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Safety and Efficacy of Seladelpar in Primary Biliary Cholangitis Patients With Cirrhosis

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Background and Objective

- Primary biliary cholangitis (PBC) is an autoimmune liver disease manifested 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 can have an impact on drug pharmacokinetics and pharmacodynamics[3]

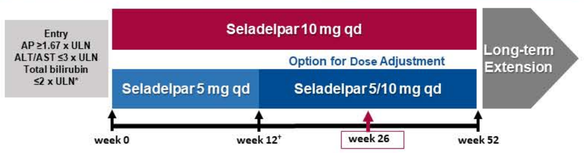
Objective

- To conduct an analysis of the safety and efficacy of seladelpar in PBC patients with cirrhosis enrolled in an ongoing phase 2 study

Methods

- Phase 2 ongoing, randomized, open-label study (NCT02955602)
- Patients with PBC and cirrhosis at entry 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
- Primary efficacy end point: AP percentage change from baseline
- Secondary end points: AP responder, changes in other liver, metabolic, and inflammatory markers
- As of January 2018, 10 patients had reached week 12 (5/10 mg, n=5; 10 mg, n=5) and 9 patients had reached week 26 (5/10 mg, n=4; 10 mg, n=5)

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.

Table 1: Diagnostic Criteria for Cirrhosis

Criteria	Seladelpar 5/10 mg	Seladelpar 10 mg
Liver biopsy	3	0
Liver elastography (e.g. FibroScan, MRE)	0	2
Ultrasound	1	2
Other (laboratory evaluation, clinical symptoms)	1	1

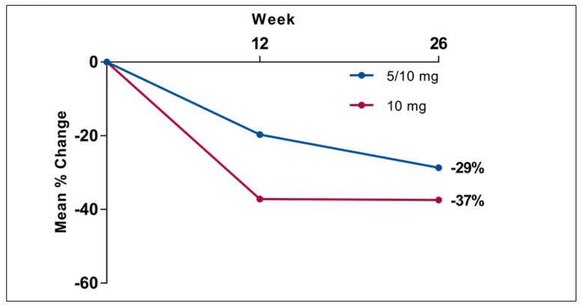
Results

Table 2: Demographic and Baseline Characteristics in Patients With Cirrhosis

Mean (SD) Parameters (Reference Range)	Seladelpar 5/10 mg (n=5)	Seladelpar 10 mg (n=5)
Age, years	54 (8)	60 (10)
Female/male	5/0	4/1
Pruritus history, n (%)	4 (80)	4 (80)
Pruritus VAS (0-100)	20 (24)	37 (28)
MELD score	6.5 (1.1)	5.7 (0.7)
AP (37-116 U/L)	246 (115)	263 (48)
GGT (7-38 U/L)	149 (85)	305 (179)
ALT (6-41 U/L)	34 (7)	66 (29)
AST (9-34 U/L)	41 (14)	56 (18)
Total bilirubin[a] (0.10-1.10 mg/dL)	0.66 [0.20]	0.80 [0.35]
Platelets (140-400 x 10^9/L)	162 (108)	175 (47)
Albumin (3.5-5.5 g/dL)	3.6 (0.5)	4.1 (0.3)
UDCA dose, mg/kg/d	11 (6)	10 (5)

VAS, visual analogue scale. [a]Median [IQR].

Figure 1: Mean AP % Change in Patients With Cirrhosis



- At 26 weeks, 3 of 4 patients on 5/10 mg and 3 of 5 patients on 10 mg had an AP <1.67 x ULN

