#AHA22

RESULTS FROM A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL EVALUATING THE EFFICACY AND SAFETY PROFILE OF BAXDROSTAT IN PATIENTS WITH TREATMENT-RESISTANT HYPERTENSION (BrigHtn Study)

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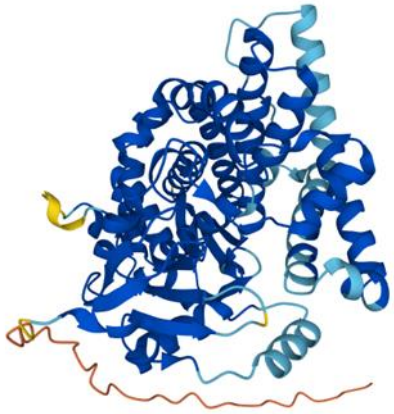
American Heart Association.

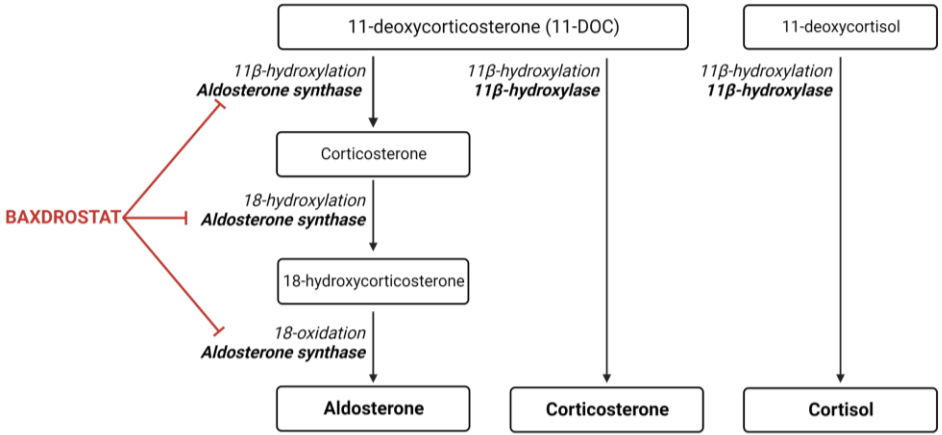
Author Disclosures

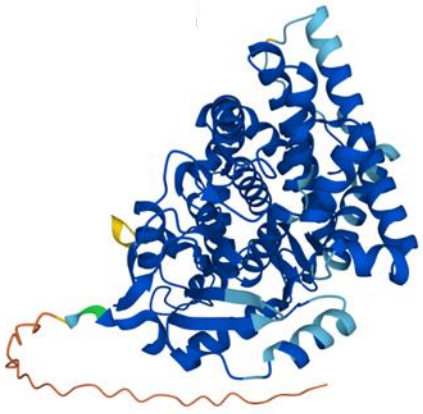
- **Mason W. Freeman, MD,** is an employee of CinCor Pharma, Inc. and receives stock-based compensation
- **Yuan-Di Halvorsen, PhD,** is an employee of CinCor Pharma Inc. and receives stock-based compensation
- **William Marshall, MD,** is an employee of CinCor Pharma, Inc. and receives stock-based compensation
- **Mackenzie Pater, PhD,** is an employee of and has equity in CinRx Pharma, LLC, which has an equity stake in CinCor Pharma, Inc.
- **Jon Isaacsohn, MD,** is an employee of and has equity in CinRx Pharma, LLC, which has an equity stake in CinCor Pharma, Inc.
- **Catherine Pearce, MBA, DHSc,** is an employee of CinCor Pharma, Inc. and receives stock-based compensation
- **Brian Murphy, MD, MPH,** is an employee of and has equity in CinRx Pharma, LLC, which has an equity stake in CinCor Pharma, Inc.
- **Deepak L. Bhatt, MD, MPH,** receives research funding from CinCor Pharma, Inc. paid to Brigham and Women's Hospital
- **Morris J. Brown, MD,** is a member of CinCor Pharma, Inc.'s scientific advisory board and receives stock-based compensation and receives research grants from National Institutes of Health Research, Medical Research Council, British Heart Foundation, and Barts Charity to study primary aldosteronism

