Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis and Elevated Bilirubin at Baseline in the Phase 3 Placebo-Controlled RESPONSE Trial

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Conclusions

- This analysis evaluates the biochemical response and safety of seladelpar in patients with primary biliary cholangitis (PBC) who had elevated total bilirubin at baseline in the RESPONSE trial
- Among this subgroup, 50% achieved the composite biochemical response after 12 months of treatment
- Reductions in alkaline phosphatase were comparable to those observed in patients with normal baseline total bilirubin, and improvements in gamma-glutamyl transferase and alanine aminotransferase with seladelpar were also noted
- Mean percent change in total bilirubin was similar between seladelpar and placebo regardless of total bilirubin level at baseline, although the number of patients with elevated total bilirubin in the placebo arm was small
- Among 20 patients with elevated total bilirubin at baseline who received seladelpar, 70% of patients reached normalization of total bilirubin by 12 months
- Overall, seladelpar was well tolerated and appeared safe in patients with PBC, regardless of their baseline total bilirubin levels

Plain Language Summary

- Primary biliary cholangitis (PBC) is a long-term liver disease that gets worse over time
- Bilirubin is a substance that doctors measure to see how well a person's liver is working
- People with PBC may have high levels of bilirubin in their blood, which can mean that their liver is not working as well as it should
- Seladelpar is a drug used to treat people with PBC
- This analysis showed how well seladelpar worked and how safe it was in people with PBC based on their levels of bilirubin at the beginning of the study
- Seladelpar helped to improve measures of liver disease in people with PBC regardless of whether their bilirubin level was high or normal at the beginning of the study
- Overall, seladelpar appeared safe and well tolerated regardless of bilirubin level before receiving seladelpar

References: **1.** European Association for the Study of the Liver. *J Hepatol.* 2017;67(1):145-72. **2.** Murillo Perez CF, et al. *Am J Gastroenterol.* 2020;115(7):1068-74. **3.** Livdelzi. US prescribing information. Gilead Sciences, Inc.; 2024. **4.** Livdelzi. UK summary of product characteristics. Gilead Sciences, Inc.; 2024. **5.** Lyvdelzi. EMA prescribing information. Gilead Sciences, Inc.; 2025. **6.** Hirschfield GM, et al. *N Engl J Med.* 2024;390(9):783-94.

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

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]
- Elevated total bilirubin in patients with PBC is an indicator of progressive disease and worse prognosis[2]
- 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[3–5]
- In the Phase 3, placebo-controlled RESPONSE trial (NCT04620733), seladelpar significantly improved biomarkers of cholestasis and pruritus vs placebo in patients with PBC over 12 months[6]

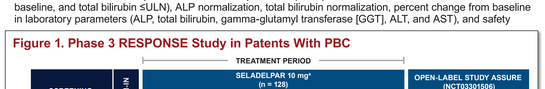
Objective

- Here, we report efficacy and safety in prespecified subgroups of patients with total bilirubin >1 × the upper limit of normal (ULN; elevated total bilirubin) or ≤1 × ULN (normal total bilirubin) at baseline in the RESPONSE trial

Methods

- Patients with PBC who had an inadequate response or intolerance to UDCA were randomized 2:1 to receive daily oral seladelpar 10 mg or placebo for 12 months (**Figure 1**)
  - Key entry criteria: Alkaline phosphatase (ALP) ≥1.67 × ULN, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN, and total bilirubin ≤2 × ULN (ULN for total bilirubin = 1.10 mg/dL)
- Prespecified subgroups of patients with total bilirubin >1 or ≤1 × ULN at baseline (elevated vs normal) were analyzed
- Outcomes included the composite biochemical response endpoint (ALP <1.67 × ULN, ALP decrease ≥15% from baseline, and total bilirubin ≤ULN), ALP normalization, total bilirubin normalization, percent change from baseline in laboratory parameters (ALP, total bilirubin, gamma-glutamyl transferase [GGT], ALT, and AST), and safety

Figure 1. Phase 3 RESPONSE Study in Patents With PBC



Primary Endpoint:
Composite response at month 12 (ALP <1.67 × ULN, ≥15% decrease in ALP, total bilirubin ≤ULN)

