Long-Term Safety of Seladelpar 10 mg With up to 5 Years of Treatment in Patients With Primary Biliary Cholangitis

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Summary

- More than 500 individual patients with primary biliary cholangitis (PBC) were exposed to seladelpar at ≤10 mg as of January 31, 2024
  - More than 450 patients had received seladelpar 10 mg (the dose studied in the Phase 3, placebo-controlled RESPONSE study [NCT04620733]) and 152 patients had received placebo
- This pooled analysis included patients with cumulative exposure to seladelpar of up to 5 years across any treatment period
- Results demonstrated that long-term seladelpar treatment appears to be tolerable, with an overall safety profile similar to that of placebo
- These data support the long-term safety of seladelpar in patients with PBC

Plain Language Summary

- More than 500 patients with primary biliary cholangitis were treated with seladelpar, including over 450 patients who received the 10 mg dose that was studied in the RESPONSE trial
- We studied safety across all treatment periods in which patients were exposed to seladelpar or placebo
- This study found that long-term seladelpar use has a safety profile that is similar to that of placebo
- These results support the long-term safety of seladelpar for treatment of patients with primary biliary cholangitis

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 Phase 3, placebo-controlled RESPONSE study (NCT04620733) in patients with PBC who had an inadequate response or intolerance to UDCA demonstrated significant improvements in cholestatic markers and additional improvements in pruritus with seladelpar 10 mg through 1 year[2]
  - Similar proportions of seladelpar- and placebo-treated patients experienced adverse events (AEs) and serious AEs (SAEs)
  - The most common AEs reported in ≥5% of patients in the seladelpar treatment group and that occurred more frequently than with placebo (with a between-group difference of ≥1%) were COVID-19, headache, abdominal pain, nausea, and abdominal distension
- Since 2016, six studies have evaluated seladelpar at ≤10 mg daily in patients with PBC[2,4-8]

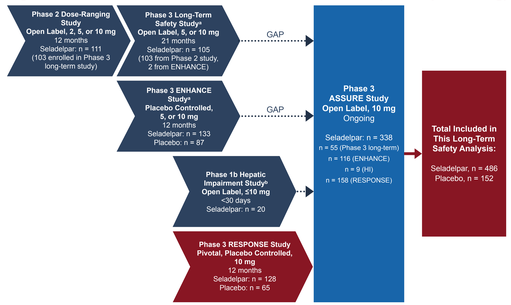
Objective

- To assess the long-term safety of seladelpar 10 mg by pooling data across 6 clinical studies

Methods

- AE data from 2 placebo-controlled and 4 open-label studies were pooled for patients treated with seladelpar 10 mg as of January 31, 2024, beginning with first exposure to seladelpar, including all exposure periods and excluding treatment gaps[2,4-8] (**Figure 1**)
  - Placebo-controlled studies included RESPONSE and ENHANCE
  - Open-label studies included a Phase 2 dose-ranging study, a Phase 3 long-term safety study, a Phase 1b PBC hepatic impairment study (*ongoing*), and ASSURE (*ongoing*)
  - Patients in the Phase 2 study, the long-term study, and ENHANCE had a treatment gap of ≥1 year from their last visit in the prior study to treatment in ASSURE. Patients in the hepatic impairment study received seladelpar for <30 days and had a variable gap (range, 27–497 days) in treatment prior to treatment in ASSURE
  - In some studies, patients started at lower doses (2 or 5 mg in the Phase 2 dose-ranging study; 5 mg in ENHANCE) and were allowed to up-titrate to 10 mg of seladelpar
- All studies except the hepatic impairment study enrolled only patients with PBC who had an inadequate response or intolerance to UDCA

Figure 1. Schematic of Patient Flow Across PBC Studies (Seladelpar ≤10 mg)

