Pharmacokinetics, pharmacodynamics, and safety results from a phase 1 multiple ascending dose study of the selective aldosterone synthase inhibitor CIN-107 (baxdrostat)

Authors: Mason W. Freeman[1], Mary Bond[2], Brian Murphy[2], James Hui[1], and Jonathan Isaacsohn[2]

Affiliations: [1]CinCor Pharma, Inc., Boston, MA, USA; [2]CinRx Pharma, LLC, Cincinnati, OH, USA

Presented by James Hui, PhD

Vice President, Clinical Pharmacology and Translational Research

CinCor Pharma, Inc.

Disclosures

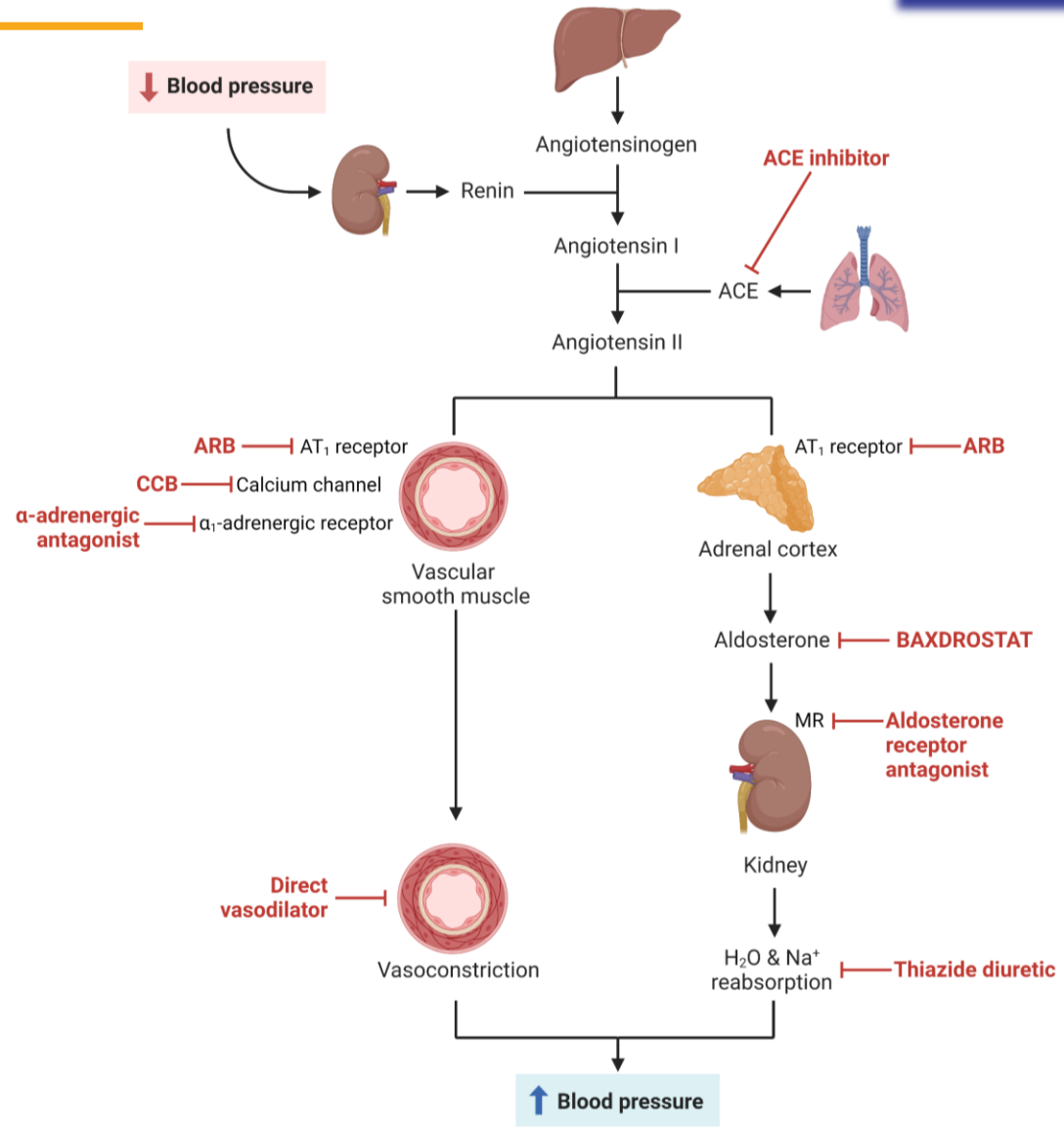
- Mason Freeman, MD, is an employee of CinCor Pharma, Inc. and receives stock-based compensation.
- James Hui, PhD, is an employee of CinCor Pharma, Inc. and receives stock-based compensation.
- Mary Bond, MS, MBA, is an employee of and has equity in CinRx Pharma, LLC, which has an equity stake in CinCor Pharma, Inc.
- Brian Murphy, MD, MPH, is an employee of and has equity in CinRx Pharma, LLC, which has an equity stake in CinCor Pharma, Inc.
- Jonathan Isaacson, MD, is an employee of and has equity in CinRx Pharma, LLC, which has an equity stake in CinCor Pharma, Inc.

