Target-HTN

Trial on the Safety and Efficacy of Lorundrostat (MLS-101) in Patients With Uncontrolled Hypertension

Luke J. Laffin MD

On Behalf of the

Target-HTN Investigators

American Heart Association

Hypertension Scientific Sessions

Insight from the Late Breaking Clinical Trials

September 10, 2023

Disclosures: Consultant / Steering Committee (Medtronic, Eli Lilly and Company, Mineralys Therapeutics, AstraZeneca, Crispr Therapeutics); Research Funding (AstraZeneca); Advisor (Gordy Health); Royalties (Belvoir Media Group, Elsevier)

Background

- Hypertension is the leading contributor to cardiovascular morbidity and mortality worldwide
- Increased global prevalence of hypertension parallels increasing rates of obesity
- Excess aldosterone production contributes to hypertension in both “classical” hyperaldosteronism and obesity-associated hypertension
- Aldosterone synthase inhibition may be an effective therapy for blood pressure driven by excess aldosterone, particularly if highly- specific for CYP11B2

Objective

To compare the safety and efficacy of **lorundrostat, an aldosterone synthase inhibitor,** with placebo, and characterize dose-dependent safety and efficacy to inform dose selection in future trials.

Trial Overview

- Prospective, randomized, double-blind, multi-center, placebo-controlled
- Adults with uncontrolled hypertension taking ≥ 2 antihypertensive medications (systolic AOBP ≥ 130 mm Hg)
- eGFR ≥ 60 mL/min/1.73m^2 and serum potassium ≤ 5.2 mmol/L
- Two separate cohorts, 8 weeks of treatment

Cohort 1

- N = 163 participants
- PRA ≤ 1.0 ng/mL/h and plasma aldosterone ≥1.0 ng/dL
- 1:1:1:1:1:1 randomization

Cohort 2

- N = 37 participants
- PRA >1.0 ng/mL/h
- 1:6 randomization

Primary Endpoint

Change in Systolic AOBP from Baseline to Week 8 Compared with Placebo (Cohort 1)

