Seladelpar for the Treatment of Primary Biliary Cholangitis: Experience with 25 Cirrhotic Patients


Background and Objective

Background
- Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by chronic cholestasis which can progress to cirrhosis, particularly in patients who have an inadequate response to ursodiol (UDCA)
- Seladelpar is a potent and selective peroxisome proliferator-activated receptor delta (PPARδ) agonist with potential as a new therapeutic agent for patients with PBC
- The initial proof of concept of seladelpar in PBC was established in a previous phase 2 clinical study in patients with an inadequate response to UDCA
- The evaluation of the safety and efficacy of seladelpar in patients with cirrhosis is important because liver impairment may have an impact on drug pharmacokinetics and pharmacodynamics

Objective
- To evaluate the safety and efficacy of seladelpar in cirrhotic patients in an ongoing open label phase 2 study in PBC

Methods
- Phase 2 ongoing, randomized, open-label study (NCT02955602)
- Patients with PBC and cirrhosis at entry and alkaline phosphatase (ALP) ≥ 1.67 x ULN who were either inadequately responding to UDCA or were intolerant of UDCA
- Patients were treated with doses of either 5 or 10 mg/day. After 12 weeks, patients receiving 5 mg could escalate to 10 mg if the ALP treatment goal was not achieved
- Primary efficacy and point A: ALP percentage change from baseline
- Secondary endpoints: Changes from baseline in ALT, total bilirubin, and pruritus visual analogue scale (VAS)

Study Design Schematic

Study Design Schematic

- Dose adjustment allowed only after Week 12

Diagnosis and Characteristics of Cirrhotic Patients

- Diagnosis was based on medical history
- Liver biopsy
- Liver elastography
- Imaging (US, CT or MRI)

- All cirrhotic patients were Child-Pugh A
- One patient had a medical history of hepatic encephalopathy (grade 1)

Results

Baseline Demographics, N = 108

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>(Reference Range)</th>
<th>Cirrhotic</th>
<th>Non-Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>51.0 (18-77)</td>
<td>57 (56)</td>
<td>56 (56)</td>
</tr>
<tr>
<td>Female/male</td>
<td>14/6</td>
<td>9/27</td>
<td>37/2</td>
</tr>
<tr>
<td>Duration of PBC, years</td>
<td>11 (6-15)</td>
<td>14 (12)</td>
<td>10 (9)</td>
</tr>
<tr>
<td>UDCA dose, mg/day</td>
<td>14 (10-17)</td>
<td>14 (10-16)</td>
<td>14 (10-16)</td>
</tr>
<tr>
<td>ALP (n = 102)</td>
<td>371-1150</td>
<td>274 (309-771)</td>
<td>371 (289-1448)</td>
</tr>
<tr>
<td>ALT (n = 102)</td>
<td>6-411</td>
<td>36 (27-58)</td>
<td>49 (20-43)</td>
</tr>
<tr>
<td>Total bilirubin (n = 102)</td>
<td>0.1-1.1 mg/dL</td>
<td>0.8 (0.3-4.1)</td>
<td>0.7 (0.3-3.6)</td>
</tr>
<tr>
<td>Platelet</td>
<td>(140-450 x 10^9/L)</td>
<td>144 (100)</td>
<td>107 (68)</td>
</tr>
<tr>
<td>INR</td>
<td>1.1 (0.5-1.2)</td>
<td>1.1 (0.5-1.2)</td>
<td>1.0 (0.5-1.2)</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5-5.5 g/dL</td>
<td>3.0 (3.0-3.0)</td>
<td>3.0 (3.0-3.0)</td>
</tr>
<tr>
<td>VAS</td>
<td>(0-100)</td>
<td>21 (15)</td>
<td>43 (30)</td>
</tr>
</tbody>
</table>

Absolute Change in Pruritus Visual Analogue Scale (VAS: 0 - 100)

References

5. Mo1473 Cymatobay Dose Titration Methods

Mo1473 Dose Titration Methods

- Dose adjustment allowed only after Week 12

Safety

- 11 serious AEs in the study; none were deemed related to seladelpar
- Three discontinuations
  - Related: Grade 1 gastroesophageal reflux in non-cirrhotic patient
- No discontinuations for transaminase elevations

- One patient on 2 mg

Summary

- Seladelpar treatment in PBC patients with cirrhosis (Child-Pugh A):
  - Maintained a potent and anti-cholestatic effect over 52 weeks
  - Appeared to be safe and was well tolerated
  - Not associated with pruritus or hepatoencephalopathy
  - Demonstrated no apparent difference in efficacy or safety between cirrhotic and non-cirrhotic patients

- A 52-week phase 3 global PBC study (ENHANCE) is currently enrolling and includes subjects with compensated cirrhosis

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