Forward-Looking Statements Disclaimer

This presentation contains certain forward-looking statements, including, but not limited to, statements related to CinCor's clinical trials, including the therapeutic potential of baxdrostat (CIN-107) and other statements that are not historical facts. Because such statements are subject to risks and uncertainties, actual results may differ from those expressed or implied by such forward-looking statements. Words such as "anticipates," "believes," "expected," "intends," "plan," "may", "will," "project", "estimate", "continue," "advance" and "future" or similar expressions are intended to identify forward-looking statements. These forward-looking statements are based on CinCor's current plans, objectives, estimates, expectations and intentions, involve assumptions that may never materialize or may prove to be incorrect and inherently involve significant risks and uncertainties, including factors beyond CinCor's control, that could cause actual results, performance, or achievement to differ materially and adversely from those anticipated or implied in the statements, including, without limitation, CinCor has incurred significant operating losses since its inception; CinCor has a limited operating history and no history of commercializing products; CinCor will require substantial additional funding to finance its operations; CinCor's business is entirely dependent at this time on the success of one drug, baxdrostat, interim, "top-line" and preliminary data from clinical trials announced or published from time to time may change; CinCor may not be successful in its efforts to expand its pipeline beyond baxdrostat; success in preclinical studies or earlier clinical trials may not be indicative of results in future clinical trials; enrollment and retention of patients in clinical trials could be delayed; CinCor relies and will rely on third parties to conduct, supervise and monitor existing clinical trials and potential future clinical trials; developments from the company's competitors and the marketplace for the company's products; and CinCor's business, operations and clinical development timelines and plans may be adversely affected by the evolving and ongoing COVID-19 pandemic and geopolitical events, including the ongoing military conflict between Russia and Ukraine and related sanctions against Russia, macroeconomic events such as rising inflation and uncertain financial markets, and matters related thereto; and other risks and uncertainties affecting the company, including those described under the caption "Risk Factors" and elsewhere in CinCor's annual report on Form 10-K for the year ended December 31, 2021 filed with the SEC on March 22, 2022, and other filings and reports that CinCor may file from time to time with the SEC, including its quarterly report on Form 10-Q for the three months ended June 30, 2022 filed with the SEC on August 8, 2022. Other risks and uncertainties of which CinCor is not currently aware may also affect the company's forward-looking statements and may cause actual results and the timing of events to differ materially from those anticipated. All forward-looking statements contained in this presentation speak only as of the date on which they were made and are based on management's assumptions and estimates as of such date. CinCor undertakes no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as may be required by law.

Introduction

- Baxdrostat is a highly potent and selective small molecule inhibitor of aldosterone synthase
- Baxdrostat represents a novel approach for the potential treatment of disorders associated with elevated aldosterone levels
  - Hypertension
  - Primary aldosteronism



Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1 receptor; CCB, calcium channel blocker; MR, mineralocorticoid receptor.

Objective

- To evaluate the safety, pharmacokinetics, and pharmacodynamics of multiple ascending doses of baxdrostat in a randomized, double-blind, placebo-controlled phase 1 study in healthy volunteers

Methods

Low-salt diet

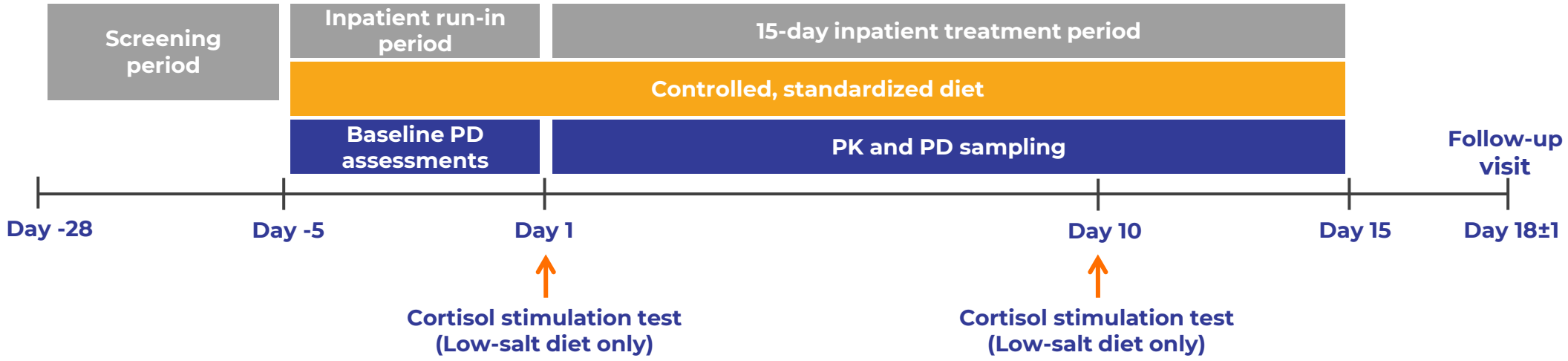
65 to 70 mEq Na^+/day and 70 to 100 mEq K^+/day