Additional Endpoints

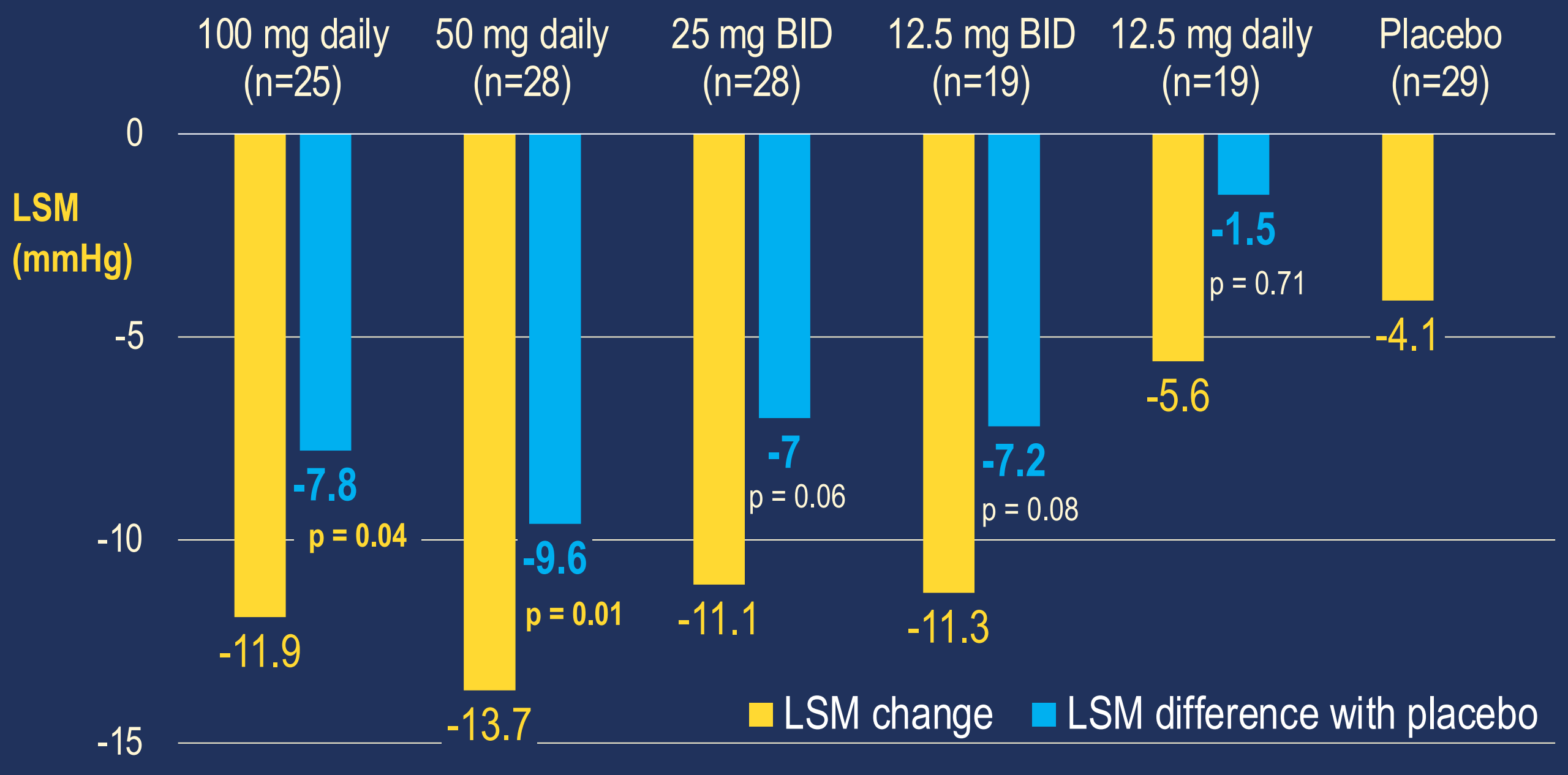
Change in Diastolic AOBP

Safety and Pharmacodynamic Biomarkers

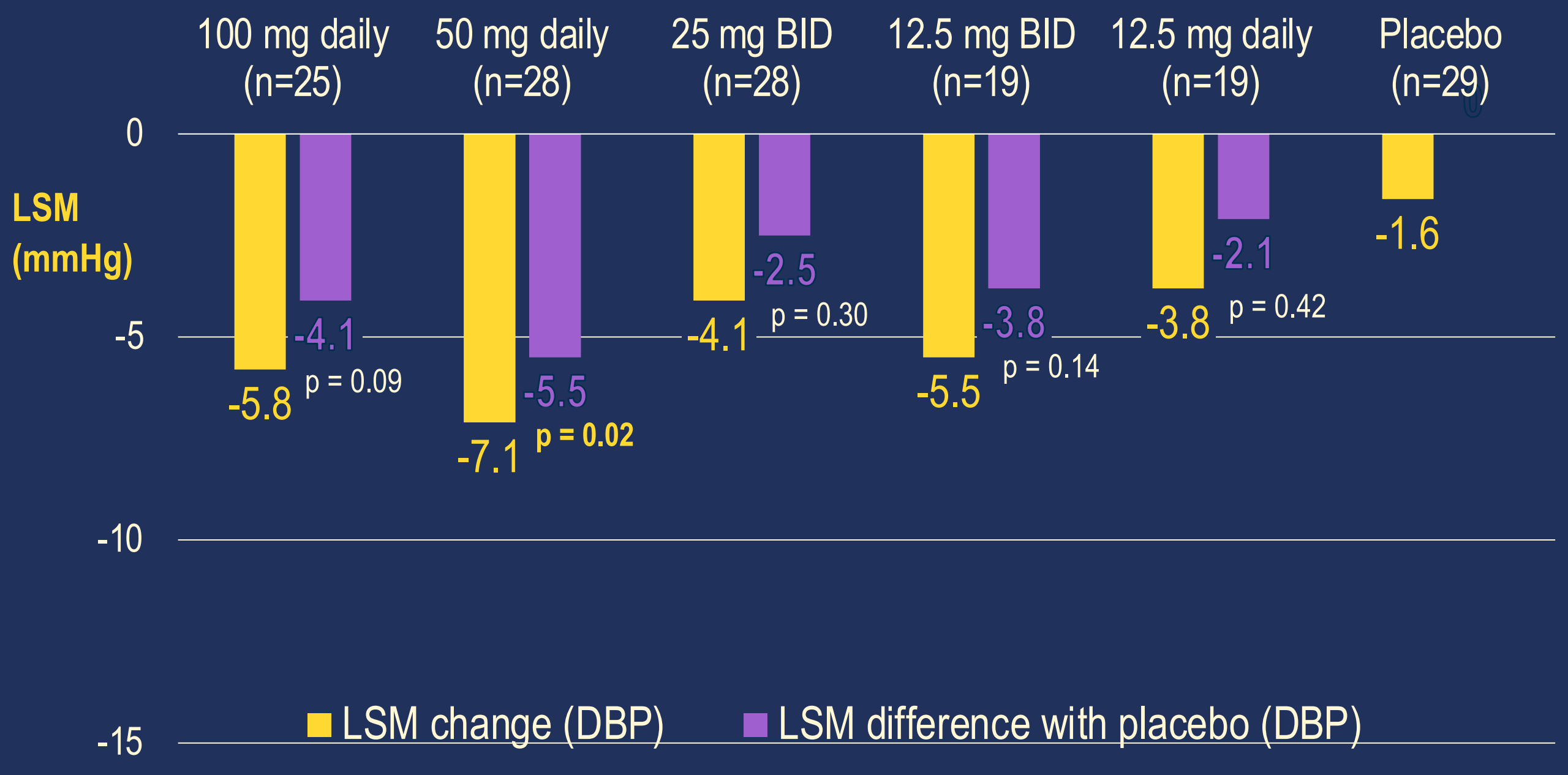
Study Participants

	Cohort 1 100 mg daily (n=30)	Cohort 1 50 mg daily (n=28)	Cohort 1 25 mg BID (n=30)	Cohort 1 12.5 mg BID (n=22)	Cohort 1 12.5 mg daily (n=23)	Cohort 1 Placebo (n=30)	Cohort 2 100mg daily (n=31)	Cohort 2 Placebo (n=6)
Age (years)	69	65	65	68	65	63	67	63
