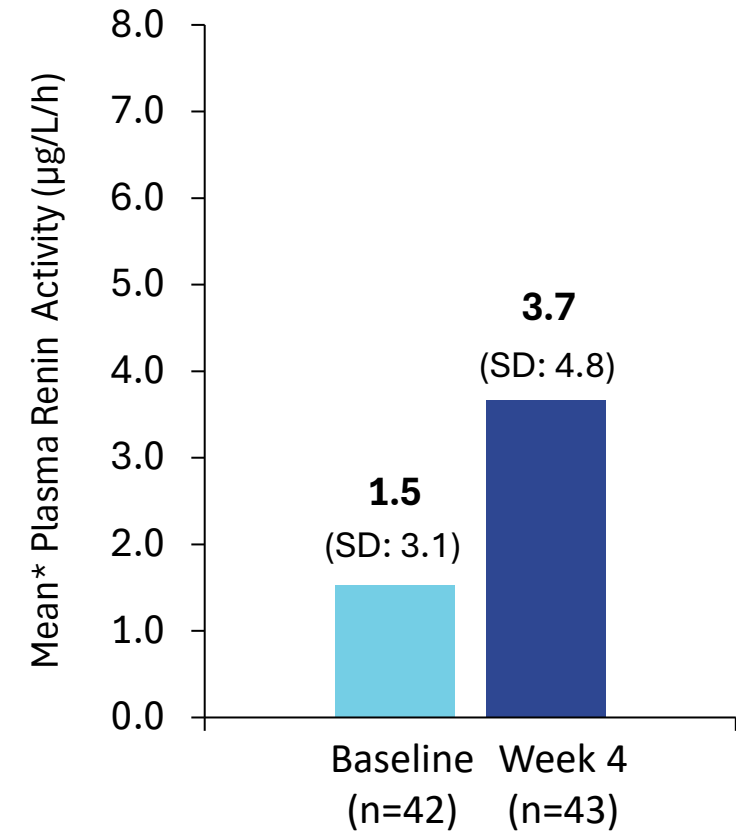
Serum Aldosterone



Aldosterone:Renin Ratio



Plasma Renin Activity



*Logarithm-transformed values.
RAAS, renin-angiotensin-aldosterone system.