Key Secondary Endpoint:
- ALP normalization at month 12[b]
- Change from baseline in pruritus NRS at 6 months in patients with baseline NRS ≥4[c]

RESPONSE study: NCT04620733. Seladelpar was administered orally once daily.
[a]Study drug given as an add-on to UDCA in patients on UDCA for at least 12 months, or as monotherapy in patients intolerant to UDCA. [b]ALP normalization was defined as ALP ≤1 × ULN. [c]Pruritus data collected via e-diary on a daily basis from the run-in visit through the first 6 months of treatment, then monthly for 7 consecutive days each month until EOT.
ALP, alkaline phosphatase; EOT, end of treatment; NRS, numeric rating scale; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Results

Table 1. Demographics and Baseline Clinical Characteristics of Patients With Total Bilirubin >1 × ULN and ≤1 × ULN at Baseline

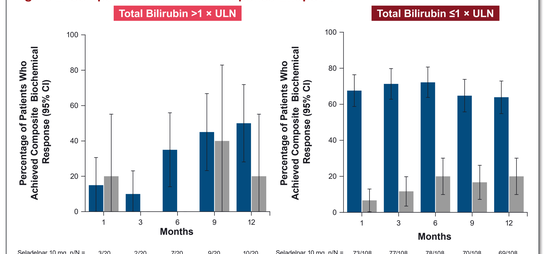
	Total Bilirubin >1 × ULN		Total Bilirubin ≤1 × ULN	
	Seladelpar 10 mg (n = 20)	Placebo (n = 5)	Seladelpar 10 mg (n = 108)	Placebo (n = 60)
Age, years, mean (SD)	52 (12.7)	60 (5.0)	57 (9.3)	57 (9.4)
Female, n (%)	19 (95)	4 (80)	104 (96)	56 (93)
Patients with cirrhosis at baseline, n (%)[a]	7 (35)	2 (40)	11 (10)	7 (12)
Portal hypertension, n (%)[b]	0	1 (50)	0	2 (29)
Child-Pugh Class A, n (%)[b]	7 (100)	2 (100)	11 (100)	7 (100)
MELD score, mean (SD)	8.1 (0.9)	8.2 (0.8)	6.5 (0.8)	6.6 (0.8)
Liver stiffness, kPa, mean (SD)	13.2 (8.5)	13.7 (6.8)	9.3 (5.6)	8.3 (3.7)
Total daily UDCA dose, mg/kg, mean (SD)	13.9 (2.2)	12.7 (0.7)	15.3 (3.2)	15.1 (3.2)
UDCA intolerance, n (%)	0	0	8 (7)	4 (7)
Previous OCA/fibrate use, n (%)	1 (5)	0	19 (18)	13 (22)
NRS ≥4, n (%)	9 (45)	2 (40)	40 (37)	21 (35)
ALP, U/L, mean (SD)[c]	384 (147.5)	399 (185.1)	302 (114.0)	307 (109.7)
Total bilirubin, mg/dL, mean (SD)[d]	1.35 (0.24)	1.48 (0.34)	0.66 (0.18)	0.68 (0.21)
<0.6 × ULN, n (%)	0	0	59 (55)	32 (53)
Direct bilirubin, mg/dL, mean (SD)[e]	0.50 (0.20)	0.52 (0.25)	0.19 (0.09)	0.19 (0.10)
GGT, U/L, mean (SD)[f]	307 (298.1)	510 (457.2)	262 (228.7)	269 (221.1)
ALT, U/L, mean (SD)[g]	57.1 (22.1)	70.2 (32.0)	45.7 (23.4)	46.4 (21.2)
AST, U/L, mean (SD)[h]	47.7 (12.5)	57.1 (19.1)	38.1 (16.3)	40.4 (15.2)
Albumin, g/dL, mean (SD)	4.1 (0.2)	4.1 (0.3)	4.2 (0.3)	4.1 (0.2)
INR, mean (SD)	1.1 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)

