

Supplemental Online Content

Laffin LJ, Rodman D, Luther JM, et al; Target-HTN Investigators. Aldosterone synthase inhibition with lorundrostat for uncontrolled hypertension. *JAMA*. Published online September 10, 2023. doi:10.1001/jama.2023.16029

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This supplemental material has been provided by the authors to give readers additional information about their work.

Target-HTN Sites

Institution	Number of participants randomized	Institution	Number of participants randomized
RC Health Concepts	2	Northwest Heart Clinical Research	0
Lundquist Institute	1	Vanderbilt	2
Jefferson City Medical Group	0	Clinical Research of West Florida, Inc.	2
PRX Research	0	WR-ClinSearch	1
Finlay Medical Research Corp	28	Ace Clinical Research Group	6
Grace Research	0	Holston Medical Group, P.C.	0
Javara Research	4	Orange County Research Center, Inc.	0
Clinical Research of West Florida - Corporate	3	Carolina Institute for Clinical Research	2
Grace Research	2	Next Phase Research	0
WR-Global Medical Research	0	Andres Patron	6
Clinical Research of South Nevada	4	Medication Management, LLC	0
Burke Primary Care	3	Vitae Research Center	7
M3 Wake Research, Inc.	1	Finlay Medical Research Corp	47
Louisiana Heart Center	0	AMR Coral Gables/Miami	2
Houston Methodist Hospital	2	Queens Hospital Medical Center	1
Javara - Privia Medical Group Georgia	3	Health Awareness, Inc.	1
Javara Inc.	0	Sundance Clinical Research	0
Javara Inc.	1	Clinical Trials Research	3
Suncoast Research Group, LLC	10	Wellness Clinical Research	1
Cleveland Clinic	0		
North Hills Medical Research	8		
Arlington Family Research Center	0		
Randolph Medical Associates	18		
Georgia Clinical Research Center, Inc.	29		

eTable 1. Select pre-specified analysis of factors anticipated to impact blood pressure lowering response to lorundrostat in cohort 1

	Body mass index (kg/m ²)		Use of thiazide-type diuretic		Race	
	25-30	>30	No	Yes	Black or African American	Other
50 mg daily dose						
LSM difference with placebo in systolic AOBP change, mmHg (90%CI)	2.2 (-7.4 to 11.8) P=0.7 <i>(n=11)</i>	-16.7 (-25.5 to -7.9) P<0.01 <i>(n=15)</i>	-4.4 (-14.0 to 5.1) P=0.44 <i>(n=12)</i>	-12.9 (-21.2 to -4.7) P=0.01 <i>(n=16)</i>	-6.9 (-16.9 to 3.2) P=0.26 <i>(n=8)</i>	-12.0 (-20.4 to -3.7) P=0.02 <i>(n=20)</i>
100 mg daily dose						
LSM difference with placebo in systolic AOBP change, mmHg (90%CI)	-4.5 (-14.5 to 5.5) P=0.46 <i>(n=10)</i>	-12.3 (-21.6 to -3.1) P=0.03 <i>(n=14)</i>	-5.3 (-15.1 to -4.4) P=0.36 <i>(n=13)</i>	-10.0 (-18.4 to -1.6) P=0.05 <i>(n=17)</i>	-7.1 (-15.8 to 1.5) P=0.17 <i>(n=15)</i>	-9.4 (-18.6 to -0.3) P=0.09 <i>(n=15)</i>

Abbreviations: AOBP – automated office blood pressure, CI – confidence interval, LSM – Least square means.

