Lorundrostat, a Novel Aldosterone Synthase Inhibitor (ASI), in Participants with Uncontrolled Hypertension, CKD, and Albuminuria: Results from Explore-CKD

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Background

- ~37 million individuals in the US have CKD, and 60% to 90% have concurrent hypertension[1,2]
- ~76% of individuals with CKD and hypertension have uncontrolled BP despite treatment with multiple antihypertensive medications[3]
- Lorundrostat is a novel ASI that has demonstrated efficacy and safety in phase 2 and 3 studies of patients with uncontrolled hypertension, including treatment-resistant hypertension[4-6]
- This is the first report of the safety and efficacy of lorundrostat in patients with CKD and uncontrolled hypertension

1. Ku E, et al. *Am J Kidney Dis*. 2019;74(1):120-31; 2. Centers for Disease Control and Prevention. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2023; 3. de Beus E, et al. *Hypertension*. 2015;66(5):998-1005; 4. Laffin LJ, et al. *N Engl J Med*. 2025;392(18):1813-23; 5. Laffin LJ, et al. *N Engl J Med*. 2025;392(18):1813-23; 6. Saxena M, et al. *JAMA*. 2025;334(5):409-18.

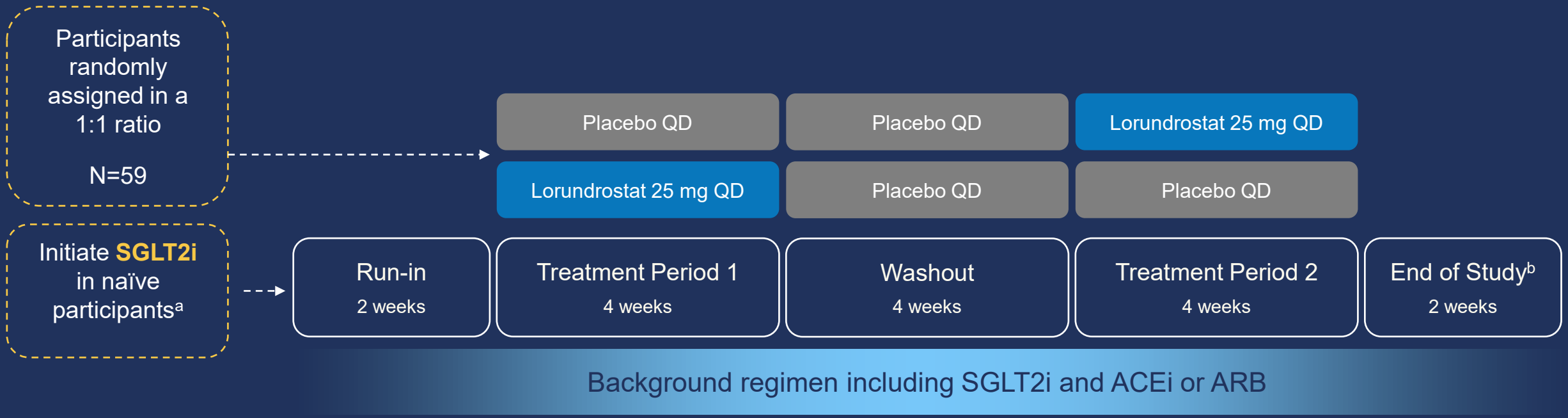
ASI, aldosterone synthase inhibition; BP, blood pressure; CKD, chronic kidney disease.

Explore-CKD: Objective

To assess the effect of lorundrostat in addition to an SGLT2i on SBP and measures of renal function in participants with uncontrolled hypertension and CKD with albuminuria

CKD, chronic kidney disease; BP, blood pressure; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Explore-CKD: Phase 2b Crossover Clinical Trial



Primary efficacy endpoint:

- Placebo-adjusted change in AOBP SBP at Week 4

Pre-specified exploratory endpoints:

- Placebo-adjusted percent change in UACR at Week 4
- Placebo-adjusted percent change in eGFR at Week 4

[a]Either study-provided commercially available dapagliflozin 10 mg QD or continue regularly prescribed SGLT2i.
[b]Participants who did not enroll in the OLE attended a 2-week End of Study safety follow-up visit.
ACEi, angiotensin converting enzyme inhibitor; AOBP, automated office blood pressure; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration; OLE, open-label extension; SBP, systolic blood pressure; QD, once daily; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UACR, urinary albumin-creatinine ratio.

