Efficacy and Safety of Seladelpar in Primary Biliary Cholangitis

52-Week Analysis of a Dose-Ranging Phase 2 Study

Primary Biliary Cholangitis (PBC)
A Progressive, Debilitating Liver Disease

- Most common autoimmune liver disease\(^1\)
  - 1 in 1000 women over the age of 40 are estimated to have PBC\(^2\)
- Inflammation and destruction of the biliary epithelial cells of intrahepatic bile ducts
- Chronic, slowly progressive, cholestatic liver disease\(^3\)
- Ultimately causes cirrhosis\(^3\)

# Current Licensed Therapies for PBC

## Limited Treatment Alternatives

<table>
<thead>
<tr>
<th>Ursodeoxycholic Acid (UDCA)</th>
<th>Obeticholic Acid (Ocaliva®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st Line</strong></td>
<td><strong>2nd Line</strong></td>
</tr>
<tr>
<td>▲ First-line therapy for PBC</td>
<td>▲ Combination therapy for UDCA-inadequate responders</td>
</tr>
<tr>
<td>▼ ~40% inadequate responders: AP &gt; 1.67 x ULN</td>
<td>▲ Monotherapy for UDCA-intolerant patients</td>
</tr>
<tr>
<td>▼ Additional 5% are intolerant to therapy</td>
<td>▲ Established AP/bilirubin as biomarkers for conditional approval</td>
</tr>
<tr>
<td></td>
<td>▼ ~50% inadequate responders</td>
</tr>
<tr>
<td></td>
<td>▼ Can cause or worsen pruritus</td>
</tr>
</tbody>
</table>

### Significant need remains for (1) improved efficacy and (2) better tolerability

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**AP**, alkaline phosphatase.  

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Seladelpar

Once-Daily Oral PPARδ Agonist for Inflammatory Liver Diseases

Bile Acid Homeostasis
- Cholesterol synthesis
- Bile acid synthesis (C4)
- Transport

Inflammation
- NFκB-dependent gene activation
- Inflammatory cytokines
- hs-C-reactive protein (CRP)

Fibrosis
- Connective tissue growth factor (CTGF)
- Stellate cell activation
- Collagen deposition

Metabolic Benefits
- LDL-C
- Cholesterol
- Lipids and increase in insulin sensitivity

CymaBay, Data on File 2018.
Seladelpar Phase 2 Study in PBC

Objective

• To evaluate the safety and efficacy of daily seladelpar treatment for up to 52 weeks from an ongoing open-label phase 2 study in PBC (NCT02955602)
• As of July 2018, results presented for 34 patients completing 52 weeks of treatment
• The 52 week time-point with a composite of AP and bilirubin as surrogates was used for regulatory approval of obeticholic acid

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Effect of AP at 1 Year Follow-up on Overall Percent Survival in Patients With PBC*

<table>
<thead>
<tr>
<th>Follow up, years</th>
<th>Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

HR AP >1.67 ≤1.67 = 2.2 (1.9-2.5)

Effect of Bilirubin at 1 Year Follow-up on Overall Percent Survival in Patients With PBC*

<table>
<thead>
<tr>
<th>Follow up, years</th>
<th>Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

HR abnormal vs normal bilirubin = 5.1 (4.3-5.9)

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*Global PBC study group
Study Design and Eligibility Criteria

Open Label, Dose Ranging, Stable UDCA Dose* or Intolerant to UDCA

Entry
AP ≥1.67 x ULN
ALT/AST ≤3 x ULN
Total Bilirubin ≤2 x ULN

AP ≥1.67 x ULN
ALT/AST ≤3 x ULN
Total Bilirubin ≤2 x ULN

Seladelpar 10 mg qd

Week 0
Week 12†
Week 52

Seladelpar 5 mg qd
Seladelpar 5/10 mg qd

Option for Dose Adjustment

Long Term Extension

Primary End Point
• AP % change from baseline

Secondary End Points
• Responder analysis defined as a composite of:
  • AP < 1.67 x ULN, ≥ 15% decrease in AP, total bilirubin ≤ ULN
  • AP normalization
  • Changes in liver, metabolic, and inflammatory markers
  • Pruritus visual analogue scale (VAS)

*UDCA therapy for prior 12 months. †At week 12 a dose adjustment in the 5/10 mg group was made based on patient response and tolerability.
CymaBay, Data on File 2018.

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## Seladelpar Phase 2 Study in PBC

### Baseline Demographics of mITT Population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>(Reference Range)</th>
<th>Seladelpar 5/10 mg (n=17)</th>
<th>Seladelpar 10 mg (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>49 (5)</td>
<td>48 (11)</td>
<td></td>
</tr>
<tr>
<td>Female/male</td>
<td>17/0</td>
<td>16/1</td>
<td></td>
</tr>
<tr>
<td>History of Pruritus, n (%)</td>
<td>11 (65)</td>
<td>14 (82)</td>
<td></td>
</tr>
<tr>
<td>Pruritus VAS</td>
<td>(0-100)</td>
<td>19 (22)</td>
<td>37 (31)</td>
</tr>
<tr>
<td>AP</td>
<td>(37-116 U/L)</td>
<td>351 (166)</td>
<td>279 (74)</td>
</tr>
<tr>
<td>ALT</td>
<td>(6-41 U/L)</td>
<td>41 (17)</td>
<td>52 (25)</td>
</tr>
<tr>
<td>Total bilirubin*</td>
<td>(0.10-1.10 mg/dL)</td>
<td>0.56 [0.50, 0.70]</td>
<td>0.75 [0.57, 1.14]</td>
</tr>
<tr>
<td>UDCA Dose, mg/kg/day</td>
<td>15 (4)</td>
<td>17 (3)</td>
<td></td>
</tr>
</tbody>
</table>

*Median [Quartiles: 25, 75]. mITT, modified intention to treat; VAS, visual analogue scale.

