Seladelpar Leads to Rapid and Sustained Alkaline Phosphatase Reduction, Regardless of Baseline Levels, Over 5 Years of Treatment in Patients with Primary Biliary Cholangitis

1157

Christopher L. Bowlus[1], Cynthia Levy[2,3], Christophe Corpechot[4], Aparna Goel[5], Kyung min Kwon[6]*, Johnny Chew[6]*, Valentina Shakhnovich[6], Xin Qi[6], Alejandra M. Villamil[7]

[1]Division of Gastroenterology and Hepatology, University of California Davis School of Medicine, Sacramento, CA, United States; [2]Division of Digestive Health and Liver Diseases, Miller School of Medicine, University of Miami, Miami, FL, United States; [3]Schiff Center for Liver Diseases, Division of Digestive Health and Liver Diseases, Miller School of Medicine, University of Miami, Miami, FL, United States; [4]Reference Center for Inflammatory Biliary Diseases and Autoimmune Hepatitis, French Network for Rare Liver Disease in Children and Adults (FILFOIE), European Reference Network RARE-LIVER, Saint-Antoine Hospital and Research Center, Assistance Publique-Hôpitaux de Paris, Sorbonne University, Paris, France; [5]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA, United States; [6]Gilead Sciences, Inc., Foster City, CA, United States; [7]The Liver Autoimmunity Unit, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

*Affiliation when this research was conducted

Copies of this poster obtained through QR (Quick Response) and/or text key codes are for personal use only and may not be reproduced without written permission of the authors.

Conclusions

- With up to 4 years of treatment, seladelpar led to rapid improvements in alkaline phosphatase (ALP) across baseline ALP quartiles
- Seladelpar led to reduced ALP even among patients not attaining ALP normalization or composite biochemical response at Month 12
- The rapid reduction in ALP, along with reductions in other markers of liver injury, was sustained at Month 48 with continued seladelpar treatment
- Stability in total bilirubin was also maintained over this period
- Seladelpar appeared well tolerated across baseline ALP levels up to Month 60

Plain Language Summary

- At the beginning of this study, people with primary biliary cholangitis (PBC) had varying levels of alkaline phosphatase (a routine blood test that reflects disease activity)
- Treatment with seladelpar reduced alkaline phosphatase and improved other markers of PBC disease activity, regardless of initial levels of alkaline phosphatase
- In this study, no people receiving seladelpar experienced serious side effects related to the treatment

References: **1.** Hirschfield GM, et al. *N Engl J Med*. 2024;390(9):783–794. **2.** Livdelzi. US Prescribing Information. Gilead Sciences, Inc.; 2026. **3.** Livdelzi. UK Summary of Product Characteristics. Gilead Sciences, Inc.; 2025. **4.** Lyvdelzi. EU Summary of Product Characteristics. Gilead Sciences, Inc.; 2026. **5.** Lammers WJ, et al. *Gastroenterology*. 2014;147(6):1338–1349.e5. **6.** Levy C, et al. *Am J Gastroenterol*. 2026;121(5):1140–1153.

Acknowledgments: We extend our thanks to the patients, their families, and all participating investigators. These studies were funded by Gilead Sciences, Inc. Medical writing and editorial support were provided by Sarah Chamdawala, MSc, and Quinn Ho, PhD, of Costello Medical, with graphic design assistance from the Creative team at Costello Medical, and funded by Gilead Sciences, Inc.

Disclosures: Conflict of interest disclosures may be viewed using the QR code at the top right.