Key Inclusion & Exclusion Criteria

Inclusion Criteria

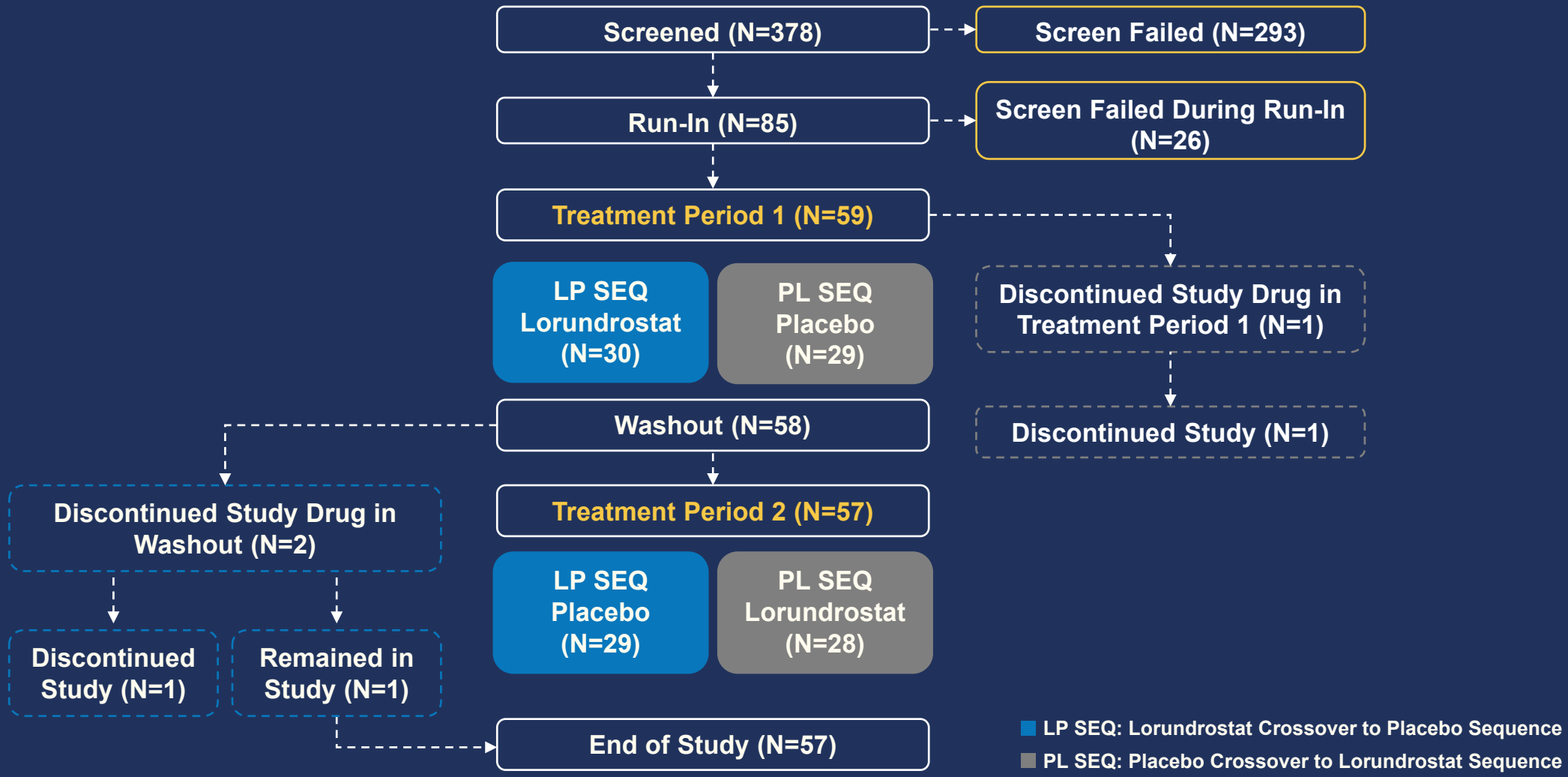
- Males or females aged ≥18 years
- AOBP SBP 135-180 mmHg
- Stage 1-3b CKD (eGFR ≥30 mL/min/1.73 m²)
- Albuminuria (first-morning void UACR 200-5000 mg/g)
- Stable treatment with an ACEi or ARB for ≥4 weeks prior to screening