- Placebo (n=6)
- 2.5 mg baxdrostat (n=9)
- 5 mg baxdrostat (n=9)

Normal-salt diet

100 to 104 mEq Na+/day and 70 to 100 mEq K^+/day

- Placebo (n=8)
- 0.5 mg baxdrostat (n=9)
- 1.5 mg baxdrostat (n=9)
- 2.5 mg baxdrostat (n=6)



Abbreviations: K^+, potassium; mEq, milliequivalent; Na^+, sodium; PD, pharmacodynamic; PK, pharmacokinetic

Baseline Demographics and Clinical Characteristics

Demographic or characteristic	Low-salt diet			Normal-salt diet			
	Pooled placebo (n=6)	2.5 mg baxdrostat (n=9)	5.0 mg baxdrostat (n=9)	Pooled placebo (n=8)	0.5 mg baxdrostat (n=9)	1.5 mg baxdrostat (n=9)	2.5 mg baxdrostat (n=6)
Age (y), mean (SD)	43.8 (6.40)	37.2 (8.67)	39.3 (10.17)	37.0 (8.72)	37.9 (8.55)	44.8 (8.60)	39.0 (9.70)
Race, n (%)							
White	2 (33.3)	4 (44.4)	5 (55.6)	5 (62.5)	3 (33.3)	3 (33.3)	4 (66.7)
Black or African American	4 (66.7)	5 (55.6)	3 (33.3)	3 (37.5)	6 (66.7)	5 (55.6)	2 (33.3)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
Other	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)							
Hispanic or Latino	1 (16.7)	0 (0.0)	2 (22.2)	1 (12.5)	2 (22.2)	1 (11.1)	0 (0.0)
Not Hispanic or Latino	5 (83.3)	9 (100.0)	7 (77.8)	7 (87.5)	7 (77.8)	8 (88.9)	6 (100.0)
Sex, n (%)							
Female	1 (16.7)	4 (44.4)	3 (33.3)	1 (12.5)	4 (44.4)	1 (11.1)	3 (50.0)
Male	5 (83.3)	5 (55.6)	6 (66.7)	7 (87.5)	5 (55.6)	8 (88.9)	(3 (50.0)
Height (cm), mean (SD)	175.3 (10.16)	168.9 (10.72)	170.1 (12.24)	170.2 (8.56)	171.5 (11.45)	173.4 (9.67)	171.7 (8.24)
Body weight (kg), mean (SD)	78.3 (13.15)	77.0 (10.99)	75.8 (12.00)	70.4 (10.98)	79.5 (11.98)	78.6 (11.29)	74.9 (5.49)
BMI (kg/m^2), mean (SD)	25.3 (2.49)	26.9 (1.41)	26.0 (1.65)	24.3 (3.21)	26.9 (1.84)	26.0 (2.45)	25.5 (2.36)