Women (%)	60%	54%	63%	64%	52%	57%	68%	67%
Black Race (%)	50%	29%	23%	32%	48%	53%	19%	33%
BMI (kg/m^2)	30.4	32.0	30.6	32.0	30.6	31.9	30.5	32.0
AOBP (mmHg)	142 / 79	140 / 85	143 / 80	143 / 82	143 /80	143 / 84	140 / 79	135 /82
≥ 3 BP meds (%)	53%	29%	53%	68%	39%	43%	36%	33%
Thiazide (%)	57%	57%	60%	59%	52%	53%	61%	83%
ACEi / ARB (%)	77%	71%	90%	77%	78%	73%	97%	83%

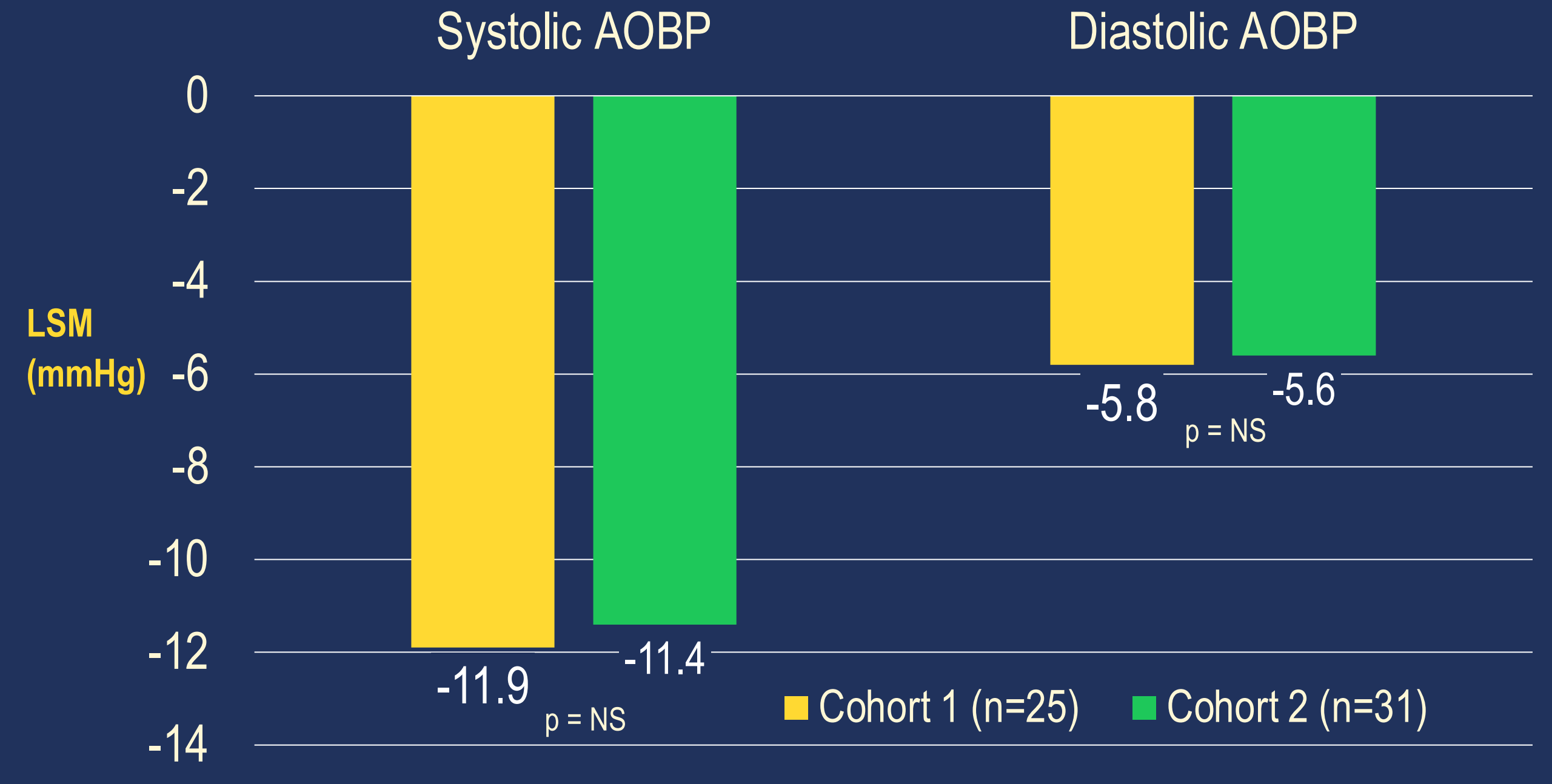
Primary Endpoint: Change in Systolic AOBP