Exclusion Criteria

- Serum potassium >5.0 mmol/L
- Serum sodium <135 mmol/L
- eGFR <30 mL/min/1.73 m^2
- Uncontrolled diabetes (HbA1c >10%)

ACEi, angiotensin converting enzyme inhibitor; AOBP, automated office blood pressure; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; UACR, urinary albumin-creatinine ratio.

Explore-CKD: Participant Flow



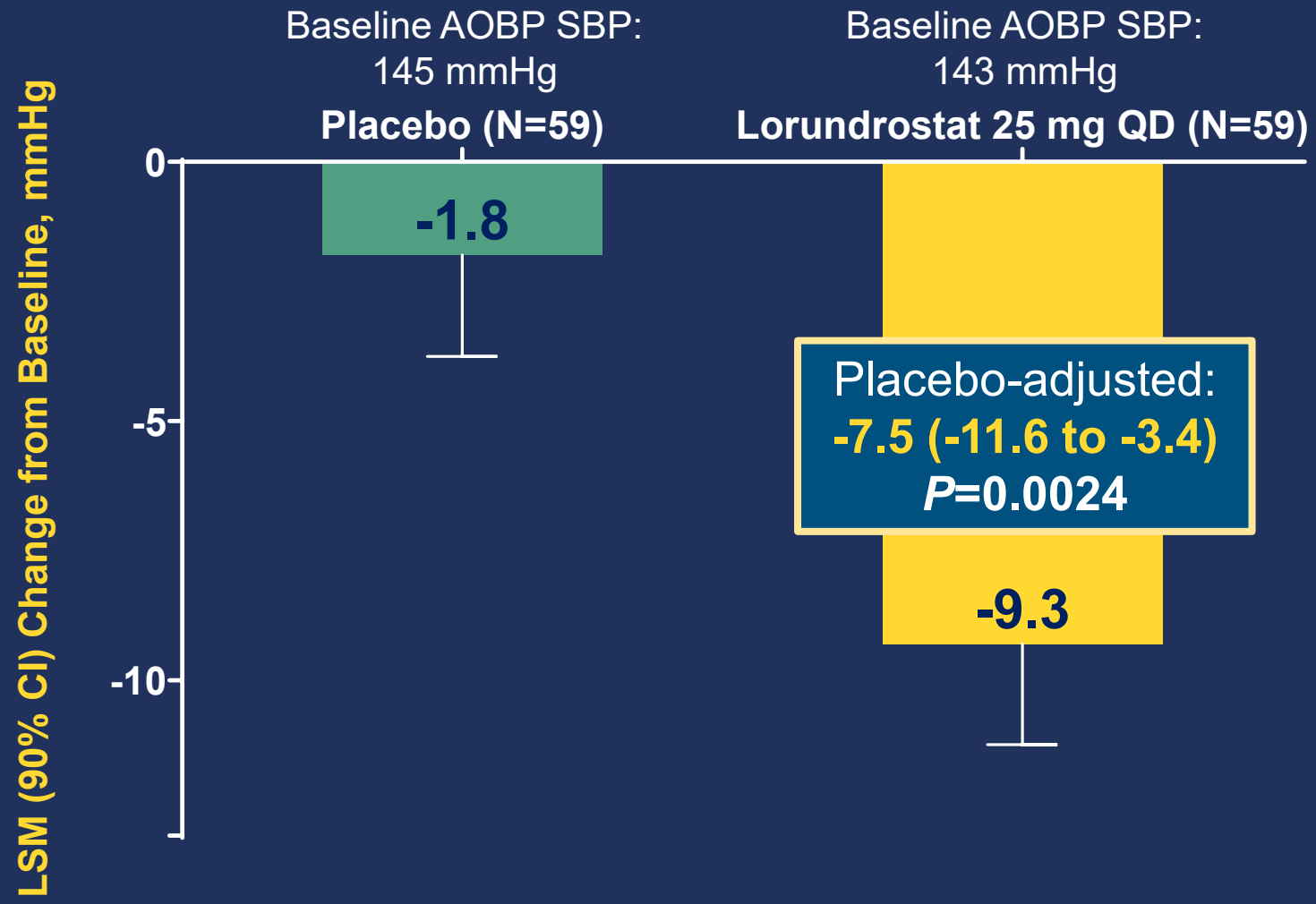
AE, adverse event; LP SEQ, lorundrostat 25 mg - placebo sequence; PL SEQ, placebo - lorundrostat 25 mg sequence.