Abbreviations: BMI, body mass index

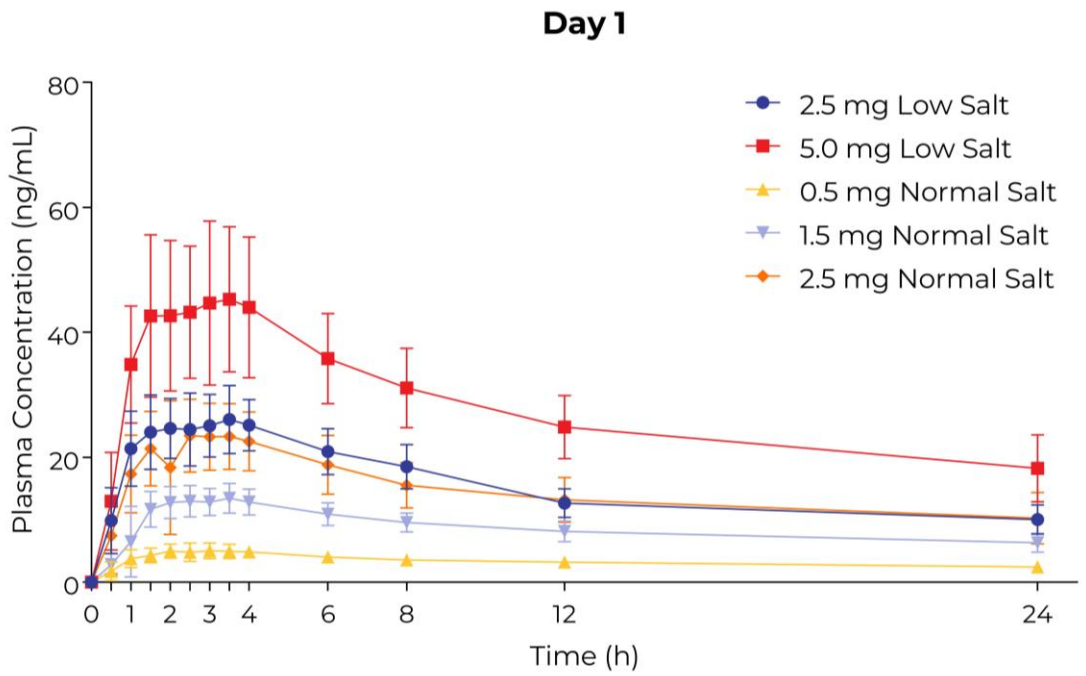
Safety Profile

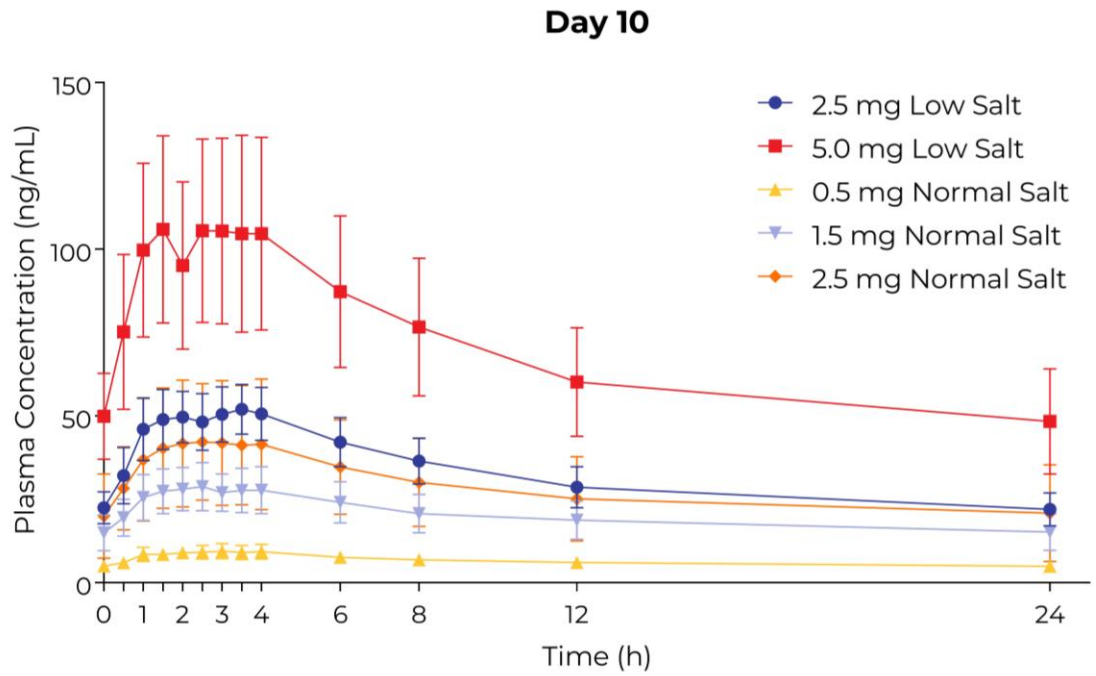
Adverse events, n (%)	Low-salt diet			Normal-salt diet			
	Pooled placebo (n=6)	2.5 mg baxdrostat (n=9)	5.0 mg baxdrostat (n=9)	Pooled placebo (n=8)	0.5 mg baxdrostat (n=9)	1.5 mg baxdrostat (n=9)	2.5 mg baxdrostat (n=6)
Any AE	2 (33.3)	3 (33.3)	3 (33.3)	1 (12.5)	1 (11.1)	1 (11.1)	3 (50.0)
Any TEAE	2 (33.3)	3 (33.3)	3 (33.3)	1 (12.5)	1 (11.1)	1 (11.1)	3 (50.0)
Palpitations	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular tachycardia	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye irritation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Abdominal pain	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
Nausea	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Viral infection	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	1 (11.1)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	1 (16.7)
Dizziness postural	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)
Dizziness	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Presyncope	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Dry throat	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Dysphonia	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any treatment-emergent SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any drug-related treatment-emergent SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

