Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis and Risk Factors for Progression Including Younger Age at Diagnosis or Higher Liver Stiffness in the Pivotal RESPONSE Study

SAT-363

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Immune-Mediated and Cholestatic Disease: Clinical Aspects

Conclusions

- Seladelpar led to similar efficacy, including alkaline phosphatase (ALP) declines and pruritus improvement, in patients with or without risk factors for primary biliary cholangitis (PBC) disease progression
- With the recent evidence highlighting the importance of achieving ALP normalisation in these high-risk populations,[1] these results suggest seladelpar may help patients reach treatment goals
- Seladelpar also appeared overall safe and well tolerated in the high-risk populations evaluated here
- Overall, these results suggest that seladelpar may benefit patients with PBC across clinical risk levels

Plain Language Summary

- Those diagnosed with PBC at a younger age (<45 years) and those with higher liver stiffness values are at higher risk for worsening PBC
- Here, we explored the effects of seladelpar in these high-risk subpopulations
- This study showed that seladelpar, a drug used to treat PBC, was both effective and safe in patients at a higher risk

References: **1.** Corpechot C, et al. *Hepatol.* 2024 Jan 1;79(1):39-48. **2.** European Association for the Study of the Liver. *J Hepatol.* 2017;67(1):145-72. **3.** Lindor KD, et al. *Hepatology.* 2019;69(1):394-419. **4.** Martini F, et al. *J Clin Med.* 2023;12:5713. **5.** Corpechot C, et al. *J Hepatol.* 2022;77:1545-53. **6.** Corpechot C, et al. *Hepatology.* 2012;56:198-208. **7.** Corpechot C, et al. *Hepatology.* 2024;79:39-48. **8.** Livdelzi. US prescribing information. Gilead Sciences, Inc.; 2024. **9.** Livdelzi. UK summary of product characteristics. Gilead Sciences, Inc.; 2024. **10.** Lyvdelzi. EMA prescribing information. Gilead Sciences, Inc.; 2025. **11.** Hirschfield GM, et al. *N Engl J Med.* 2024;390:783-94.

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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[2]
- Earlier age of PBC onset is associated with worse prognosis,[2,3] with younger age at diagnosis (Dx) linked to increased mortality rates[4]
- Liver stiffness measurement (LSM) has emerged as a valuable noninvasive tool for risk stratification in PBC, with higher baseline LSM at treatment initiation associated with worse long-term outcomes[5-7]
- 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[8-10]
- In the Phase 3 RESPONSE trial (NCT04620733), seladelpar significantly improved cholestasis biomarkers and pruritus compared with placebo in patients with PBC[11]

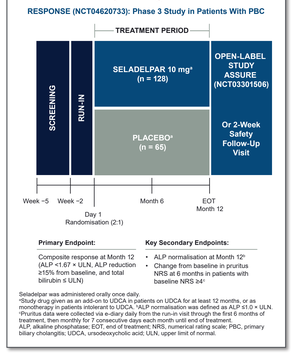
Objective

- To investigate the efficacy and safety of seladelpar in 2 high-risk subgroups of patients with PBC in the RESPONSE trial

Methods

- Patients with PBC were randomised 2:1 to receive daily oral seladelpar 10 mg or placebo for 12 months (**Figure 1**); detailed study design has been previously presented[11]
- Two high-risk subgroups were defined post hoc:
  - Age <45 years vs ≥45 years at PBC Dx (younger age at PBC Dx and older age at PBC Dx, respectively)
  - LSM ≥10 kPa vs <10 kPa at study entry (higher LSM at baseline and lower LSM at baseline, respectively)
- Efficacy endpoints at Month 12 included composite biochemical response (alkaline phosphatase [ALP] <1.67 × upper limit of normal [ULN], ALP reduction ≥15% from baseline, and total bilirubin ≤ ULN), ALP normalisation, deep response (ALP ≤ ULN and total bilirubin ≤ ULN), mean percent changes in ALP and additional parameters of interest (total bilirubin, alanine aminotransferase, aspartate aminotransferase [ALT], and gamma-glutamyl transferase [GGT]), and changes in pruritus numerical rating scale (NRS) in patients with moderate to severe pruritus, defined as NRS ≥4 at baseline in RESPONSE
- Safety was also assessed

