Seladelpar Leads to Durable and Significant Decrease in the Pruritogenic Cytokine IL-31, Associated With Pruritus Improvement: Long-Term Data From the ASSURE Study

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Conclusions

- Interleukin-31 (IL-31) is a known pruritogenic cytokine elevated in patients with primary biliary cholangitis
- Seladelpar led to sustained reductions in IL-31 and total bile acid levels through Month 36
- IL-31 was higher in patients with increased pruritus burden, and greater reductions in IL-31 were observed among patients with meaningful improvement of pruritus (numeric rating scale reduction of ≥3)
- Alongside existing evidence, these findings suggest a potential mechanistic link between seladelpar treatment, and pruritus improvement

Plain Language Summary

- Primary biliary cholangitis is a serious, long-term disease that damages the liver and the drainage system in the liver that helps remove bile and toxins from the body
- Itching is a common symptom in people with primary biliary cholangitis
- Seladelpar is an approved treatment for primary biliary cholangitis that helps reduce itching
- Bile acids, which are part of bile, and a protein called interleukin-31 may play a role in causing itching
- In this study, seladelpar lowered interleukin-31 and bile acid levels, which may help explain some of the improvement in itching seen with seladelpar

References: **1.** European Association for the Study of the Liver. *J Hepatol.* 2017;67(1):145-72. **2.** Onofrio FQ, et al. *Gastroenterol Hepatol (N Y).* 2019;15(3):145-54. **3.** Trivella J, et al. *Hepatol Commun.* 2023;7(6):e0179. **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;390:793-94. **8.** Kremer AE, et al. *Hepatology.* 2024;80(1):27-37.

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Introduction

- Primary biliary cholangitis (PBC) is a chronic, autoimmune, cholestatic liver disease that disproportionately affects women and is associated with progressive liver injury and significant symptom burden[1]
- Up to 80% of people with PBC experience pruritus, which can substantially reduce quality of life[2,3]
- 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 Phase 3, placebo-controlled RESPONSE study (NCT04620733), seladelpar significantly improved alkaline phosphatase (ALP) and pruritus in patients with PBC[7]
- Interleukin-31 (IL-31) is a known pruritogenic cytokine elevated in patients with PBC[8]
- Bile acids are also implicated as components of pruritogenic signaling pathways in cholestatic pruritus, including in PBC[8]
- While the pathogenesis of cholestatic itch remains uncertain, bile acids and IL-31 have been implicated[8]
- IL-31 levels have been shown to be correlated with bile acid levels in PBC patients (ENHANCE study; NCT03602560), suggesting bile acid levels are proximal to the regulation of IL-31 release[8]

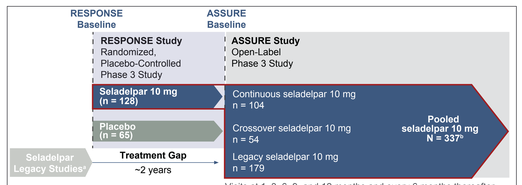
Objective

- To evaluate long-term changes in IL-31 and their association with pruritus and bile acids in patients with PBC treated with seladelpar up to 36 months from an interim analysis of the ongoing Phase 3 open-label ASSURE study (NCT03301506)

Methods

- Patients enrolled in ASSURE directly from RESPONSE or after participation in prior legacy seladelpar studies and received open-label seladelpar 10 mg once daily (**Figure 1**)
  - Patients were pooled at seladelpar initiation in either RESPONSE or ASSURE
- Patients with baseline and at least 1 post-baseline IL-31 concentration were included in this post hoc analysis
- Baseline numeric rating scale (NRS) was used to classify patients into subgroups with higher (NRS ≥4) and lower (NRS <4) pruritus severity
- Serum IL-31 concentrations were determined using a single-molecule array ultrasensitive immunoassay (lower limit of quantitation of 0.024 pg/mL)
- Serum bile acids in samples were analyzed quantitatively by liquid chromatography tandem mass spectrometry (Metabolon, Durham, NC, USA); total bile acids were then calculated as the sum of 12 bile acids, excluding UDCA, tauroursodeoxycholic acid, and glycoursodeoxycholic acid
- IL-31 levels were assessed over time in the overall population
- Baseline IL-31 levels were compared by baseline NRS groups (NRS ≥4 vs NRS <4)
- Changes in IL-31 by NRS improvement status (≥3 points decline vs less improvement) were also assessed
- Total bile acid concentration was assessed over time in the overall population
- Correlations between IL-31 and NRS or total bile acids were evaluated using Spearman's rank correlation (rho; ρ)
- Data cutoff for IL-31 and bile acid biomarker datasets: January 31, 2025