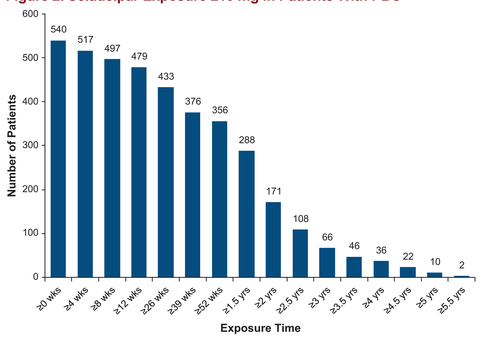


Studies included in this analysis: Phase 2 dose-ranging study (NCT02955602), Phase 3 long-term safety study (NCT03301506), Phase 3 ENHANCE study (NCT03602560), Phase 1b HI study (NCT04950764), Phase 3 registrational RESPONSE study (NCT04620733), and Phase 3, open-label ASSURE study (NCT03301506). The 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; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

- Seladelpar cumulative exposure was summarized for all dose levels ≤10 mg
- Placebo exposure was pooled from the 2 placebo-controlled studies
- Exposure-adjusted patient incidences of AEs, including SAEs, were summarized for patients who received seladelpar 10 mg
  - AEs of interest included liver-, muscle-, and renal-related AEs and were identified based on a predefined search strategy
  - AEs within any given category were recorded as a single occurrence per patient, even if multiple events were experienced
  - Patient exposure was not censored after the occurrence of an AE in the calculation of total exposure

Results

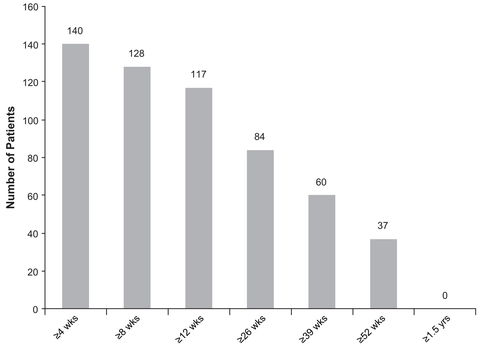
Figure 2. Seladelpar Exposure ≤10 mg in Patients With PBC



Data cutoff: January 31, 2024.
If a patient had a single treatment course, exposure duration was calculated as the last dose date of the treatment course minus the first dose date of the treatment course plus 1 day. If a patient had 2 treatment courses, exposure duration was calculated as the sum of durations in the first and second treatment courses. Time on the drug was cumulative exposure minus any treatment gaps resulting from time between studies.
PBC, primary biliary cholangitis; wks, weeks; yrs, years.

- 540 unique patients with PBC were exposed to seladelpar at ≤10 mg (**Figure 2**)
  - 171 were exposed for ≥2 years; 66 were exposed for ≥3 years; 36 were exposed for ≥4 years; 10 were exposed for ≥5 years
- As of the data cutoff date, a total of 486 patients with PBC had received seladelpar 10 mg
  - 355 patients were treated for ≥1 year, 170 for ≥2 years, 66 for ≥3 years, 36 for ≥4 years, and 10 for ≥5 years

Figure 3. Placebo Exposure in Patients With PBC



PBC, primary biliary cholangitis; wks, weeks; yrs, years.

- Placebo exposure included 152 patients (**Figure 3**)
  - 117 were treated for ≥12 weeks and 84 for ≥26 weeks
    - There were 57 patients who received placebo in RESPONSE that completed the month 12 visit but did not receive a full 365 days of treatment

Table 1. Overall Summary of Exposure-Adjusted Patient Incidence of AEs

Exposure-Adjusted AEs per 100 Patient-Years	Seladelpar 10 mg n = 486 (E = 865.1 Years)	Placebo n = 152 (E = 89.9 Years)
Patients with ≥1 AE	48.3	132.3
Grade ≥3 AEs (per CTCAE)	9.8	12.2
SAEs	8.0	7.8
Treatment-related SAEs	0	0
AEs leading to treatment discontinuation	2.9	5.6
AEs leading to study discontinuation	2.0	3.3
AEs leading to death	0.2	0
Pruritus AEs	9.7	26.7

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.

