Pharmacokinetics of the Novel Nonsteroidal Mineralocorticoid Receptor Antagonist Ocedurenone (KBP-5074) in Individuals with Moderate Hepatic Impairment

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KBP BIOSCIENCES PTE. LTD.

- Disclosures:
- **James McCabe, Vincent Benn, Jay Zhang, Fred Yang are employees of KBP Biosciences**

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ABSTRACT

TITLE:
Pharmacokinetics of the novel nonsteroidal mineralocorticoid receptor antagonist Ocedurenone in individuals with moderate hepatic impairment

BACKGROUND:
Ocedurenone is a selective nonsteroidal mineralocorticoid receptor antagonist (MRA). This study assessed the effect of moderate hepatic impairment on the pharmacokinetics (PK), safety, and tolerability of Ocedurenone.

OBJECTIVE:
This study was designed to provide information on the PK, safety, and tolerability after a single dose of Ocedurenone in individuals with hepatic impairment compared to those with normal hepatic function. This study also evaluated the plasma protein binding of Ocedurenone in individuals with hepatic impairment compared to those with normal hepatic function.

METHOD:
This was an open, nonrandomized, multi-center study investigating the PK, safety, and tolerability of a single oral dose of 0.5 mg Ocedurenone to male and female subjects with moderate hepatic impairment (Child-Pugh B score 7-9) compared to normal healthy control subjects. Twelve subjects (6 subjects with moderate impairment and 6 healthy control subjects) were enrolled. All subjects received a single oral dose of 0.5 mg Ocedurenone on Day 1 after an overnight fast of ≥10 hours. Each healthy control subject was matched by age (±10 years), BMI (±20%), and sex to a moderate hepatic impairment subject. Serial blood collections were obtained through 264 hours postdose for plasma levels of Ocedurenone. Plasma protein binding was analyzed, and safety and tolerability were monitored.

RESULT:
Following a single oral dose of 0.5 mg, Ocedurenone was steadily absorbed with median T_{max} values of 4.00 and 3.00 hours, respectively. After reaching C_{max}, the disposition of Ocedurenone appeared to be biphasic. The geometric mean $t_{1/2}$ values for the moderate hepatic impairment group and normal healthy control group were 75.6 and 65.7 hours, respectively. Systemic exposure to Ocedurenone as assessed by AUC was 23.5% to 26.6% lower in subjects with moderate hepatic impairment versus healthy subjects, whereas C_{max} was 41.2 % lower. Ocedurenone was determined to be >99.7% bound to proteins in plasma. Given the low percentage of unbound drug, it was not deemed appropriate to calculate the PK parameters for unbound drug. Ocedurenone was safe and well tolerated in all participants.

CONCLUSION:
Small decreases of AUC and C_{max} upon systemic exposure to Ocedurenone in subjects with moderate hepatic impairment demonstrate low hepatic extraction and is consistent with the observation that Ocedurenone is cleared predominantly in the gastrointestinal tract vs the kidney.

Considering the long half-life and small decrease in AUC and C_{max}, a dose adjustment does not appear to be warranted in patients with moderate hepatic impairment.

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BACKGROUND

- **Ocedurenone, a novel highly protein-bound and highly selective non-steroidal mineralocorticoid receptor antagonist (MRA), is currently under development, for the treatment of uncontrolled hypertension in patients with chronic kidney disease (CKD).**
- **Ocedurenone selectively binds to recombinant human mineralocorticoid receptor (MR) with much higher affinity then to recombinant human glucocorticoid, progesterone, and androgen receptors and has a higher antagonistic activity to the MR than steroidal MRAs (ie, spironolactone and eplerenone) and non-steroidal finerenone (1-3).**
- **A phase 2b clinical trial (BLOCK-CKD) in subjects with stage 3b/4 CKD (eGFR 15-44 mL/min/1.73 m^2) demonstrated significant blood pressure lowering and that neither hyperkalemia nor reductions in kidney function were limiting factors to the use of Ocedurenone (4).**

