ENHANCE: Safety and Efficacy of Seladelpar in Patients With Primary Biliary Cholangitis

Gideon Hirschfield, FRCP, PhD
Toronto Centre for Liver Disease, University of Toronto
@autoimmuneliver
Disclosures

Gideon Hirschfield, FRCP, PhD

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

- CymaBay Therapeutics
- Falk Pharma
- Genfit
- GSK
- Intercept
- Morphic Therapeutic
- Mirum
- Pliant
- Roche
ENHANCE: Safety and Efficacy of Seladelpar in Patients With Primary Biliary Cholangitis

A PHASE 3 INTERNATIONAL, RANDOMIZED, PLACEBO-CONTROLLED STUDY


Sponsor: CymaBay Therapeutics, Inc
Primary Biliary Cholangitis (PBC)

1 in 1000 women over 40 years of age live with PBC

- Chronic, destructive, autoimmune, cholestatic liver disease
- Bile duct injury, portal inflammation, cholestasis, progressive liver fibrosis
- Elevated serum markers of biliary injury: Alkaline phosphatase (ALP), Total bilirubin
- Symptoms including fatigue and pruritus

Healthy liver → Cholestasis → Impaired quality and quantity of life → Progression:
- Inflammation
- Progressive Biliary Fibrosis
- Cirrhosis

END STAGE LIVER DISEASE
- Portal hypertension
- Liver failure
- Hepatocellular carcinoma
- Liver transplantation
- Death

1 in 1000 women over 40 years of age live with PBC

Slides are the property of CymaBay Therapeutics and AASLD. Permission is required from both CymaBay Therapeutics and AASLD for reuse.
Primary Biliary Cholangitis (PBC)

1 in 1000 women over 40 years of age live with PBC

Chronic, destructive, autoimmune, cholestatic liver disease

Bile duct injury, portal inflammation, cholestasis, progressive liver fibrosis

Elevated serum markers of biliary injury:
Alkaline phosphatase (ALP)
Total bilirubin

Symptoms including fatigue and pruritus

ALP and total bilirubin are biochemical surrogates of disease activity that highlight an individual’s risk of disease progression

Treatment goals recognize the importance of normalizing ALP and total bilirubin

Unmet Need Remains Despite Existing Treatments
Opportunity for new therapy addressing disease activity and symptom burden

**1ST LINE**

Ursodeoxycholic Acid (UDCA)

- 1st-line therapy for PBC

- ~40% are inadequate responders with ALP ≥1.67x ULN
- Additional ~5% are intolerant to therapy
- UDCA therapy does not improve pruritus or other symptoms associated with PBC

**2ND LINE**

Obeticholic Acid (Ocaliva®)

- Add-on therapy for UDCA inadequate responders
- Monotherapy for patients intolerant to UDCA
- ALP/bilirubin as biomarkers for accelerated approval

- ~50% are inadequate responders
- Pruritus can worsen or be caused

Seladelpar is a potentially improved 2nd-line treatment for PBC

Seladelpar
The only potent and selective PPARδ agonist in development for liver disease

 Decrease Bile Acids\(^1\)
- ▼ Cholesterol synthesis
- ▼ Bile acid synthesis (C4)
- ▲ Transport

 Anti-fibrotic\(^2\)
- ▼ Profibrotic genes
- ▼ Stellate cell activation
- ▼ Collagen synthesis/deposition

 Anti-inflammatory\(^1\)
- ▼ NF\(\kappa\)B-dependent gene activation
- ▼ Inflammatory cytokines
- ▼ hs-C-reactive protein

 Increase Lipid Metabolism\(^3\)
- ▼ Cholesterol/LDL-C
- ▲ Fatty acid oxidation
- ▲ Insulin sensitivity

Targets all important cell types in liver disease

PPAR\(\delta\), peroxisome proliferator-activated receptor delta.
ENHANCE Phase 3 Study (Original Design)

Key Inclusion Criteria

- 18 to 75 years old, male or female with a diagnosis of PBC based on any 2 of the following criteria:
  - History of ALP above 1.0x ULN for at least 6 months
  - Positive AMA titer (>1:40 on immunofluorescence or M2 positive by ELISA) or positive PBC-specific ANA
  - Documented liver biopsy results consistent with PBC
- UDCA for the past 12 months (stable dose) OR intolerant to UDCA
- ALP ≥1.67x ULN; ALT/AST ≤3x ULN; total bilirubin ≤2x ULN

Seladelpar was administered orally once daily.