Correspondence: Christopher L. Bowlus, clbowlus@ucdavis.edu

Introduction

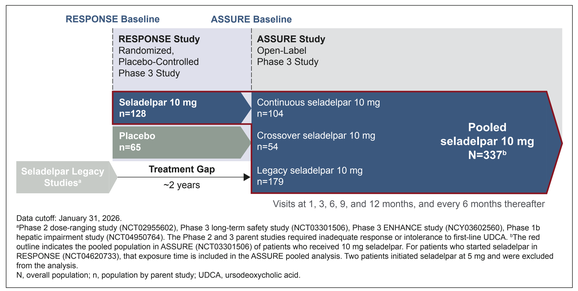
- Seladelpar is a first-in-class delpar (selective peroxisome proliferator-activated receptor delta [PPARδ] agonist) indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA or as monotherapy in patients who are unable to tolerate UDCA[1–4]
- Alkaline phosphatase (ALP) is a key marker of disease activity in PBC, and patients present with variable ALP levels at baseline; reduction in ALP levels is associated with reduced risk of negative long-term outcomes[5]
- In the pivotal placebo-controlled, Phase 3 RESPONSE trial (NCT04620733), seladelpar significantly reduced ALP levels compared with placebo[1]
- The ongoing, open-label, Phase 3 ASSURE study (NCT03301506)[6] assesses the long-term impact of seladelpar treatment in PBC, including its impact on ALP and other biochemical markers of disease progression, as well as long-term safety

Objective

- To evaluate changes in ALP over time across different baseline ALP quartiles, and at different thresholds of ALP response, in patients receiving seladelpar treatment for up to 5 years

Methods

Figure 1. Study Design



Data cutoff: January 31, 2026.
[a]Phase 2 dose-ranging study (NCT02955602), Phase 3 long-term safety study (NCT03301506), Phase 3 ENHANCE study (NCY03602560), Phase 1b hepatic impairment study (NCT04950764). The Phase 2 and 3 parent studies required inadequate response or intolerance to first-line UDCA. [b]The red outline indicates the pooled population in ASSURE (NCT03301506) of patients who received 10 mg seladelpar. For patients who started seladelpar in RESPONSE (NCT04620733), that exposure time is included in the ASSURE pooled analysis. Two patients initiated seladelpar at 5 mg and were excluded from the analysis.
N, overall population; n, population by parent study; UDCA, ursodeoxycholic acid.

Seladelpar Treatment Duration at Data Cutoff

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients who completed treatment through time point, n (%)	325 (96)	298 (88)	243 (72)	116 (34)	2 (<1)

- Patients rolled over directly from RESPONSE or enrolled after prior participation in a legacy study and received open label seladelpar 10 mg daily in ASSURE (**Figure 1**)
- This analysis is based on a pooled population of all patients enrolled in ASSURE where baseline was defined as the time of seladelpar initiation in RESPONSE or ASSURE. The data cutoff for this interim analysis was January 31, 2026
- Patients were pooled and categorized by baseline ALP quartile, defined as: ALP (U/L) <198.5, Q1; ≥198.5 to <259, Q2; ≥259 to <352, Q3; and ≥352, Q4; ALP changes from baseline across quartiles were assessed for up to 48 months in this interim analysis. Other outcomes evaluated across baseline ALP quartiles included:
  - Additional biochemical markers of liver injury, gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and total bilirubin (TB)
  - Proportions of patients attaining ALP reductions of ≥20%, ≥30%, or ≥40% from baseline
- Additional subgroup analysis evaluated up to Month 48 were:
  - ALP changes from baseline among patients who did not attain ALP normalization and/or composite biochemical response (CBR; defined as ALP <1.67 × upper limit of normal [ULN], ≥15% reduction in ALP, and TB ≤ULN) at Month 12 versus those who did achieve either endpoint
- Patients who had PBC-related clinical outcomes (death, liver transplantation, Model for End-Stage Liver Disease score ≥15 for at least 2 consecutive visits, ascites requiring treatment, hospitalization for decompensation event [esophageal varices hemorrhage, spontaneous bacterial peritonitis, hepatic encephalopathy]) or who met liver safety criteria that led to seladelpar discontinuation (i.e., intercurrent events) were considered non-responders for all subsequent time points
- Safety was assessed by patient incidence of adverse events (AEs) up to Month 60, stratified by baseline ALP
  - Liver-related AEs were identified based on a prespecified search strategy of preferred terms