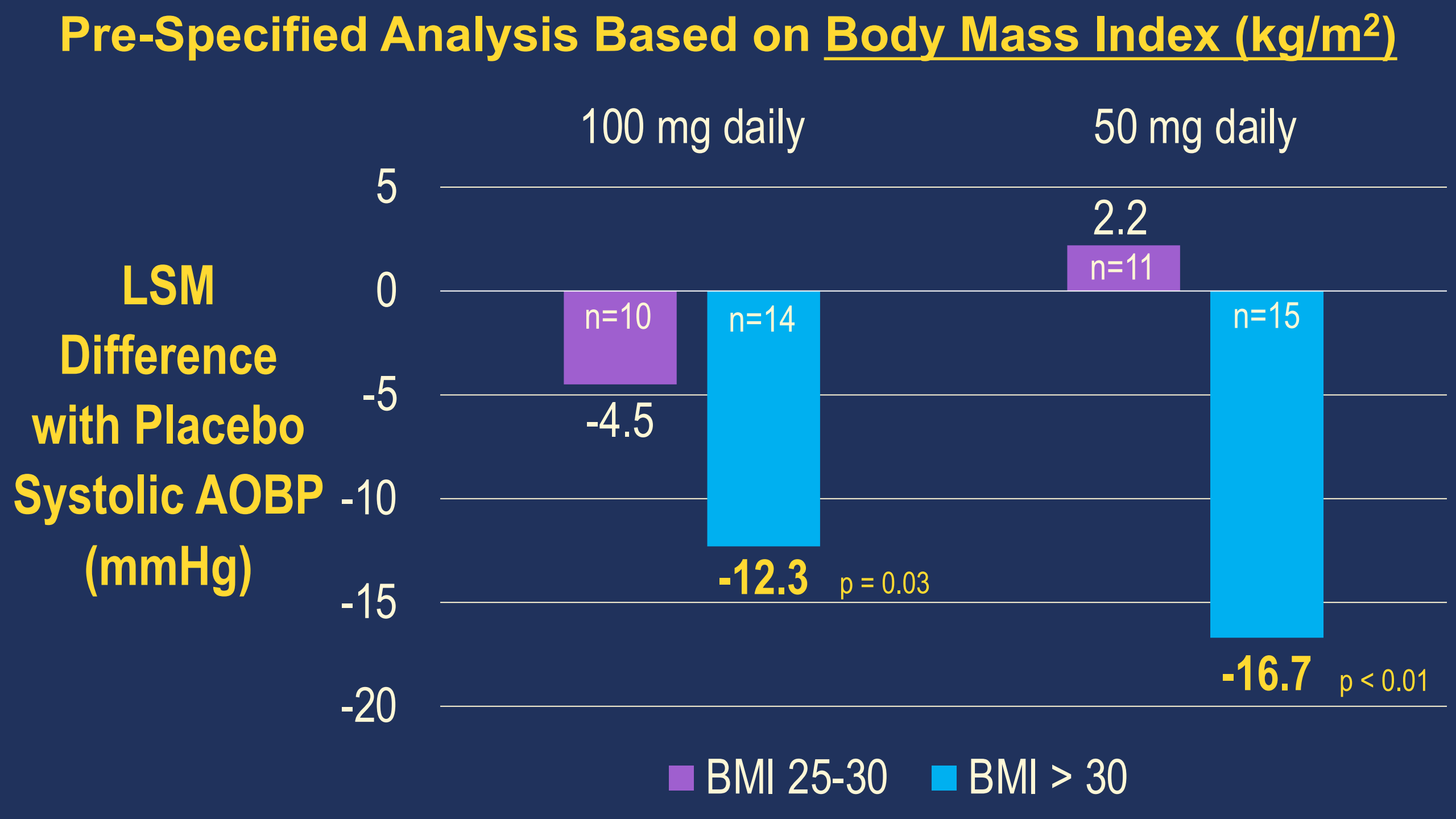
Secondary Endpoint: Change in Diastolic AOBP