Safety

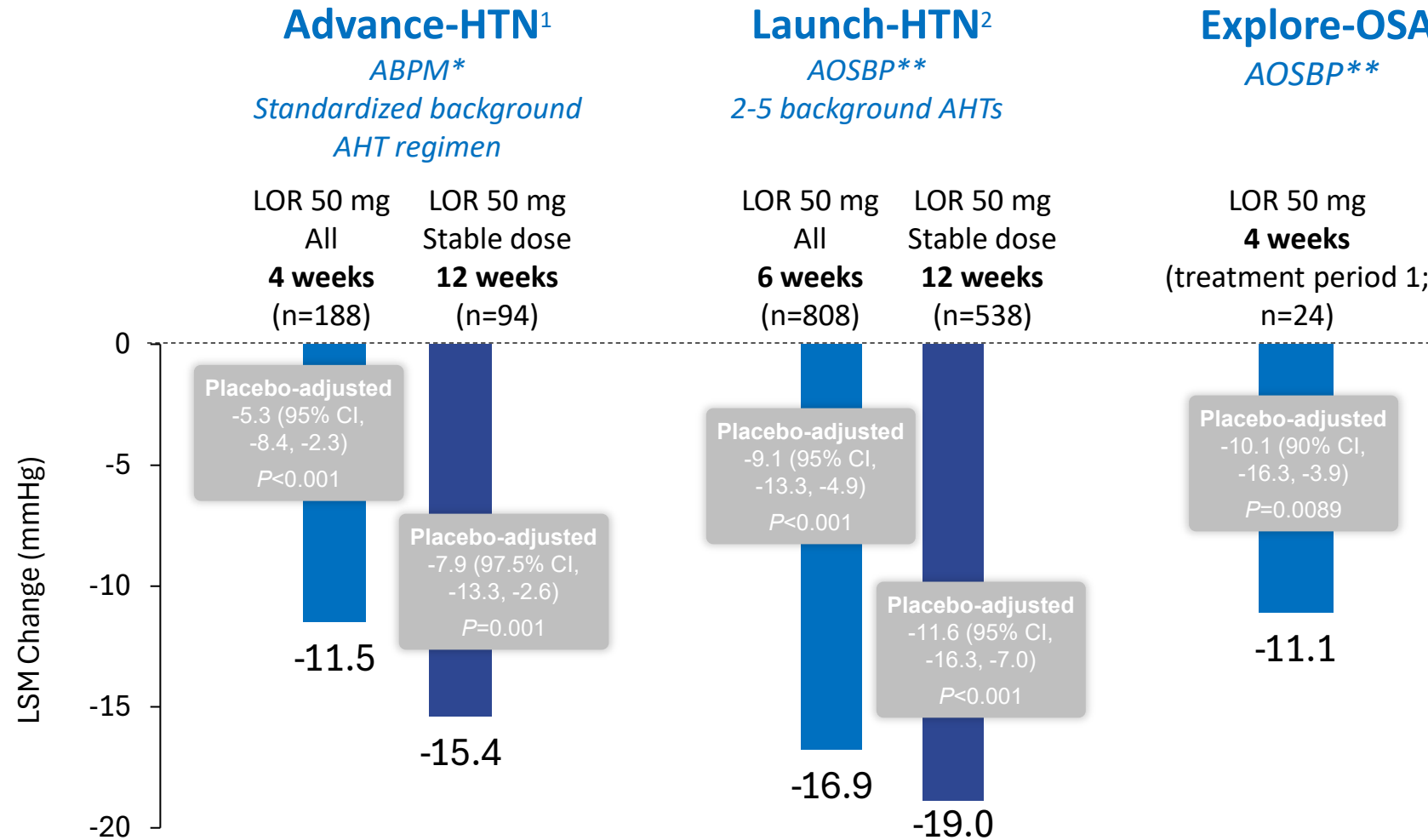
AESIs, n (%)	Placebo (n=47)	Lorundrostat (n=45)
Severely elevated BP ^a	3 (6.4)	0 (0)
Reduction in eGFR ^b	0 (0)	1 (2.2)
Symptomatic hypotension	0 (0)	0 (0)
Hyperkalemia (>5.5 mmol/L) ^b	0 (0)	0 (0)
Hyponatremia ^b	0 (0)	0 (0)
Hypocortisolism ^c	0 (0)	0 (0)

- 1 participant had ≥25% change in eGFR (Cystatin-C) on lorundrostat treatment; none had ≥50% change
- There were no serum potassium elevations >5.5 mmol/L
- Placebo-adjusted LSM change in serum potassium at Week 4: +0.302 mmol/L (90% CI: 0.164, 0.441; *P*=0.0007)

Safety analysis set: All participants who received at least one dose of study drug.

^aAOBP SBP >180 mmHg or AOBP DBP >110 mmHg. ^bTrial drug had to be modified due to the adverse event (dose reduction, dose hold, or permanent dose discontinuation). ^cConfirmed by ACTH stimulation test and required discontinuation of trial drug. ACTH, adrenocorticotrophic hormone; AESI, adverse event of special interest; AOBP, automated office blood pressure; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

SBP Reduction in Pivotal Trials in Uncontrolled HTN Showed Continued Improvement out to 12 weeks



ABPM, ambulatory blood pressure monitoring; AHT, antihypertensive therapy; AOSBP, automated office systolic blood pressure; HTN, hypertension; LOR, lorundrostat; LSM, least squares mean; SBP, systolic blood pressure.

1. Laffin LJ, et al. *N Engl J Med*. 2025;392(18):1813-1823. 2. Saxena M, et al. *JAMA*. 2025;334(5):409-418.

*24-hour average ambulatory SBP
**Automated office SBP

Summary

In Explore-OSA, including 67% adults with severe OSA and more than one-third on PAP, there was no evidence of efficacy in AHI response after 4 weeks of lorundrostat

Four weeks of lorundrostat achieved significant SBP reductions in adults with moderate-to-severe OSA and HTN

The magnitude of BP reduction was consistent with pivotal lorundrostat trials in uncontrolled and treatment-resistant HTN^{1,2}

There was no evidence of significant safety events, including hyperkalemia

A longer-term cardiovascular outcomes trial of lorundrostat is warranted

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Participants



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Site Staff**



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