Seladelpar Treatment Resulted in Correlated Decreases in Serum IL-31 and Pruritus in Patients with Primary Biliary Cholangitis (PBC)

Post-Hoc Results from the Phase 3 Randomized, Placebo-Controlled ENHANCE Study

Andreas E. Kremer
Marlyn J. Mayo, Gideon M. Hirschfield, Cynthia Levy, Christopher L. Bowlus, David E. Jones, Jeff D. Johnson, Charles A. McWherter, and Yun-Jung Choi

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Disclosure

Andreas E. Kremer

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

- Abbvie, AstraZeneca, AOP Orphan, Bayer, CymaBay, Escient, Eisai, Falk, FMC, Gilead, GSK, Intercept, Mirum, Medscape, MSD, Myr, Newbridge, Novartis, Lilly, Roche, Viofor
Seladelpar
Targets all important 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

Increase Lipid Metabolism
- Cholesterol/LDL-C
- Fatty acid oxidation

Anti-Fibrotic
- Profibrotic genes
- Stellate cell activation
- Collagen synthesis/deposition

Regulates Genes That Control Pathways in Liver Health and Disease
## Seladelpar Studies with PBC Patients

**Daily oral add-on to UDCA dose, or as monotherapy when intolerant**

<table>
<thead>
<tr>
<th>PBC studies</th>
<th>Phase 2 open-label study</th>
<th>ENHANCE Phase 3 study</th>
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</table>
| **Key Eligibility** | ▪ Diagnosis of PBC  
▪ ALT/AST ≤ 3 x ULN  
▪ Prior UDCA ≥ 12 months or intolerant | ▪ ALP ≥ 1.67 x ULN  
▪ Total Bilirubin ≤ 2 x ULN |

### Study Design

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month 3</th>
<th>1 Year</th>
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<tbody>
<tr>
<td><strong>Dose Adjustment</strong></td>
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<tr>
<td>Seladelpar 5 mg</td>
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<tr>
<td>Seladelpar 10 mg (n = 48)</td>
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<tr>
<td>Seladelpar 5/10 mg (n = 42)</td>
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<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month 3</th>
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<tbody>
<tr>
<td><strong>Placebo</strong> (n = 55)</td>
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<tr>
<td>Seladelpar 5 mg (n = 53)</td>
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<td>Seladelpar 10 mg (n = 53)</td>
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### Measurements

<table>
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<tr>
<th></th>
<th>Baseline</th>
<th>Month 3</th>
<th>1 Year</th>
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<tbody>
<tr>
<td><strong>Pruritus Visual Analog Scale (VAS, 0-100)</strong></td>
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<tr>
<td><strong>Serum total bile acids</strong></td>
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<tr>
<td><strong>Serum IL-31</strong></td>
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<th></th>
<th>Baseline</th>
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<tr>
<td><strong>Pruritus Numerical Rating Scale (NRS, 0-10)</strong></td>
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<td><strong>Serum total bile acids</strong></td>
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<td><strong>Serum IL-31</strong></td>
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<tr>
<td><strong>Serum autotaxin</strong></td>
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<tr>
<td><strong>Other cytokines (IL-4, IL-13 and IL-33)</strong></td>
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Seladelpar Improved Pruritus in Patients with PBC
Patients with moderate to severe pruritus

**Phase 2 open-label study**

- **PBC patients with VAS ≥ 40**
  - 5/10 mg (n=12)
  - 10 mg (n=15)
  - VAS scale 0-100

**ENHANCE phase 3 study**

- **PBC patients with NRS ≥ 4**
  - Placebo (n=18)
  - Seladelpar 5 mg (n=17)
  - Seladelpar 10 mg (n=18)
  - NRS scale 0-10

- **Change in VAS at 1 Year**
  - Mean (SE)
  - 5/10 mg (n=12)
  - 10 mg (n=15)

- **Change in NRS at Month 3**
  - LS Mean (SE)
  - Placebo (n=18)
  - Seladelpar 5 mg (n=17)
  - Seladelpar 10 mg (n=18)

- **p-values**
  - p=0.02
  - p=0.48
  - p=0.09
  - p=0.02
IL-31 in Pruritic Skin Diseases

- **IL-31 is elevated** in tissue or serum of patients with pruritic skin diseases (atopic dermatitis, prurigo nodularis).
- IL-31 is primarily produced by T helper 2 (Th2) cells, although other innate immune cells can also produce IL-31.
- The **dimeric IL-31 receptor** is expressed by various cell types, including peripheral sensory nerves, epidermal keratinocytes, and immune cells.
- **Animals** (mouse, dog, monkey and human) treated with IL-31 exhibited increased scratching behavior, and treatments targeting IL-31 reduced scratching.
- **Nemolizumab**, a human monoclonal anti-IL-31 RA antibody, significantly reduced pruritus in patients with atopic dermatitis in phase III trial.