eTable 2. Change in pharmacodynamic biomarkers compared with baseline

	100 mg daily Cohort 1* (n=30)	50 mg daily (n=28)	25 mg BID (n=30)	12.5 mg BID (n=22)	12.5 mg daily (n=23)	Placebo Cohort 1*(n=30)	100mg daily, Cohort 2* (n=31)	Placebo, Cohort 2* (n=6)
Baseline serum aldosterone, mean (SD), ng/dL	6.57 (3.29)	6.21 (3.83)	6.57 (4.37)	6.71 (3.43)	7.04 (3.75)	6.46 (3.39)	6.32 (3.47)	5.96 (1.84)
Week 4 serum aldosterone, mean (SD), ng/dL	3.97 (4.19)	3.90 (5.27)	3.10 (3.25)	4.51 (3.75)	6.06 (4.62)	6.79 (4.77)	5.02 (4.84)	5.84 (3.14)
Change in serum aldosterone, mean (SD), ng/dL	-2.88 (4.44)	-2.56 (3.72)	-3.39 (4.22)	-2.42 (2.78)	-1.05 (4.33)	0.14 (3.68)	-1.19 (5.38)	-0.11 (3.39)
Baseline plasma renin activity, mean (SD), ng/mL/h	0.96 (2.12)	1.26 (3.01)	1.10 (2.24)	1.30 (1.90)	0.95 (1.07)	0.54 (0.44)	5.42 (7.05)	5.53 (8.66)
Week 4 plasma renin activity, mean (SD), ng/mL/h	3.87 (6.31)	3.94 (9.16)	2.86 (4.22)	5.99 (11.27)	1.80 (3.57)	0.69 (0.97)	12.64 (12.08)	4.10 (2.49)
Change in plasma renin activity, mean (SD), ng/mL/h	2.85 (6.27)	2.60 (9.34)	1.66 (2.40)	4.65 (11.27)	0.78 (3.44)	0.15 (0.78)	7.10 (13.03)	-1.43 (7.00)
Baseline morning serum cortisol, mean (SD), ug/dL	11.28 (3.55)	10.81 (2.74)	10.58 (2.51)	10.20 (2.98)	9.45 (4.11)	10.51 (3.45)	11.12 (3.47)	10.51 (2.66)
Week 8 morning serum cortisol, mean (SD), ug/dL	16.68 (9.09)	15.66 (7.10)	15.53 (8.26)	12.32 (7.65)	12.52 (8.79)	14.20 (8.59)	25.40 (6.75)	28.07 (5.40)
Change in morning serum cortisol, mean (SD), ug/dL	5.03 (7.63)	4.85 (6.78)	4.94 (7.73)	1.88 (7.40)	3.23 (8.37)	3.57 (7.46)	14.24 (8.11)	17.55 (7.15)
Baseline eGFR, mean (SD), ml/min/1.73m ²	77.35 (13.95)	77.18 (14.05)	80.85 (12.37)	81.70 (16.28)	77.87 (18.69)	81.63 (17.31)	79.90 (13.10)	83.92 (18.59)
Week 8 eGFR, mean (SD), ml/min/1.73m ²	68.42 (20.14)	72.54 (16.89)	75.11 (14.81)	76.32 (19.63)	76.00 (21.00)	83.83 (17.32)	72.42 (16.32)	79.83 (15.78)
Change in eGFR, mean (SD), ml/min/1.73m ²	-7.83 (11.62)	-4.64 (9.87)	-5.55 (9.22)	-6.66 (7.92)	-3.67 (8.10)	0.95 (7.06)	-7.95 (9.13)	-4.08 (3.94)

*Cohort 1 = plasma renin activity ≤ 1.0 ng/mL/h, Cohort 2 = plasma renin activity >1.0 ng/mL/h. Abbreviations: BID – twice daily, eGFR – estimated glomerular filtration rate, SD-standard deviation

eTable 3. Observed 24-hour ambulatory blood pressure changes among all cohort 1 participants

	Placebo (n=26)	12.5 mg BID (n=16)	25 mg BID (n=26)	12.5 mg daily (n=15)	50 mg daily (n=28)	100 mg daily Cohort 1 (n=24)
Mean 24-hour ABPM, Baseline to End of Treatment						
Mean (SE) change in SBP, mmHg	-0.8 (2.1)	-5.7 (3.2)	-8.7 (3.1)	-5.2 (4.3)	-1.8 (3.0)	-8.9 (2.4)
Mean 24-hour Central Blood Pressure Assessed by Pulse Wave Velocity during ABPM						
Mean (SE) change in SBP, mmHg	-0.6 (2.2)	-8.0 (4.7)	-10.6 (3.5)	0.6 (5.6)	-4.3 (3.1)	-11.0 (2.8)
Mean Overnight ABPM, Baseline to End of Treatment						
Mean (SE) change in SBP, mmHg	-3.5 (2.5)	-7.5 (4.0)	-6.0 (3.1)	-5.4 (5.4)	2.4 (4.8)	-11.5 (2.9)