Introduction

- **Lowering aldosterone activity can lower blood pressure**
- **Baxdrostat lowers aldosterone activity by inhibiting hormonal synthesis**
  - **Highly potent and selective oral, small molecule inhibitor of aldosterone synthase (ASI)**
  - **Off-target inhibition of cortisol synthesis has thwarted previous ASI development**







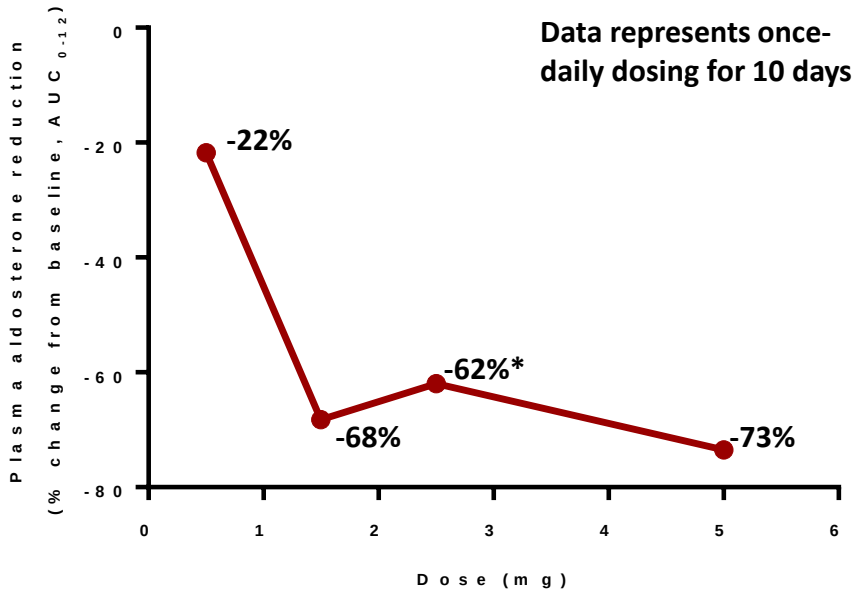
ALDOSTERONE SYNTHASE

Enzymes are 93% sequence similar

'CORTISOL SYNTHASE'
(11β-hydroxylase)

BrigHtn Dose Selection Based on Multiple Ascending Dose Human Volunteer Study

Baxdrostat caused a sustained, dose-dependent reduction of plasma aldosterone



Data are least squares means. *Low and normal salt diet combined (n=56).
Abbreviation: AUC_{0-12}, area under the curve from time 0 to 12 hours.

Study Design

Randomized, double-blind, placebo-controlled, multicenter, parallel-group, dose-ranging study

Key Inclusion Criteria

- On a stable regimen of ≥3 antihypertensive agents (1 of which is a diuretic) for at least 4 weeks prior to randomization
- ≥70% adherent to antihypertensive medication regimen
- Has a seated blood pressure ≥130/80 mm Hg

Key Exclusion Criteria

- Estimated glomerular filtration rate <45 mL/min/1.73m^2

Primary Endpoint (12 weeks)