METHOD

- **This was an open-label, nonrandomized, multi-center, single-dose study investigating the pharmacokinetics (PK), safety, and tolerability of a single dose of Ocedurenone administered orally in male and female subjects with moderate hepatic impairment compared to subjects with normal hepatic function. A total of approximately 12 subjects (6 subjects with moderate impairment and 6 matched-control healthy subjects) were enrolled in and completed the study. Subjects received a single oral dose of 0.5 mg Ocedurenone on Day 1 following an overnight fast of at least 10 hours.**
- **Child-Pugh (CP) scoring was used to determine the level of hepatic impairment. Subjects were enrolled into the following groups based on their CP score or confirmation of normal hepatic function at screening:**
  - **Group 1: Matched-control healthy subjects with normal hepatic function**
  - **Group 2: Subjects with moderate hepatic impairment (CP Class B, score of 7 to 9)**
- **Serial blood collections were obtained from pre-dose and post-dose for analysis of plasma concentrations of Ocedurenone. Blood samples for analysis of Ocedurenone plasma protein binding were also collected.**
- **Safety was monitored with recording of AEs, clinical laboratory evaluations (clinical chemistry, hematology, and urinalysis), vital sign measurements, 12-lead ECGs, and physical examination findings during the study.**

RESULT

- **Single doses of Ocedurenone appeared to be safe and well tolerated when administered to subjects with moderate hepatic impairment and healthy subjects with normal hepatic function in this study. One subject in the moderate hepatic impairment group experienced 1 treatment-related TEAE of nausea, mild in severity, which resolved without intervention. No TEAEs were reported by any subjects in the normal hepatic function group. There were no SAEs during the study and no TEAE led to premature discontinuation of a subject from the study. There were no clinically significant findings in the clinical laboratory evaluations, vital sign data, 12-lead ECG, or physical examination data during the study.**

PK Results

Following a single oral dose of 0.5 mg Ocedurenone to subjects with moderate hepatic impairment (N=6) and normal hepatic function (N=6), Ocedurenone was steadily absorbed with median Tmax values of 4.00 hours (range 2.00 to 12.0) and 3.00 hours (range: 2.00 to 24.0), respectively. After reaching Cmax, the disposition of Ocedurenone appeared to be biphasic. The geometric mean t1/2 values for the moderate hepatic impairment and normal hepatic function groups were 75.6 hours (range: 63.1 to 90.1 hours) and 65.7 hours (range: 56.7 to 73.1 hours), respectively (Table 1 and Figure 1).

Figure 1. Arithmetic Mean (+SD) Plasma Concentrations of Ocedurenone Following a Single Oral Dose (Linear and Semi-logarithmic Scale)

Table 1. Summary of the Pharmacokinetic Parameters for Ocedurenone Following a Single Oral Dose

Parameter	Normal Hepatic Function (N=6)	Moderate Hepatic Impairment (N=6)
$AUC_{0\text{-tlast}}$(h*ng/mL)	750 (12.9) [6]	551 (16.6) [6]
$AUC_{0\text{-}\infty}$ (h*ng/mL)	800 (14.0) [6]	612 (16.8) [6]
$\%AUC_{extrap}$ (%)	6.07 (26.1) [6]	9.66 (28.4) [6]
C_{max} (ng/mL)	9.74 (12.3) [6]	5.72 (22.9) [6]
t_{max} (h)	3.00 (2.00, 24.0) [6]	4.00 (2.00, 12.0) [6]
$t_{1/2}$ (h)	65.7 (9.9) [6]	75.6 (13.1) [6]
CL/F (L/h)	0.625 (14.0) [6]	0.817 (16.8) [6]
Vz/F (L)	59.2 (12.5) [6]	89.1 (20.3) [6]

CONCLUSION

- **A single 0.5-mg dose of Ocedurenone was safe and well tolerated when administered to subjects with moderate hepatic impairment and healthy subjects with normal hepatic function.**
- **Ocedurenone was steadily absorbed with median T_{max} values of 4.00 and 3.00 hours, respectively. After reaching C_{max}, the disposition of Ocedurenone appeared to be biphasic. The geometric mean $t_{1/2}$ values for the moderate hepatic impairment group and normal hepatic function group were 75.6 and 65.7 hours, respectively. Ocedurenone systemic exposure, as assessed by AUC were 23.5% to 26.6% lower following administration to subjects with moderate hepatic impairment versus healthy subjects with normal hepatic function, whereas C_{max} was 41.2 % lower. Therefore, the difference in exposure based on C_{max} and AUCs is considered statistically significant.**
- **The unbound of Ocedurenone at 4 and 12 hours postdose from subjects enrolled ranged from 0.115 to 0.296%.**
- **Small decreases of AUC and C_{max} upon systemic exposure to Ocedurenone in subjects with moderate hepatic impairment demonstrate low hepatic extraction and is consistent with the observation that Ocedurenone is cleared predominantly in the gastrointestinal tract vs the kidney.**
- **Considering the long half-life and small decrease in AUC and C_{max}, a dose adjustment does not appear to be warranted in patients with moderate hepatic impairment.**

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