Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis and Cirrhosis, Including Those With Clinical Signs of Portal Hypertension: Interim Results From the Open-Label ASSURE Study With up to 4 Years of Treatment

SAT-287

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Immune-Mediated and Cholestatic Disease: Clinical Aspects

Conclusions

- Seladelpar demonstrated sustained biochemical efficacy up to 3 years in patients with primary biliary cholangitis (PBC) and cirrhosis, a population at high risk for disease progression
- In this analysis of patients with PBC and cirrhosis (~50% with features consistent with portal hypertension), seladelpar treatment for up to 4 years was generally safe and well tolerated, and there were no new safety signals
- These data highlight the medical complexity of patients with PBC and cirrhosis, who require ongoing disease management and remain at high risk for clinical worsening; optimizing therapy response prior to cirrhosis development in patients at risk for progression, including alkaline phosphatase normalisation, should be considered

Plain Language Summary

- Primary biliary cholangitis (PBC) is a long-term liver disease that can lead to liver scarring (cirrhosis) and liver failure
- Seladelpar is an approved, effective drug used to treat people with PBC; previous studies have shown that seladelpar is a safe and effective treatment
- In this study, we show that seladelpar remained safe and effective with long-term use in patients with advanced liver disease such as cirrhosis and signs of portal hypertension (increased pressure in the vein leading to the liver)

References: **1.** European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-72. **2.** Lindor KD, et al. *Hepatology*. 2019;69(1):394-419. **3.** Kowdley KV, et al. *Am J Gastroenterol*. 2023;118:232-42. **4.** Livdelzi. US prescribing information. Gilead Sciences, Inc.; 2024. **5.** Livdelzi. UK summary of product characteristics. Gilead Sciences, Inc.; 2024. **6.** Lyvdelzi. EMA *prescribing information*. Gilead Sciences, Inc.; 2025. **7.** Hirschfield GM, et al. *N Engl J Med*. 2024;390(9):783-94. **8.** Levy C, et al. *Am J Gastroenterol*. 2026;121(5):1140-53. **9.** Gordon SC, et al. *Hepatol Commun*. 2026;10(5):e0918.

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Introduction

- Primary biliary cholangitis (PBC) is a chronic, autoimmune, cholestatic liver disease associated with progressive liver injury and significant symptom burden[1]
- PBC can cause fibrosis, which eventually progresses to cirrhosis if inadequately treated[2]
- In patients with PBC, a diagnosis of portal hypertension represents advancing cirrhosis and a heightened risk for adverse clinical outcomes[3]
- Seladelpar is a first-in-class delpar (selective peroxisome proliferator–activated receptor delta [PPARδ] agonist) indicated for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients who are unable to tolerate UDCA[4-6]
- In the pivotal Phase 3, placebo-controlled RESPONSE study (NCT04620733), seladelpar had similar efficacy in patients with or without compensated cirrhosis and a safety profile generally similar to that of placebo at Month 12 of treatment[7]
- The ongoing, open label, Phase 3 ASSURE study (NCT03301506) study enrolled patients with PBC from the RESPONSE trial and from legacy seladelpar studies and included patients with compensated cirrhosis, allowing for ongoing evaluation of safety and efficacy in this population[8]

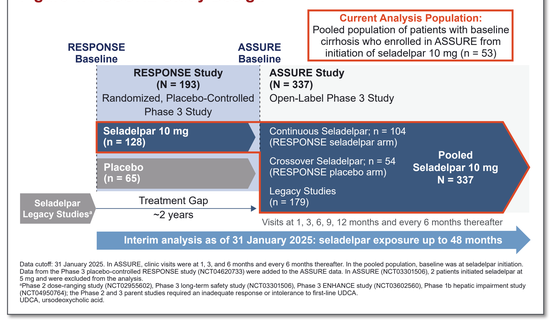
Objective

- To evaluate the long-term efficacy and safety of seladelpar in patients with PBC and compensated cirrhosis (including those with features suggestive of portal hypertension) in the ongoing, open-label, Phase 3 ASSURE study[8]

