Efficacy and safety of seladelpar in patients with primary biliary cholangitis and alkaline phosphatase levels between 1 and 1.67 × upper limit of normal: interim results from the open-label ASSURE study

SAT-316

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Immune-mediated and cholestatic disease: Clinical aspects

Conclusions

- Among patients with primary biliary cholangitis enrolled in ASSURE with alkaline phosphatase (ALP) levels between 1–1.67 × upper limit of normal, seladelpar led to high rates of ALP normalisation up to 24 months, which is increasingly recognised as a treatment goal[6–7]
- Seladelpar treatment led to sustained reductions in cholestatic and liver injury markers and pruritus up to 24 months
- Seladelpar was well tolerated in this population, with no new safety signals

Plain Language Summary

- Patients with primary biliary cholangitis enrolled in ASSURE with alkaline phosphatase (a routine blood test that reflects disease activity) between 1–1.67 times higher than normal levels were found to have lasting decreases in alkaline phosphatase levels with up to 24 months of seladelpar treatment
- Seladelpar was well tolerated in this group of patients

References: **1.** Hirschfield GM, et al. *N Engl J Med.* 2024;390(9):783–794. **2.** Livdelzi. US prescribing information. Gilead Sciences, Inc.; 2024. **3.** Livdelzi. UK Summary of Product Characteristics. Gilead Sciences, Inc.; 2024. **4.** Lyvdelzi. EU Summary of Product Characteristics. Gilead Sciences, Inc.; 2025. **5.** Levy C, et al. *Am J Gastroenterol.* 2025; ePub ahead of print. **6.** Murillo Perez CF, et al. *Am J Gastroenterol.* 2020;115(7):1066–1074. **7.** Kowdley KV, et al. *Aliment Pharmacol Ther.* 2025;63(4):522–537. **8.** Corpechot C, et al. *Hepatology.* 2024;79(1):39–48.

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Introduction

- Seladelpar is a first-in-class delpar (selective peroxisome proliferator-activated receptor delta [PPARδ] agonist) indicated for the treatment of primary biliary cholangitis (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[1–4]
- The pivotal Phase 3 RESPONSE study (NCT04620733) established the safety and efficacy of seladelpar in patients with alkaline phosphatase (ALP) levels ≥1.67 × upper limit of normal (ULN)[1]
- The ongoing, open-label, Phase 3 ASSURE study (NCT03301506)[5] enrolled patients who previously participated in RESPONSE or earlier legacy seladelpar trials; as a long-term safety study, ALP elevation was not required for enrolment
- Therapeutic interventions with the potential to normalise biochemical markers of PBC have not been extensively evaluated in patients with ALP <1.67 × ULN, despite evidence suggesting that ALP normalisation leads to improved clinical outcomes in patients with PBC[6–8]

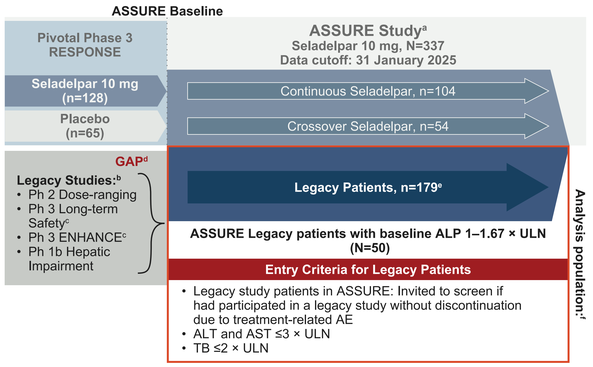
Objective

- To evaluate the efficacy and safety of seladelpar in inadequate responders as defined by ALP between 1–1.67 × ULN at baseline, from an interim analysis of the ongoing ASSURE study

Methods

- Patients enrolled in the open-label ASSURE study received seladelpar 10 mg once daily (**Figure 1**)
- Data for this post hoc analysis included patients from legacy seladelpar studies who enrolled in ASSURE with ALP levels >1 × ULN but <1.67 × ULN at baseline of ASSURE (cutoff: 31 January 2025)
- Efficacy endpoints for this analysis included **composite ALP normalisation** (defined as ALP ≤1 × ULN and ≥15% reduction in ALP), ALP normalisation (defined as ALP ≤1 × ULN), change from baseline in cholestatic and liver injury markers, change in liver stiffness measurement (LSM), and change in pruritus numerical rating scale (NRS) among patients with moderate to severe pruritus (NRS ≥4) at baseline through Month 24
  - Laboratory serum values were assessed at baseline, Months 1, 3, 6, 9, 12 and every 6 months thereafter
  - LSM was assessed using vibration-controlled transient elastography (FibroScan) at baseline and every 12 months thereafter; LSM values with confirmed interquartile range/LSM ratio ≥30% were excluded to ensure data reliability
  - Pruritus NRS (0–10 rating of worst itch in the past 24 hours) was collected daily through Month 6 and then at study visits thereafter
- Safety was assessed by patient incidence of adverse events (AEs)