[a]In this analysis, cirrhosis was defined as a 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 × 10⁹ cells/µL with a serum albumin level <3.5 g/dL or an INR >1.3 (not due to antithrombotic agent use); or a total bilirubin level >1 × ULN, the presence of radiologic evidence of cirrhosis (a nodular liver) with concurrent splenomegaly, or clinical determination by the investigator. [b]Percentage of patients with cirrhosis. [c]The ULN for ALP is 110 U/L in men and women. [d]The ULN for total bilirubin is 1.10 mg/dL in men and women. [e]The ULN for direct bilirubin is 0.30 mg/dL in men and women. [f]The ULN for GGT is 52 U/L in men and 38 U/L in women. [g]The ULN for ALT is 41 U/L in men and women. [h]The ULN for AST is 34 U/L in men and women.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; MELD, model for end-stage liver disease; NRS, numeric rating scale; OCA, obeticholic acid; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

- Of the 193 patients in RESPONSE, 128 received seladelpar and 65 received placebo
  - A total of 25 patients (13%; 20 seladelpar, 5 placebo) had elevated total bilirubin at baseline
- Patients with elevated total bilirubin at baseline had higher mean ALP (seladelpar, 384 U/L; placebo, 399 U/L) and higher rates of cirrhosis (seladelpar, 35% [7/20]; placebo, 40% [2/5]) at baseline compared with patients with normal total bilirubin at baseline (ALP: seladelpar, 302 U/L; placebo, 307 U/L; cirrhosis: seladelpar, 10% [11/108]; placebo, 12% [7/60]; **Table 1**)

Results

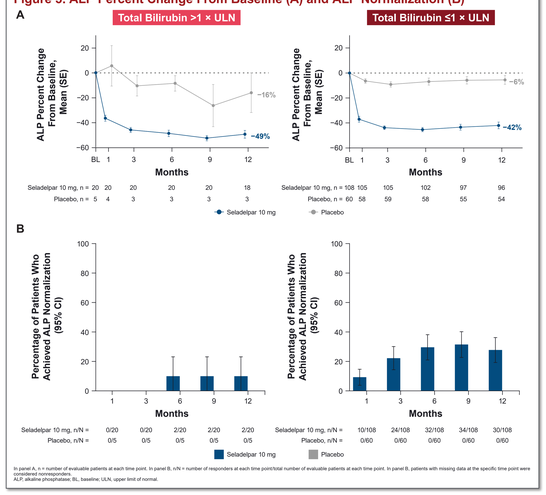
Figure 2. Composite Biochemical Response Endpoint



n/N = number of responders at each time point/total number of evaluable patients at each time point. The composite biochemical response endpoint included ALP <1.67 × ULN, ALP decrease ≥15% from baseline, and total bilirubin ≤ULN. Patients with missing data at the specific time point were considered nonresponders.
ALP, alkaline phosphatase; ULN, upper limit of normal.

- At 12 months, 50% (10/20) of patients receiving seladelpar with elevated total bilirubin at baseline achieved the composite biochemical response endpoint compared with 20% (1/5) of patients receiving placebo; 64% (69/108) of patients receiving seladelpar with normal total bilirubin at baseline achieved the composite biochemical response endpoint compared with 20% (12/60) of those on placebo (**Figure 2**)

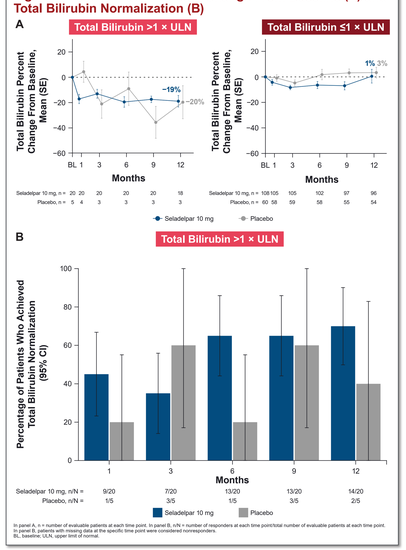
Figure 3. ALP Percent Change From Baseline (A) and ALP Normalization (B)



In panel A, n = number of evaluable patients at each time point. In panel B, n/N = number of responders at each time point/total number of evaluable patients at each time point. In panel B, patients with missing data at the specific time point were considered nonresponders.
ALP, alkaline phosphatase; BL, baseline; ULN, upper limit of normal.