Methods

- Patients from RESPONSE and legacy seladelpar studies enrolled in ASSURE and received seladelpar 10 mg once daily (**Figure 1**)
- Patients with cirrhosis at baseline were pooled for this analysis (data cutoff date: 31 January 2025); cirrhosis was defined per protocol using ≥1 of the following criteria (details previously published)[9]:
  - Clinical history of cirrhosis, clinical conditions consistent with liver cirrhosis and/or portal hypertension, or presence of radiologic evidence of cirrhosis (a nodular liver) with or without concurrent splenomegaly
  - Liver stiffness >16.9 kPa by FibroScan at screening
  - Laboratory findings including low platelets and low serum albumin
  - Clinical determination by the investigator
- Post hoc, patients were identified as having features consistent with portal hypertension if they met ≥1 criterion at baseline: platelets <140 × 10^3/µL, albumin <1.0 × the lower limit of normal, total bilirubin >1.0 × the upper limit of normal (ULN), ascites, or a medical history of varices or portal hypertension
- Baseline was defined as the time of seladelpar initiation in RESPONSE or ASSURE
- Efficacy endpoints through Month 36 included composite biochemical response (alkaline phosphatase [ALP] <1.67 × ULN, ≥15% decrease in ALP, and total bilirubin ≤1.0 × ULN), ALP normalisation, and other laboratory changes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], total bilirubin)
- Safety was assessed by the incidence and severity of adverse events (AEs) and changes in laboratory parameters and includes data up to 4 years of treatment
- PBC clinical outcomes were adjudicated by an external committee and were defined as death, liver transplantation, Model for End-Stage Liver Disease (MELD) score ≥15 at ≥2 consecutive visits, ascites requiring treatment, and hospitalisation for new onset or recurrence of decompensating events (eg, variceal bleeding, hepatic encephalopathy [West Haven criteria ≥2], and spontaneous bacterial peritonitis)

Figure 1. ASSURE Study Design



Data cutoff: 31 January 2025. In ASSURE, clinic visits were at 1, 3, and 6 months and every 6 months thereafter. In the pooled population, baseline was at seladelpar initiation. Data from the Phase 3 placebo-controlled RESPONSE study (NCT04620733) were added to the ASSURE data. In ASSURE (NCT03301506), 2 patients initiated seladelpar at 5 mg and were excluded from the analysis.
*Phase 2 dose-ranging study (NCT02955602), Phase 3 long-term safety study (NCT03301506), Phase 3 ENHANCE study (NCT03602560), Phase 1b hepatic impairment study (NCT04950764); the Phase 2 and 3 parent studies required an inadequate response or intolerance to first-line UDCA.
UDCA, ursodeoxycholic acid.

Results

- In total, 53/337 (16%) patients had cirrhosis at baseline; most were Child-Pugh Class A, with 4/53 (8%) Child-Pugh Class B (**Table 1**)
- Baseline mean (SD) ALP was 267.5 (113.7) U/L, total bilirubin was 0.98 (0.45) mg/dL, and liver stiffness was 20.6 (14.7) kPa; 29/53 (55%) met ≥1 criterion consistent with portal hypertension

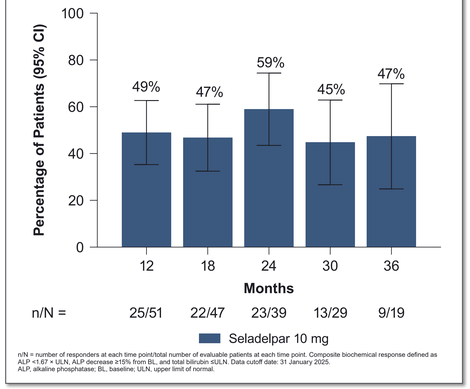
Table 1. Baseline Characteristics of Patients With Cirrhosis

	Seladelpar 10 mg (n = 53)
Age, years, mean (SD)	60.4 (9.07)
Female, n (%)	48 (91)
BMI, kg/m², mean (SD)	27.2 (5.47)
Duration of PBC, years, mean (SD)	11.5 (6.51)
Child-Pugh Class	
Child-Pugh Class A, n (%)	49 (92)
Child-Pugh Class B, n (%)	4 (8)
One or more clinical signs of portal hypertension, n (%)	29 (55)
Liver stiffness, kPa, mean (SD)	20.6 (14.66)
ALP, U/L, mean (SD)	267.5 (113.69)
ALT, U/L, mean (SD)	39.6 (17.17)
GGT, U/L, mean (SD)	242.1 (222.28)
Total bilirubin, mg/dL, mean (SD)	0.98 (0.449)
AST, U/L, mean (SD)	42.0 (16.66)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; PBC, primary biliary cholangitis.

- Among evaluable patients, 25/51 (49%) achieved a composite biochemical response at Month 12, which was sustained up to Month 36 (**Figure 2**)

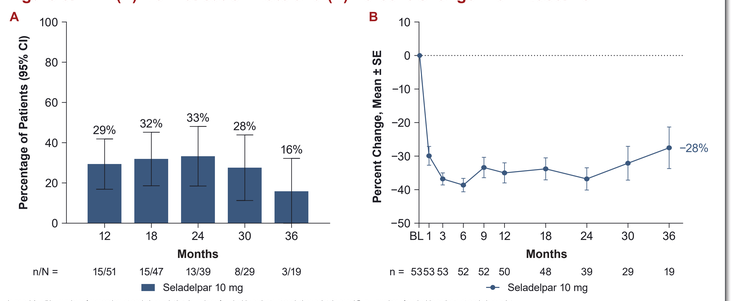
Figure 2. Composite Biochemical Response Among Patients With Cirrhosis Through 36 Months of Seladelpar Treatment



n/N = number of responders at each time point/total number of evaluable patients at each time point. Composite biochemical response defined as ALP <1.67 × ULN, ALP decrease ≥15% from BL, and total bilirubin ≤ULN. Data cutoff date: 31 January 2025.
ALP, alkaline phosphatase; BL, baseline; ULN, upper limit of normal.