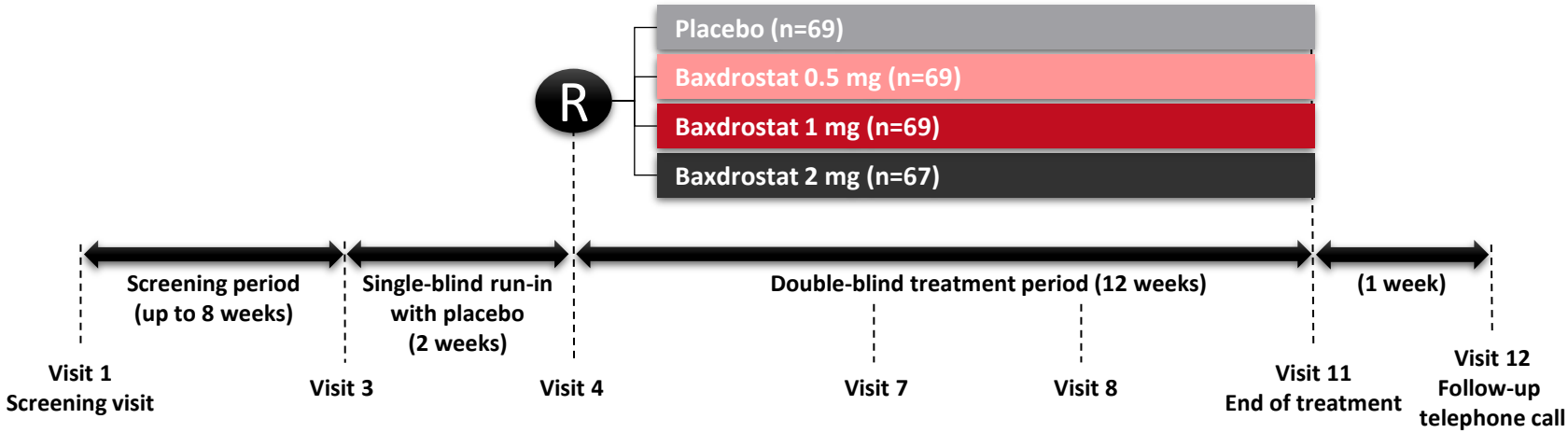
- Change from baseline in mean seated systolic blood pressure compared to placebo

Secondary Endpoint

- Change from baseline in mean seated diastolic blood pressure compared to placebo

Exploratory Endpoints

- Pharmacokinetic and pharmacodynamic analyses



Baseline Demographics

Well-balanced randomization across all cohorts

Demographic	Placebo (n=69)	0.5 mg baxdrostat (n=69)	1 mg baxdrostat (n=70)	2 mg baxdrostat (n=67)
Age — mean ± SD, yr	63.8±10.8	61.5±10.3	62.7±10.1	61.2±10.8
Male sex — no. (%)	42 (61)	36 (52)	37 (53)	38 (57)
Race — no. (%)				
White	51 (74)	45 (65)	48 (69)	47 (70)
Black	16 (23)	22 (32)	20 (29)	19 (28)
Asian	2 (3)	1 (1)	2 (3)	1 (1)
American Indian or Alaska Native	0	1 (1)	0	0
Hispanic or Latino ethnic group — no. (%)	30 (43)	33 (48)	23 (33)	32 (48)