Results

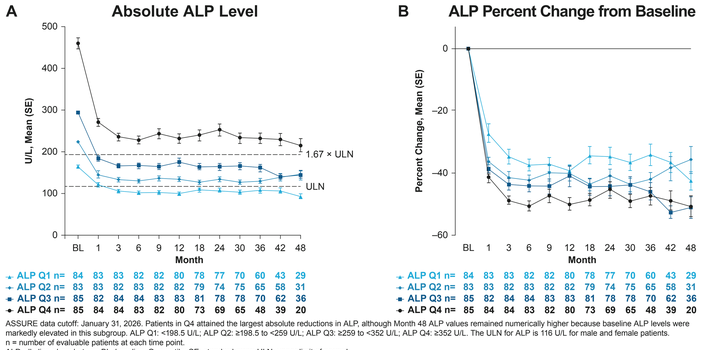
Table 1. Demographics and Baseline Characteristics

	SEL 10 mg				
	Q1 <198.5 U/L ALP (N=84)	Q2 ≥198.5 to <259 U/L ALP (N=83)	Q3 ≥259 to <352 U/L ALP (N=85)	Q4 ≥352 U/L ALP (N=85)	Total (N=337)
Age at screening, years, mean (SD)	61.7 (8.6)	56.9 (9.5)	57.3 (9.2)	56.4 (10.7)	58.1 (9.7)
Age group at PBC diagnosis, years, n (%)					
<50	38 (45.2)	50 (60.2)	49 (57.6)	48 (56.5)	185 (54.9)
≥50	46 (54.8)	33 (39.8)	36 (42.4)	37 (43.5)	152 (45.1)
Sex, female, n (%)	79 (94.0)	79 (95.2)	79 (92.9)	81 (95.3)	318 (94.4)
Race, white, n (%)	74 (88.1)	72 (86.7)	74 (87.1)	71 (83.5)	291 (86.4)
Body mass index, kg/m², mean (SD)	27.0 (6.0)	28.5 (6.5)	27.0 (5.0)	26.8 (5.6)	27.3 (5.8)
On UDCA, n (%)	82 (97.6)	79 (95.2)	81 (95.3)	78 (91.8)	320 (95.0)
Cirrhosis, n (%)	16 (19.0)	12 (14.5)	12 (14.1)	12 (14.1)	52 (15.4)
Child-Pugh A, n (%)[a]	15 (93.8)	11 (91.7)	10 (83.3)	12 (100.0)	48 (92.3)
Liver stiffness, kPa, mean (SD)	9.7 (9.0)	9.7 (7.5)	10.0 (5.6)	10.9 (9.8)	10.0 (8.1)
INR, mean (SD)	1.0 (0.09)	1.0 (0.08)	1.0 (0.08)	1.0 (0.08)	1.0 (0.08)
Albumin, g/dL, mean (SD)	4.2 (0.3)	4.2 (0.3)	4.1 (0.3)	4.1 (0.3)	4.1 (0.3)
ALP, U/L,[b] mean (SD)	165 (24.8)	225 (16.6)	296 (26.8)	461 (121.3)	287 (128.2)
AST, U/L,[b] mean (SD)	28 (10.3)	35 (12.1)	39 (12.3)	49 (20.5)	38 (16.3)
ALT, U/L,[b] mean (SD)	28 (11.8)	40 (16.6)	46 (19.1)	58 (29.6)	43 (23.0)
GGT, U/L,[b] mean (SD)	123 (93.1)	171 (132.9)	261 (218.4)	383 (256.8)	235 (211.5)
TB, mg/dL,[b] mean (SD)	0.6 (0.3)	0.7 (0.3)	0.8 (0.4)	0.8 (0.3)	0.8 (0.3)
Pruritus NRS, mean (SD)	2.0 (2.7)	2.4 (2.7)	3.0 (2.9)	3.7 (2.9)	2.8 (2.8)

