Safety of Seladelpar in Primary Biliary Cholangitis Patients With Cirrhosis and Clinical Signs of Portal Hypertension: Data From the ENHANCE and RESPONSE Studies

WED-171

Aliya Gulamhusein[1], Michael K Porayko[2], Andrea Galli[3], Francesca Carubbi[4], Xin Qi[5], Sarah Proehl[5], Daria B Crittenden[5], Stuart C Gordon[6,7]

[1]Division of Gastroenterology and Hepatology, Toronto Centre for Liver Disease, University of Toronto, Toronto, ON, Canada; [2]Department of Hepatology, Vanderbilt University, Nashville, TN, USA; [3]Azienda Ospedaliero Universitaria Careggi Gastroenterologia Clinica, Firenze, Italy; [4]Metabolic Medicine Unit, Azienda Ospedaliero Universitaria di Modena, University of Modena and Reggio Emilia, Modena, Italy; [5]Gilead Sciences, Inc., Foster City, CA, USA; [6]Division of Hepatology, Henry Ford Hospital, Wayne State University School of Medicine, Detroit, MI, USA; [7]Michigan State University College of Medicine, East Lansing, MI, USA

Conclusions

- In this pooled analysis of patients with primary biliary cholangitis (PBC) from the ENHANCE and RESPONSE studies who had a diagnosis of cirrhosis as well as clinical signs of portal hypertension (PHT), safety outcomes and liver-related adverse events (AEs) were overall similar between seladelpar and placebo
- In this subpopulation of patients, treatment with seladelpar was associated with a lower postbaseline incidence of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN) and elevated total bilirubin (TB) >2 × ULN compared with placebo
- Overall, these data suggest that seladelpar can be safely administered as a second-line treatment to patients with PBC who have cirrhosis and signs of PHT
- Although the sample size in this analysis was small, the findings are consistent with those seen more broadly in prior studies of seladelpar in patients with PBC and compensated cirrhosis

Plain Language Summary

- Primary biliary cholangitis (PBC) is a long-term liver disease that can lead to liver scarring (cirrhosis) and high blood pressure in liver veins (portal hypertension, or PHT), as well as liver failure
- Here, researchers looked at pooled results from two Phase 3 studies of seladelpar, a medication approved for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as a stand-alone therapy in patients who are unable to tolerate UDCA, to understand the safety of seladelpar compared with placebo in patients with cirrhosis and clinical signs of PHT
- The study found that seladelpar appeared to be safe and well tolerated in patients with PBC who had cirrhosis and clinical signs of PHT, which is consistent with the findings of prior studies

References: **1.** European Association for the Study of the Liver. *J Hepatol.* 2017;67:145-72. **2.** Warnes T, et al. *Liver Int.* 2023;43(1):139-46. **3.** Hirschfield G, et al. *N Engl J Med.* 2024;390(9):783-94. **4.** Ocaliva (obeticholic acid). Prescribing Information. Intercept Pharmaceuticals, Inc.; April 2022. **5.** Livdelzi. US prescribing information. Gilead Sciences, Inc.; 2024. **6.** Livdelzi. UK Summary of Product Characteristics. Gilead Sciences, Inc.; 2024. **7.** Seladelpar Gilead. EMA prescribing information. Gilead Sciences, Inc.; 2025. **8.** Hirschfield G, et al. *Hepatology.* 2023;78(2):397-415. **9.** Hirschfield GM, et al. *N Engl J Med.* 2024;390:783-94. Supplementary appendix. **10.** Trivedi P, et al. AASLD. 2024.

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

Introduction

- PBC is a chronic, progressive, autoimmune, cholestatic liver disease that can cause cirrhosis and PHT[1-3]
- Obeticholic acid, a second-line treatment for PBC, is contraindicated in patients with decompensated cirrhosis or a prior decompensation event and compensated cirrhosis with evidence of PHT[4]; however, other second-line treatments are available
- Seladelpar is a first-in-class delpar (selective peroxisome proliferator–activated receptor delta [PPARδ] agonist) indicated for the treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as monotherapy in patients who are unable to tolerate UDCA[5-7]
- In two Phase 3, placebo-controlled studies (ENHANCE [NCT03602560] and RESPONSE [NCT04620733]), seladelpar significantly reduced biochemical cholestasis and pruritus in patients with PBC and had a safety profile similar to that of placebo, including among patients with compensated cirrhosis (primary analyses at month 3 in ENHANCE and month 12 in RESPONSE)[3,8]
- Seladelpar has appeared safe in patients with PBC who have cirrhosis and a diagnosis of PHT in clinical studies, although samples sizes were small[9]
- In addition, long-term (≥5 years) seladelpar treatment has been demonstrated to be tolerable, with an overall safety profile similar to placebo, and no treatment-related serious AEs (SAEs) reported[10]