Baseline Clinical Characteristics

Well-balanced randomization across all cohorts

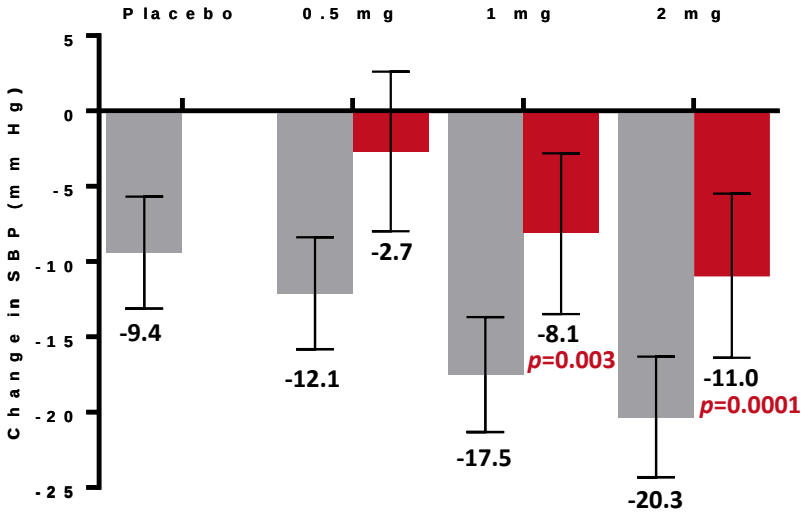
Characteristic*	Placebo (n=69)	0.5 mg baxdrostat (n=69)	1 mg baxdrostat (n=70)	2 mg baxdrostat (n=67)
Body-mass index — kg/m²	32.1±5.3	33.2±5.3	31.9±5.2	33.3±5.1
Seated systolic blood pressure — mmHg	148.9±12.4	147.6±12.5	147.7±13.1	147.3±11.8
Seated diastolic blood pressure — mmHg	88.2±6.1	87.6±7.7	87.7±6.0	88.2±7.1
Glomerular filtration rate — ml/min/1.73 m²	85.5±17.5	81.0±20.4	83.2±20.6	85.2±19.4
Background antihypertensive drug — no. (%)				
Diuretic	69 (100)	69 (100)	70 (100)	67 (100)
Beta blocker	47 (68)	44 (64)	41 (59)	35 (52)
Calcium channel blocker	47 (68)	44 (64)	49 (70)	47 (70)
Agent acting on the RAAS	63 (91)	64 (93)	65 (93)	64 (96)
General antihypertensive	9 (13)	8 (12)	11 (16)	8 (12)

*Plus-minus values are mean ± SD.
Abbreviation: RAAS, renin-angiotensin-aldosterone system.

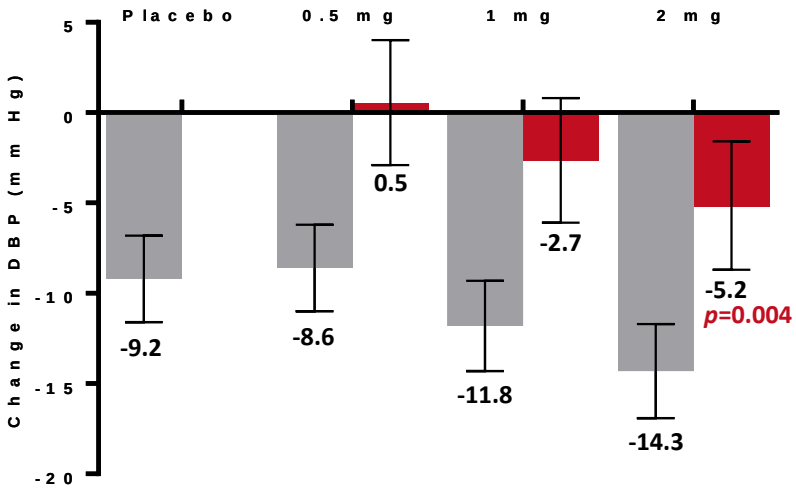
Primary and Secondary Endpoints

Reduction of SBP (-20.3 mm Hg) and DBP (-14.3 mm Hg) at the 2-mg dose
Statistically significant placebo-corrected reduction of SBP (-11.0 mm Hg) and DBP (-5.2 mm Hg) at the 2-mg dose

Change in systolic blood pressure (mm Hg)



Change in diastolic blood pressure (mm Hg)



Data are least squares mean ± 95% confidence interval.
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

Safety Profile

Baxdrostat was well tolerated; no SAEs were deemed related to baxdrostat

Event — no. (%)	Placebo (n=69)		0.5 mg baxdrostat (n=69)		1 mg baxdrostat (n=69)		2 mg baxdrostat (n=67)	
	No. of patients (%)	No. of events	No. of patients (%)	No. of events	No. of patients (%)	No. of events	No. of patients (%)	No. of events
Any SAE	2 (3)	3	0	0	2 (3)	3	6 (9)*	12
Any treatment-emergent adverse event	28 (41)	50	24 (35)	38	36 (52)	77	32 (48)	67
Adverse event of special interest†	0	0	1 (1)	1	5 (7)	6	2 (3)	3
Hyponatremia	0	0	0	0	2 (3)	2	1 (2)	1
Hypotension	0	0	0	0	1 (1)	1	0	0
Potassium ≥6.0mEq/L‡	0	0	0	0	2 (3)	2	1 (2)	1
Potassium level between 5.5 and 5.9 mmol/L on at least 2 consecutive occasions	0	0	1 (1)	1	2 (3)	2	1 (2)	1

*Patient with urosepsis had 6 SAEs; none were deemed related to baxdrostat.

