Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis in the RESPONSE Trial: A Phase 3 International, Randomized, Placebo-Controlled Study

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Sponsor: CymaBay Therapeutics, Inc.

Presented by Gideon Hirschfield, FRCP, PhD
Toronto Centre for Liver Disease
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- Professor of Medicine, University of Toronto

I disclose the following financial relationship(s) with a commercial interest:

**Consulting**
- CymaBay Therapeutics
- Escient
- Gilead
- GlaxoSmithKline
- Intercept/Advanz
- Ipsen
- Kowa
- Mirum
- Pliant

**Lectures, presentations, speaker bureaus, manuscript writing, or educational events**
- GlaxoSmithKline
- Intercept
- Ipsen
Primary Biliary Cholangitis (PBC)
Approximately 1 in 1000 women over 40 years of age live with PBC

- Chronic, progressive, autoimmune, cholestatic liver disease
- Serum markers of cholestasis are prognostic
  - Alkaline phosphatase (ALP)
  - Total bilirubin (TB)
- Frequently symptomatic
  - Pruritus
  - Fatigue

Seladelpar

First-in-Class, Potent, Selective Delpar (PPARδ Agonist) Targeting Multiple Cell Types and Processes in PBC

**Improves Cholestasis**
- Bile acid synthesis
- ALP
- GGT

**Hepatocytes and Cholangiocytes**

**Reduces Pruritus**
- Bile acids
- Serum IL-31*

**Hepatocytes**

**Reduces Markers of Inflammation**
- Inflammatory cytokines
- Inflammatory lipid mediators
- ALT

**Macrophages and Kupffer Cells**

**Increases Lipid Metabolism**
- Cholesterol/LDL-C/triglycerides
- Fatty acid oxidation

**Seladelpar**
- Potent PPARδ engagement

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*Although the mechanism of pruritus in PBC is yet to be fully elucidated, reductions in IL-31 may be related to pruritus improvement, which was observed in the ENHANCE study.*


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EMA, European Medicines Agency; FDA, Food and Drug Administration; IL-31, interleukin-31; LDL-C, low-density lipoprotein cholesterol; PPARδ, peroxisome proliferator-activated receptor delta.

* *
RESPONSE: Phase 3 Study Design

**Entry Criteria**
- PBC and inadequate response or intolerance to UDCA
- ALP ≥ 1.67 × ULN
- ALT/AST ≤ 3 × ULN
- Total bilirubin ≤ 2 × ULN
- Compensated cirrhosis allowed

**Stratification**
- ALP < 350 U/L vs ALP ≥ 350 U/L
- Pruritus NRS < 4 vs NRS ≥ 4

**TREATMENT PERIOD**

<table>
<thead>
<tr>
<th>SELADELPAR 10 mg</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 128)</td>
<td>(N = 65)</td>
</tr>
</tbody>
</table>

**ENTRY CRITERIA**
- PBC and inadequate response or intolerance to UDCA
- ALP ≥ 1.67 × ULN
- ALT/AST ≤ 3 × ULN
- Total bilirubin ≤ 2 × ULN
- Compensated cirrhosis allowed

**STRATIFICATION**
- ALP < 350 U/L vs ALP ≥ 350 U/L
- Pruritus NRS < 4 vs NRS ≥ 4

**RESPONSE: Phase 3 Study Design**

**PRIMARY ENDPOINT – COMPOSITE RESPONDER RATE AT MONTH 12**
ALP < 1.67 × ULN; ALP decrease ≥ 15%; total bilirubin ≤ 1 × ULN

**KEY SECONDARY ENDPOINTS**
- ALP normalization rate (ALP ≤ 1 × ULN) at Month 12
- Change in pruritus NRS at Month 6 in patients with baseline NRS ≥ 4

Seladelpar was administered orally once daily.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; EOT, end of treatment; NRS, Numerical Rating Scale; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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### Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 65)</th>
<th>Seladelpar 10 mg (N = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>60 (92.3%)</td>
<td>123 (96.1%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>57.0 (9.2)</td>
<td>56.6 (10.0)</td>
</tr>
<tr>
<td>Duration of disease, years</td>
<td>8.6 (6.5)</td>
<td>8.2 (6.7)</td>
</tr>
<tr>
<td>On UDCA, n (%)</td>
<td>61 (93.8%)</td>
<td>120 (93.8%)</td>
</tr>
<tr>
<td>Pruritus NRS ≥ 4, n (%)</td>
<td>23 (35.4%)</td>
<td>49 (38.3%)</td>
</tr>
<tr>
<td>Cirrhosis, n (%)</td>
<td>9 (13.8%)</td>
<td>18 (14.1%)</td>
</tr>
<tr>
<td>ALP, U/L</td>
<td>313.8 (117.7)</td>
<td>314.6 (123.0)</td>
</tr>
<tr>
<td>TB, mg/dL</td>
<td>0.74 (0.3)</td>
<td>0.77 (0.3)</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>48.2 (22.8)</td>
<td>47.4 (23.5)</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>41.7 (16.0)</td>
<td>39.6 (16.1)</td>
</tr>
<tr>
<td>GGT, U/L</td>
<td>287.5 (249.6)</td>
<td>269.0 (240.0)</td>
</tr>
</tbody>
</table>