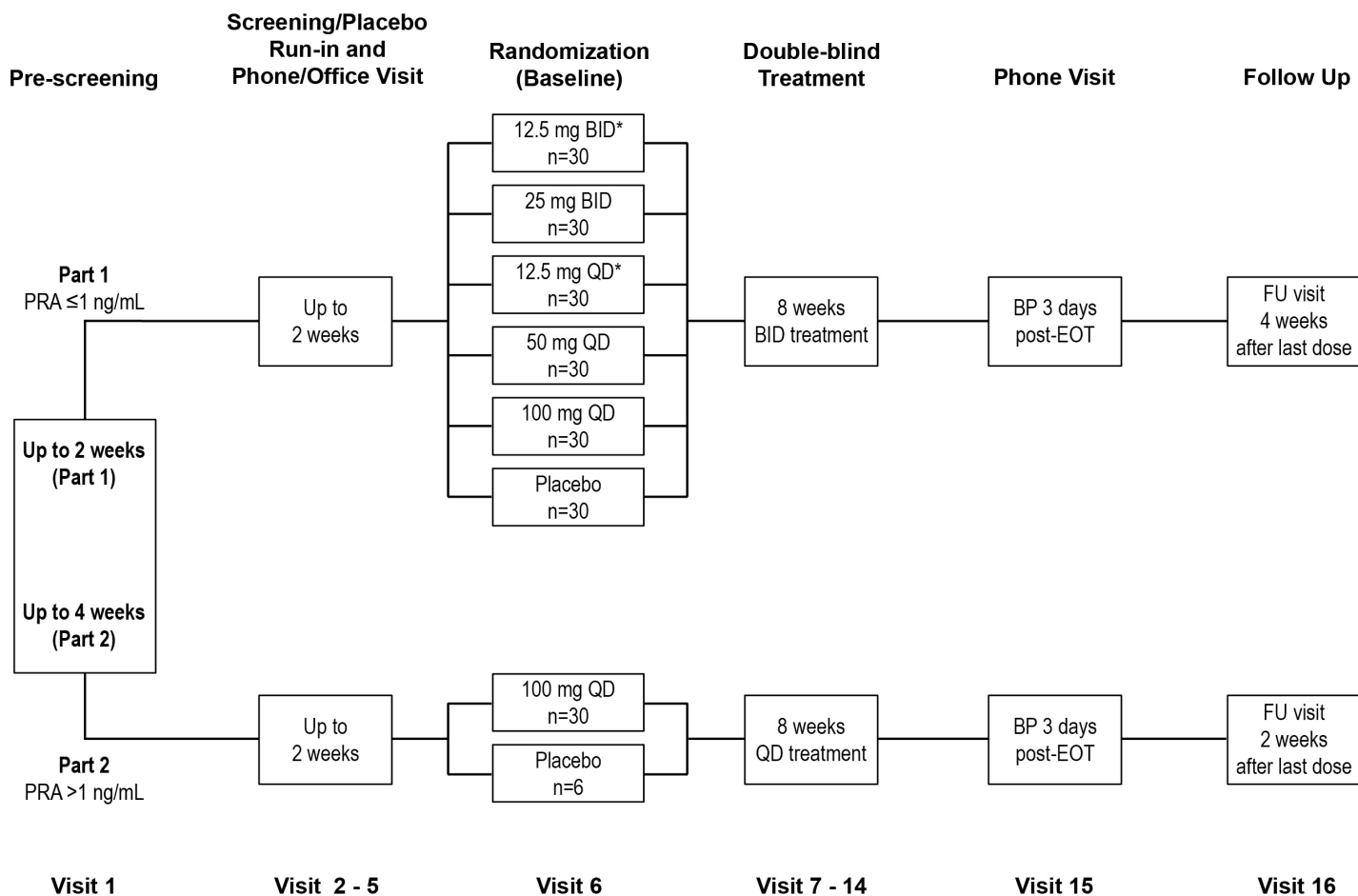
Abbreviations: ABPM – ambulatory blood pressure monitoring, BID – twice daily, LSM - Least-square means, SBP – systolic blood pressure, SE – standard error

eTable 4. Observed 24-hour ambulatory blood pressure changes among cohort 1 participants with baseline 24-hour mean systolic blood pressure > 130 mm Hg

