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

Mo1473

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## Background and Objective

### Background

- Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by chronic cholestasis which can progress to cirrhosis, particularly in patients who have an inadequate response to ursodeoxycholic acid (UDCA)[1]
- Seladelpar is a potent and selective peroxisome proliferator-activated receptor delta (PPARδ) agonist with potential as a new therapeutic agent for patients with PBC[2]
- The initial proof of concept of seladelpar in PBC was established in a previous phase 2 clinical study in patients with an inadequate response to UDCA[2]
- The evaluation of the safety and efficacy of seladelpar in patients with cirrhosis is important because liver impairment may have an impact on drug pharmacokinetics and pharmacodynamics[3]

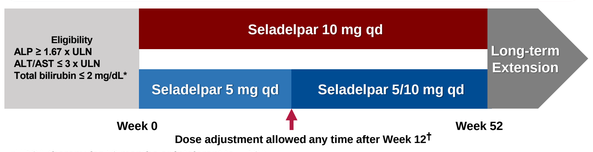
### Objective

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

## Methods

- Phase 2 ongoing, randomized, open-label study (NCT02955602)
- Patients with PBC and cirrhosis at entry and alkaline phosphatase [ALP] ≥1.67 x upper limit of normal [ULN] who were either inadequately responding to UDCA or were intolerant of UDCA
- Patients were treated with doses of either 5 or 10 mg/day. After 12 weeks, patients receiving 5 mg could escalate to 10 mg if the ALP treatment goal was not achieved
- Primary efficacy end point: ALP percentage change from baseline
- Secondary end points: Changes from baseline in ALT, Total bilirubin, and pruritus visual analogue scale (VAS)
- Safety: Evaluation of adverse events, serious adverse events, discontinuations, and safety labs

## Study Design Schematic




*UDCA therapy for 12 months or intolerant to UDCA.
†At week 12, a dose adjustment in the 5/10 mg group was made based on patient response and tolerability.

## 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)

| Cirrhosis Determination | |
|---|---|
| Method | N |
| Liver biopsy | 8 |
| Liver elastography (FibroScan ®, MRE) | 3 |
| Imaging (US/CT/MRI) | 14 |
| Total | 25 |

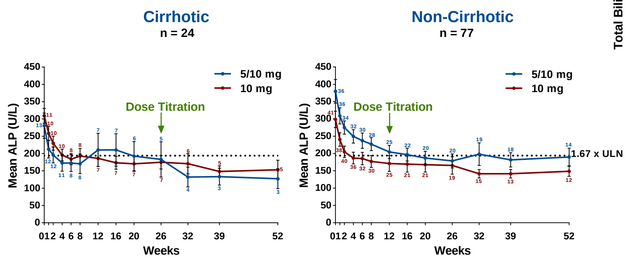
## Results

### Baseline Demographics, N = 108

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

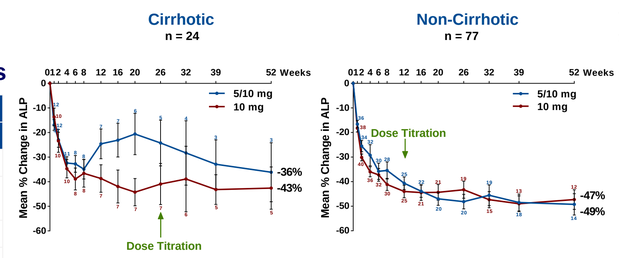
* All parameters are Mean (SD)
‡ A significant difference was observed between cirrhotic and non-cirrhotic patients

