Long-Term Efficacy and Safety of Open-Label Seladelpar Treatment in Patients With Primary Biliary Cholangitis: Pooled Interim Results for up to 3 Years From the ASSURE Study

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Summary

- This long-term, pooled analysis from the ongoing, open-label, Phase 3 ASSURE study (NCT03301506) investigated the efficacy and safety of daily seladelpar 10 mg in 337 patients with primary biliary cholangitis, of whom 124 had ≥24 months of seladelpar exposure
- By month 30, seladelpar resulted in a durable and sustained biochemical response in 81% of patients (30/37) and an alkaline phosphatase normalization rate of 41% (15/37)
- A robust reduction in pruritus, assessed by daily e-diary through month 6, was observed with seladelpar treatment
- Seladelpar continues to appear safe and well tolerated, showing no new safety signals or changes in the frequency of adverse events after up to 3 years of exposure

Plain Language Summary

Please scan the QR code for an expanded version of this plain language summary.

- ASSURE (NCT03301506) is an ongoing study that includes patients who participated in the Phase 3 RESPONSE study (NCT04620733) and prior seladelpar trials
- Here, we show data for 337 patients with primary biliary cholangitis, including 124 patients with up to or beyond 2 years of seladelpar treatment
- A lower alkaline phosphatase level is considered the main result that shows seladelpar is working
- A "biochemical response" was defined by having an alkaline phosphatase level <1.67 times the upper limit of normal, at least a 15% reduction in alkaline phosphatase levels, and a normal total bilirubin level
- After 2.5 years of seladelpar, 81% of patients (30/37) demonstrated a biochemical response to seladelpar
- Forty-one percent of patients (15/37) had a normal alkaline phosphatase level after 2.5 years of seladelpar
- Additionally, patients in this study reported improvements in itching over 6 months of taking seladelpar
- Throughout 3 years of seladelpar treatment, the rate of adverse events did not appear to change in the ASSURE study

Introduction

- Primary biliary cholangitis (PBC) is a chronic, progressive, autoimmune, cholestatic liver disease that affects approximately 1 in 1000 women over 40 years of age[1]
- Seladelpar is a first-in-class delpar (selective peroxisome proliferator–activated receptor delta [PPARδ] agonist) targeting multiple cell types and processes in PBC[2]
  - In August 2024, seladelpar was granted accelerated approval in the United States for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as a monotherapy in patients unable to tolerate UDCA[3]
- The ASSURE study (NCT03301506) is an ongoing, open-label, long-term, Phase 3 trial of seladelpar in patients with PBC rolling over from the placebo-controlled, Phase 3 RESPONSE trial (NCT04620733) or with prior participation in legacy seladelpar trials[2,4-8]
- Interim results from the ASSURE study, reported separately for patients rolling over from RESPONSE or the legacy studies, were previously presented and demonstrated that seladelpar exhibited[9]
  - A durable effect on markers of cholestasis and liver injury maintained for up to 2 years in patients continuing seladelpar in ASSURE after completing RESPONSE
  - Similar effects in legacy patients starting seladelpar in ASSURE

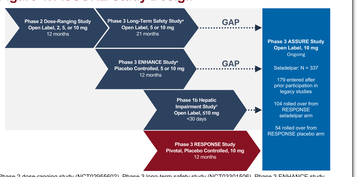
Objective

- To assess the pooled interim efficacy and safety for all patients in the ASSURE study for up to 3 years

Methods

- Patients could enter ASSURE from the RESPONSE study or from legacy seladelpar studies (**Figure 1**)
  - For patients who had received seladelpar in RESPONSE and then rolled over into ASSURE, exposure to seladelpar during RESPONSE was included in the analysis
  - Baseline (BL) was based on first exposure to seladelpar in ASSURE or RESPONSE
- Key efficacy endpoints included: Composite biochemical response (alkaline phosphatase [ALP] <1.67 × the upper limit of normal [ULN], ALP decrease ≥15%, and total bilirubin ≤ULN), ALP normalization, and other liver biochemistries
- Pruritus was recorded using a numerical rating scale (NRS; 0–10 rating of worst itch in the past 24 hours) collected daily by e-diary through month 6; change from BL was assessed through month 6 in patients with moderate to severe pruritus (NRS ≥4) at BL
  - After month 6, pruritus NRS was collected only at study visits, and these data were not summarized
- Efficacy endpoints and pruritus outcomes are reported among the number of evaluable patients for each measure
- Exposure-adjusted adverse events (AEs) were calculated for each year on study as incidence per 100 patient-years

