Pharmacokinetics and Pharmacodynamics of Seladelpar, a Potent and Selective PPAR-δ Agonist, in Patients with Primary Biliary Cholangitis


INTRODUCTION

Primary Biliary Cholangitis (PBC) is a serious and potentially life-threatening autoimmune disease of the liver characterized by inflammation and destruction of intrahepatic bile ducts resulting in cholestasis and accumulation of toxic bile acids (BA).

Seladelpar, a selective PPAR-δ receptor agonist (MBX-8025), is a potent anti-cholestatic agent. In an ongoing Phase 2 study (EudraCT 2016-002996-91), PBC subjects with an inadequate response or intolerance to ursodeoxycholic acid (UDCA) are being evaluated for the safety and anti-cholestatic efficacy of seladelpar. We evaluated the plasma exposure of seladelpar in a subset of PBC subjects from the current study. We also explored the relationship between the exposure of seladelpar and its anti-cholestatic activity.

A mass balance study in rats provided further information on absorption, metabolism and excretion of seladelpar.

METHODS

PBC Low Dose Study

- Phase 2 ongoing, 52-week, multicenter, randomized open-label study
- PBC subjects with inadequate response to or intolerant to UDCA (Alkaline Phosphatase (AP) ≥ 1.67x ULN)
- Seladelpar oral daily dosing of 2.5 or 10 mg in capsules
- Targeting an enrollment of approximately 116 subjects
- PK planned for a subset of PBC study subjects
  - 2 mg: up to 6 subjects
  - 5 mg and 10 mg: up to 12 subjects per group
- Timed collection of blood samples over 24 hours for concentrations of seladelpar on Day 1 and either Week 2 or Week 12
- PK-PD relationships between seladelpar AUCs and biochemical parameters were analyzed by a linear regression model

Seladelpar Mass Balance Study in Rats

- To determine the routes and rates of excretion with mass balance and tissue distribution of seladelpar
- Male and female Sprague-Dawley rats
- Single oral dose of [14C] seladelpar at 15 mg/kg (200 μCi/kg)
- Sample collection at intervals up to 168 hours
- Tissue Distribution: 33-34 tissues were analyzed for seladelpar-related radioactivity at 2, 8, 24, 48, 72 and 168 hours
- Elimination: feces, urine sample collection up to 168 hours
- Biliary excretion using bile-duct cannulated rats up to 72 hours
- Carcasses were subjected to quantitative whole body autoradiography

RESULTS

Baseline Characteristics of PBC Population

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Dose</th>
<th>N</th>
<th>Cov (mg/mL)</th>
<th>Time (hr)</th>
<th>AUC0-24 (ng·hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>2 mg</td>
<td>5</td>
<td>25 (14)</td>
<td>1.5 (0.7)</td>
<td>169 (34)</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>6</td>
<td>140 (101)</td>
<td>5.7 (7.6)</td>
<td>1171 (458)</td>
</tr>
<tr>
<td>Week 2</td>
<td>2 mg</td>
<td>2</td>
<td>29 (12)</td>
<td>1.6 (6.0)</td>
<td>287 (120)</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>6</td>
<td>88 (23)</td>
<td>2.8 (2.2)</td>
<td>851 (246)</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>5</td>
<td>142 (53)</td>
<td>2.9 (1.6)</td>
<td>1387 (257)</td>
</tr>
</tbody>
</table>

Seladelpar PK Profile

Dose Proportionality

Day 1

Week 2

PK-PD Correlation

GTT

Direct Bilirubin

Haptoglobin

hs-CRP

Total Cholesterol

AST

Tissue Distribution over Time in Rats

Single vs. Multiple Dose

AUC0-24 h

Male Rat

Female Rat

Mass Balance in Rats

Biliary Excretion in Bile Duct Cannulated Rats

CONCLUSION

- In a rat mass balance study, no accumulation in any tissue; after 24 hours the radioactivity was limited to the gastrointestinal tract and other excretory organs
- In bile duct cannulated rats, the majority of radioactivity appeared in the bile in the first 24 hours; the main route of elimination was fecal excretion
- Approximately dose proportional increases were observed in Crmax and AUC0-24h for seladelpar in PBC subjects dosed from 2 to 10 mg
- In PBC subjects, seladelpar was rapidly absorbed and had a profile consistent with once-daily oral regimen

Changes in cholestatic and anti-inflammatory pharmacodynamic markers correlated with seladelpar exposure (AUC0-24h) in PBC subjects

INVESTIGATORS

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