Results from a phase 1 multiple ascending dose study demonstrating safety and selectivity of the aldosterone synthase inhibitor baxdrostat

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INTRODUCTION

Baxdrostat (CIN-107) is a highly potent, selective, and competitive small molecule inhibitor of aldosterone synthase that is a potential treatment for disorders associated with elevated aldosterone levels, including hypertension and primary aldosteronism. This randomized, double-blind, placebo-controlled phase 1 study evaluated the safety, pharmacokinetics, and pharmacodynamics of multiple ascending doses of baxdrostat in healthy volunteers.

METHODS

Subjects were randomized into 5 cohorts to receive baxdrostat or placebo once daily for 10 days. Cohorts 1 and 2 were placed on a low salt diet (65 to 70 mEq Na+/day and 70 to 100 mEq K+/day) to stimulate aldosterone production and were administered 2.5 or 5.0 mg oral baxdrostat, respectively. Cohorts 1 and 2 also underwent an adrenocorticotropic hormone (ACTH) challenge to increase aldosterone and cortisol levels in order to evaluate the specificity of baxdrostat for targeting aldosterone synthase. Cohorts 3, 4, and 5 were placed on a normal salt diet (100 to 104 mEq Na+/day and 70 to 100 mEq K+/day) and were administered 1.5, 2.5, or 0.5 mg oral baxdrostat, respectively. In all cohorts, blood samples were collected prior to and after dosing on days 1 and 10 for measurement of plasma baxdrostat concentrations to characterize single-dose and steady-state pharmacokinetics. Pharmacodynamic measurements included plasma aldosterone, cortisol, and electrolytes **(Figure 1)**. Safety assessments included adverse events, physical examination, electrocardiograms, ortho-static vital signs, and clinical laboratory evaluations.

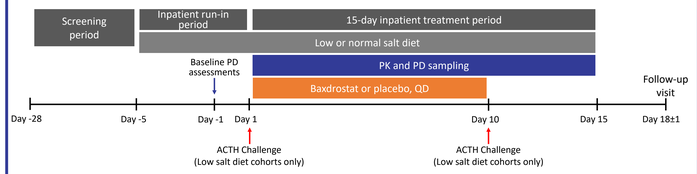

Figure 1. Study Design.
Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic; QD, once a day.

RESULTS

54 subjects completed the study. There were no deaths, serious adverse events, or discontinuations due to treatment-emergent adverse events (TEAEs). Overall, 6 (14.3%) subjects receiving baxdrostat and 3 (21.4%) subjects receiving placebo experienced a TEAE that was considered related to the study drug. All TEAEs in subjects receiving baxdrostat were mild in severity **(Table 1)**.

RESULTS

Table 1. Summary of Study Drug-Related Adverse Events

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 study drug-related TEAE	2 (33.3)	2 (22.2)	1 (11.1)	1 (12.5)	1 (11.1)	0 (0.0)	2 (33.3)
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)
Nausea	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)
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)

Abbreviation: TEAE, treatment-emergent adverse event.

Plasma concentrations of baxdrostat increased proportionally with ascending doses. Baxdrostat was rapidly absorbed, with peak concentrations observed within 4 hours after dosing. The concentration of plasma baxdrostat declined in an apparent biphasic manner with a half-life of 26 to 31 hours **(Figure 2)**. Additional PK parameters are presented in **Table 2**.

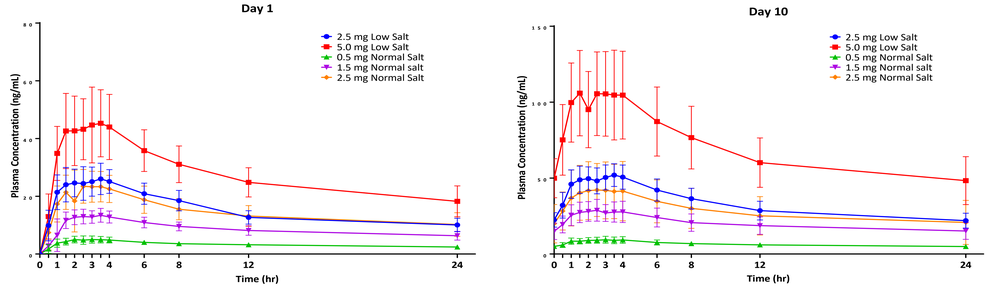

Figure 2. Plasma Baxdrostat Concentration vs. Time on Days 1 and 10
Plasma baxdrostat concentration (ng/mL) by scheduled time point and treatment. Data are mean ± standard deviation.