Primary Endpoint: Month 12 Composite Biochemical Response
ALP < 1.67 × ULN, ≥ 15% Decrease in ALP, Total Bilirubin ≤ ULN

P value by Cochran–Mantel–Haenszel (CMH) test.

Subjects Achieving Composite Response (%)

- Placebo: 20.0%
- Seladelpar 10 mg: 61.7%

n/N =
- Placebo: 13/65
- Seladelpar 10 mg: 79/128

Approximately 6 in 10 patients achieved the biochemical composite response at Month 12

P < 0.0001

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ALP Change From Baseline

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo n</th>
<th>Seladelpar 10 mg n</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>65</td>
<td>128</td>
</tr>
<tr>
<td>M1</td>
<td>62</td>
<td>125</td>
</tr>
<tr>
<td>M3</td>
<td>62</td>
<td>125</td>
</tr>
<tr>
<td>M6</td>
<td>61</td>
<td>122</td>
</tr>
<tr>
<td>M9</td>
<td>58</td>
<td>117</td>
</tr>
<tr>
<td>M12</td>
<td>57</td>
<td>114</td>
</tr>
</tbody>
</table>

BL, baseline; LS, least squares; M, month.

*P < 0.0001 at all time points.

Seladelpar 10 mg -42.4% -133.9 U/L
Placebo -4.3% -16.9 U/L
Key Secondary Endpoint: ALP Normalization at Month 12

Subjects Achieving ALP Normalization (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0/65</td>
</tr>
<tr>
<td>Seladelpar 10 mg</td>
<td>32/128</td>
</tr>
</tbody>
</table>

$P < 0.0001$

1 in 4 patients treated with seladelpar normalized ALP

$P$ value by CMH test.

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Seladelpar Significantly Improved Serum Markers of Liver Injury and Lipid Profile

% ALT Change

% LDL Cholesterol Change

% GGT Change

% Triglycerides Change

*P < 0.0001 vs placebo. †P < 0.005 vs placebo. ‡P < 0.05 vs placebo.

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Seladelpar Significantly Improved Pruritus
Subjects With Baseline NRS ≥ 4

Key Secondary Endpoint:
Change in Pruritus NRS at Month 6

Change From Baseline
in NRS (LS Mean ± SE)

Placebo
Seladelpar 10 mg

n = 20
45

Change From Baseline
in NRS (LS Mean ± SE)

P < 0.005

‡

Change in Pruritus NRS Over Time

Placebo
Seladelpar 10 mg

MMRM analysis in subjects with baseline NRS ≥ 4 using weekly averages. Baseline pruritus NRS is defined as the mean of all daily recorded scores during the run-in period and on Day 1. The n values represent the number of subjects with available data at each time point.

*P < 0.005 vs placebo. †P < 0.05 vs placebo.

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In the Overall Population, Seladelpar Both Had a Durable Effect on Pruritus and Reduced the Pruritogenic Cytokine IL-31

In the Overall Population, Seladelpar Both Had a Durable Effect on Pruritus and Reduced the Pruritogenic Cytokine IL-31

<table>
<thead>
<tr>
<th></th>
<th>Placebo n = 65</th>
<th>M1 64</th>
<th>M3 63</th>
<th>M6 61</th>
<th>M9 56</th>
<th>M12 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seladelpar 10 mg n = 128</td>
<td>128</td>
<td>124</td>
<td>121</td>
<td>108</td>
<td>105</td>
<td></td>
</tr>
</tbody>
</table>

**Change From Baseline in Pruritus NRS (LS Mean ± SE)**

- Placebo
- Seladelpar 10 mg

**% Change From Baseline in Serum IL-31 (LS Mean ± SE)**

- M3 56
- M6 53
- M12 50

MMRM analysis in the overall population using weekly averages. Baseline pruritus NRS is defined as the mean of all daily recorded scores during the run-in period and on Day 1. The n values represent the number of subjects with available data at each time point.

*P < 0.0001 vs placebo. †P < 0.005 vs placebo. ‡P < 0.05 vs placebo.