Figure 1. ASSURE Study Design



Phase 2 dose-ranging study (NCT02955602), Phase 3 long-term safety study (NCT03301506), Phase 3 ENHANCE study (NCT03602560), Phase 1b HI study (NCT04950764), Phase 3 registrational RESPONSE study (NCT04620733), and Phase 3, open-label ASSURE study (NCT03301506). The Phase 2 and 3 parent studies required an inadequate response or intolerance to first-line UDCA. Data cutoff January 31, 2024.
*Terminated early. †Patients were eligible to enroll in ASSURE after completing the study, but they had to meet screening criteria and had variable time to entry into ASSURE.
HI, hepatic impairment; UDCA, ursodeoxycholic acid.

Results

Table 1. Ongoing Study, Patients as of January 31, 2024

Time Point[a]	12 Months	18 Months	24 Months	30 Months
Patients in the pooled analysis	282	237	124	34

[a]Treatment exposure was defined as (the date of the last seladelpar dose in ASSURE − the date of the first seladelpar dose in ASSURE).

- As of the data cutoff date (January 31, 2024), 337 patients enrolled in ASSURE, of whom 124 had ≥24 months of seladelpar exposure (**Table 1**)

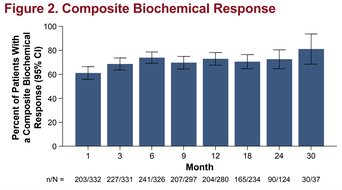
Table 2. Demographics and Baseline Clinical Characteristics

	Seladelpar 10 mg Overall N = 337
Age, years, mean (SD)	58.1 (9.7)
Female sex, n (%)	318 (94)
Race, n (%)	
American Indian or Alaska Native	11 (3)
Asian	24 (7)
Black or African American	7 (2)
White	291 (86)
Other[a]	4 (1)
BMI, kg/m², mean (SD)	27.3 (5.8)
Patients with cirrhosis at baseline, n (%)	55 (16)
Child-Pugh class A	51 (93)
Child-Pugh class B	4 (7)
Portal hypertension, n (% of patients with cirrhosis)	9 (16)
MELD score ≥12, n (%)	2 (<1)
ALP, U/L, mean (SD)	287.5 (128.4)
Total bilirubin, mg/dL, mean (SD)	0.8 (0.3)
NRS ≥4, n (%)	107 (32)
NRS, mean (SE)	6.3 (0.2)

[a]"Other" consisted of 2 patients who declined to answer and 2 patients who had missing data.
ALP, alkaline phosphatase; BMI, body mass index; MELD, model for end-stage liver disease; NRS, numerical rating scale.

- At BL, the mean (SD) age was 58.1 (9.7) years, most patients (94%) were female, and 16% of patients had cirrhosis (**Table 2**)

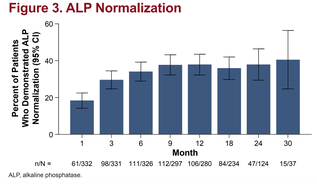
Figure 2. Composite Biochemical Response



- The composite biochemical response endpoint was met in 73% (204/280), 73% (90/124), and 81% (30/37) of patients at months 12, 24, and 30, respectively (**Figure 2**)

Results

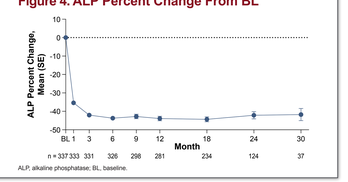
Figure 3. ALP Normalization



ALP, alkaline phosphatase.