Table 2. Summary of Single Dose and Steady-State Plasma PK Parameters of Baxdrostat

Plasma PK Parameter	Low salt diet		Normal salt diet		
	2.5 mg baxdrostat (n=9)	5.0 mg baxdrostat (n=9)	0.5 mg baxdrostat (n=9)	1.5 mg baxdrostat (n=9)	2.5 mg baxdrostat (n=6)
Day 1					
$C_{max,D1}$ (ng/mL), mean (CV%)	28.09 (21.0)	47.33 (26.0)	5.36 (23.3)	14.03 (16.0)	26.18 (18.2)
$T_{max,D1}$ (h), median (min, max)	3.0 (1.0, 4.0)	3.0 (1.5, 4.0)	2.0 (1.0, 4.0)	2.5 (1.0, 4.0)	3.0 (2.0, 4.0)
$AUC_{0\text{-}24hr}$ (h·ng/mL), mean (CV%)	365.79 (17.9)	657.85 (20.9)	79.47 (21.8)	205.31 (17.9)	343.98 (26.9)
Day 10					
$C_{max,D10}$ (ng/mL), mean (CV%)	53.96 (14.0)	113.44 (22.8)	9.72 (23.3)	29.94 (20.4)	43.88 (42.6)
$T_{max,D10}$ (h), median (min, max)	2.0 (1.0, 4.0)	3.0 (1.5, 4.0)	2.0 (1.0, 3.5)	2.5 (1.0, 4.0)	3.0 (2.5, 4.0)
$AUC_{0\text{-}tau}$ (h•ng/mL), mean (CV%)	782.99 (18.3)	1659.41 (26.5)	155.19 (23.0)	479.67 (28.8)	676.51 (50.8)
$t_{1/2}$ (h), mean (CV%)	28.37 (16.8)	29.36 (22.0)	31.16 (18.6)	29.92 (25.8)	25.55 (23.3)

Abbreviations: $AUC_{0\text{-}24h}$ = area under the plasma concentration-time curve from time 0 to 24 hours post-dose; $AUC_{0\text{-}tau}$ = area under the plasma concentration-time curve over a dosing interval; $C_{max,D1}$ = maximum observed plasma concentration on Day 1; $C_{max,D10}$ = maximum observed plasma concentration on Day 10; CV = coefficient of variability; max = maximum; min = minimum; PK = pharmacokinetic(s); $t_{1/2}$ = terminal phase elimination half-life; T_{max} = time to maximum observed plasma concentration.

A dose-dependent reduction of plasma aldosterone was observed with baxdrostat doses ≥1.5 mg, regardless of normal or low salt diet. Decreases in plasma aldosterone were observed starting on Day 1 and were sustained, with levels reduced by approximately 51-73% on Day 10 **(Figure 3)**. Baxdrostat's inhibition of aldosterone synthase had no meaningful impact on plasma cortisol **(Figure 4)**. Baxdrostat resulted in mild dose-dependent decreases in plasma sodium levels and increases in potassium levels, as would be expected from the observed reduction in aldosterone.

RESULTS

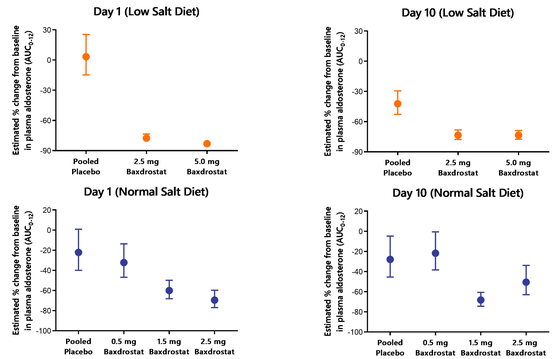

Figure 3. Baxdrostat Reduces Plasma Aldosterone Levels in a Dose-dependent Manner
Estimated percent change from baseline (Day -1) in plasma aldosterone area under the pharmacodynamic effect-time curve from time 0 to 12 hours post-dose on Day 1 and Day 10. Data are least squares mean and 90% confidence intervals. AUC indicates area under the curve.

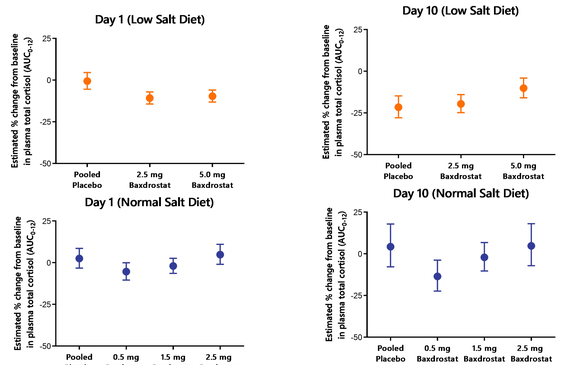

Figure 4. Baxdrostat Does Not Have a Meaningful Effect on Plasma Cortisol Levels
Estimated percent change from baseline (Day -1) in plasma cortisol (total) area under the pharmacodynamic effect-time curve from time 0 to 12 hours post-dose on Day 1 and Day 10. Data are least squares mean and 90% confidence intervals. AUC indicates area under the curve.

CONCLUSIONS

Oral administration of baxdrostat was safe and well tolerated in all subjects and resulted in dose-dependent increases in plasma baxdrostat 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 and support continued study in ongoing phase 2 clinical trials evaluating the efficacy and safety of baxdrostat for treatment-resistant or uncontrolled hypertension and primary aldosteronism.