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

Phase 2 Open Label Study in PBC

Disclosures

Prof Marlyn J Mayo discloses the following potential conflicts of interest:

*Clinical Trial Agreements*: CymaBay Therapeutics, Intercept Pharmaceuticals, Mallinckrodt Pharmaceuticals, Salix Pharmaceuticals, TARGET PharmaSolutions, GlaxoSmithKline

*Advisory/Consulting Agreements*: CymaBay Therapeutics, TARGET PharmaSolutions, Cara Diagnostics, Regeneron Pharmaceuticals, GlaxoSmithKline

This clinical trial was designed and sponsored by CymaBay Therapeutics, California, USA
Primary Biliary Cholangitis (PBC) and Its Treatment

- Chronic, slowly progressive, cholestatic liver disease
- Inflammation and destruction of intrahepatic bile ducts
- May ultimately lead to cirrhosis

Ursodeoxycholic Acid (UDCA)

1st Line

- ▲ First line therapy for PBC
- ▼ ~40% inadequate responders
- ▼ Additional 5% are intolerant to therapy

Obeticholic Acid (Ocaliva®)

2nd Line

- ▲ Add-on therapy for UDCA inadequate responders
- ▲ Monotherapy for UDCA intolerant patients
- ▲ ALP/bilirubin as cholestatic biomarkers
- ▼ ~50% inadequate responders
- ▼ Can cause or worsen pruritus

Seladelpar
A selective delta PPAR agonist

- Oral, once-daily medication
- Potent and selective PPARδ agonist
  - EC$_{50}$ = 2 nM
  - 630-Fold selective over PPARα
  - Inactive against PPARγ
  - Clinical activity down to 5 mg
- Non-bile acid small molecule
Seladelpar
Targets multiple pathways and cell types in liver disease

Decrease Bile Acids
- Cholesterol synthesis
- Bile acid synthesis (C4)
- Transport

Anti-Inflammatory
- NFκB-dependent gene activation
- Inflammatory cytokines
- hs-C-Reactive Protein

Anti-Fibrotic
- Connective Tissue Growth Factor
- Stellate cell activation
- Collagen synthesis/deposition

Increase Lipid Metabolism
- Cholesterol/LDL-C
- Fatty acid oxidation
- Insulin sensitivity
Open Label Phase 2 Study in PBC Patients with Inadequate Response or Intolerance to UDCA

Entry Criteria: ALP ≥ 1.67 x ULN; ALT & AST ≤ 3 x ULN; Total Bilirubin ≤ 2 mg/dL after UDCA for 12 months or intolerant to UDCA

Seladelpar 10 mg

Seladelpar 5 mg

Seladelpar 5 mg or 10 mg

Long Term Extension

Primary Efficacy: % Change in ALP from baseline

Secondary Efficacy: ALT, Total bilirubin, and pruritus visual analog scale (VAS)

Safety: Adverse events, serious adverse events, discontinuations, and safety labs

Dose adjustment allowed any time after Week 12
Seladelpar Phase 2 Study in PBC
Cirrhotic subgroup analysis

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

(EudraCT: 2016-002996-91; NCT02955602)
Diagnosis and Characteristics of Cirrhotic Patients

- Diagnosis was based on medical history
  - Liver biopsy
  - Liver elastography
  - Imaging (Ultrasound, CT or MRI)
- All cirrhotic patients were Child-Pugh A
- One patient had a medical history of hepatic encephalopathy (grade 1)

<table>
<thead>
<tr>
<th>Cirrhosis Determination</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver biopsy</td>
<td>8</td>
</tr>
<tr>
<td>Elastrography (FibroScan®/ MRE)</td>
<td>3</td>
</tr>
<tr>
<td>Imaging (US/ CT/ MRI)</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
</tr>
</tbody>
</table>
Baseline Demographics, $N = 108$

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>(Reference Range)</th>
<th>Cirrhotic 5/10 mg n = 14</th>
<th>Cirrhotic 10 mg n = 11</th>
<th>Non-Cirrhotic 5/10 mg n = 39</th>
<th>Non-Cirrhotic 10 mg n = 44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td>57 (8)</td>
<td>61 (10)</td>
<td>58 (8)</td>
<td>56 (10)</td>
</tr>
<tr>
<td>Female/male, n</td>
<td></td>
<td>14/0</td>
<td>9/2</td>
<td>37/2</td>
<td>41/3</td>
</tr>
<tr>
<td>Duration of PBC, years</td>
<td></td>
<td>11 (8)</td>
<td>12 (4)</td>
<td>10 (6)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>UDCA dose, mg/kg/d</td>
<td></td>
<td>14 (4)</td>
<td>17 (3)</td>
<td>14 (4)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>ALP (37-116 U/L)</td>
<td></td>
<td>274 (128)</td>
<td>309 (71)</td>
<td>371 (200)</td>
<td>292 (148)</td>
</tr>
<tr>
<td>ALT (6-41 U/L)</td>
<td></td>
<td>38 (27)</td>
<td>56 (24)</td>
<td>49 (26)</td>
<td>43 (22)</td>
</tr>
<tr>
<td>Total bilirubin (0.10-1.10 mg/dL)</td>
<td></td>
<td>0.78 (0.34)</td>
<td>0.99 (0.41)</td>
<td>0.73 (0.36)</td>
<td>0.78 (0.29)</td>
</tr>
<tr>
<td>Platelet (140-400 x 10⁹/L)</td>
<td></td>
<td>144 (90)</td>
<td>187 (68)</td>
<td>242 (73)</td>
<td>255 (71)</td>
</tr>
<tr>
<td>INR</td>
<td></td>
<td>1.1 (0.1)</td>
<td>1.1 (0.1)</td>
<td>1.0 (0.1)</td>
<td>1.0 (0.1)</td>
</tr>
<tr>
<td>Albumin (3.5-5.5 g/dL)</td>
<td></td>
<td>3.8 (0.4)</td>
<td>3.9 (0.5)</td>
<td>4.1 (0.3)</td>
<td>4.1 (0.3)</td>
</tr>
<tr>
<td>VAS (0-100)</td>
<td></td>
<td>21 (15)</td>
<td>43 (30)</td>
<td>25 (26)</td>
<td>28 (28)</td>
</tr>
</tbody>
</table>

