Effect of Seladelpar on Pruritus in Primary Biliary Cholangitis: 26-Week Analysis of an Ongoing International, Randomized, Dose-Ranging Phase 2 Study

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Background and Objective

- Primary biliary cholangitis (PBC) is an idiopathic inflammatory liver disease that is characterized by the destruction of intrahepatic bile ducts[1]
- As many as 70% of patients with PBC experience pruritus during the course of the disease, which dramatically reduces quality of life (QoL)[2]
- Seladelpar, a potent and selective peroxisome proliferator-activated receptor delta (PPARδ) agonist, is a candidate therapy for patients with inflammatory liver diseases, including PBC and non-alcoholic steatohepatitis (NASH)[3,4]
- The evaluation of pruritus through 26 weeks represents a key secondary outcome for the upcoming phase 3 seladelpar PBC study (ENHANCE)

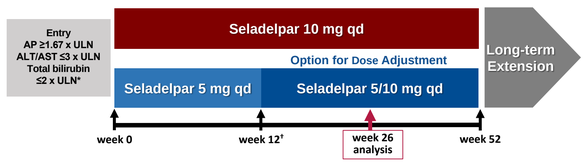
Objective

- To understand the effect of seladelpar on pruritus after 26 weeks of treatment in an ongoing phase 2 PBC study

Methods

- Phase 2 ongoing, randomized, open-label study (NCT02955602)
- Patients with PBC and alkaline phosphatase [AP] ≥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/d. After 12 weeks, patients receiving 5 mg could escalate to 10 mg if the AP treatment goal was not achieved
- Data were evaluated through the first 26 weeks of treatment
- Pruritus was assessed with a visual analogue scale (VAS, 0-100), 5-D itch, and PBC-40 questionnaire. The 5-D itch measures five dimensions of pruritus: duration, degree, direction, disability, and distribution. The PBC-40 is a patient-derived, disease-specific QoL measure developed and validated for use in PBC. It consists of 40 questions grouped by different dimensions, with fatigue being the most prominent

Study Schematic Design



*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.

Results

Table 1: Baseline Demographics

Mean (SD) mITT Parameters (Reference Range)	Seladelpar 5/10 mg (n=25)	Seladelpar 10 mg (n=26)
Age, years	58 (7)	58 (9)
Female/male	25/0	24/2
BMI, kg/m^2	26 (5)	26 (5)
Pruritus history, n (%)	15 (60)	18 (69)
Pruritus VAS (0-100)	18 (22)	35 (32)
5-D itch (5-25)	10 (5)	12 (5)
AP (37-116 U/L)	328 (160)	294 (141)
ALT (6-41 U/L)	40 (19)	49 (22)
Total bilirubin[a] (0.10-1.10 mg/dL)	0.60 (0.50, 0.73)	0.75 (0.63, 1.14)
UDCA dose, mg/kg/d	15 (3)	15 (4)

mITT, modified intention to treat. [a]Median (Quartiles: 25, 75).

Figure 1: VAS Score

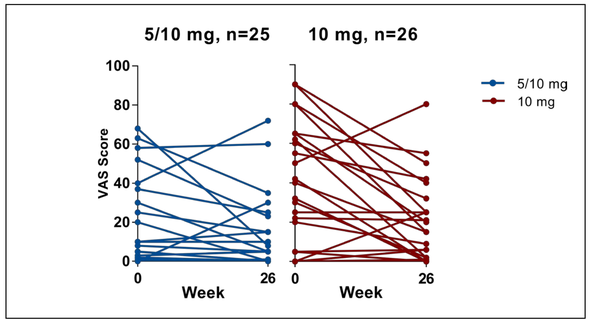


Figure 2: VAS Absolute Change From Baseline

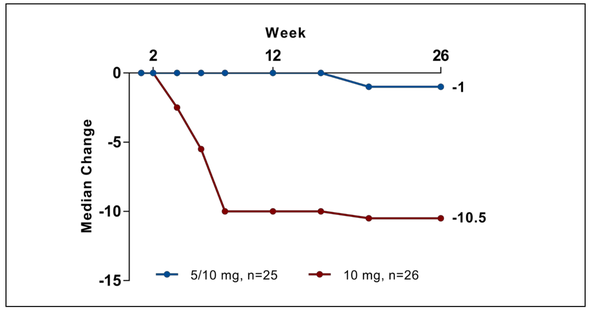
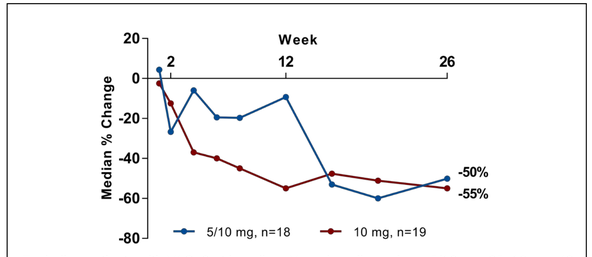


Figure 3: VAS % Change From Baseline



Excluding patients with VAS=0 at baseline. Mean baseline values: 5/10 mg=25; 10 mg=48.

Figure 4: 5-D Itch Absolute Change From Baseline

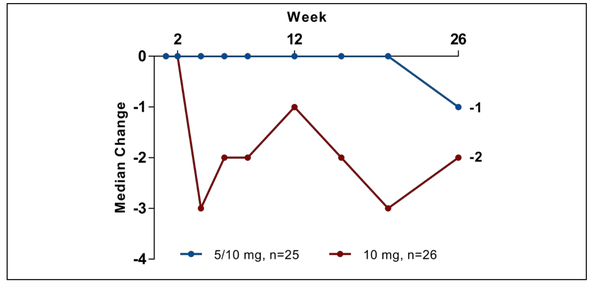


Figure 5: 5-D Itch % Change From Baseline

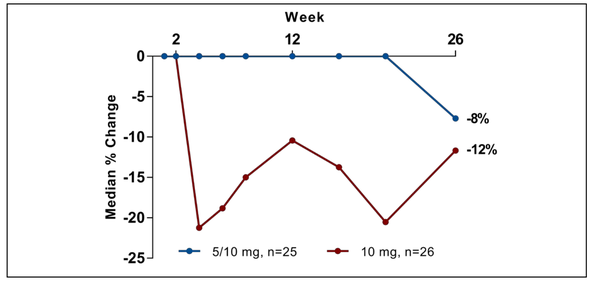


Table 2: PBC-40 % Change From Baseline at Week 26

Median (Reference Range)	Seladelpar 5/10 mg (n=25)	Seladelpar 10 mg (n=26)
PBC-40, total (34-200)	-6	-6
PBC-40, fatigue (11-55)	-7	-12
PBC-40, itch (3-15)	-9	-13

Median baseline values: Total, 5/10 mg=105; 10 mg=91; Fatigue, 5/10 mg=30; 10 mg=30; Itch, 5/10 mg=4; 10 mg=4.5.

Safety

Table 3: Safety Population

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

[a]One patient entered the study with intense pruritus and discontinued seladelpar 10 mg after 5 days due to an increase in pruritus, possibly related to PBC.

Summary

- In this population of patients with PBC, seladelpar was not associated with drug-induced pruritus
- Improvements in pruritus measures (VAS, 5-D itch, and PBC-40) were observed
- Seladelpar appears to be generally safe and well tolerated
- A phase 3 placebo-controlled study of seladelpar (ENHANCE) has been initiated in PBC and will further evaluate pruritus

References

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