- At 12 months, mean percent change in ALP with seladelpar was similar in patients with or without elevated total bilirubin (−49% and −42%, respectively); this magnitude of reduction was not seen in either subgroup of patients who received placebo (elevated total bilirubin, −16%; normal total bilirubin, −6%; **Figure 3A**)
- Among patients who received seladelpar, 10% (2/20) with elevated total bilirubin at baseline achieved ALP normalization at 12 months, as did 28% (30/108) with normal total bilirubin at baseline; no patient receiving placebo demonstrated ALP normalization regardless of baseline total bilirubin level (**Figure 3B**)

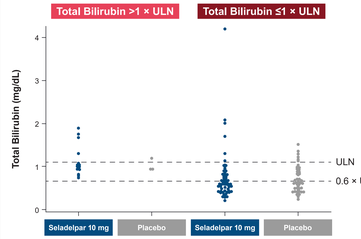
Figure 4. Total Bilirubin Percent Change From Baseline (A) and Total Bilirubin Normalization (B)



In panel A, n = number of evaluable patients at each time point. In panel B, n/N = number of responders at each time point/total number of evaluable patients at each time point.
BL, baseline; ULN, upper limit of normal.

- Mean percent change in total bilirubin was similar between seladelpar and placebo in both subgroups (**Figure 4A**), although standard errors were wide for the placebo group with elevated total bilirubin
- Among patients with elevated total bilirubin at baseline, 70% (14/20) receiving seladelpar achieved total bilirubin normalization at 12 months compared with 40% (2/5) receiving placebo (**Figure 4B**)

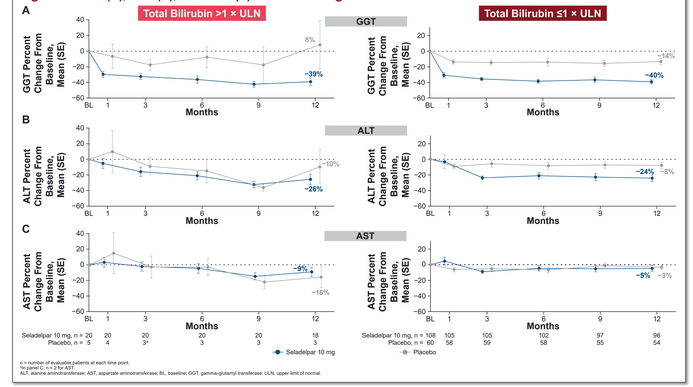
Figure 5. Absolute Total Bilirubin at Month 12 Among Patients With Total Bilirubin >1 × ULN and ≤1 × ULN at Baseline



ULN, upper limit of normal.

- No patients with elevated total bilirubin at baseline achieved a value <0.6 × ULN at 12 months. Among patients with normal total bilirubin at baseline, 62% (67/108) who received seladelpar reached total bilirubin <0.6 × ULN at 12 months compared with 50% (30/60) who received placebo (**Figure 5**)

Figure 6. GGT (A), ALT (B), and AST (C) Percent Change From Baseline



n = number of evaluable patients at each time point.
*In panel C, n = 2 for AST.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; GGT, gamma-glutamyl transferase; ULN, upper limit of normal.

- Decreases in GGT were observed with seladelpar regardless of baseline total bilirubin level (**Figure 6A**)
- In the elevated total bilirubin group, ALT percent change was similar for seladelpar and placebo (**Figure 6B**)
- AST remained relatively stable through 12 months across both treatment groups regardless of baseline total bilirubin level (**Figure 6C**)
- Interpretation of the efficacy data is limited by the small number of placebo patients with elevated total bilirubin at baseline

Table 2. Overall Safety Among Patients With Total Bilirubin >1 × ULN and ≤1 × ULN at Baseline