TEAEs are defined as any AE, regardless of relationship to the study drug, which began after the first dose was administered. Abbreviations: AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Pharmacokinetics

- Plasma concentrations of baxdrostat increased proportionally with ascending doses
- Baxdrostat was rapidly absorbed
- Peak concentrations were observed within 4 hours after dosing
- Mean terminal half-life was 26-31 hours



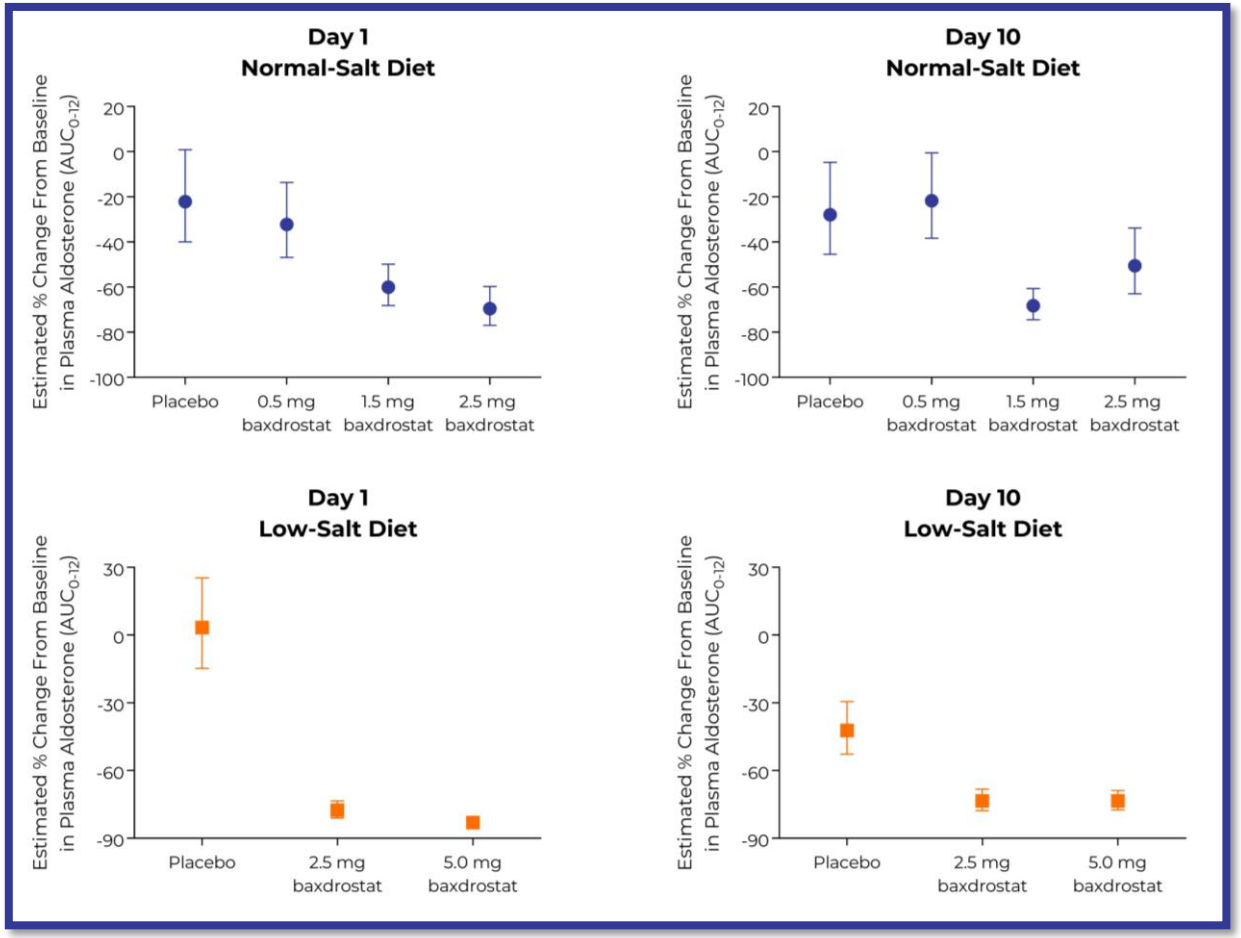


Estimated percentage change from baseline (day −1) in plasma aldosterone area under the pharmacodynamic effect-time curve from time 0 to 12 hours postdose on day 1 and day 10. Data are least squares mean and 90% confidence intervals.

