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

James McCabe, Vincent Benn, Jay Zhang, Fred Yang
KBP BIOSCIENCES PTE. LTD.
• Disclosures:
  • James McCabe, Vincent Benn, Jay Zhang, Fred Yang are employees of KBP Biosciences
ABSTRACT

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 glucocorticosterone, progesterone, and androgen receptors and has a higher antagonistic activity to the MR than steroidal MRAs (ie, spironolactone and eplerenone) and non-steroidal flumenidine (1-3).

- A phase 2b clinical trial (BLOCK CKD) in subjects with stage 3b-4 CKD (eGFR 15-44 mL/min/1.73 m²) 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, 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 7-8) 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 210 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 analysis was performed, and safety and tolerability were monitored.

RESULTS:
- Following a single oral dose of 0.5 mg Ocedurenone was steadily absorbed with median Tmax values of 4.00 and 3.00 hours, respectively. After reaching Cmax, the disposition of Ocedurenone appeared to be biphasic. The geometric mean AUC values for the moderate hepatic impairment group and normal healthy control group were 75.6 and 65.7 hours, respectively. Ocedurenone systemically exposure, as assessed by AUC was 23.5% to 26.6% lower following administration to subjects with moderate hepatic impairment versus healthy subjects with normal hepatic function. Ocedurenone systemic exposure, as assessed by AUC was 23.5% to 26.6% lower following administration to subjects with moderate hepatic impairment versus healthy subjects with normal hepatic function. Since Ocedurenone was well tolerated and safety were well tolerated in all participants.

CONCLUSION:
- Small decreases in AUC and Cmax 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 Cmax, a dose adjustment does not appear to be warranted in patients with moderate hepatic impairment.

For additional information please contact:
James McCabe MD
Deputy Chief Medical Officer
KBP BIOSCIENCES PTE. LTD.
Email: james.mccabe@kbpbiosciences.com

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Hepatic Function</th>
<th>Moderate Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng/mL/h)</td>
<td>79.2 (14.0) [6]</td>
<td>61.2 (14.0) [6]</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>0.60 (0.20, 0.80) [6]</td>
<td>0.80 (0.20, 0.80) [6]</td>
</tr>
<tr>
<td>Cmin (ng/mL)</td>
<td>0.29 (0.10, 0.45) [6]</td>
<td>0.40 (0.10, 0.45) [6]</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>4.00 (1.40, 2.00)</td>
<td>0.61 (1.40, 2.00)</td>
</tr>
<tr>
<td>Vz (L)</td>
<td>79.2 (14.0) [6]</td>
<td>58.1 (20.0) [6]</td>
</tr>
</tbody>
</table>

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 than to recombinant human glucocorticosterone, progesterone, and androgen receptors and has a higher antagonistic activity to the MR than steroidal MRAs (ie, spironolactone and eplerenone) and non-steroidal flumenidine (1-3).

- A phase 2b clinical trial (BLOCK CKD) in subjects with stage 3b-4 CKD (eGFR 15-44 mL/min/1.73 m²) 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, 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 7-8) 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 210 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 analysis was performed, and safety and tolerability were monitored.

RESULTS:
- Following a single oral dose of 0.5 mg Ocedurenone was steadily absorbed with median Tmax values of 4.00 and 3.00 hours, respectively. After reaching Cmax, the disposition of Ocedurenone appeared to be biphasic. The geometric mean AUC values for the moderate hepatic impairment group and normal healthy control group were 75.6 and 65.7 hours, respectively. Ocedurenone systemically exposure, as assessed by AUC was 23.5% to 26.6% lower following administration to subjects with moderate hepatic impairment versus healthy subjects with normal hepatic function. Since Ocedurenone was well tolerated and safety were well tolerated in all participants.

CONCLUSION:
- Small decreases in AUC and Cmax 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 Cmax, a dose adjustment does not appear to be warranted in patients with moderate hepatic impairment.

REFERENCES