	Placebo (n=20)	12.5 mg BID (n=12)	25 mg BID (n=19)	12.5 mg daily (n=14)	50 mg daily (n=14)	100 mg daily Cohort 1 (n=21)
Mean 24-hour ABPM, Baseline to End of Treatment						
Mean (SE) change in SBP, mmHg	-2.1 (2.3)	-7.1 (4.0)	-12.1 (3.8)	-5.6 (4.6)	-7.5 (4.7)	-9.9 (2.7)
Mean 24-hour Central Blood Pressure Assessed by Pulse Wave Velocity during ABPM, Baseline to End of Treatment						
Mean (SE) change in SBP, mmHg	-1.4 (2.5)	-7.4 (5.2)	-13.1 (4.1)	-0.6 (6.2)	-10.8 (2.7)	-12.9 (2.8)
Mean Overnight ABPM, Baseline to End of Treatment						
Mean (SE) change in SBP, mmHg	-3.9 (2.3)	-6.4 (5.1)	-9.6 (4.0)	-5.6 (5.9)	-0.1 (6.8)	-12.3 (3.2)

Abbreviations: ABPM – ambulatory blood pressure monitoring, BID – twice daily, SBP – systolic blood pressure, SD – standard deviation

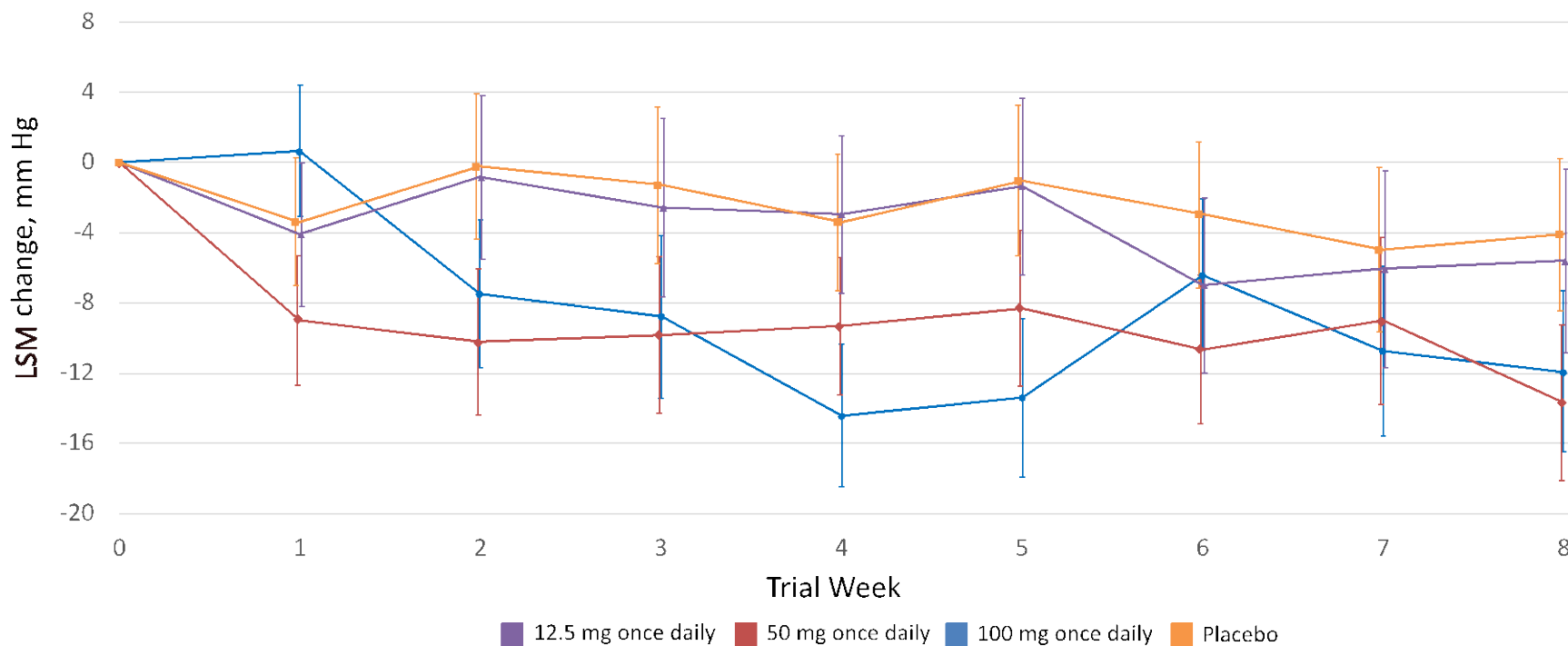
eFigure 1. Study design schema



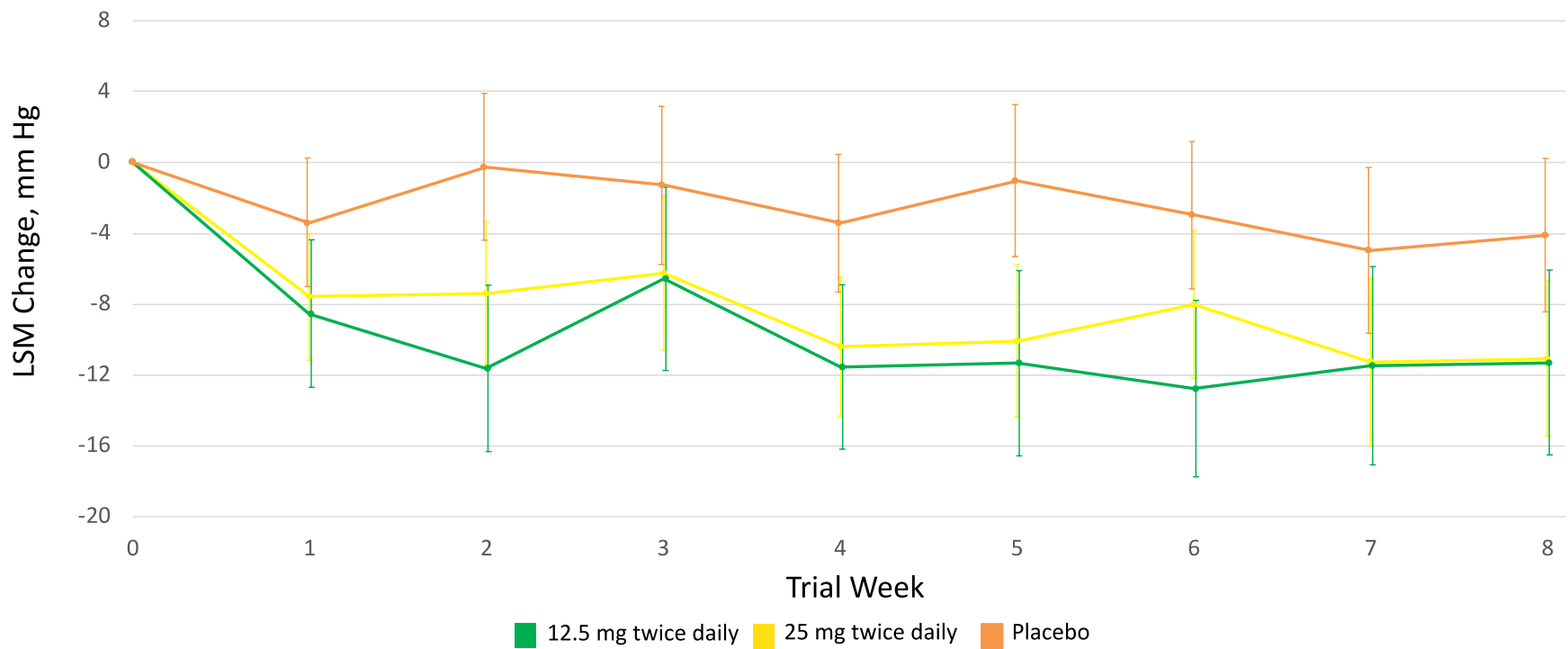
* - Randomization to the 12.5 mg daily and twice daily was stopped following interim analysis due to sub-maximal efficacy