Pharmacodynamics

Plasma Aldosterone

- A dose-dependent reduction of plasma of aldosterone occurred with baxdrostat doses ≥1.5 mg, regardless normal or low salt diet
- Decreases in plasma aldosterone started on Day 1 and were sustained, with levels reduced by approximately 51-73% on Day 10



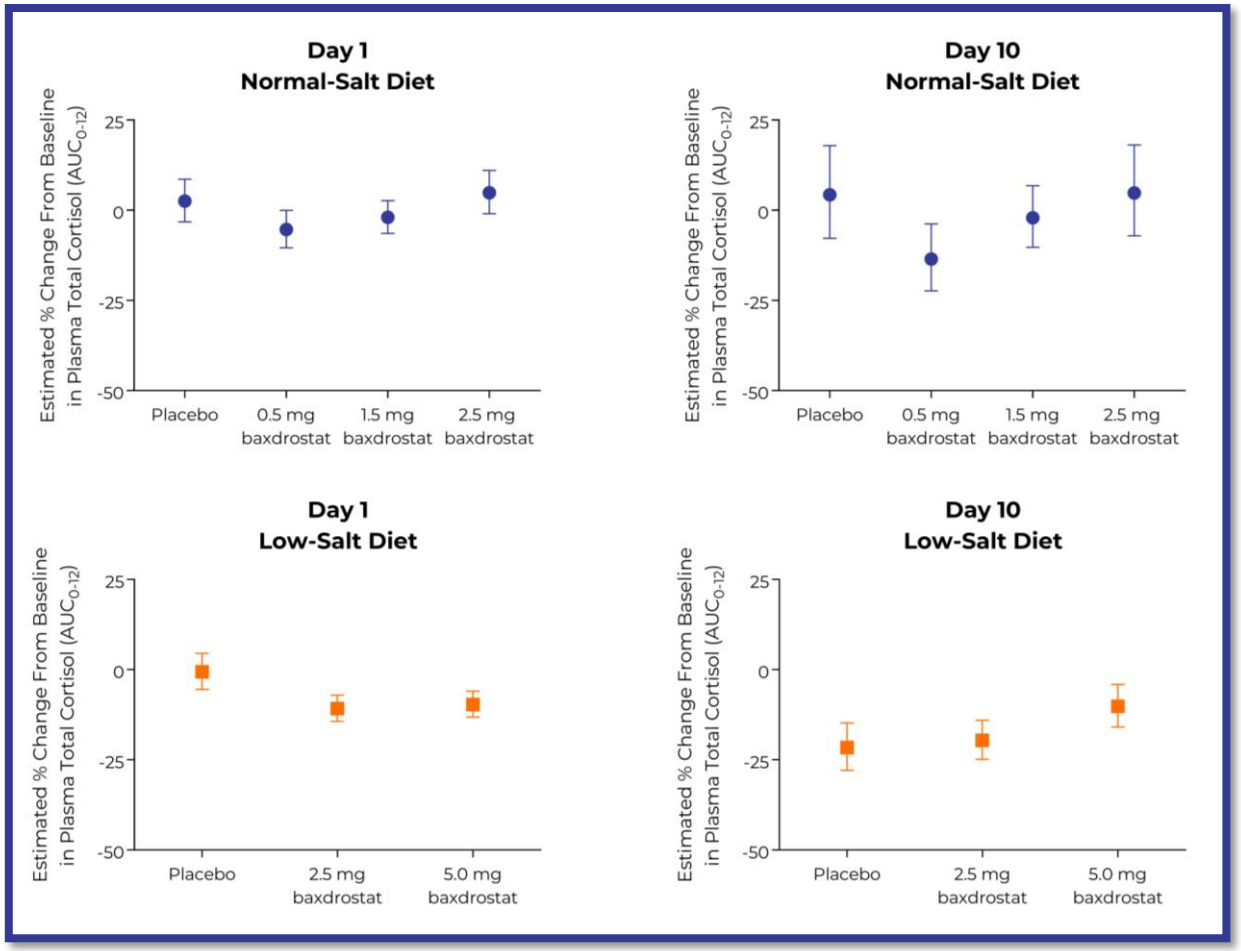
Estimated percentage change from baseline (day −1) in plasma aldosterone area under the pharmacodynamic effect-time curve from time 0 to 12 hours postdose on day 1 and day 10. Data are least squares mean and 90% confidence intervals.