- In total, 15/51 (29%) patients achieved ALP normalisation at Month 12, and 3/19 (16%) with available data had normal ALP at Month 36 (**Figure 3A**)
- Mean percent change from baseline in ALP was −35% at Month 12 and −28% at Month 36 (**Figure 3B**)

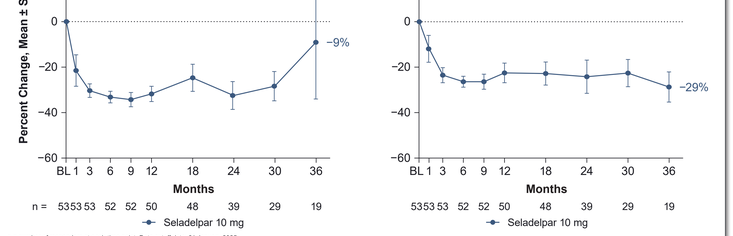
Figure 3. ALP (A) Normalisation Rate and (B) Percent Change From Baseline



In panel A, n/N = number of responders at each time point/total number of evaluable patients at each time point. In panel B, n = number of evaluable patients at each time point.
Data cutoff date: 31 January 2025.
ALP, alkaline phosphatase; BL, baseline.

- Decreases in GGT and ALT were observed with seladelpar in patients with cirrhosis (**Figure 4**)

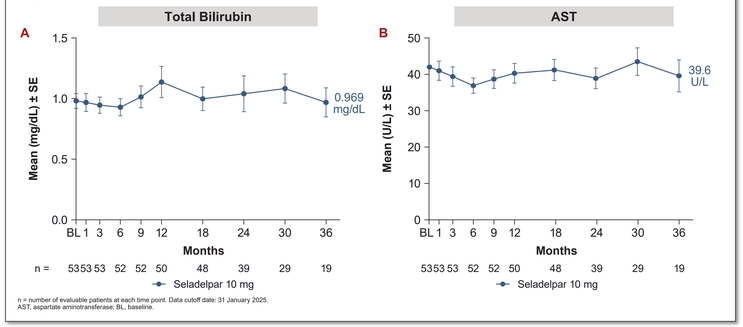
Figure 4. Percent Change From Baseline in (A) GGT and (B) ALT



n = number of responders at each time point. Data cutoff date: 31 January 2025.
ALT, alanine aminotransferase; BL, baseline; GGT, gamma-glutamyl transferase.

- Total bilirubin and AST remained overall stable through Month 36 (**Figure 5**)

Figure 5. Mean (A) Total Bilirubin and (B) AST Over Time



n = number of evaluable patients at each time point. Data cutoff date: 31 January 2025.
AST, aspartate aminotransferase; BL, baseline.

- AEs were reported in 50/53 (94%) patients (**Table 2**)
- With up to 4 years of follow-up, 32% of patients with cirrhosis experienced a serious AE (SAE); none were treatment related
  - No pattern in SAEs was observed with respect to the type of event or time to onset
  - In total, 3 SAEs were associated with a protocol-defined PBC clinical outcome

Table 2. Overall Safety

Patient Incidence, n (%)	Seladelpar 10 mg (n = 53)
Any AE	50 (94)
Grade ≥3 AEs (per CTCAE)	21 (40)
SAEs	17 (32)
Treatment-related SAEs	0
AEs leading to treatment discontinuation	8 (15)
AEs leading to death	0

All AEs listed were treatment emergent unless otherwise stated.
Data cutoff date: 31 January 2025.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious AE.

- Four patients experienced protocol-defined PBC clinical outcomes as of the data cutoff; no events were assessed as related to seladelpar
  - One patient developed ascites requiring treatment at approximately 24 months
  - One patient had MELD scores ≥15 for 2 visits in a row after 18 months
  - Two patients met criteria for both events after approximately 12 months of treatment
- Overall, 8 patients discontinued treatment due to AEs, of which 4 were liver related:
  - Events included disease progression, hepatorenal syndrome, and blood bilirubin increased (2 patients)
  - All liver-related events were assessed as unlikely or unrelated to seladelpar by the investigator
  - Time to discontinuation ranged from ~12 months to 3 years
- When patients with cirrhosis were treated with seladelpar, the overall exposure-adjusted patient incidence of liver-related AEs was 15 per 100 patient-years, which remained stable through Month 48 and was similar to the exposure-adjusted incidence among patients with cirrhosis in the placebo arm of the RESPONSE trial over 1 year (17 per 100 patient-years)

Limitations

- Cirrhosis was diagnosed clinically, and this analysis did not account for patients who developed cirrhosis during the study
- Features suggestive of portal hypertension were defined post hoc
- The study is currently ongoing, so the number of evaluable patients at later time points is limited