*All parameters are Mean (SD)
Alkaline Phosphatase through Week 52
Comparable decrease in cirrhotics and non-cirrhotics

Cirrhotic
\( n = 24 \)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>5/10 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.67 x ULN</td>
<td>1.67 x ULN</td>
</tr>
<tr>
<td>5/10 mg</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>10 mg</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Mean (SE); Numbers indicate the number of patients

Non-Cirrhotic
\( n = 77 \)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>5/10 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.67 x ULN</td>
<td>1.67 x ULN</td>
</tr>
<tr>
<td>5/10 mg</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>10 mg</td>
<td>34</td>
<td>32</td>
</tr>
</tbody>
</table>

Mean (SE); Numbers indicate the number of patients
Percent Change in Alkaline Phosphatase through Week 52

Comparable decrease in cirrhotics and non-cirrhotics

<table>
<thead>
<tr>
<th>Cirrhotic</th>
<th>Non-Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 24</td>
<td>n = 77</td>
</tr>
<tr>
<td>Mean % Change in ALP</td>
<td>Mean % Change in ALP</td>
</tr>
<tr>
<td>-36%</td>
<td>-47%</td>
</tr>
<tr>
<td>-43%</td>
<td>-49%</td>
</tr>
</tbody>
</table>

Dose Titration

Mean (SE); Numbers indicate the number of patients
ALT through Week 52
Comparable decrease in cirrhotics and non-cirrhotics

Cirrhotic
n = 24

Weeks
Mean ALT (U/L)
0 20 40 60 80 100
5/10 mg 10 mg

Non-Cirrhotic
n = 77

Weeks
Mean ALT (U/L)
0 20 40 60 80 100
5/10 mg 10 mg

Mean (SE); Numbers indicate the number of patients.
Total Bilirubin

Stable across cirrhotics and non-cirrhotics

Mean (SE); numbers indicate the number of patients
Absolute Change in Pruritus Visual Analogue Scale (VAS: 0-100)

No increase in cirrhotics and non-cirrhotics

Baseline VAS: 5/10 mg: 19
10 mg: 43

Baseline VAS: 5/10 mg: 25
10 mg: 27
Adverse Events
Safety summary

- 11 serious AEs in the study*; none were deemed related to seladelpar
- Three discontinuations
  - Related: Grade 1 gastroesophageal reflux in non-cirrhotic patient
  - Unrelated: Pneumonia & pruritus (both patients with cirrhosis)
- No discontinuations for transaminase elevations

<table>
<thead>
<tr>
<th>Most Common Adverse Events</th>
<th>Cirrhotic</th>
<th>Non-Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5/10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>n = 14</td>
<td>n = 11</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (7%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (7%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (14%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>UTI</td>
<td>0 (0%)</td>
<td>2 (18%)</td>
</tr>
</tbody>
</table>

*One patient on 2 mg
### Adverse Events

*Well tolerated across cirrhotics and non-cirrhotics*

<table>
<thead>
<tr>
<th>Adverse Event (AE) Category</th>
<th>5/10 mg</th>
<th>10 mg</th>
<th>5/10 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 14</td>
<td>n = 11</td>
<td>n = 39</td>
<td>n = 44</td>
</tr>
<tr>
<td>Patients with at least 1 AE</td>
<td>10 (71%)</td>
<td>8 (73%)</td>
<td>29 (74%)</td>
<td>30 (68%)</td>
</tr>
<tr>
<td>Any AE ≥ Grade 3</td>
<td>1 (7%)</td>
<td>1 (9%)</td>
<td>4 (10%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Any treatment-related AE</td>
<td>5 (36%)</td>
<td>2 (18%)</td>
<td>9 (23%)</td>
<td>11 (25%)</td>
</tr>
<tr>
<td>Any treatment-related AE ≥ Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any AE with outcome of death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any SAE</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Any treatment-related SAE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any AE leading to discontinuation from Seladelpar</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Seladelpar treatment in PBC patients with cirrhosis (Child-Pugh A):

- Maintained a potent anti-cholestatic effect over 52 weeks
- Appeared to be safe and was well tolerated
- Not associated with pruritus or hepatotoxicity
- 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 including subjects with compensated cirrhosis
We gratefully acknowledge study patients, investigators, site staff and CB8025-21629 team!

- **USA**
  - Guy Neff, Michael Galambos, Goel Aparna, Marlyn Mayo, Brian Borg, Stuart Gordon, Stephen Harrison, Paul Thuluvath, Cynthia Levy, Carmen Stanca, Bruce Bacon, Tarek Hassanein, Joseph Odin, Mitchell Shiffman, John Vierling, David Bernstein, Charles Landis, Adam Peyton, Norman Gitlin

- **UK**
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- **Germany**
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- **Canada**
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- **CymaBay**
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Thank You