Abbreviation: AUC, area under the curve

Pharmacodynamics

Plasma Cortisol

- Baxdrostat had no meaningful impact on plasma cortisol levels



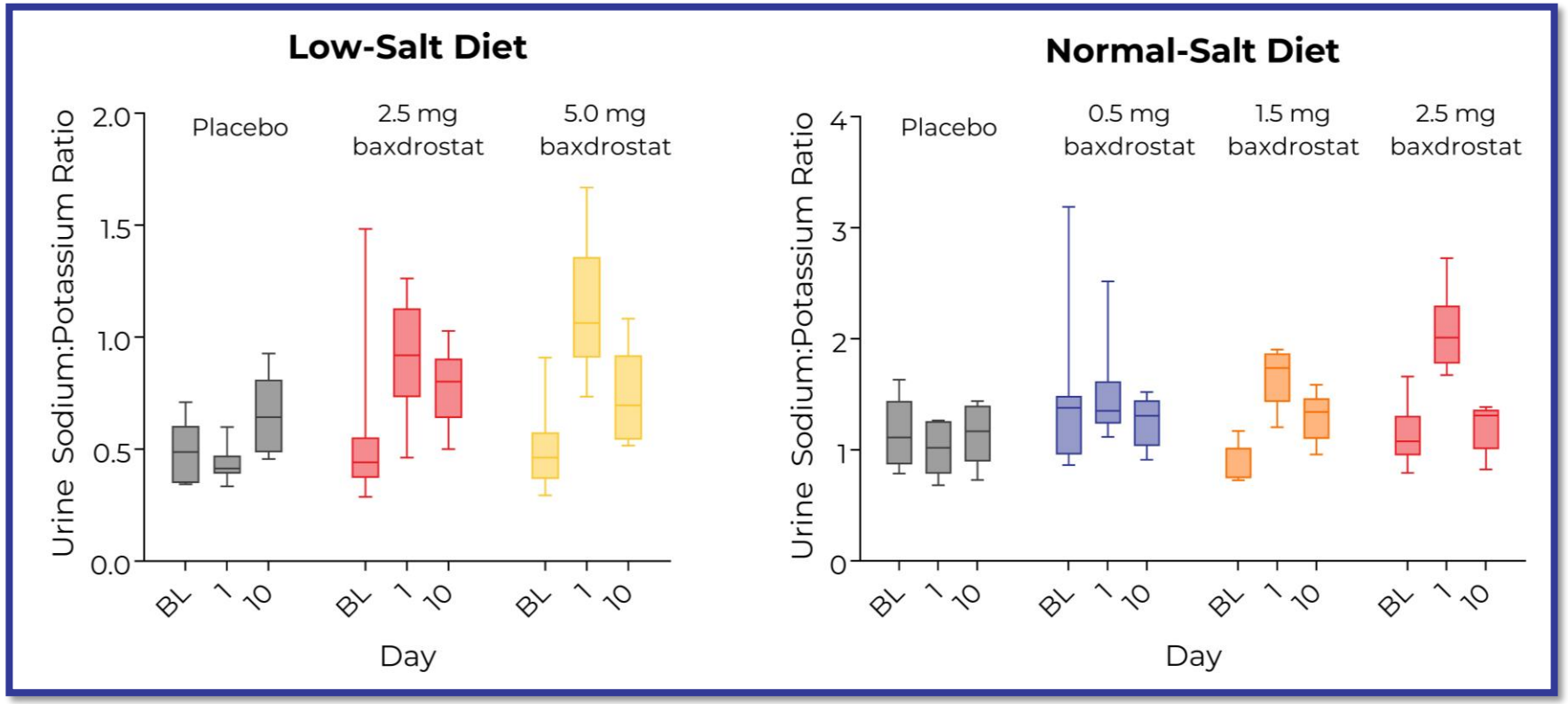
Estimated percentage change from baseline (day −1) in plasma cortisol (total) area under the pharmacodynamic effect-time curve from time 0 to 12 hours postdose on day 1 and day 10. Data are least squares mean and 90% confidence intervals.

Abbreviation: AUC, area under the curve

Pharmacodynamics

Urinary Sodium and Potassium

- The sodium:potassium ratio increased on Day 1 and diminished by Day 10
- This effect was mediated by greater elimination of sodium on Day 1 compared to Day 10