†Adverse events of special interest were hypotension, hyponatremia, or elevated potassium levels that required clinical intervention.

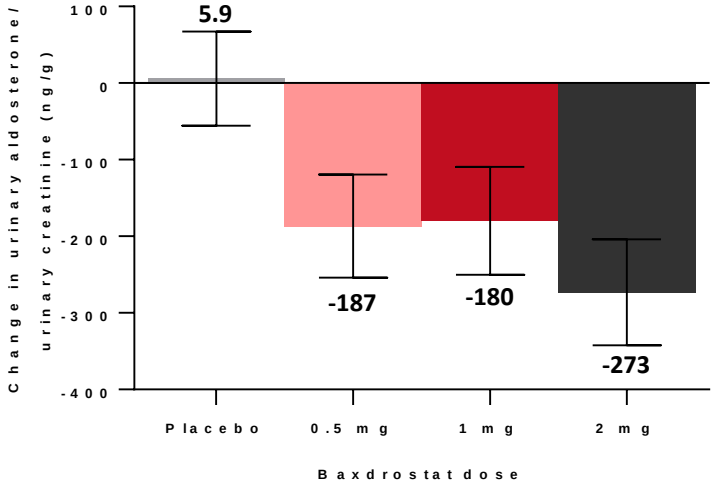
‡One patient had a potassium level between 5.5 and 5.9 mmol per liter as well as a potassium level of 6.0 mmol per liter or higher, and these measurements were counted as the same event; thus, a total of six patients with hyperkalemia had an adverse event of special interest.

Abbreviation: SAE, serious adverse event.

Baxdrostat Reduces Aldosterone

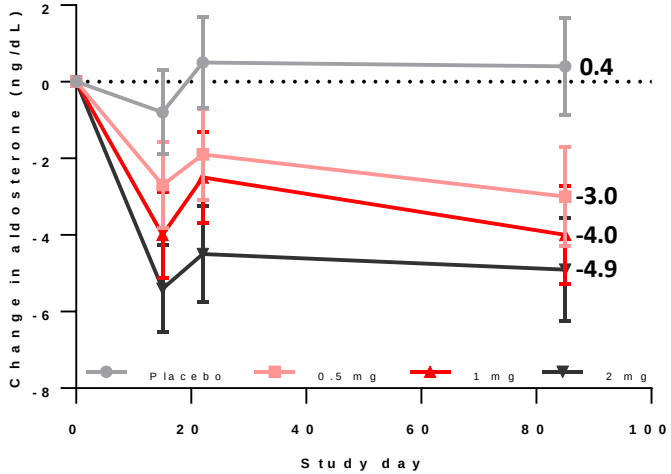
Dose-dependent reductions in aldosterone support the biological effect of baxdrostat

24-h urinary aldosterone normalized to U_{CR} at day 85



	Placebo	0.5 mg	1 mg	2 mg
Baseline 24-h urine aldosterone concentration, mean ± SD, ng/g	364±228	437±264	398±233	431±399