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Seladelpar Reductions in Pruritus Were Accompanied by Improvements in Sleep Disturbance

**NRS ≥ 4 Population**

**Overall Population**

*P < 0.0001 vs placebo. †P < 0.005 vs placebo. ‡P < 0.05 vs placebo.*
**Safety Overview: Summary of Adverse Events**

No Meaningful Differences Between Placebo and Seladelpar

<table>
<thead>
<tr>
<th>Safety Population, n (%)</th>
<th>Placebo (N = 65)</th>
<th>Seladelpar 10 mg (N = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at least 1 AE</td>
<td>55 (84.6)</td>
<td>111 (86.7)</td>
</tr>
<tr>
<td>Any treatment-related AE</td>
<td>8 (12.3)</td>
<td>22 (17.2)</td>
</tr>
<tr>
<td>Any treatment-related AE ≥ Grade 3 (CTCAE)</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 SAE</td>
<td>4 (6.2)</td>
<td>9 (7.0)</td>
</tr>
<tr>
<td>Any treatment-related SAE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any AE leading to study drug discontinuation</td>
<td>3 (4.6)</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td>Liver-related AEs*</td>
<td>6 (9.2)</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td>Muscle-related AEs*</td>
<td>5 (7.7)</td>
<td>8 (6.3)</td>
</tr>
</tbody>
</table>

All AEs were treatment emergent. Treatment-related AEs were per investigator assessment.
AE, adverse event; SAE, serious adverse event.
*A liver and muscle AEs were identified by predefined search strategy.
†ASSURE, NCT03301506.

96% of eligible patients completing treatment agreed to enter open-label safety study†
<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Placebo (N = 65)</th>
<th>Seladelpar 10 mg (N = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19</td>
<td>10 (15.4)</td>
<td>23 (18.0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10 (15.4)</td>
<td>6 (4.7)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6 (9.2)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3.1)</td>
<td>10 (7.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5 (7.7)</td>
<td>7 (5.5)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>5 (7.7)</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (1.5)</td>
<td>9 (7.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4 (6.2)</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (6.2)</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (4.6)</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>2 (3.1)</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4 (6.2)</td>
<td>5 (3.9)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 (6.2)</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (6.2)</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td>Vertigo positional</td>
<td>4 (6.2)</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

All AEs were treatment emergent.
The RESPONSE Phase 3 Study Met Both Primary and Key Secondary Endpoints
Seladelpar Improved Markers of Disease Activity and Pruritus in Patients With PBC

- Significantly more patients met the composite biochemical endpoint and ALP normalization with seladelpar vs placebo at Month 12
  - Approximately 6 in 10 patients met the primary composite endpoint
  - Approximately 1 in 4 patients met the key secondary endpoint of ALP normalization
  - Mean reduction in ALP was 42% or 133.9 U/L at Month 12

- The improvement in pruritus at Month 6 in patients with moderate to severe itch was highly statistically significant

- In the overall population, seladelpar reduced pruritus as well as the pruritogenic cytokine IL-31 through Month 12

- Treatment with seladelpar decreased ALT, GGT, triglycerides, and LDL cholesterol

- Seladelpar appeared safe and well tolerated
Acknowledgements

We gratefully acknowledge the study patients, investigators, site staff, and the RESPONSE team.

Countries involved in the global RESPONSE study:

Argentina  Germany  Poland
Australia  Greece  Romania
Austria  Hungary  Russia
Belgium  Israel  Spain
Canada  Italy  Switzerland
Chile  Republic of Korea  Turkey
Czech Republic  Mexico  UK
France  New Zealand  USA

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Thank you!
Appendix
## RESPONSE Patient Disposition

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Placebo (N = 65)</th>
<th>Seladelpar 10 mg (N = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomized and treated</td>
<td>65 (100.0)</td>
<td>128 (100.0)</td>
</tr>
<tr>
<td>Subjects who completed treatment</td>
<td>57 (87.7)</td>
<td>118 (92.2)</td>
</tr>
<tr>
<td>Subjects who discontinued treatment</td>
<td>8 (12.3)</td>
<td>10 (7.8)</td>
</tr>
<tr>
<td>Primary reason for treatment discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>4 (6.2)</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td>Withdrawal of informed consent</td>
<td>2 (3.1)</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td>Significant protocol deviation</td>
<td>1 (1.5)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1 (1.5)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Eligible subjects who agreed to enter ASSURE*,+</td>
<td>54 (96.4)</td>
<td>106 (96.4)</td>
</tr>
</tbody>
</table>

All randomized subjects analysis set. The N and n values represent the total number of subjects and the number of subjects in each category, respectively.

*Includes subjects who completed RESPONSE, were eligible to enroll in the open-label study ASSURE and agreed to the open-label study; subjects in Russia were not eligible for ASSURE due to operational complexities.

†Percentages based on number of subjects eligible for ASSURE who completed treatment in RESPONSE (56 subjects in placebo, 110 subjects in seladelpar, 166 subjects overall).