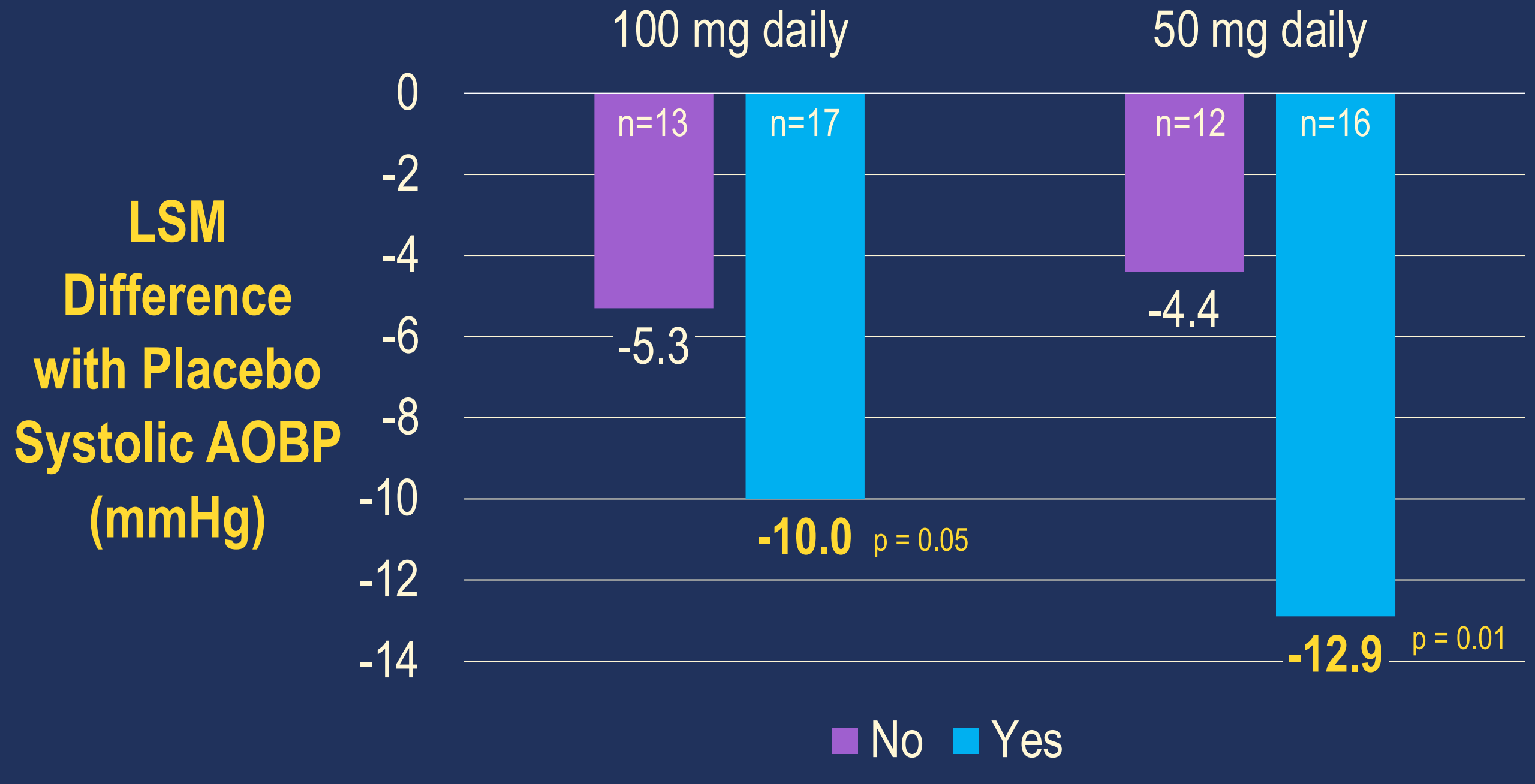
100 mg Daily: Difference Between Cohort 1 and 2



Pre-Specified Analysis Based on Body Mass Index (kg/m²)



Pre-Specified Analysis Based on Use of Thiazide-Type Diuretic



Adverse events

	Cohort 1 100 mg daily (N=30)	Cohort 1 50 mg daily (N=28)	Cohort 1 25 mg BID (N=30)	Cohort 1 12.5 mg BID (N=22)	Cohort 1 12.5 mg daily (N=23)	Cohort 1 Placebo (N=30)	Cohort 2 100mg daily (n=31)	Cohort 2 Placebo (n=6)
Serious AE (%)	0%	0%	0%	0%	9%[b]	0%	3%[c]	0%
Any AE (%)[a]	57%	43%	67%	59%	70%	40%	61%	17%
Hypotension (%)	3%	0%	0%	1%	0%	0%	3%	0%

[a] Participants counted once at highest-grade abnormality

[b] One participant worsening of pre-existing CAD and one participant metastatic cancer to their peritoneum