	Total Bilirubin >1 × ULN		Total Bilirubin ≤1 × ULN	
Patient Incidence, n (%)	Seladelpar 10 mg (n = 20)	Placebo (n = 5)	Seladelpar 10 mg (n = 108)	Placebo (n = 60)
Any AE	19 (95)	5 (100)	92 (85)	50 (83)
Grade ≥3 AEs (per CTCAE)	3 (15)	1 (20)	11 (10)	4 (7)
SAEs	2 (10)	1 (20)	7 (6)	3 (5)
Treatment-related SAEs	0	0	0	0
AEs leading to treatment discontinuation	1 (5)[a]	1 (20)[b]	3 (3)[c]	2 (3)[d]
AEs leading to death	0	0	0	0

All AEs listed are treatment emergent unless otherwise stated.
[a]One patient experienced a grade 3 SAE of coagulopathy attributed to rifampicin. [b]One patient experienced a grade 2 AE of overlap syndrome. [c]One patient experienced a grade 2 AE of disease progression (adjudicated by the CERC as not indicative of drug-induced liver injury), 1 patient experienced a grade 1 AE of increased liver function test (adjudicated by the CERC as not indicative of drug-induced liver injury), and 1 patient experienced a grade 3 SAE of papillary thyroid cancer. [d]One patient experienced a grade 2 AE of hypertriglyceridemia, and 1 patient experienced a grade 4 SAE of suicide attempt.
AE, adverse event; CERC, critical event review committee; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious AE; ULN, upper limit of normal.

- Adverse events (AEs) were reported in 95% and 85% of patients who received seladelpar with elevated total bilirubin and normal total bilirubin at baseline, respectively, with similar percentages seen in the placebo group (**Table 2**)
- No treatment-related serious AEs or deaths were reported

Table 3. Liver-Related AEs Among Patients With Total Bilirubin >1 × ULN and ≤1 × ULN at Baseline

	Total Bilirubin >1 × ULN		Total Bilirubin ≤1 × ULN	
Patient Incidence, n (%)	Seladelpar 10 mg (n = 20)	Placebo (n = 5)	Seladelpar 10 mg (n = 108)	Placebo (n = 60)
AEs potentially reflecting liver-related toxicity[a]	1 (5)	1 (20)	7 (6)	5 (8)
Hepatic cirrhosis	0	0	3 (3)[b]	1 (2)
Blood bilirubin increased	0	0	1 (1)	1 (2)
Liver function test increased	0	0	1 (1)	1 (2)
Ascites	0	0	1 (1)[b]	0
Drug-induced liver injury[c]	0	0	1 (1)	0
Hepatic lesion	0	0	1 (1)	0
Hepatomegaly	1 (5)	0	0	0
Hyperbilirubinemia	0	0	0	1 (2)
Nonalcoholic fatty liver disease	0	0	0	1 (2)
Esophageal varices hemorrhage	0	0	1 (1)	0
Portal hypertensive gastropathy	0	1 (20)	0	0

All AEs listed are treatment emergent.
[a]Liver-related AEs were identified by a predefined search strategy. [b]One patient experienced both hepatic cirrhosis and ascites. [c]The drug-induced liver injury event was assessed as related to a concomitant medication (amoxicillin without clavulanic acid) and not related to the study drug; study drug was interrupted, but subsequently, the patient was able to resume study drug and complete the treatment period.
AE, adverse event; ULN, upper limit of normal.

- The overall rates of liver-related AEs were similar (normal total bilirubin group) or lower (elevated total bilirubin group) in the seladelpar arm vs the placebo arm (**Table 3**)
- AEs potentially reflecting liver-related toxicity occurred in 5% (1/20) and 20% (1/5) of patients receiving seladelpar vs placebo, respectively, among those who had elevated total bilirubin at baseline
- Among patients with normal total bilirubin at baseline, AEs potentially reflecting liver-related toxicity occurred in 6% (7/108) and 8% (5/60) of patients receiving seladelpar and placebo, respectively
- All liver-related AEs reported in the seladelpar group were grade ≤2 in severity, with the exception of one grade 3 event of variceal hemorrhage in a patient with cirrhosis at baseline; details of this case have been previously published[6]