- The exposure-adjusted patient incidence (per 100 patient-years) for seladelpar 10 mg was 48.3 for AEs, 8.0 for SAEs, and 9.8 for Grade ≥3 AEs (**Table 1**). There were no treatment-related SAEs
- The exposure-adjusted patient incidence (per 100 patient-years) for patients in the placebo group was 132.3 for AEs (rate reflective of shorter exposure time for placebo patients), 7.8 for SAEs, and 12.2 for Grade ≥3 AEs
- AEs leading to treatment discontinuation occurred in 2.9 patients per 100 patient-years in patients treated with seladelpar and 5.6 per 100 patient-years in those treated with placebo

Table 2. Overall Exposure-Adjusted AEs by Preferred Term[a]

Exposure-Adjusted AEs per 100 Patient-Years	Seladelpar 10 mg n = 486 (E = 865.1 Years)	Placebo n = 152 (E = 89.9 Years)
Patients with ≥1 AE	48.3	132.3
Pruritus	9.3	26.7
COVID-19	8.1	11.1
Nausea	7.7	7.8
Urinary tract infection	6.6	4.5
Fatigue	6.4	13.3
Diarrhea	6.2	7.8
Arthralgia	6.1	10.0
Headache	6.0	3.3
Abdominal pain upper	5.3	6.7
Nasopharyngitis	4.9	7.8
Abdominal pain	4.4	2.2
Upper respiratory tract infection	3.9	8.9
Cough	3.7	5.6
Dizziness	3.6	1.1
Vomiting	3.5	5.6
Dyspepsia	3.2	4.5
Abdominal distension	3.1	5.6
Constipation	3.0	5.6
Gastroesophageal reflux disease	3.0	3.3

AEs were coded using MedDRA version 24.0. All AEs listed are treatment emergent.
[a]AEs by preferred term reported for AEs occurring in ≥3 patients per 100 patient-years in the seladelpar group.
AE, adverse event; E, patients' sum of exposure; MedDRA, Medical Dictionary for Regulatory Activities.

- The most common exposure-adjusted AEs reported were consistent with findings from the pivotal RESPONSE study[2] (**Table 2**)

Table 3. Exposure-Adjusted AEs of Interest by Preferred Term[a]

Exposure-Adjusted AEs per 100 Patient-Years	Seladelpar 10 mg n = 486 (E = 865.1 Years)	Placebo n = 152 (E = 89.9 Years)
Patients with ≥1 liver-related AE[b]	6.1	13.3
Alanine aminotransferase increased	0.9	2.2
Blood bilirubin increased	0.6	3.3
Liver function test increased	0.6	1.1
Hepatic cirrhosis	0.5	1.1
Hyperbilirubinemia	0.5	1.1
Portal hypertensive gastropathy	0.1	1.1
Ultrasound liver abnormal	0.1	1.1
Patients with ≥1 muscle-related AE[b]	6.9	8.9
Myalgia	2.9	3.3
Muscle spasms	2.2	2.2
Fibromyalgia	0.7	1.1
Musculoskeletal stiffness	0.1	3.3
Patients with ≥1 renal-related AE[b]	0.7	0

All AEs listed are treatment emergent.
[a]AEs by preferred term reported for AEs occurring in >1 patient per 100 patient-years in either treatment group. [b]AEs of interest were identified by a predefined search strategy.
AE, adverse event; E, patients' sum of exposure.

- Exposure-adjusted AEs of interest (liver-, muscle-, and renal-related AEs) are reported in **Table 3**

Table 4. Exposure-Adjusted Laboratory Parameters of Interest

Exposure-Adjusted AEs per 100 Patient-Years	Seladelpar 10 mg n = 486 (E = 865.1 Years)	Placebo n = 152 (E = 89.9 Years)
Liver-related laboratory parameters		
ALT or AST >3 × ULN	5.1	13.4
Muscle-related laboratory parameters		
CK >3 × ULN	1.0	3.3
CK >5 × ULN	0.5	2.2

All AEs listed are treatment emergent.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; E, patients' sum of exposure; ULN, upper limit of normal.

- Elevations in liver enzymes and creatine kinase were more common among patients receiving placebo in this exposure-adjusted analysis (**Table 4**)

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.** Mayo MJ, et al. *Aliment Pharmacol Ther.* 2024;59(2):186-200. **5.** Bowlus CL, et al. *J Hepatol.* 2022;77(2):353-64. **6.** Hirschfield GM, et al. *Hepatology.* 2023;78(2):397-415. **7.** NCT04950764. https://clinicaltrials.gov/study/NCT04950764. Accessed September 24, 2024. **8.** NCT03301506. https://clinicaltrials.gov/study/NCT03301506. Accessed September 24, 2024.

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