- ALP normalization rates increased through month 12 and were sustained in 41% (15/37) of patients through month 30 (**Figure 3**)

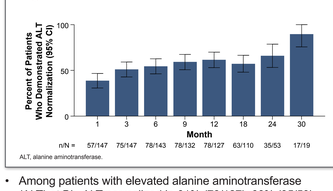
Figure 4. ALP Percent Change From BL



ALP, alkaline phosphatase; BL, baseline.

- Improvements in ALP levels were seen as early as month 1 and were maintained through month 30 (**Figure 4**)

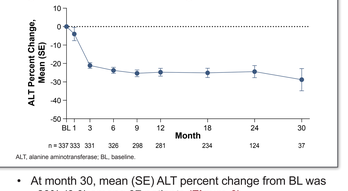
Figure 5. ALT Normalization



ALT, alanine aminotransferase.

- Among patients with elevated alanine aminotransferase (ALT) at BL, ALT normalized in 61% (78/127), 66% (35/53), and 90% (17/19) of patients at months 12, 24, and 30, respectively (**Figure 5**)

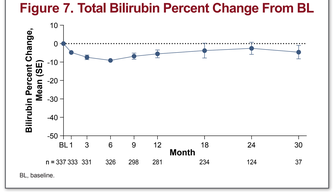
Figure 6. ALT Percent Change From BL



ALT, alanine aminotransferase; BL, baseline.

- At month 30, mean (SE) ALT percent change from BL was –29% (6.0) among 37 patients (**Figure 6**)

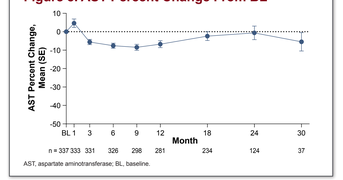
Figure 7. Total Bilirubin Percent Change From BL



BL, baseline.

- At month 30, mean (SE) total bilirubin percent change from BL was –5% (3.6) among 37 patients (**Figure 7**)

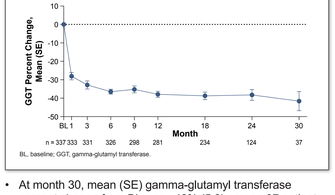
Figure 8. AST Percent Change From BL



AST, aspartate aminotransferase; BL, baseline.

- Through 30 months of treatment with seladelpar, aspartate aminotransferase levels remained stable (**Figure 8**)

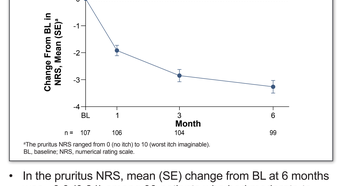
Figure 9. GGT Percent Change From BL



BL, baseline; GGT, gamma-glutamyl transferase.

- At month 30, mean (SE) gamma-glutamyl transferase percent change from BL was –42% (5.2) among 37 patients (**Figure 9**)

Figure 10. Change in Pruritus NRS



*The pruritus NRS ranged from 0 (no itch) to 10 (worst itch imaginable).
BL, baseline; NRS, numerical rating scale.

- In the pruritus NRS, mean (SE) change from BL at 6 months was −3.3 (0.24) among 99 patients who had moderate to severe pruritus at BL (**Figure 10**)

Table 3. Safety Overview

Exposure-Adjusted AEs per 100 Patient-Years	Seladelpar 10 mg Overall N = 337 (E = 575.7 Years)	Seladelpar 10 mg Year 1 N = 337 (E = 313.7 Years)	Seladelpar 10 mg Year 2 N = 280 (E = 214.4 Years)	Seladelpar 10 mg Year 3 N = 124 (E = 47.6 Years)
Patients with ≥1 AE	50.2	85.8	70.0	63.0
Grade ≥3 AEs (per CTCAE)	8.3	9.6	8.4	8.4
SAEs	6.9	7.7	6.5	6.3
Treatment-related SAEs	0	0	0	0
AEs leading to treatment discontinuation	2.4	2.2	3.3	0
AEs leading to study discontinuation	1.6	1.6	1.9	0
AEs leading to death	0.2	0	0.5	0

All AEs listed are treatment emergent unless otherwise stated.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; E, patients' sum of exposure; SAE, serious adverse event.