Figure 1. Study Design



[a]Study drug administered orally once daily as an add-on to UDCA or as monotherapy in patients intolerant to UDCA; the ongoing open-label ASSURE study (NCT03301506) includes patients previously enrolled in legacy seladelpar studies and RESPONSE (NCT04620733; data cutoff: 31 January 2025). [b]Legacy studies include the Phase 2 dose-ranging study (NCT02955602), Phase 3 long-term safety study (NCT03301506), Phase 3 ENHANCE study (NCT03602560), and Phase 1b hepatic impairment study (NCT04950764). The Phase 2 and 3 parent studies required an inadequate response or intolerance to first-line UDCA. [c]These studies had an early termination. [d]Treatment gaps between legacy studies and ASSURE ranged from 4 weeks (Phase 1b impairment study) to 212 weeks (Phase 3 ENHANCE study). [e]In ASSURE, 1 patient initiated seladelpar at 5 mg and was excluded from the primary analysis; [f]For this ASSURE legacy analysis, 28 patients previously participated in ENHANCE, 16 in the long-term safety study, and 6 in the hepatic impairment study, with a gap ranging from 4 to 163 weeks between each prior legacy study and ASSURE.
AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ph, phase; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Results

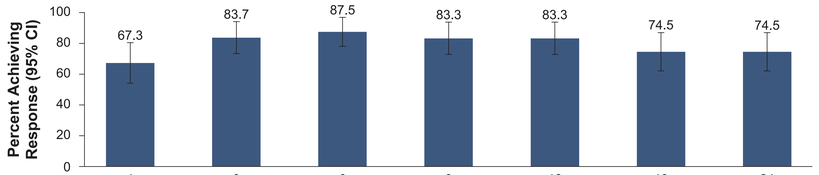
Table 1. Demographics and Baseline Characteristics

	Seladelpar 10 mg (N=50)
Age at screening, years, mean (SD)	61.9 (8.8)
Age at PBC diagnosis, years, mean (SD)	51 (8.0)
Age group at PBC diagnosis, n (%)	
<50 years	22 (44.0)
≥50 years	28 (56.0)
Female, n (%)	49 (98.0)
Race, white, n (%)	43 (86.0)
Body mass index, kg/m², mean (SD)	27.2 (6.4)
On UDCA, n (%)	48 (96.0)
Cirrhosis, n (%)	12 (24.0)
Child-Pugh A, n (%)[a]	11 (91.7)
ALP, U/L,[b] mean (SD)	156 (21.7)
AST, U/L,[b] mean (SD)	30 (12.1)
ALT, U/L,[b] mean (SD)	28 (11.6)
GGT, U/L,[b] mean (SD)	117 (75.9)
TB, mg/dL,[b] mean (SD)	0.64 (0.3)
≥0.6 × ULN, n (%)	16 (32.0)
Patients with moderate to severe pruritus,[c] n (%)	10 (20.0)
Pruritus NRS, mean (SD)	6.0 (1.6)
GLOBE score >0.3, n (%)	20 (40.0)
Liver stiffness, kPa, mean (SD)	10.4 (10.8)

[a]Percentage of patients with cirrhosis. [b]ALP ULN=116 U/L; AST ULN=34 U/L; ALT ULN=41 U/L; GGT ULN=52 U/L for male patients, 38 U/L for female patients; TB ULN=1.10 mg/dL. [c]Defined as pruritus NRS ≥4.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; NRS, numerical rating scale; PBC, primary biliary cholangitis; SD, standard deviation; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

- 50 patients from legacy seladelpar studies enrolled in ASSURE, with ALP 1–1.67 × ULN at baseline, were included in this analysis; 47 patients had reached Month 24 at the time of data cutoff
- At baseline, 24.0% (12/50) had cirrhosis, and 44.0% (22/50) were aged <50 years at PBC diagnosis; many patients had PBC progression risk factors (younger age, cirrhosis, or GLOBE score >0.3; **Table 1**)