Baseline Demographics & Clinical Characteristics

	Total (N=59)
Mean age (SD), years	64.6 (10.14)
Female, n (%)	18 (30.5)
White, n (%)	39 (66.1)
African American/Black, n (%)	10 (16.9)
Baseline BMI, mean (SD), kg/m^2	33.1 (7.10)
eGFR (cystatin C), mean (SD), mL/min/1.73 m^2	43.0 (14.97)
eGFR (creatinine), mean (SD), mL/min/1.73 m^2	54.6 (21.08)
Baseline UACR (spot), geometric mean (SD), mg/g	517 (2.51)
Diabetes, n (%)	45 (76.3)
SGLT2i naïve at screening, n (%)	26 (44.1)
Seated AOBP SBP, mean (SD), mmHg	148.9 (10.37)

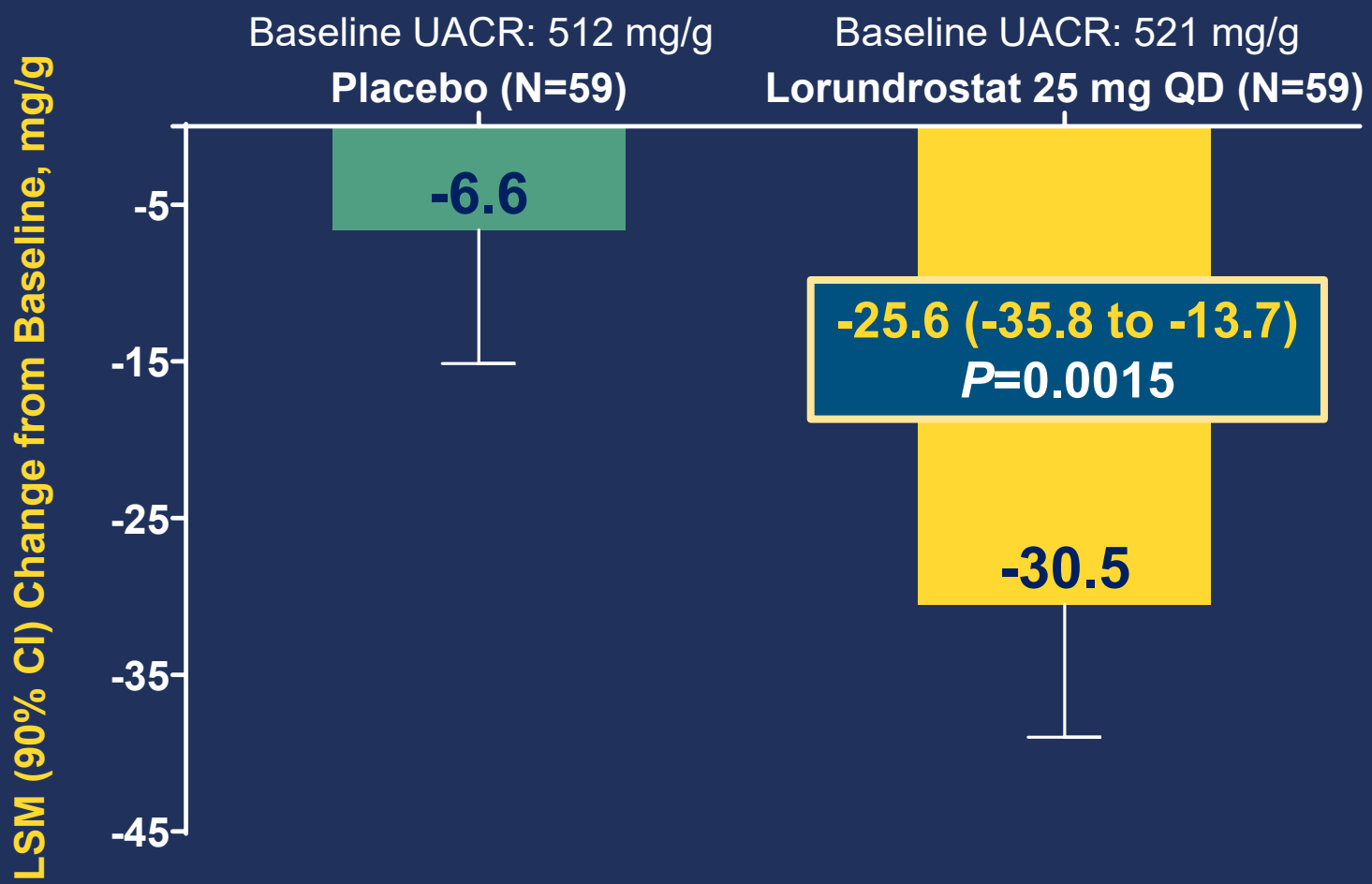
AOBP, automated office blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urinary albumin-to creatinine ratio.