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 (NCT03602560), 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)

Results

- A total of 284 patients were included in the IL-31 data analysis set; 93 had a baseline NRS ≥4 (**Table 1**)

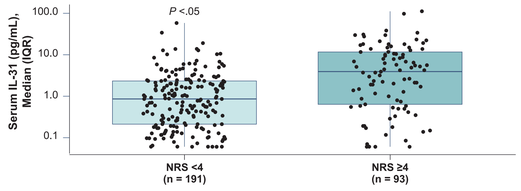
Table 1. Baseline Demographic and Clinical Characteristics of IL-31 Analysis Set

	Baseline NRS ≥4 (n = 93)	Overall Population (N = 284)
Age, years, mean (SD)	55.3 (10.6)	58.4 (9.6)
Female, n (%)	87 (94)	269 (95)
Patients with cirrhosis at baseline, n (%)	19 (20)	44 (15)
Child-Pugh class A, n (% of patients with cirrhosis)	17 (89)	42 (95)
ALP, U/L, mean (SD)	314.9 (125.9)	285.1 (119.1)
TB, mg/dL, mean (SD)	0.8 (0.4)	0.7 (0.3)
Duration of PBC, years, mean (SD)	9.1 (5.4)	9.9 (6.3)
Pruritus NRS, mean (SD)	6.3 (1.6)	2.8 (2.9)
IL-31, pg/mL, mean (SD)	8.9 (15.8)	4.4 (10.4)
IL-31, pg/mL, median (IQR)	3.7 (0.6, 11.0)	1.1 (0.3, 4.0)

ALP, alkaline phosphatase; IL-31, interleukin-31; NRS, numeric rating scale; PBC, primary biliary cholangitis; TB, total bilirubin.

- Baseline median (IQR) IL-31 level was higher in patients with NRS ≥4 vs NRS <4 (3.70 [0.60, 11.00] pg/mL vs 0.81 [0.20, 2.20] pg/mL; **Figure 2**)

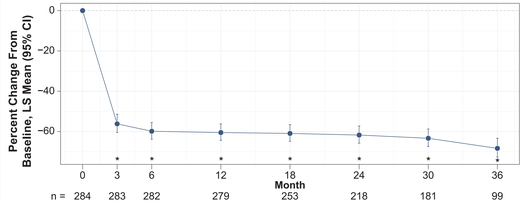
Figure 2. Baseline IL-31 by Baseline NRS Subgroup



P-value shown is from Wilcoxon rank-sum tests.
IL-31, interleukin-31; NRS, numeric rating scale.

- IL-31 reduction with seladelpar treatment was rapid and sustained up to Month 36 in the overall population (least-squares mean [95% CI], –68% [–63%, –73%]; **Figure 3**) and in patients with baseline NRS ≥4 (–74% [–66%, –80%]; data not shown)

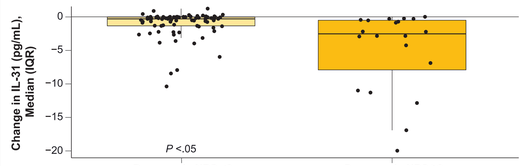
Figure 3. Percent Change From Baseline in Serum IL-31 Over Time in the Overall Population



n represents the number of patients who had baseline and corresponding post-baseline IL-31 values.
*P <.05 at indicated time point compared with baseline level.
IL-31, interleukin-31; LS, least-squares.