CymaBay, Data on File 2018.
Seladelpar Phase 2 Study in PBC
Rapid and Sustained Activity Through Week 52

Mean Percent AP Change

Week

2 12 26 52

Mean % Change

-60 -40 -20 0

Dose adjustment for 5/10 mg group

*P<0.0001 for both groups compared to baseline values
Mean ± SEM

Decreases in AP >45% observed at 5/10 mg and 10 mg

CymaBay, Data on File 2018.
Seladelpar Phase 2 Study in PBC
Meaningful and Sustained Activity Through Week 52

Mean AP from Baseline to Week 52

- 5/10 mg, n=17
- 10 mg, n=17

Substantial improvement with AP < 1.67 x ULN

CymaBay, Data on File 2018.
Seladelpar Phase 2 Study in PBC
Responder Analysis at Week 52

Composite Responder Rate

<table>
<thead>
<tr>
<th>Seladelpar</th>
<th>5/10 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder Rate, %</td>
<td>59%</td>
<td>71%</td>
</tr>
</tbody>
</table>

AP Normalization

<table>
<thead>
<tr>
<th>Seladelpar</th>
<th>5/10 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP Normalization, %</td>
<td>24%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Up to 71% of patients achieved the composite efficacy end point

CymaBay, Data on File 2018.
Seladelpar Phase 2 Study in PBC

Stable Total Bilirubin Levels Through Week 52

Median Total Bilirubin

Median total bilirubin remains normal with 5/10 mg and 10 mg
Seladelpar Phase 2 Study in PBC

Significant Decreases in Transaminase Through Week 52

**Median Percent ALT Change**

- Dose adjustment for 5/10 mg group

**Mean ALT**

- No transaminase safety signal was observed

CymaBay, Data on File 2018.

*P<0.0001, compared to baseline values

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## Seladelpar Phase 2 Study in PBC

### Additional Markers of Interest

#### Percent Change in Other Biochemical Markers from Baseline to Week 52

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
<th>(Reference range)</th>
<th>Seladelpar 5/10 mg (n=17)</th>
<th>P-value</th>
<th>Seladelpar 10 mg (n=17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>% change from baseline</td>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td>(50-130 mg/dL)</td>
<td>140 (28)</td>
<td>-13% (13)</td>
<td>0.0005</td>
<td>143 (47)</td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
<td>(35-60 mg/dL)</td>
<td>82 (21)</td>
<td>+4 (23)</td>
<td>NS</td>
<td>74 (27)</td>
</tr>
<tr>
<td>GGT</td>
<td></td>
<td>(Female: 7-38, Male: 11-52 U/L)</td>
<td>140 (28)</td>
<td>-37% (34)</td>
<td>0.0004</td>
<td>286 (223)</td>
</tr>
<tr>
<td>hs-CRP*</td>
<td></td>
<td>(0.0 – 3.0 mg/L)</td>
<td>3 [2, 6]*</td>
<td>-14% (-69, 180)†</td>
<td>NS</td>
<td>3 [2, 6]*</td>
</tr>
</tbody>
</table>

*Median (Quartiles: 25, 75). †Median (Min, Max).
CymaBay, Data on File 2018.
Seladelpar Phase 2 Study in PBC

Patient Reported Pruritus: VAS Through Week 52

Median Change in VAS

- In patients with baseline itch, the median changes in VAS were -30% and -66% in the 5/10 mg and 10 mg groups, respectively

Dose adjustment for 5/10 mg group

Median VAS

Treatment was not associated with increased pruritus

CymaBay, Data on File 2018.
# Seladelpar Phase 2 Study in PBC
## Safety Population Adverse Event (AE) Profile

<table>
<thead>
<tr>
<th>AE Category</th>
<th>Seladelpar 5/10 mg (n=64) n (%)</th>
<th>Seladelpar 10 mg (n=55) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>50 (78)</td>
<td>38 (69)</td>
</tr>
<tr>
<td>Any AE ≥ grade 3</td>
<td>6 (9)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Any treatment-related AE</td>
<td>20 (31)</td>
<td>13 (24)</td>
</tr>
<tr>
<td>Any treatment-related AE ≥ grade 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any AE with outcome of death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any serious AE (SAE)</td>
<td>6 (9)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Any treatment-related SAE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any AE leading to discontinuation from seladelpar</td>
<td>2 (3)</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Most Common AEs (≥ 10%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>14 (22)</td>
<td>10 (18)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (13)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (14)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (14)</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

CymaBay, Data on File 2018.
Seladelpar Phase 2 Study in PBC

Safety Summary

• There were 11 serious AEs in the study; none were deemed related to seladelpar
• No ≥ grade 3 ALT elevations
• No discontinuations for transaminase elevations
• Three discontinuations
  – One discontinuation for a grade 1 gastroesophageal reflux was deemed related to seladelpar
  – Two discontinuations (pneumonia & worsening of pruritus) were deemed unrelated to seladelpar
• Overall, no increase in pruritus
Seladelpar for PBC
Summary and Next Steps

• Seladelpar maintained a potent anti-cholestatic effect over 52 weeks
• Up to 71% of patients achieved the composite efficacy end point
• Overall, seladelpar was generally safe, well tolerated, and not associated with pruritus

A 52-week phase 3 global PBC study (ENHANCE) has been initiated to further confirm these results
Acknowledgements

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Thank You

A study of Primary Biliary Cholangitis