ASSURE data cutoff: January 31, 2026. [a]Percentage out 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;[1] TB ULN=1.10 mg/dL.[4]
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; NRS, numerical rating scale; PBC, primary biliary cholangitis; Q, quartile; SD, standard deviation; SEL, seladelpar; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

- Overall, 337 patients were included in the analysis; baseline demographics were similar across baseline ALP quartiles (**Table 1**)
- Baseline disease characteristics were different across ALP quartiles; GGT, ALT, and TB increased with ALP, while cirrhosis prevalence and measures of hepatic synthetic function (international normalized ratio and albumin) remained generally similar across quartiles

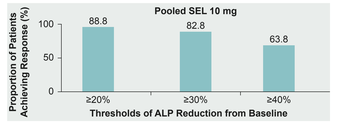
Figure 2. ALP Changes Over Time by Baseline ALP Quartile in Patients Treated with Seladelpar

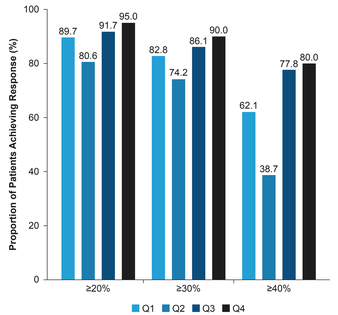


ASSURE data cutoff: January 31, 2026. Patients in Q4 attained the largest absolute reductions in ALP, although Month 48 ALP values remained numerically higher because baseline ALP levels were markedly elevated in this subgroup. ALP Q1: <198.5 U/L; ALP Q2: ≥198.5 to <259 U/L; ALP Q3: ≥259 to <352 U/L; ALP Q4: ≥352 U/L. The ULN for ALP is 116 U/L for male and female patients.
n = number of evaluable patients at each time point.
ALP, alkaline phosphatase; BL, baseline; Q, quartile; SE, standard error; ULN, upper limit of normal.

- Reductions in ALP were observed as early as Month 1, and sustained through Month 48 in all quartiles (mean percent change from baseline [standard error; SE] at Month 48: Q1, −42.4% [3.0]; Q2, −35.7% [4.3]; Q3, −51.1% [3.6]; Q4, −50.7% [3.4]; **Figure 2**)
- Of 330 patients evaluable at Month 12, 115 (34.8%) attained ALP normalization and 228 (69.1%) attained CBR
  - Among the 215/330 (65.2%) patients who did not attain ALP normalization at Month 12 and the 102/330 (30.9%) patients who did not attain CBR at Month 12, ALP levels reduced over the treatment period; at Month 48, mean (SE) ALP percent changes from baseline were −43.5% (2.7) and −34.7% (6.2), respectively
- Patients with high baseline ALP levels who did not attain ALP normalization or CBR at Month 12 still experienced biochemical improvement with continued treatment

Figure 3. Attainment of Different Thresholds of ALP Reduction with Seladelpar at Month 48



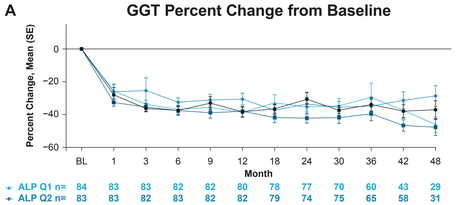


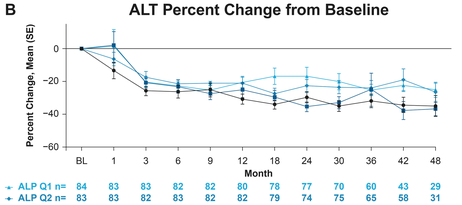
ALP Q1 n/N=	**26/29**	**24/29**	**18/29**
ALP Q2 n/N=	**25/31**	**23/31**	**12/31**
ALP Q3 n/N=	**33/36**	**31/36**	**28/36**
ALP Q4 n/N=	**19/20**	**18/20**	**16/20**

ASSURE data cutoff: January 31, 2026. ALP Q1: <198.5 U/L; ALP Q2: ≥198.5 to <259 U/L; ALP Q3: ≥259 to <352 U/L; ALP Q4: ≥352 U/L. Threshold of ALP reduction was defined as the percentage decrease in ALP from baseline. n/N = number of responders/number of evaluable patients at Month 48.
ALP, alkaline phosphatase; Q, quartile; SEL, seladelpar.