[C] Participant had hyponatremia that resolved upon drug discontinuation

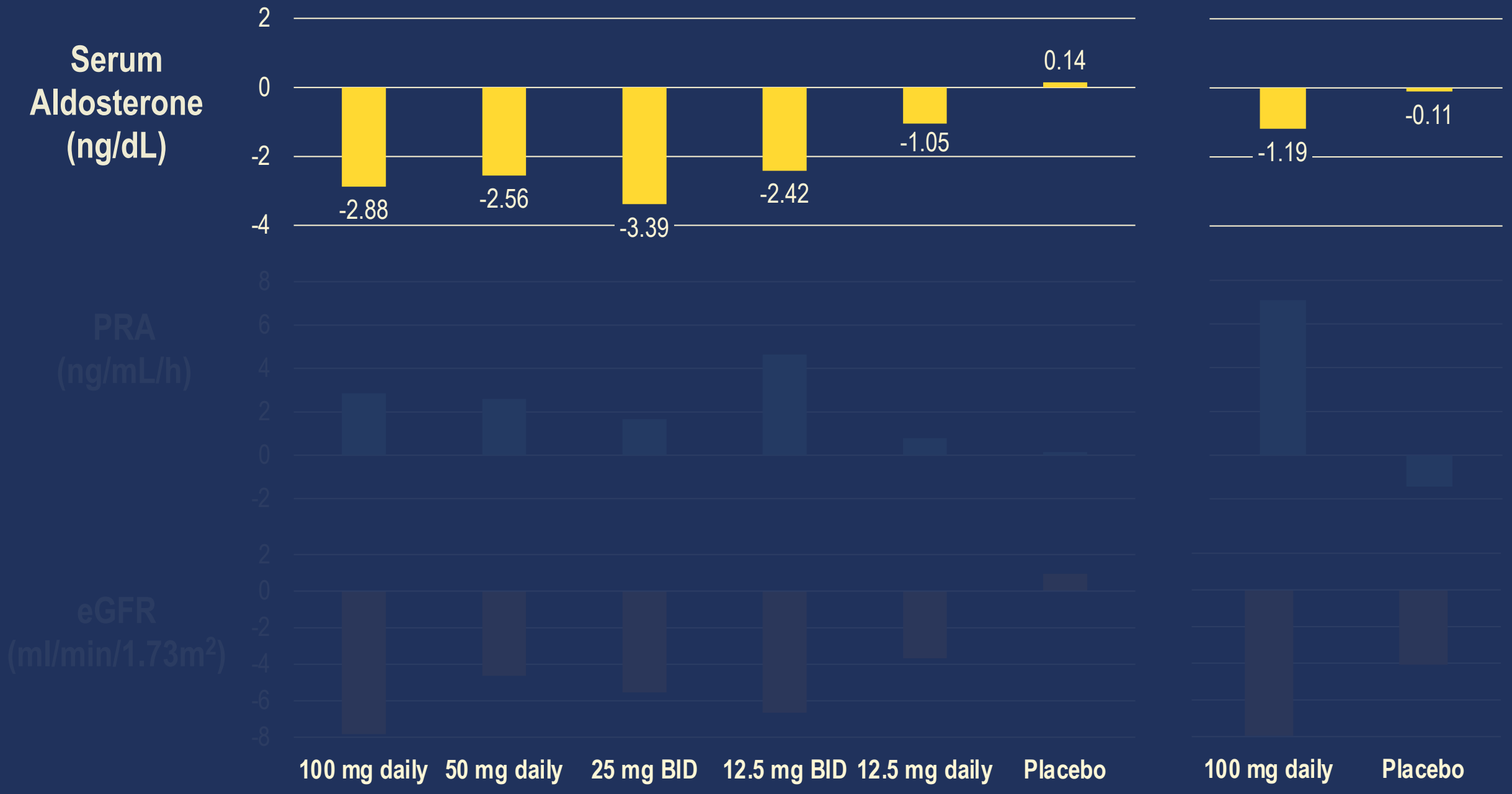
Serum potassium changes

	Cohort 1 100 mg daily (N=30)	Cohort 1 50 mg daily (N=28)	Cohort 1 25 mg BID (N=30)	Cohort 1 12.5 mg BID (N=22)	Cohort 1 12.5 mg daily (N=23)	Cohort 1 Placebo (N=30)	Cohort 2 100mg daily (n=31)	Cohort 2 Placebo (n=6)
Mean change in K^+ (mmol/L)	0.29	0.25	0.34	0.32	0.31	0.03	0.21	-0.05
Participants with K^+ 5.6 - 6.0 mmol/L (%)	16%	4%	7%	9%	13%	0%	6%	0%
Participants with K^+ 6.1 - 6.5 mmol/L (%)	0%	0%	3%	5%	4%	0%	3%	0%
Participants with K^+ > 6.5 mmol/L (%)	3%	4%	0%	0%	0%	0%	0%	0%