Kabashima et al, Front Med, 2021
Pearson et al, Vet Sci, 2023
Lewis et al, J Eur Acad Dermatol Venereol, 2017
Hawro et al, Allergy, 2014
Serum IL-31: PBC Patients vs. Healthy Volunteers (HV)

Healthy volunteers: age, sex and BMI matched with PBC patients (ENHANCE)

- IL-31 was elevated in previous studies (Mu et al, Immunological Investigations, 2021; Xu et al, Hepatology, 2023)
FXR Agonist Increased Serum IL-31 Levels

- FXR agonist, cilofexor, dose-dependently increased serum IL-31 levels in noncirrhotic NASH patients
- Significantly higher IL-31 levels in cilofexor-treated NASH patients with severe pruritus
- FXR agonist OCA elevated serum human IL-31 levels in PXB mice with humanized liver

Xu et al, Hepatology, 2023
Substantial Reduction of Serum IL-31 by Seladelpar After 3 Months

ENHANCE phase 3 study with seladelpar in patients with PBC

**IL-31**

**IL-31 % Change**

**IL-31 (pg/mL)**

- Placebo (n=55)
- Seladelpar 5 mg (n=53)
- Seladelpar 10 mg (n=53)

BL: Baseline
M3: Month 3

- IL-31 % Change at Month 3
  - Placebo: BL -60, M3 -30, +31%
  - Seladelpar 5 mg: BL -60, M3 -30, -30%
  - Seladelpar 10 mg: BL -60, M3 -60, -52%

*p-values indicated for statistical significance.*
Serum IL-31 Correlates with Pruritus NRS

ENHANCE phase 3 study with seladelpar in patients with PBC

Baseline IL-31 vs. Baseline NRS

Changes in IL-31 vs. Change in NRS

- Placebo (r=0.36, p=0.0080)
- 5 mg (r=0.44, p=0.0011)
- 10 mg (r=0.54, p<0.0001)
Patients with Pruritus Improvement Showed Greater Decrease in Serum IL-31 Levels

ENHANCE phase 3 study with seladelpar in patients with PBC

Changes in IL-31 by Decrease in Pruritus NRS

Decrease in NRS < 2

- Placebo
- Seladelpar 5 mg
- Seladelpar 10 mg

Decrease in NRS ≥ 2

- Placebo
- Seladelpar 5 mg
- Seladelpar 10 mg
Phase 2 Study Confirms IL-31 and Pruritus Results

Open-label phase 2 study with seladelpar in patients with PBC

IL-31

Baseline IL-31 vs. VAS

Changes in IL-31 vs. VAS at 1 Year
IL-31 is Correlated with Total Bile Acids

ENHANCE phase 3 study with seladelpar in patients with PBC

Baseline IL-31 vs. Total Bile Acids

Total Bile Acids

Changes in IL-31 and Total Bile Acids

- Placebo (r=0.26, p=0.068)
- 5 mg (r=0.06, p=0.66)
- 10 mg (r=0.63, p<0.0001)
No Effect of Seladelpar on Other Cytokines Known to Be Associated with IL-31 and Pruritus

ENHANCE phase 3 study with seladelpar in patients with PBC

**IL-4**

**IL-13**

**IL-33**

Placebo 5 mg 10 mg

BL: Baseline  M3: Month 3
No Effect of Seladelpar on Autotaxin Levels

ENHANCE phase 3 study with seladelpar in patients with PBC

![Graph showing the effect of Seladelpar on Autotaxin levels]

**Graph Details:**
- **Autotaxin (ng/mL)**
- **BL**: Baseline
- **M3**: Month 3
- **Placebo**
- **5 mg**
- **10 mg**
- **p-values:**
  - BL to M3 (Placebo): p=0.24
  - BL to M3 (5 mg): p=0.49
  - BL to M3 (10 mg): p=0.86
Conclusions

- IL-31 levels were increased over 30-fold in PBC patients compared to healthy volunteers.
- Baseline IL-31 level is correlated with pruritus NRS and bile acid levels.
- Seladelpar treatment for 3 month and up to 1 year led to significant and substantial reductions in IL-31.
- Greater reduction in IL-31 was observed in patients with a significant improvement in pruritus (NRS ≥ 2).
- Decreases in IL-31 levels were associated with improvements in pruritus and decreases in total bile acids.