Seladelpar or placebo was administered as an add-on to UDCA therapy for patients who tolerated UDCA; for patients with UDCA intolerance, the study drug was administered as a monotherapy.

The study was discontinued because of unexpected histological findings that were later determined to be pre-existing in the nonalcoholic steatohepatitis seladelpar program.

Seladelpar or placebo was administered as an add-on to UDCA therapy for patients who tolerated UDCA; for patients with UDCA intolerance, the study drug was administered as a monotherapy.

Key Inclusion Criteria

- 18 to 75 years old, male or female with a diagnosis of PBC based on any 2 of the following criteria:
  - History of ALP above 1.0x ULN for at least 6 months
  - Positive AMA titer (>1:40 on immunofluorescence or M2 positive by ELISA) or positive PBC-specific ANA
  - Documented liver biopsy results consistent with PBC
- UDCA for the past 12 months (stable dose) OR intolerant to UDCA
- ALP ≥1.67x ULN; ALT/AST ≤3x ULN; total bilirubin ≤2x ULN

ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; ELISA, enzyme-linked immunosorbent assay; ULN, upper limit of normal.

Seladelpar was administered orally once daily.

Seladelpar or placebo was administered as an add-on to UDCA therapy for patients who tolerated UDCA; for patients with UDCA intolerance, the study drug was administered as a monotherapy.

The study was discontinued because of unexpected histological findings that were later determined to be pre-existing in the nonalcoholic steatohepatitis seladelpar program.

Seladelpar or placebo was administered as an add-on to UDCA therapy for patients who tolerated UDCA; for patients with UDCA intolerance, the study drug was administered as a monotherapy.

The study was discontinued because of unexpected histological findings that were later determined to be pre-existing in the nonalcoholic steatohepatitis seladelpar program.
ENHANCE Design and Analysis Plan

Blinded analysis after early termination. The safety analysis set included any patient who received at least 1 dose of study drug. The mITT analysis set included any patient randomized and dosed.

**Study Population**
- Intolerance or inadequate response to UDCA
- ALP ≥1.67x ULN, bilirubin ≤2x ULN
- Includes patients with severe pruritus

**Design**
- Seladelpar 10 mg and 5/10 mg titration vs placebo (1:1:1 randomization)
- Stratified by ALP value (<350 U/L vs ≥350 U/L) and pruritus Numerical Rating Scale (NRS) (<4 vs ≥4)

**Endpoints**
**Amended Endpoints (No dose titration prior to Month 6)**
- **Primary Endpoint:** Composite responder rate at Month 3*
- **Key Secondary Endpoints:**
  - ALP normalization at Month 3
  - Change from baseline in pruritus NRS at Month 3 (patients with baseline NRS ≥4)
- **Other Secondary Endpoints:**
  - Previous 3 endpoints at Month 6

**Enrolled Patients**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Seladelpar 5 mg</th>
<th>Seladelpar 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety/mITT Population</td>
<td>87</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Month 3</td>
<td>56</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>Month 6</td>
<td>23</td>
<td>26</td>
<td>20</td>
</tr>
</tbody>
</table>

*Composite responder: ALP <1.67x ULN, ≥15% decrease in ALP, total bilirubin ≤ULN.

mITT, modified intention-to-treat.
### Demographic and Baseline Characteristics

**mITT population**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=87)</th>
<th>Seladelpar 5 mg (n=89)</th>
<th>Seladelpar 10 mg (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>85 (98%)</td>
<td>82 (92%)</td>
<td>83 (93%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>56 (8)</td>
<td>55 (10)</td>
<td>56 (9)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>80 (92%)</td>
<td>83 (93%)</td>
<td>77 (87%)</td>
</tr>
<tr>
<td>Duration of PBC, years</td>
<td>8 (6)</td>
<td>8 (6)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>History of Pruritus, n (%)</td>
<td>57 (66%)</td>
<td>66 (74%)</td>
<td>65 (73%)</td>
</tr>
<tr>
<td>Pruritus NRS ≥4</td>
<td>27 (31%)</td>
<td>27 (30%)</td>
<td>27 (30%)</td>
</tr>
<tr>
<td>UDCA Dose, mg/kg/day</td>
<td>15 (3)</td>
<td>16 (4)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>UDCA Intolerant, n (%)</td>
<td>2 (2%)</td>
<td>6 (7%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>ALP, ULN: 116 U/L</td>
<td>293 (106)</td>
<td>290 (104)</td>
<td>291 (109)</td>
</tr>
<tr>
<td>ALT, ULN: 41 U/L</td>
<td>44 (21)</td>
<td>48 (21)</td>
<td>47 (21)</td>
</tr>
<tr>
<td>AST, ULN: 34 U/L</td>
<td>37 (17)</td>
<td>40 (14)</td>
<td>40 (15)</td>
</tr>
<tr>
<td>GGT, ULN: 38 U/L</td>
<td>229 (193)</td>
<td>231 (212)</td>
<td>243 (228)</td>
</tr>
<tr>
<td>Total bilirubin, ULN: 1.1 mg/dL</td>
<td>0.71 (0.32)</td>
<td>0.76 (0.35)</td>
<td>0.72 (0.32)</td>
</tr>
<tr>
<td>Immunoglobulin M, ULN: 230 mg/dL</td>
<td>358 (264)</td>
<td>332 (202)</td>
<td>316 (181)</td>
</tr>
</tbody>
</table>