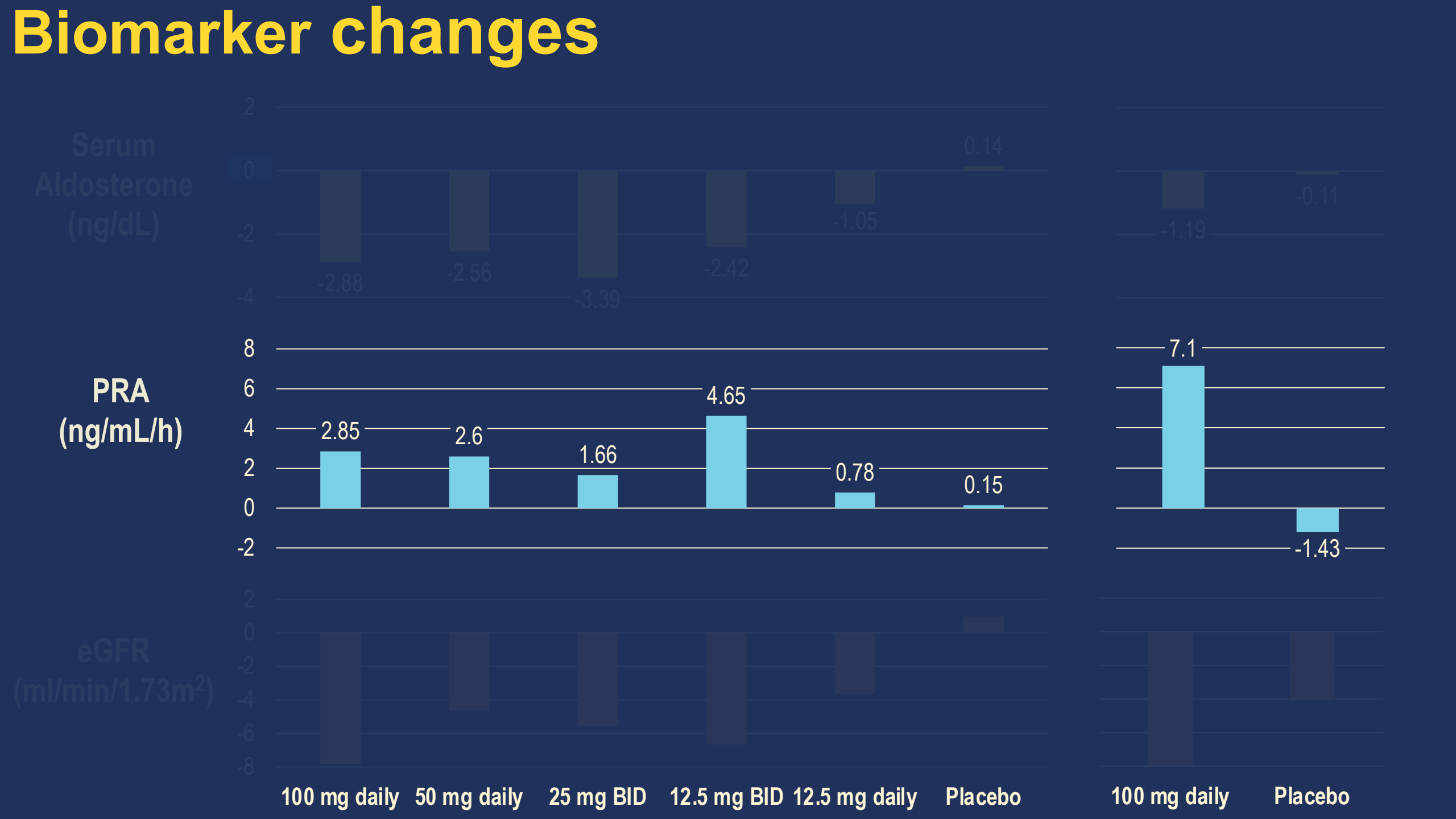
Affected individuals were counted once at highest-grade abnormality

Hemolyzed blood samples with serum potassium levels that were not reproducible on repeat testing were not included