Figure 2. Composite ALP Normalisation Through 24 Months of Seladelpar Treatment



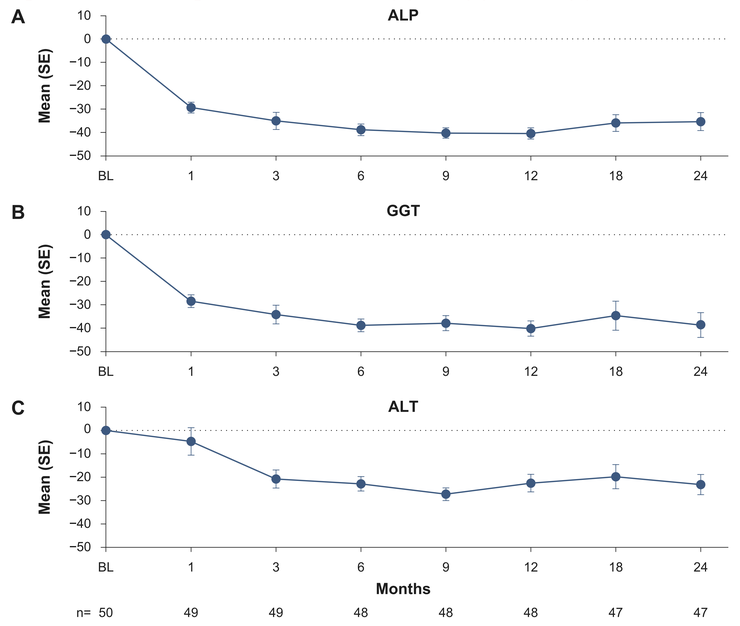
n/N=	33/49	41/49	42/48	40/48	40/48	35/47	35/47
ALP ≤1 × ULN, n (%)[a]	33 (67.3)	41 (83.7)	42 (87.5)	41 (85.4)	40 (83.3)	37 (78.7)	36 (76.6)
≥15% reduction in ALP, n (%)[a]	42 (85.7)	44 (89.8)	44 (91.7)	43 (89.6)	45 (93.8)	40 (85.1)	40 (85.1)

Seladelpar 10 mg

Patients who missed assessment while on treatment were defined as non-responders at that time point; patients who discontinued treatment due to an AE or PBC clinical outcome, or due to needing to initiate prohibited medication requiring ongoing treatment, were defined as non-responders indefinitely. Response rate (n/N) = number of responders/number of response evaluable patients; composite responder status defined as ALP ≤1 × ULN and ALP reduction from baseline ≥15%. [a]Percentage of response evaluable patients.
AE, adverse event; ALP, alkaline phosphatase; CI, confidence interval; PBC, primary biliary cholangitis; ULN, upper limit of normal.

- Rapid and sustained composite ALP normalisation was achieved with seladelpar treatment; 83.3% (40/48) at Month 12 and 74.5% (35/47) at Month 24 (**Figure 2**)
  - Composite ALP normalisation was achieved with seladelpar treatment in 75.0% (24/32; 95% confidence interval [CI]: 60.0% to 90.0%) and 60.0% (15/25; 95% CI: 40.8% to 79.2%) of patients at Month 30 and Month 36, respectively
- Rapid and sustained ALP normalisation was achieved with seladelpar; 83.3% (40/48) at Month 12 and 76.6% (36/47) at Month 24 (**Figure 2**)
  - ALP normalisation was achieved with seladelpar treatment in 75.0% (24/32; 95% CI: 60.0% to 90.0%) and 60.0% (15/25; 95% CI: 40.8% to 79.2%) of patients at Month 30 and Month 36, respectively
- LSM remained stable over time with median change and median percent change from baseline of −0.3 kPa and −4.8% at Month 24, respectively
- Pruritus improvement was observed with seladelpar among patients with moderate to severe pruritus at baseline (n=10); mean (standard error) NRS change from baseline was −3.2 (0.7) at Month 12 and −2.7 (0.7) at Month 24

Figure 3. Percent Change from Baseline in ALP (A), GGT (B), and ALT (C)



n = number of evaluable patients at each time point.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; BL, baseline; GGT, gamma-glutamyl transferase; SE, standard error.

- Seladelpar led to sustained ALP reduction, with mean change of −40.4% at Month 12 and −35.3% at Month 24 (**Figure 3A**)
- Gamma-glutamyl transferase (GGT) and alanine aminotransferase (ALT) levels demonstrated consistent reductions through 24 months of seladelpar treatment: GGT and ALT mean change −40.1% and −22.9% at Month 12; −38.6% and −23.5% at Month 24, respectively (**Figures 3B–3C**)
- Mean total bilirubin (TB) remained stable overall, with mean change of −7.8% at Month 12 and −3.1% at Month 24
- Among patients who had TB ≥0.6 × ULN at baseline, 40% (6/15) achieved TB <0.6 × ULN at Month 24

Table 2. Overall Safety Outcomes

n (%)	Seladelpar 10 mg (N=50)
Any AE (at least one)	40 (80.0)
Serious AE[a]	2 (4.0)
Treatment-related serious AE	0
Grade 3 or higher AE[b]	5 (10.0)
AE with action taken as permanent withdrawal of study drug	0
AE leading to death	0

All AEs listed were treatment-emergent. TEAEs that began on or after the date when seladelpar was initiated up to 30 days after 2 years of seladelpar treatment were included. Adverse events were coded using MedDRA version 27.1, and severity grades were defined by CTCAE Version 5.0. [a]Serious AEs reported were Grade 3 pleuritic pain and Grade 2 rotator cuff syndrome, both of which caused hospitalisation; dose was not changed in either instance. [b]Grade 3 or higher AEs reported were pleuritic pain, renal mass, sciatica, squamous cell carcinoma and ankle fracture.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

- Overall, 80.0% (40/50) of patients experienced an AE, with no patients discontinuing treatment due to AEs (**Table 2**)
  - Serious AEs occurred in 4.0% (2/50) of patients, both of which were unrelated to treatment