- In the overall population, 88.8%, 82.8%, and 63.8% of patients attained ALP reductions of ≥20%, ≥30%, and ≥40%, respectively, at Month 48 (**Figure 3**)

Figure 4. GGT and ALT Changes Over Time by Baseline ALP Quartile in Patients Treated with Seladelpar





ASSURE data cutoff: January 31, 2026. n = number of evaluable patients at each time point.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; BL, baseline; GGT, gamma-glutamyl transferase; Q, quartile; SE, standard error.

- Reductions in GGT were similar across all quartiles (mean [SE] percent change from baseline at Month 48: Q1, −46.2% [4.7]; Q2, −28.7% [6.3]; Q3, −47.8% [5.0]; Q4, −37.2% [5.6]; **Figure 4A**)
- Reductions in ALT were also observed across baseline ALP quartiles at similar magnitudes, and were sustained through Month 48 (mean [SE] percent change from baseline: Q1, −25.1% [4.6]; Q2, −26.6% [5.6]; Q3, −36.9% [4.2]; Q4, −34.9% [6.4]; **Figure 4B**)
- TB remained stable through Month 48 across ALP quartiles

Table 2. Overall Safety Outcomes

n (%)	SEL 10 mg				
	Q1 <198.5 U/L ALP (N=84)	Q2 ≥198.5 to <259 U/L ALP (N=83)	Q3 ≥259 to <352 U/L ALP (N=85)	Q4 ≥352 U/L ALP (N=85)	Total (N=337)
Any AE (at least one)	81 (96.4)	83 (100.0)	84 (98.8)	79 (92.9)	327 (97.0)
Serious AE[a]	17 (20.2)	26 (31.3)	14 (16.5)	22 (25.9)	79 (23.4)
Treatment-related serious AE	0	0	0	0	0
Grade 3 or higher AE	20 (23.8)	31 (37.3)	15 (17.6)	22 (25.9)	88 (26.1)
AE with action taken as permanent withdrawal of study drug	9 (10.7)	8 (9.6)	7 (8.2)	16 (18.8)	40 (11.9)
AE leading to death[b]	2 (2.4)	0	0	1 (1.2)	3 (0.9)

ASSURE data cutoff: January 31, 2026. All AEs listed were treatment-emergent. TEAEs that began on or after the date when seladelpar was initiated up to 30 days after the date of the last seladelpar dose were included. Adverse events were coded using MedDRA version 28.1, and severity grades were defined by CTCAE Version 5.0. [a]Serious AEs adjudicated as PBC clinical outcomes were esophageal varices hemorrhage (Q1, Q3, Q4), autoimmune hemolytic anemia (Q4), intracranial hemorrhage (Q1), metastatic lung cancer (Q1), and pneumonia (Q1). [b]The three adverse events leading to death included autoimmune hemolytic anemia, metastatic lung cancer, and an intracranial hemorrhage associated with a head injury. All events were assessed by the Investigators as not related to seladelpar.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; PBC, primary biliary cholangitis; Q, quartile; SEL, seladelpar; TEAE, treatment-emergent adverse event.

- AEs were reported in 327 (97.0%) patients overall, with similar proportions observed across ALP quartiles (**Table 2**)
  - Incidence of AEs leading to discontinuation was greatest in Q4; however, there was no change to the overall safety profile of seladelpar across quartiles