Primary Endpoint: Placebo-Adjusted Change in AOBP SBP at Week 4



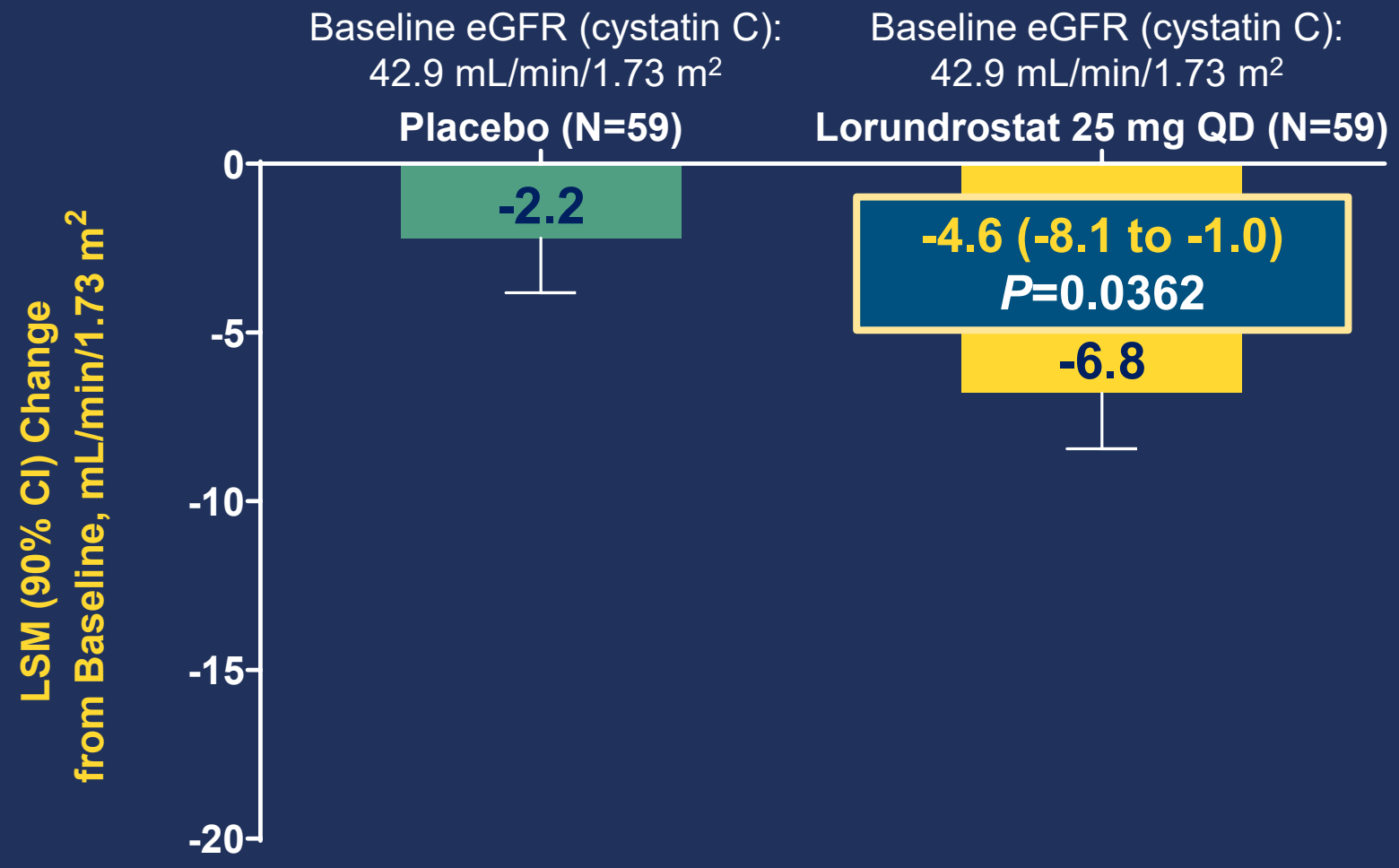
AOBP, automated office blood pressure; CI, confidence interval; LSM, least square means; QD, once daily; SBP, systolic blood pressure.

Exploratory Endpoint: Percent Change in Spot UACR at Week 4



CI, confidence interval; LSM, least square means; QD, once daily; UACR, urinary albumin-to creatinine ratio.

Exploratory Endpoint: Percent Change in eGFR (Cystatin C) at Week 4



CI, confidence interval; eGFR, estimated glomerular filtration rate; LSM, least square means; QD, once daily.

Participants with event, n (%)	Placebo (N=57)	Lorundrostat (N=58)
Treatment-related TEAE	8 (14.0)	16 (27.6)
Treatment-related TEAEs by worst severity		
Mild	6 (10.5)	5 (8.6)
Moderate	2 (3.5)	10 (17.2)
Severe	0	1 (1.7)
Serum potassium >6.0 mmol/L – Adjudicated per protocol[a]	0	3 (5.2)
SAE	0	2 (3.4)
AESI	1 (1.8)	10 (17.2)
TEAE leading to discontinuation of study drug	1 (1.8)[b]	2 (3.4)[c]
Death	0	0

[a]During the adjudication process, any elevated value confirmed to be hemolyzed or spurious was removed from the evaluation; [b]Retinal detachment; [c]Hyperkalemia/acute kidney injury and CKD worsening.
AESI, adverse event of special interest; CKD, chronic kidney disease; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Conclusions

- In Explore-CKD, lorundrostat added to SGLT2i significantly reduced AOBP SBP and albuminuria in participants with CKD and uncontrolled hypertension
- This parallel reduction is anticipated to provide meaningful benefits in CKD-associated cardiorenal outcomes
- Lorundrostat was well tolerated, with modest changes in potassium and eGFR
- Lorundrostat demonstrated reductions in AOBP SBP in participants with CKD and uncontrolled hypertension, suggesting that lorundrostat may provide benefits in CKD-associated cardiorenal outcomes

AOBP, automated office blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

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