Serum aldosterone

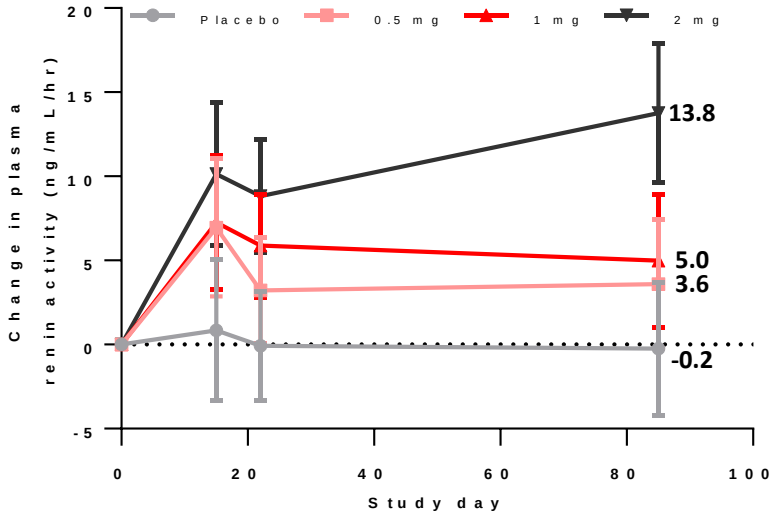


	Placebo	0.5 mg	1 mg	2 mg
Baseline serum aldosterone concentration, mean ± SD, ng/dL	6.7±4.8	6.9±4.2	7.9±5.8	8.4±5.5

Data are least squares mean ± 95% confidence interval.
Abbreviation: U_{CR}, urinary creatinine.

Baxdrostat Increases Plasma Renin Activity

Increased plasma renin activity is an indicator of baxdrostat's effect on lowering salt and fluid retention*



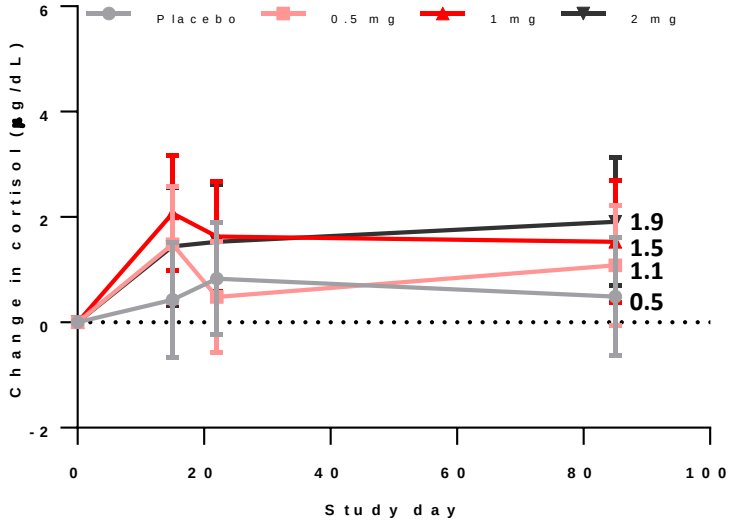
	Placebo	0.5 mg	1 mg	2 mg
Baseline plasma renin activity, mean ± SD, ng/mL/h	**4.5±6.7**	**3.1±5.2**	**5.2±10.8**	**6.7±10.4**

*Increased plasma renin activity is expected with RAAS blockade and is also observed in patients treated with ACEi and ARBs.

Data are least squares mean ± 95% confidence interval.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; RAAS, renin-angiotensin-aldosterone system.

Baxdrostat Does Not Reduce Cortisol

Baxdrostat is selective for aldosterone synthase



	Placebo	0.5 mg	1 mg	2 mg
Baseline serum cortisol, mean ± SD, µg/dL	8.9±3.6	9.6±4.0	9.7±4.1	10.3±4.0

Data are least squares mean ± 95% confidence interval.

Conclusions

- 2 mg baxdrostat significantly and substantially reduced systolic and diastolic blood pressure in patients with treatment-resistant hypertension
- Baxdrostat reduced aldosterone levels and increased plasma renin activity without reducing cortisol, supporting its biological effect and selectivity
- Baxdrostat demonstrated a favorable safety profile and was well tolerated
- Baxdrostat has the potential to treat disorders associated with aldosterone excess, including hypertension and primary hyperaldosteronism

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

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THANK YOU

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Scientific Sessions

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