GGT, gamma-glutamyl transferase.
Mean (SD) unless otherwise specified.
Primary Composite Endpoint Achieved at 3 months
ALP <1.67x ULN, ≥15% decrease in ALP, total bilirubin ≤ULN

78% of patients on seladelpar 10 mg achieved the primary composite endpoint with high statistical significance at 3 months

(n=78) Placebo (n=80) 5 mg (n=79) 10 mg
10.3 47.5 64.6

(n=56) Placebo (n=56) 5 mg (n=55) 10 mg
12.5 57.1 78.2

(n=23) Placebo (n=26) 5 mg (n=20) 10 mg
21.7 61.5 70.0

*ns, not significant. P values by Cochran-Mantel-Haenszel (CMH) test. CymaBay, Data on File 2020.*
Key Secondary Endpoint Achieved: ALP Normalization Rate
ALP ≤1x ULN

Month 1

Month 3

Month 6

27% of patients on seladelpar 10 mg normalized ALP by 3 months

P values by CMH test.
CymaBay, Data on File 2020.
ALP Relative and Absolute Change at Month 3

Significant dose-dependent relative and absolute reductions in ALP were observed at 3 months.

LS Mean and P values by analysis of covariance (ANCOVA).
CymaBay, Data on File 2020.
ALT Normalization at Month 3
Patients with baseline ALT >ULN

In patients with elevated baseline ALT on seladelpar 10 mg

50% normalized ALT by 3 months

*P* values by CMH test.
CymaBay, Data on File 2020.
### Improvement in Other Serum Liver Tests

Month 1, 3, and 6 treatment effects in mITT population

#### Seladelpar demonstrated broad anti-cholestatic and anti-inflammatory effects

<table>
<thead>
<tr>
<th>mITT population</th>
<th>Placebo</th>
<th>Seladelpar 5 mg</th>
<th>Seladelpar 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 1 (n=78)</td>
<td>Month 3 (n=56)</td>
<td>Month 6 (n=23)</td>
</tr>
<tr>
<td>ALT % Change</td>
<td>-2.0%</td>
<td>-4.0%</td>
<td>2.4%</td>
</tr>
<tr>
<td>GGT % Change</td>
<td>-6.7%</td>
<td>-6.5%</td>
<td>0.1%</td>
</tr>
<tr>
<td>AST % Change</td>
<td>1.3%</td>
<td>-0.2%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Total bilirubin % Change</td>
<td>-1.3%</td>
<td>0.9%</td>
<td>1.7%</td>
</tr>
<tr>
<td>IgM % Change</td>
<td>-2.6%</td>
<td>-5.7%</td>
<td>-3.4%</td>
</tr>
</tbody>
</table>

IgM, immunoglobulin M.
Key Secondary Endpoint Achieved: Treatment Improvement in Pruritus

Patients with baseline NRS ≥4

In patients with moderate and severe pruritus (baseline NRS of 6.2), significant improvements in pruritus were seen with seladelpar 10 mg at 3 months.
Dose-Ordered Reductions in Pruritus NRS Observed at Month 3

Patients with baseline NRS ≥4

Dose-ordered reductions in NRS were seen at 3 months in patients with moderate and severe pruritus

- **≥2-point Reduction**: Placebo 33.3%, 5 mg 50.0%, 10 mg 68.4%
  - *P* = 0.0361

- **≥3-point Reduction**: Placebo 16.7%, 5 mg 38.9%, 10 mg 42.1%
  - *P* = 0.0361

- **≥4-point Reduction**: Placebo 5.6%, 5 mg 22.2%, 10 mg 36.8%
  - *P* = 0.0183

*P* values by CMH test. Non-significant *P* values not shown.