- In patients receiving seladelpar 10 mg, exposure-adjusted AEs were observed in 86, 70, and 63 patients per 100 patient-years at months 12, 24, and 36, respectively (**Table 3**)
- No treatment-related serious AEs occurred
- One fatal outcome was due to autoimmune hemolytic anemia
  - The investigator and sponsor deemed this event to be unrelated to seladelpar

Table 4. Common AEs by Preferred Term[a]

Exposure-Adjusted AEs per 100 Patient-Years	Seladelpar 10 mg Overall N = 337 (E = 575.7 Years)	Seladelpar 10 mg Year 1 N = 337 (E = 313.7 Years)	Seladelpar 10 mg Year 2 N = 280 (E = 214.4 Years)	Seladelpar 10 mg Year 3 N = 124 (E = 47.6 Years)
Patients with ≥1 AE	50.2	85.8	70.0	63.0
COVID-19	11.5	16.3	7.0	10.5
Pruritus	6.8	7.3	7.5	4.2
Nausea	5.2	7.0	3.3	2.1
Fatigue	4.9	4.8	6.1	0
Urinary tract infection	4.7	5.1	5.1	6.3
Diarrhea	4.5	7.0	2.3	0
Headache	4.5	7.0	2.3	0
Arthralgia	4.0	5.1	4.2	0
Nasopharyngitis	4.0	5.4	3.7	2.1
Abdominal pain upper	3.6	4.1	3.3	2.1
Abdominal pain	3.5	3.8	3.3	2.1

All AEs listed are treatment emergent.
[a]AEs by preferred term reported for AEs occurring in ≥3 patients per 100 patient-years in the overall population.
AE, adverse event; E, patients' sum of exposure.

- COVID-19, pruritus, and nausea were the most common AEs reported in the overall population of patients treated with seladelpar 10 mg (**Table 4**)

Table 5. AEs of Interest

Exposure-Adjusted AEs per 100 Patient-Years	Seladelpar 10 mg Overall N = 337 (E = 575.7 Years)	Seladelpar 10 mg Year 1 N = 337 (E = 313.7 Years)	Seladelpar 10 mg Year 2 N = 280 (E = 214.4 Years)	Seladelpar 10 mg Year 3 N = 124 (E = 47.6 Years)
Patients with ≥1 liver-related AE[a]	5.0	5.7	5.1	2.1
Patients with ≥1 muscle-related AE[a]	4.3	5.4	3.7	0
Patients with ≥1 renal-related AE[a]	0.2	0.3	0	0

All AEs listed are treatment emergent. Liver-related AEs were defined using the broad Hepatic disorders SMQ, with exclusion of the sub-SMQs Congenital, familial, neonatal and genetic disorders of the liver; Liver infections; and Pregnancy-related hepatic disorders. Muscle-related AEs were defined using the broad Myalgia FMQ v2.1. Renal-related AEs were defined using the broad Acute renal failure SMQ v24.0.
[a]AEs of interest were identified by a predefined search strategy.
AE, adverse event; E, patients' sum of exposure; FMQ, Food and Drug Administration Medical Query; SMQ, Standardized Medical Dictionary for Regulatory Affairs Query.

- The rates of exposure-adjusted liver-, muscle-, and renal-related AEs remained stable or decreased over 3 years of seladelpar exposure (**Table 5**)
- Most AEs of interest were Grade 1 or 2 in severity

References: **1.** European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-72. **2.** Hirschfield GM, et al. *N Engl J Med*. 2024;390(9):783-94. **3.** Livdelzi. US prescribing information. Gilead Sciences, Inc.; 2024. **4.** NCT03301506. https://clinicaltrials.gov/study/NCT03301506. Accessed September 24, 2024. **5.** Hirschfield GM, et al. *Hepatology*. 2023;78(2):397-415. **6.** Bowlus CL, et al. *J Hepatol*. 2022;77(2):353-64. **7.** Mayo MJ, et al. *Aliment Pharmacol Ther*. 2024;59(2):186-200. **8.** NCT04950764. https://clinicaltrials.gov/study/NCT04950764. Accessed September 24, 2024. **9.** Trivedi PJ, et al. Poster presented at: EASL 2024; June 5–8; 2024; Milan, Italy. Poster ST-13.

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