### ALP through Week 52

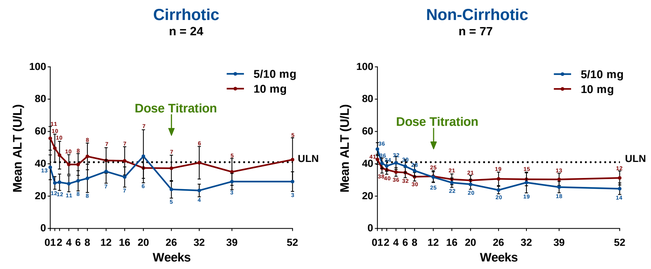



Mean (SE); Numbers indicate the number of patients

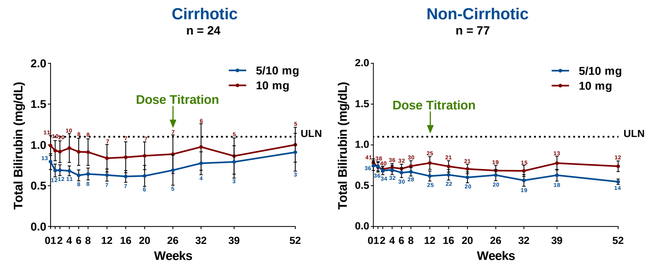
### Percent Change in ALP through Week 52



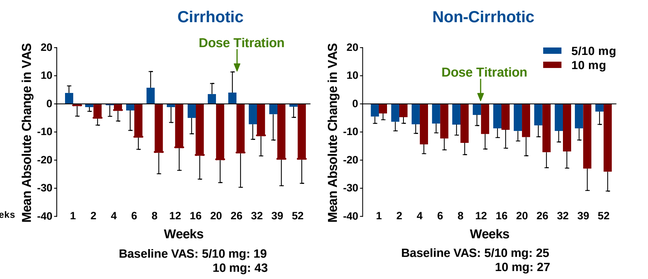

### ALT through Week 52




### Total Bilirubin




### Absolute Change in Pruritus Visual Analogue Scale (VAS: 0 - 100)




Baseline VAS: 5/10 mg: 19, 10 mg: 43
Baseline VAS: 5/10 mg: 25, 10 mg: 27

### Safety

- 11 serious AEs in the study*; none were deemed related to seladelpar
- Three discontinuations
  - Related: Grade 1 gastroesophageal reflux in non-cirrhotic patient
  - Unrelated: (1) Pneumonia, (2) pruritus (both in cirrhotic patients)
- No discontinuations for transaminase elevations

*One patient on 2 mg

| Adverse Event (AE) Category | Cirrhotic 5/10 mg n = 14 | Cirrhotic 10 mg n = 11 | Non-Cirrhotic 5/10 mg n = 39 | Non-Cirrhotic 10 mg n = 44 |
|---|---|---|---|---|
| Patients with at least 1 AE | 10 (71%) | 8 (73%) | 29 (74%) | 30 (68%) |
| Any AE ≥ Grade 3 | 1 (7%) | 1 (9%) | 4 (10%) | 3 (7%) |
| Any treatment-related AE | 5 (36%) | 2 (18%) | 9 (23%) | 11 (25%) |
| Any treatment-related AE ≥ Grade 3 | 0 | 0 | 0 | 0 |
| Any AE with outcome of death | 0 | 0 | 0 | 0 |
| Any SAE | 2 | 1 | 3 | 4 |
| Any treatment-related SAE | 0 | 0 | 0 | 0 |
| Any AE leading to discontinuation from Seladelpar | 1 | 1 | 1 | 0 |

| Most Common Adverse Events | Cirrhotic 5/10 mg n = 14 | Cirrhotic 10 mg n = 11 | Non-Cirrhotic 5/10 mg n = 39 | Non-Cirrhotic 10 mg n = 44 |
|---|---|---|---|---|
| Pruritus | 1 (7%) | 2 (18%) | 7 (18%) | 8 (18%) |
| Arthralgia | 1 (7%) | 1 (9%) | 3 (8%) | 4 (9%) |
| Fatigue | 2 (14%) | 2 (18%) | 3 (8%) | 2 (5%) |
| UTI | 0 (0%) | 2 (18%) | 4 (10%) | 3 (7%) |

## Summary

- Seladelpar treatment in PBC patients with cirrhosis (Child-Pugh A):
  - Maintained a potent and 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

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## References

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2. Jones D, et al. *Lancet Gastroenterol Hepatol.* 2017;2(10):716-726.
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