CymaBay, Data on File 2020.
## Safety Overview

Summary of treatment-emergent adverse events

<table>
<thead>
<tr>
<th>Safety Population, n (%)</th>
<th>Placebo (n=87)</th>
<th>Seladelpar 5 mg (n=89)</th>
<th>Seladelpar 10 mg (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 AE</td>
<td>64 (73.6)</td>
<td>56 (62.9)</td>
<td>58 (65.2)</td>
</tr>
<tr>
<td>Any treatment-related AE</td>
<td>16 (18.4)</td>
<td>25 (28.1)</td>
<td>15 (16.9)</td>
</tr>
<tr>
<td>Any treatment-related AE ≥ Grade 3 (CTCAE)*</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>
</tr>
<tr>
<td>Any SAE</td>
<td>3 (3.4)</td>
<td>3 (3.4)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Any treatment-related SAE</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any AE leading to study drug discontinuation</td>
<td>2 (2.3)</td>
<td>2 (2.2)</td>
<td>2 (2.2)</td>
</tr>
</tbody>
</table>

*No Grade 3 ALT/AST elevations.*

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event.
## Treatment-Emergent Adverse Events

Occurring in ≥5% of patients in any randomized treatment

<table>
<thead>
<tr>
<th>Safety Population, n (%)</th>
<th>Placebo (n=87)</th>
<th>Seladelpar 5 mg (n=89)</th>
<th>Seladelpar 10 mg (n=89)</th>
<th>Seladelpar Total (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain upper</td>
<td>3 (3.4)</td>
<td>8 (9.0)</td>
<td>6 (6.7)</td>
<td>14 (7.9)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11 (12.6)</td>
<td>3 (3.4)</td>
<td>10 (11.2)</td>
<td>13 (7.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (4.6)</td>
<td>5 (5.6)</td>
<td>7 (7.9)</td>
<td>12 (6.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1.1)</td>
<td>5 (5.6)</td>
<td>7 (7.9)</td>
<td>12 (6.7)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2 (2.3)</td>
<td>6 (6.7)</td>
<td>4 (4.5)</td>
<td>10 (5.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5 (5.7)</td>
<td>5 (5.6)</td>
<td>4 (4.5)</td>
<td>9 (5.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (2.3)</td>
<td>5 (5.6)</td>
<td>3 (3.4)</td>
<td>8 (4.5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>2 (2.2)</td>
<td>5 (5.6)</td>
<td>7 (3.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (9.2)</td>
<td>2 (2.2)</td>
<td>4 (4.5)</td>
<td>6 (3.4)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0</td>
<td>5 (5.6)</td>
<td>1 (1.1)</td>
<td>6 (3.4)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5 (5.7)</td>
<td>2 (2.2)</td>
<td>1 (1.1)</td>
<td>3 (1.7)</td>
</tr>
</tbody>
</table>
## Treatment-Emergent Serious Adverse Events

### Safety Population, n (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n=87)</th>
<th>Seladelpar 5 mg (n=89)</th>
<th>Seladelpar 10 mg (n=89)</th>
<th>Seladelpar Total (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one serious TEAE</td>
<td>3 (3.4)</td>
<td>3 (3.4)</td>
<td>1 (1.1)</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Any treatment-related SAE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### List of SAEs by preferred term

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Seladelpar 5 mg</th>
<th>Seladelpar 10 mg</th>
<th>Seladelpar Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulitis</td>
<td>0</td>
<td>0</td>
<td>1 (1.1)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Pyelonephritis acute</td>
<td>1 (1.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cognitive disorder</td>
<td>0</td>
<td>1 (1.1)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Partial seizures</td>
<td>1 (1.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>0</td>
<td>1 (1.1)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>0</td>
<td>1 (1.1)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Rectal polyp</td>
<td>1 (1.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Safety and Efficacy of Seladelpar in Patients With PBC

- 78% of patients achieved primary endpoint with 10 mg dose
- Seladelpar 10 mg had a statistically significant effect on ALP normalization
- Seladelpar 10 mg had a statistically significant reduction in pruritus
- 10 mg dose is optimal with consistently greater effects on all endpoints
- Overall, seladelpar was generally safe and well tolerated

A 52-week Phase 3 global registration study (RESPONSE) to begin enrolling patients in Q1 2021
Acknowledgements

We gratefully acknowledge the study patients, investigators, site staff, and the ENHANCE team!

Argentina  Australia  Austria  Belgium  Canada  Chile  France  Germany  Greece  Hungary  Israel  Italy  Korea  Mexico  Netherlands  New Zealand  Poland  Romania  Russia  Spain  UK  USA
Thank You