Figure 2: Mean AP % Change in Non-cirrhotic Patients

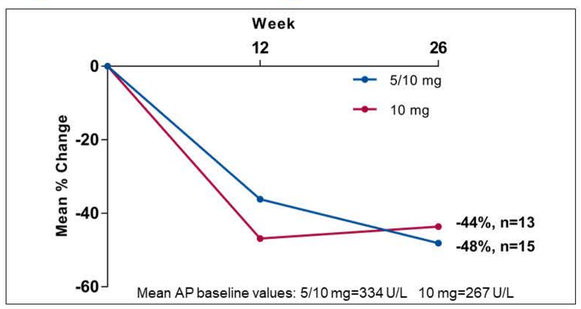


Figure 3: Median ALT % Change in Patients With Cirrhosis

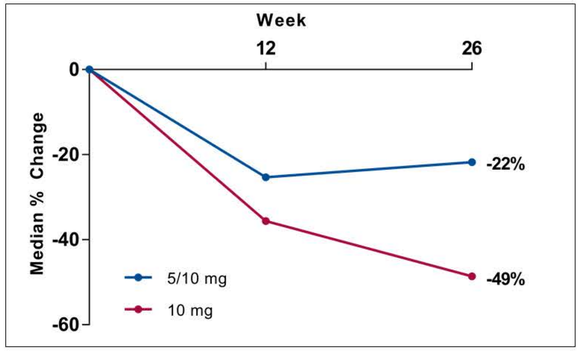


Figure 4: Median Total Bilirubin in Patients With Cirrhosis

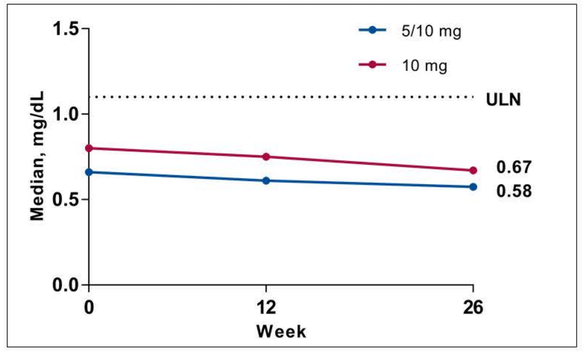


Table 3: Mean % Change From Baseline in Other Markers in Patients With Cirrhosis

Mean (SD) Parameter	Seladelpar 5/10 mg		Seladelpar 10 mg	
	Week 12	Week 26	Week 12	Week 26
Albumin	4.5 (4.5)	4 (5)	0.3 (4.7)	-4 (4)
Platelets	17 (27)	4.0 (14.1)	-2 (14)	-7.1 (5.8)
AST	4 (34)	-1 (24)	-11 (6)	-12 (28)
GGT	-5 (26)	-17 (41)	-23 (31)	-23 (39)
VAS[a]	3	0	-5	-10

[a]median absolute change.

Safety

Table 4: Adverse Events Occurring in Patients With Cirrhosis

Adverse Event[a] n (%)	Seladelpar 5/10 mg (n=5)	Seladelpar 10 mg (n=5)
Pruritus	1 (20)	1 (20)
Abdominal distension	1 (20)	1 (20)
Fatigue	2 (40)	1 (20)
Cough	2 (40)	0
Dry mouth	1 (20)	1 (20)
Abdominal tenderness	1 (20)	1 (20)

[a]Adverse events occurring in ≥2 patients receiving seladelpar.

- SAE: Pneumonia in a patient with a history of COPD, deemed unrelated to seladelpar. Drug was discontinued due to this event
- No other discontinuations and no hepatic decompensation events were observed
- No ≥ grade 3 ALT elevations

Summary

- The decrease in AP was comparable in cirrhotic and non-cirrhotic patients
- No transaminase safety signal was observed
- Seladelpar appeared to be generally safe and well tolerated with no decompensation reported
- The results support the further evaluation of seladelpar in compensated cirrhotic PBC patients
- A phase 3 placebo-controlled study of seladelpar (ENHANCE) has been initiated

References

1. Kumagi T, Heathcote EJ. *Orphanet J Rare Dis.* 2008;3:1. doi: 10.1186/1750-1172-3-1.
2. Jones D, et al. *Lancet Gastroenterol Hepatol.* 2017;2(10):716-726.
3. Weersink RA, et al. *BMJ Open.* 2016;6(10):e012991. doi:10.1136/bmjopen-2016-012991.

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