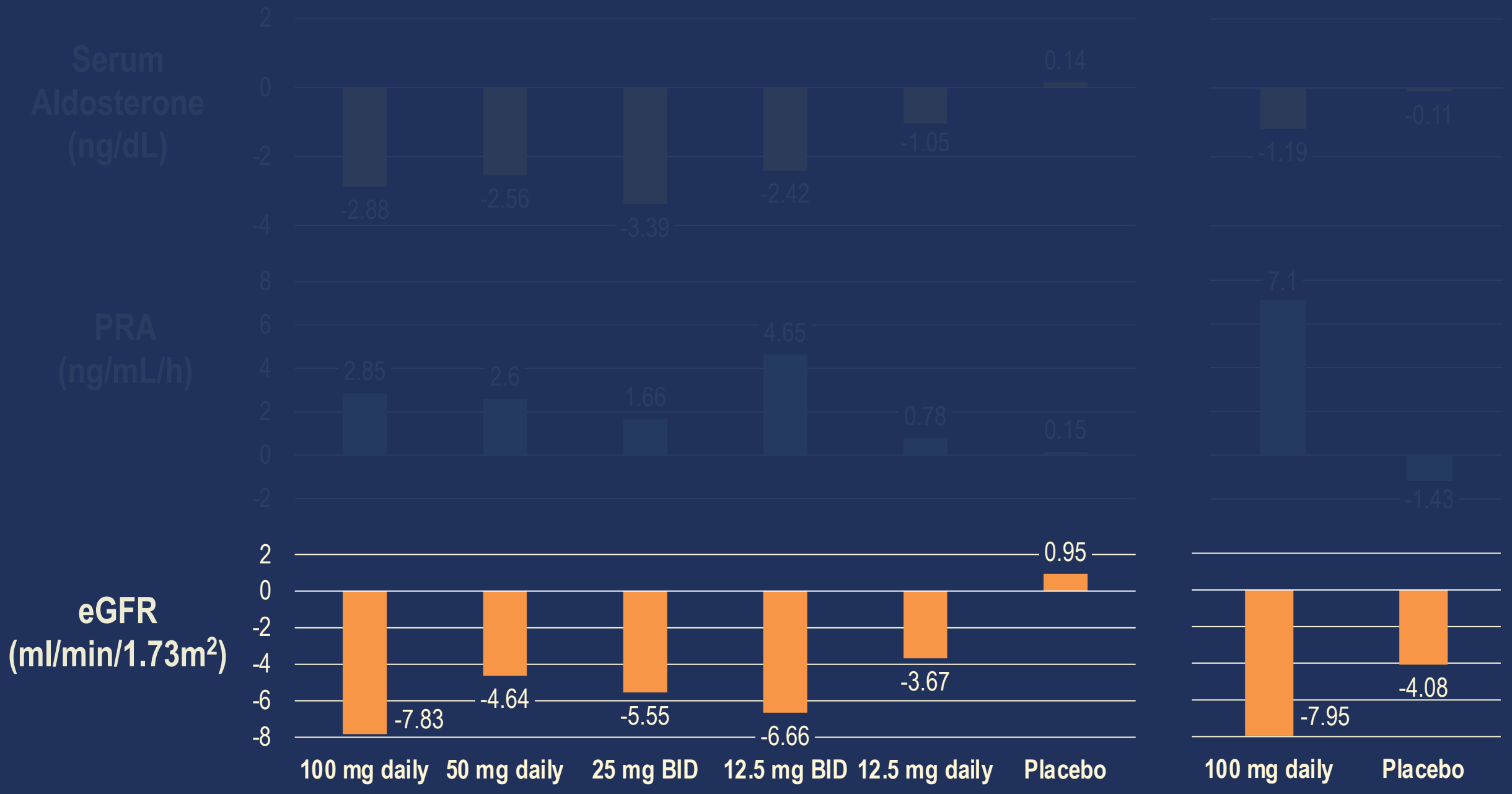
Biomarker changes



Biomarker changes



Biomarker changes



Limitations

- Phase 2 dose-finding study
- Use of AOBP, rather than ABPM, for primary endpoint
- Participants on varying background antihypertensive regimens

Conclusions

- Lorundrostat was well tolerated and reduced systolic AOBP
- BP reduction particularly evident among participants with obesity
- Small expected increases in potassium and declines in eGFR
- Results support further study of lorundrostat as a treatment for uncontrolled hypertension, particularly with the 50 mg daily dose

Acknowledgements

Target-HTN Participants

43 sites across the United States

Target-HTN Investigators

Mineralys Therapeutics

Jon Congleton, David Rodman MD, Jessica Ibbitson, among others

Co-authors

David Rodman MD, James M. Luther MD, Anand Vaidya MD, Matthew R. Weir MD, Natasa Rajicic ScD, BT Slingsby MD PhD, and Steven E. Nissen MD

Simultaneous Publication

Research

JAMA | Original Investigation

Aldosterone Synthase Inhibition With Lorundrostat for Uncontrolled Hypertension

The Target-HTN Randomized Clinical Trial

Luke J. Laffin, MD; David Rodman, MD; James M. Luther, MD; Anand Vaidya, MD; Matthew R. Weir, MD; Natasa Rajicic, ScD; B. T. Slingsby, MD, PhD; Steven E. Nissen, MD; for the Target-HTN Investigators

Cleveland Clinic

Every life deserves world class care.

laffinl@ccf.org
@ljlaffin