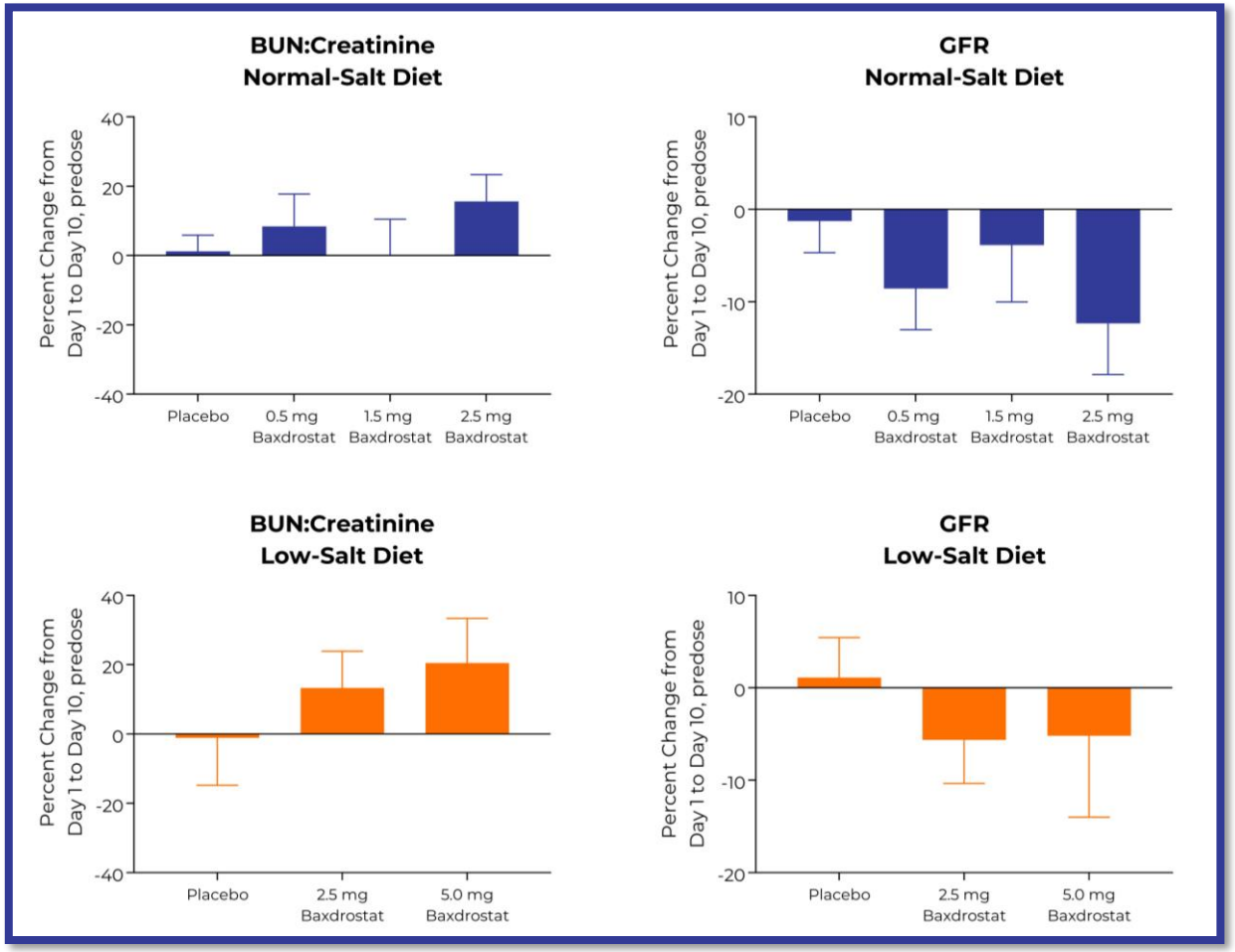


Urine sodium-potassium ratio at baseline (BL), day 1, and day 10. Box whiskers show interquartile range (box) and minimum-maximum (whiskers) for sodium or potassium from 24-hour urine collections.

Pharmacodynamics

BUN, Creatinine, and GFR

- There was a mild increase in the BUN:creatinine ratio
- A mild reduction in the glomerular filtration rate (<15%) occurred
- These results suggests that baxdrostat produced a mild diuretic effect



Percent change in the blood urea nitrogen-creatinine ratio and glomerular filtration rate from Day 1 to Day 10, predose. Data are mean ± SD.

Abbreviations: BUN, blood urea nitrogen; GFR, glomerular filtration rate

Conclusions

- Baxdrostat demonstrated a compelling safety profile and was well tolerated
- Baxdrostat demonstrated dose-proportional increases in plasma concentration with a half-life that supports once-daily dosing
- The dose-dependent decrease in plasma aldosterone and lack of effect on cortisol demonstrate the selective blockade of aldosterone synthase
- Baxdrostat produced a transient increase in sodium excretion and mild diuretic effect
- We believe these results support our continued study in ongoing phase 2 clinical trials evaluating the efficacy and safety of baxdrostat for treatment-resistant or uncontrolled hypertension and primary aldosteronism