Results From a Phase 1 Study Demonstrating the Safety and Pharmacokinetics of the Aldosterone Synthase Inhibitor CIN-107 in Subjects With Varying Degrees of Renal Function

Mason W. Freeman[1], Yuan-Di Halvorsen[1], Mary Bond[2], Brian Murphy[2], and Jonathan Isaacsohn[2]

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

Introduction

Hypertension and chronic kidney disease are common comorbidities exacerbated by elevated aldosterone levels.[1] Baxdrostat (CIN-107) is a highly selective, oral small-molecule inhibitor of aldosterone synthase with the potential to lower blood pressure and slow the progression of kidney disease in subjects with varying degrees of renal function.[2,3]

Given the high prevalence of renal impairment in patients with hypertension, it is important to determine whether a baxdrostat dose adjustment may be required due to pharmacokinetic (PK) differences (eg, renal clearance, systemic exposure) in patients with impaired renal function.

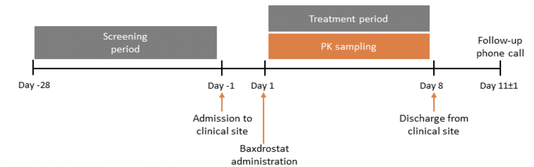
This study assessed the safety, tolerability, and PK of a single oral dose of baxdrostat administered to subjects with varying degrees of renal function.

Methods

Subjects were enrolled into renal function groups based on estimated glomerular filtration rate (eGFR). The groups were control (eGFR ≥60 mL/min), moderate to severe renal impairment (eGFR 15 to 59 mL/min), and kidney failure (eGFR <15 mL/min, including subjects on dialysis). A single 10-mg dose of baxdrostat was administered, followed by 7 days of PK sampling of blood and urine (**Figure 1**).

Safety was assessed based on adverse events, clinical laboratory evaluations, vital signs, electrocardiograms (ECGs), and physical examinations.

Figure 1. Study Design



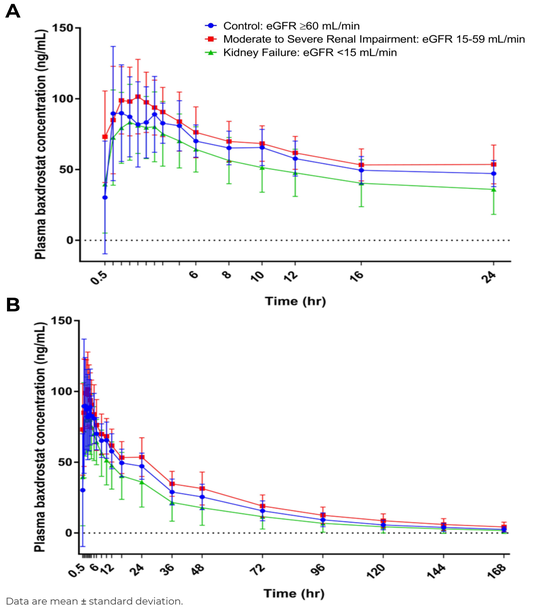
Abbreviation: PK, pharmacokinetic.

Results

Thirty-two subjects completed the study. The plasma concentration-time curves (**Figure 2**) and PK parameters (**Table 1**) of baxdrostat in all groups were similar.

The cumulative amount of excreted baxdrostat in the moderate to severe renal impairment group was similar to that of the control group; however, inadequate urine production in the kidney failure group resulted in minimal excretion of baxdrostat (**Figure 3**). Mean renal clearance of baxdrostat was unchanged between subjects with moderate to severe renal impairment and control subjects (data not shown).

Figure 2. Plasma Baxdrostat Concentration by Renal Function Group Over Time



Data are mean ± standard deviation.

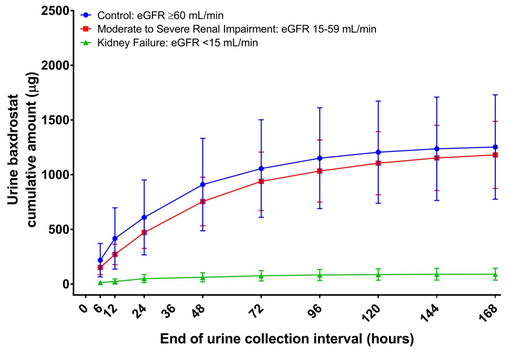
Results (cont'd)

Table 1. Plasma PK Parameters of Baxdrostat

PK Parameter, mean (SD)	Control, eGFR ≥60 mL/min (n=10)	Moderate to severe renal impairment, eGFR 15-59 mL/min (n=11)	Kidney failure, eGFR <15 mL/min (n=12)
C_{max} (ng/mL)	108.02 (25.5)	110.06 (23.2)	96.05 (26.8)
T_{max} (h)	2.10 (1.6)	1.82 (1.0)	1.63 (0.8)
$AUC_{0\text{-}last}$ (h·ng/mL)	3377.10 (917.1)	4012.53 (1192.5)	2567.48 (1362.9)
$AUC_{0\text{-}inf}$ (h·ng/mL)	3530.92 (1032.8)	4340.95 (1486.6)	2661.74 (1461.8)
$t_{1/2}$ (h)	35.63 (12.1)	42.14 (16.5)	29.70 (10.5)
CL/F (L/h)	3.06 (0.9)	2.60 (1.0)	5.07 (2.9)

Abbreviations: $AUC_{0\text{-}last}$, area under the plasma concentration-time curve from time 0 to time of last quantifiable plasma concentration; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time 0 to infinity; CL/F, apparent plasma clearance; C_{max}, maximum observed plasma concentration; h, hour(s); L, liter(s); mL, milliliter(s); min, minutes; ng, nanogram(s); PK, pharmacokinetic; SD, standard deviation; $t_{½}$, terminal phase elimination half-life; T_{max}, time to maximum observed plasma concentration.

Figure 3. Cumulative Baxdrostat Excretion in Urine by Renal Function Group Over Time



Data are mean ± standard deviation.
Abbreviations: eGFR, estimated glomerular filtration rate; mL, milliliter(s); ng, nanogram(s).

There were no deaths, and only 1 mild drug-related adverse event (diarrhea) occurred. There were no clinically meaningful changes in laboratory values, vital signs, physical examinations, or ECGs.

Conclusions

- Our results demonstrate that a single dose of baxdrostat was well-tolerated in subjects with varying degrees of renal function, including those with moderate to severe renal impairment or kidney failure (on hemodialysis).
- Renal impairment did not significantly affect systemic exposure or clearance of baxdrostat.
- The PK properties of baxdrostat do not suggest that altered dosing will be necessary in patients with impaired renal function, including those with end-stage renal disease.

References

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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. 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.

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