Objective

- To present pooled safety data from ENHANCE and RESPONSE in a subgroup of patients with cirrhosis and clinical signs of PHT

Methods

Figure 1. ENHANCE and RESPONSE Study Designs

Entry Criteria

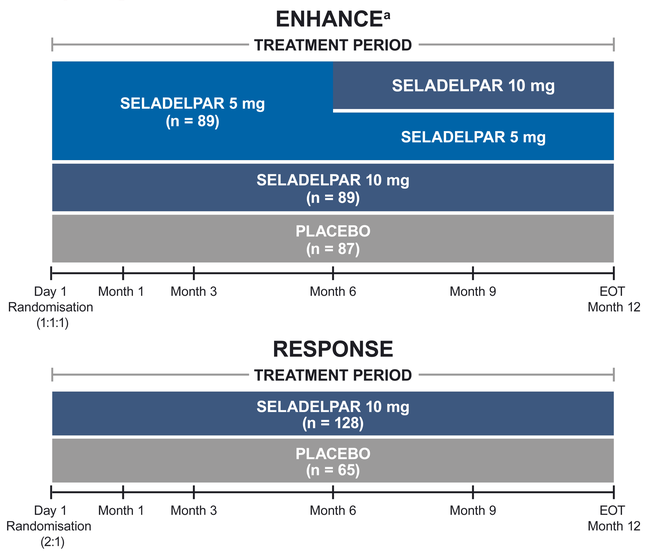
- PBC and UDCA for the past 12 months (stable dose) or intolerant to UDCA
- ALP ≥1.67 × ULN
- ALT and AST ≤3 × ULN
- TB ≤2 × ULN
- Compensated cirrhosis allowed

Definition of Cirrhosis

- History of liver biopsy showing cirrhosis (eg, Ludwig stage 4 or Ishak stage 5)
- Current or a history of decompensated liver disease
- Liver stiffness >16.9 kPa by FibroScan
- The combination of a platelet count <140 × 10^3 cells/μL, with a serum albumin level <3.5 g/dL, an international normalised ratio >1.3 (not due to antithrombotic agent use), or a TB level > 1.0 × ULN
- The presence of radiologic evidence of cirrhosis (a nodular liver) with concurrent splenomegaly
- Clinical determination by the investigator

Stratification

- ALP <350 U/L vs ALP ≥350 U/L
- Pruritus NRS <4 vs NRS ≥4



Study drug administered orally once daily as an add-on to UDCA or as monotherapy in patients intolerant to UDCA.
[a]Primary endpoint was amended to be month 3 before unblinding due to early termination.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOT, end of treatment; NRS, numeric rating scale; PBC, primary biliary cholangitis; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

- In ENHANCE and RESPONSE, patients with PBC who had an inadequate response or intolerance to UDCA were randomised to receive seladelpar or placebo for 12 months (**Figure 1**)
  - ENHANCE was terminated early with endpoints amended to month 3 prior to unblinding because of unexpected histological findings in a concurrent Phase 2 study of seladelpar in patients with nonalcoholic steatohepatitis, which were deemed unrelated to seladelpar by an independent committee of pathologists and hepatologists[6]
- A diagnosis of cirrhosis was documented at baseline
- Patients with cirrhosis were identified post hoc as having clinical signs of PHT at baseline if any of the following were present: thrombocytopenia (platelet count <140 × 10^3 cells/μL); low albumin (serum albumin level <3.5 g/dL); elevated TB (TB >1 × ULN); or medical history of PHT, varices, or ascites
- This analysis presents pooled safety data (AEs, liver-related AEs, and any liver-related laboratory abnormality [ALT or AST >3 × ULN and TB >2 × ULN]) in the subpopulation of patients with cirrhosis and clinical signs of PHT who received seladelpar (5 mg, 5/10 mg, and 10 mg) vs placebo from ENHANCE and RESPONSE for all available time points through month 12 of each study
  - Liver-related AEs were identified by a predefined search strategy

Results

Table 1. Baseline Demographics and Clinical Characteristics of Patients with PBC, Cirrhosis, and Clinical Signs of PHT