- At Month 36, patients with NRS improvement ≥3 points had greater median (IQR) reductions in IL-31 (–2.80 [–10.80, –0.52] pg/mL; n = 21) compared with patients with lower NRS improvement (–0.30 [–1.32, –0.04] pg/mL; n = 76; **Figure 4**)

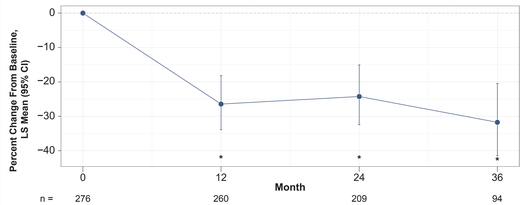
Figure 4. Changes in IL-31 by Decrease in Pruritus NRS at Month 36



P-value shown is from Wilcoxon rank-sum tests.
One outlier from the "Decrease in NRS ≥3" group (change in IL-31 = –88.2 pg/mL) was removed for visualization purposes.
IL-31, interleukin-31; NRS, numeric rating scale.

- Total bile acid reductions were sustained up to Month 36 in the overall population (least-squares mean [95% CI], –31.7% [–20.5%, –41.4%]; **Figure 5**)

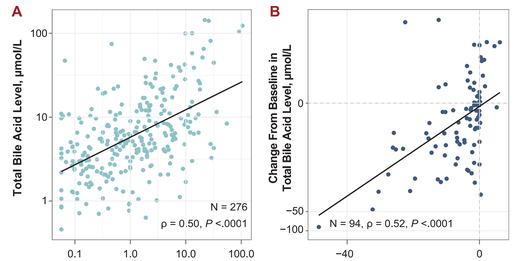
Figure 5. Percent Change From Baseline in Total Bile Acid (Excluding UDCA, TUDCA, GUDCA) Over Time in the Overall Population



n represents the number of patients who had baseline and corresponding post-baseline total bile acid values.
*P <.05 at indicated time points compared with baseline level.
GUDCA, glycoursodeoxycholic acid; LS, least-squares; TUDCA, tauroursodeoxycholic acid; UDCA, ursodeoxycholic acid.

- IL-31 and total bile acids were correlated at baseline (ρ = 0.50; *P* <.0001; **Figure 6A**), as were changes from baseline to Month 36 (ρ = 0.52; *P* <.0001; **Figure 6B**)

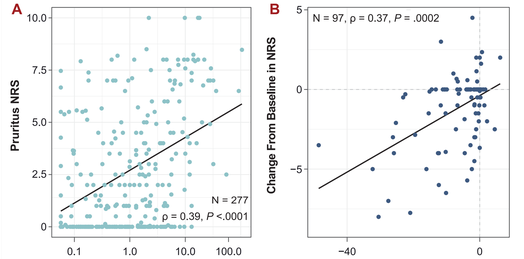
Figure 6. Correlations of (A) IL-31 With Serum Total Bile Acid Level at Baseline, and (B) Absolute Change From Baseline in Serum IL-31 With Absolute Change From Baseline in Total Bile Acid Level at 36 Months in the Overall Population



[a]The x-axis and y-axis are displayed on log scales.
[b]The x-axis and y-axis are displayed on symmetric log (pseudo-log) scales.
IL-31, interleukin-31.

- Baseline IL-31 levels were correlated with baseline NRS (ρ = 0.39; *P* <.0001; **Figure 7A**), as were changes from baseline to Month 36 in IL-31 and NRS (ρ = 0.37; *P* = .0002; **Figure 7B**)

Figure 7. Correlations of (A) IL-31 With Pruritus NRS at Baseline and (B) Absolute Change From Baseline in Serum IL-31 With Absolute Change From Baseline in Pruritus NRS at Month 36 in the Overall Population



[a]The x-axis is displayed on log scale.
[b]The x-axis is displayed on symmetric log (pseudo-log) scale.
IL-31, interleukin-31; NRS, numeric rating scale.

Limitations

- IL-31 is one of the pruritogenic mediators involved in the mechanism underlying pruritus in PBC
- The analytical performance of IL-31 measurement may be influenced by biological and technical variability
- The study is currently ongoing, so the number of evaluable patients at later time points is limited