Abbreviations: BID – twice daily, BP – blood pressure, EOT- end of treatment, FU – follow-up, PRA – plasma renin activity, QD –daily

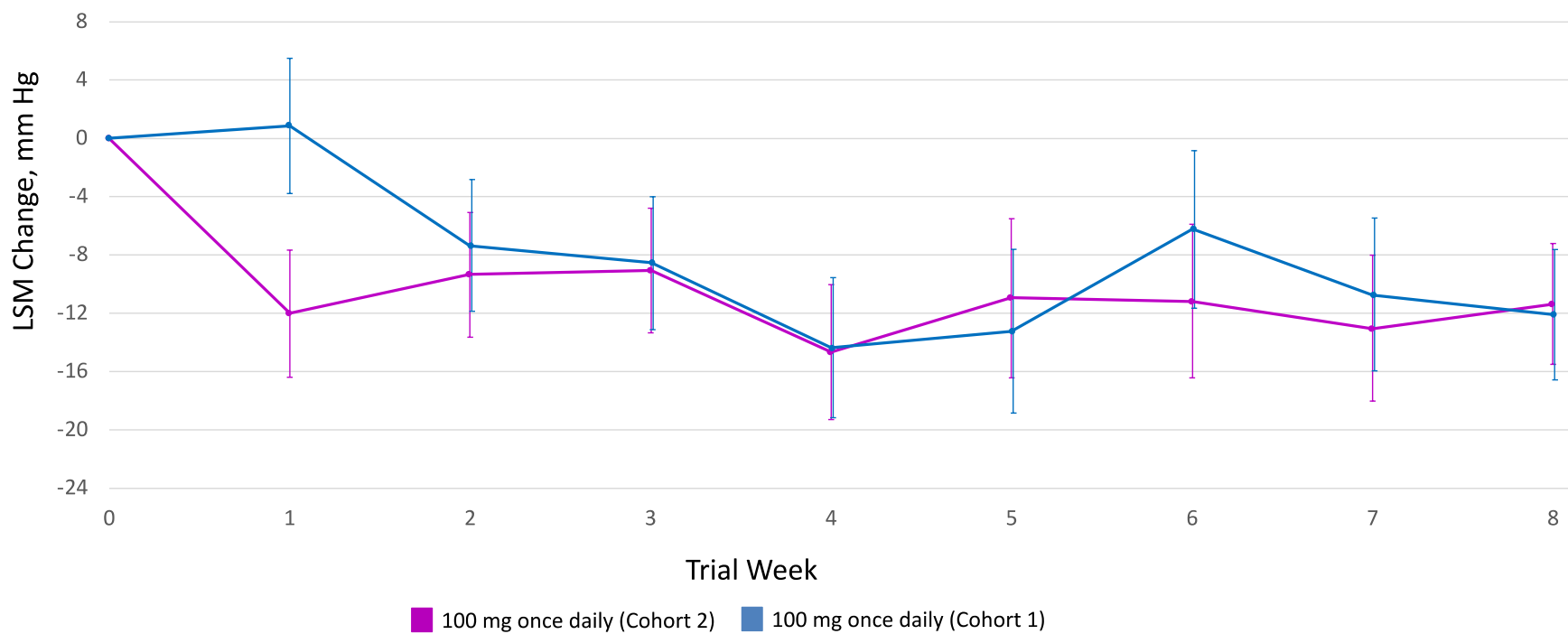
eFigure 2. Weekly automated office systolic blood pressure changes with lorundrostat



Weekly least-squares mean (LSM) change in systolic automated office blood pressure from baseline among participants taking once daily lorundrostat or placebo in cohort 1. Error bars represent 90% confidence intervals.