	Seladelpar 5 mg (n = 6)	Seladelpar 10 mg (n = 15)	Any Seladelpar (n = 21)	Placebo (n = 6)
Age, years, mean (SD)	54.0 (10.7)	57.3 (11.7)	56.3 (11.3)	53.0 (12.2)
Female, n (%)	5 (83)	14 (93)	19 (90)	4 (67)
ALP, U/L, mean (SD)	285.9 (139.7)	323.9 (160.1)	313.0 (152.1)	343.9 (167.9)
TB, mg/dL, mean (SD)	1.3 (0.4)	1.2 (0.3)	1.2 (0.3)	1.3 (0.6)
Duration of PBC,[a] years, mean (SD)	7.5 (5.4)	9.5 (7.5)	8.9 (6.9)	9.6 (4.8)
Liver stiffness,[b] kPa, mean (SD)	17.3 (10.8)	22.6 (12.3)[c]	21.0 (11.8)[d]	17.4 (3.5)[e]

Patient demographics and clinical characteristics were present at baseline and identified in the PHT post hoc analysis.
[a]Duration is years from diagnosis date to the informed consent date. [b]Assessment performed via FibroScan. [c]n = 14. [d]n = 20. [e]n = 5.
ALP, alkaline phosphatase; PBC, primary biliary cholangitis; PHT, portal hypertension; TB, total bilirubin.

- Among 56 patients who were diagnosed with cirrhosis at baseline across the 2 studies, 27 had signs of PHT at baseline—21 patients randomised to seladelpar (15 of whom were on 10 mg) and 6 randomised to placebo (**Table 1**)
- The disease characteristics were generally similar between the patients randomised to seladelpar or placebo (**Table 1**)

Table 2. Summary of AEs

Patient Incidence, n (%)	Seladelpar 5 mg (n = 6)	Seladelpar 10 mg (n = 15)	Any Seladelpar (n = 21)	Placebo (n = 6)
Any AE	3 (50)	12 (80)	15 (71)	5 (83)
Grade ≥3 AEs	0	1 (7)	1 (5)	1 (17)
SAEs	0	1 (7)	1 (5)	1 (17)
Treatment-related SAEs	0	0	0	0
AE with action taken as permanent study drug discontinuation[a]	0	1 (7)	1 (5)	2 (33)
AEs leading to death	0	0	0	0

All AEs were treatment emergent unless otherwise stated.
[a]None of the AEs leading to drug discontinuation were treatment related.
AE, adverse event.

- Overall, 5/6 (83%) of patients on placebo and 15/21 (71%) of patients on seladelpar experienced an AE (**Table 2**)
- SAEs occurred in 1/6 (17%) patients on placebo and 1/21 (5%) patients on seladelpar; all were deemed unrelated to the study drug
- Of those randomised to placebo, 2/6 (33%) patients discontinued treatment due to an AE compared with 1/21 (5%) patients randomised to seladelpar

Table 3. Liver-Related Safety

Patient Incidence, n (%)	Seladelpar 5 mg (n = 6)	Seladelpar 10 mg (n = 15)	Any Seladelpar (n = 21)	Placebo (n = 6)
Liver-related AEs, total	0	3 (20)	3 (14)	2 (33)
Hepatomegaly	0	2 (13)	2 (10)	0
Ascites	0	1 (7)	1 (5)	0
Hyperbilirubinaemia	0	0	0	1 (17)
Portal hypertensive gastropathy	0	0	0	1 (17)

All AEs were treatment emergent unless otherwise stated.
These data were based on a pre-defined search strategy.
AE, adverse event.

- Incidences of liver-related AEs were similar across patients on placebo (2/6, 33%) or seladelpar (3/21, 14%); these events included hepatomegaly, ascites, hyperbilirubinaemia, and portal hypertensive gastropathy (**Table 3**)

Table 4. Liver-Related Laboratory Abnormalities Reported Postbaseline

Patient Incidence, n (%)	Seladelpar 5 mg (n = 6)	Seladelpar 10 mg (n = 15)	Any Seladelpar (n = 21)	Placebo (n = 6)
Any liver-related laboratory abnormality[a]	0	1 (7)	1 (5)	2 (33)
ALT or AST >3 × ULN	0	1 (7)	1 (5)	2 (33)
TB >2 × ULN	0	0	0	2 (33)

[a]Patients who met any of the individual subcategories at any postbaseline time point.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; ULN, upper limit of normal.

- Liver-related laboratory abnormalities occurred in 2/6 (33%) placebo-treated patients and 1/21 (5%) seladelpar-treated patients (**Table 4**)
  - Of those with liver-related laboratory abnormalities, 1 patient randomised to placebo discontinued treatment (due to hyperbilirubinaemia)