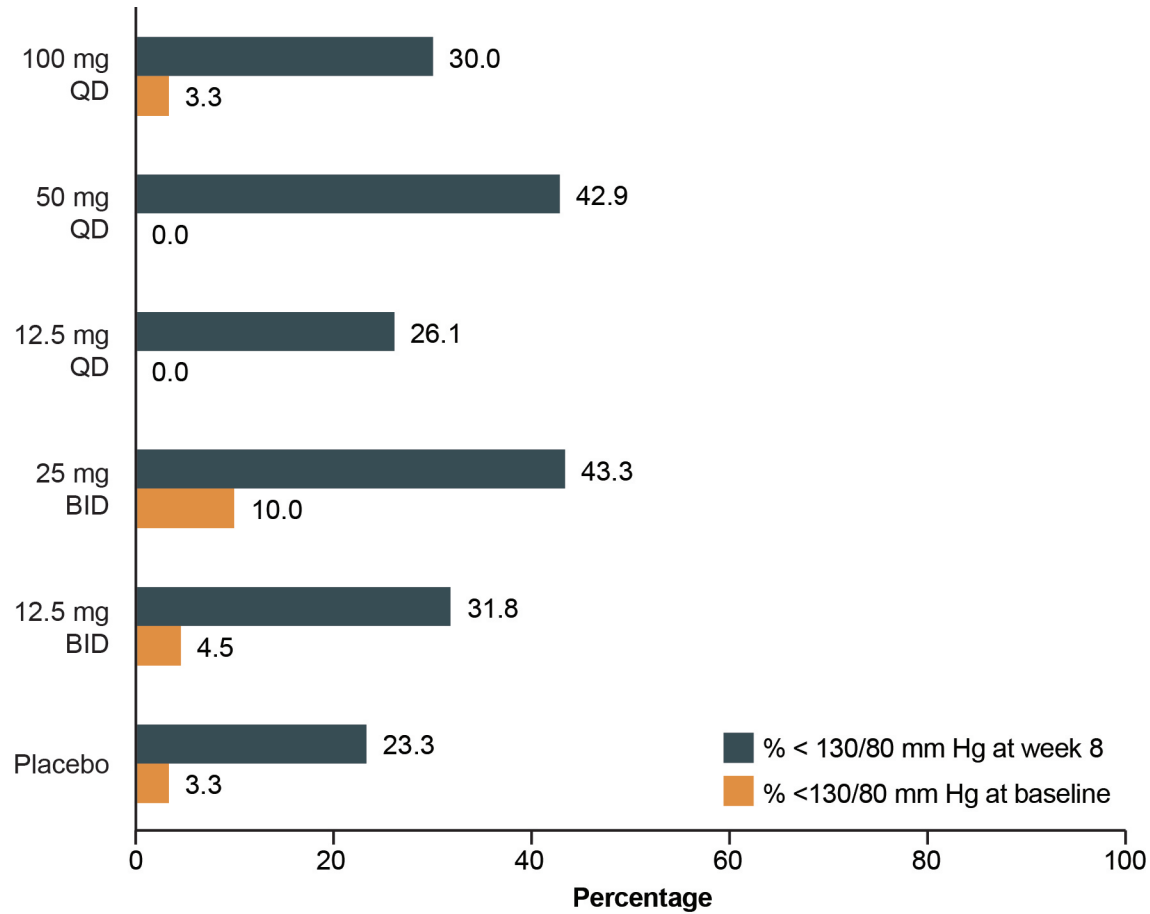


Weekly least-squares mean (LSM) change in systolic automated office blood pressure from baseline among participants taking twice daily lorundrostat or placebo in cohort 1. Error bars represent 90% confidence intervals.



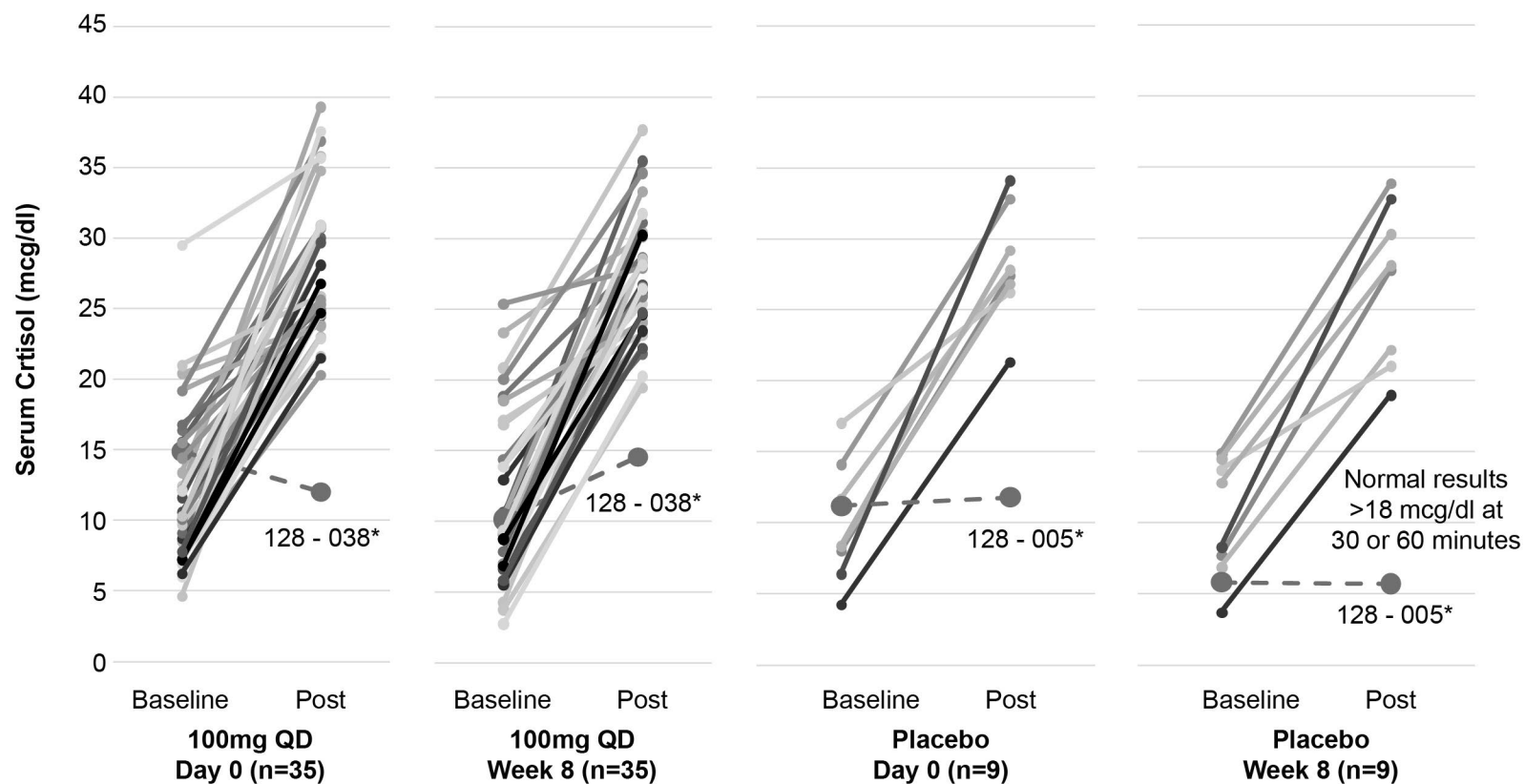
Weekly least-squares mean (LSM) change in systolic automated office blood pressure from baseline among participants taking 100 mg once daily lorundrostat in cohort 2 (plasma renin activity >1.0 ng/mL/h) compared with 100 mg once daily lorundrostat in cohort 1 (plasma renin activity ≤ 1.0 ng/mL/h) in cohort 1. Error bars represent 90% confidence intervals.

eFigure 3. Proportion of participants with automated office blood pressure < 130/80 mmHg at week 8 compared with baseline among cohort 1 participants



Abbreviations: BID – twice daily, QD - daily

eFigure 4. Cosyntropin-stimulated cortisol production after 8 weeks of lorundrostat treatment



COVID-19 necessitated supply chain shortages in cosyntropin did not allow all trial participants to undergo ACTH stimulation testing.

*Participants at study site 128 did not receive proper administration of cosyntropin

Abbreviations: QD –daily