Figure 1. Study Design



Results

- Among 193 patients enrolled, 65 were aged <45 years at Dx (seladepar, n = 40; placebo, n = 25) and 52 had a baseline LSM ≥10 kPa (seladelpar, n = 36; placebo, n = 16)
- Patients diagnosed at a younger age had numerically higher cirrhosis rates (17% vs 13%) and similar ALP levels (316 vs 313 U/L) at baseline, compared with patients diagnosed at an older age, at the subgroup level
  - Within patients aged <45 years at Dx, those who were randomised to seladelpar had numerically higher mean LSM, mean ALP, and rates of cirrhosis at baseline compared with the placebo arm (**Table 1A**)
- Patients with baseline LSM ≥10 kPa had higher cirrhosis rates (44% vs 2%), and higher baseline ALP (350 vs 300 U/L) compared with patients with LSM <10 kPa, at the subgroup level
  - Within the LSM ≥10 kPa high-risk subgroup, patients randomised to seladelpar had numerically higher mean LSM (16.6 vs 14.6 kPa) and similar rates of cirrhosis compared with the placebo arm (**Table 1B**)

Table 1. Baseline Characteristics by (A) Age and (B) LSM

A

	Younger Age (<45 years) at PBC Dx (N = 65)		Older Age (≥45 years) at PBC Dx (N = 128)	
	Seladelpar 10 mg (n = 40)	Placebo (n = 25)	Seladelpar 10 mg (n = 88)	Placebo (n = 40)
Age, years, mean (SD)	47.5 (8.8)	48.6 (6.5)	60.7 (7.5)	62.3 (6.2)
Female, n (%)	38 (95)	25 (100)	85 (97)	35 (88)
Patients with cirrhosis at BL, n (%)	8 (20)	3 (12)	10 (11)	6 (15)
Child-Pugh Class A, n (%) of patients with cirrhosis	8 (100)	3 (100)	10 (100)	6 (100)
LSM, kPa, mean (SD)[a]	11.2 (7.8)	8.4 (3.0)	9.3 (5.2)	9.0 (4.8)
ALP, U/L, mean (SD)[b]	322.6 (101.3)	305.7 (96.0)	310.9 (132.0)	318.9 (130.3)
ALP ≥350 U/L, n (%)	17 (43)	6 (24)	18 (20)	12 (30)
ALT, U/L, mean (SD)[c]	61.1 (21.4)	54.4 (21.2)	41.3 (21.8)	44.4 (23.2)
AST, U/L, mean (SD)[d]	47.4 (14.7)	45.0 (16.6)	36.1 (15.6)	39.6 (15.5)
GGT, U/L, mean (SD)[e]	282.0 (167.4)	255.9 (172.9)	263.1 (267.3)	307.3 (287.7)
Total bilirubin, mg/dL, mean (SD)[f]	0.83 (0.34)	0.71 (0.35)	0.74 (0.30)	0.76 (0.29)
Pruritus NRS, mean (SD)	4.0 (2.9)	3.1 (2.8)	2.6 (2.7)	2.9 (3.1)
Pruritus NRS level ≥4, n (%)	20 (50)	10 (40)	29 (33)	13 (33)

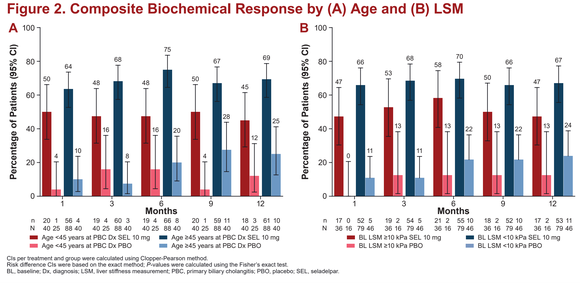
B

	Higher LSM (≥10 kPa) at Baseline (N = 52)		Lower LSM (<10 kPa) at Baseline (N = 125)	
	Seladelpar 10 mg (n = 36)	Placebo (n = 16)	Seladelpar 10 mg (n = 79)	Placebo (n = 46)
Age, years, mean (SD)	55.9 (12.4)	54.8 (9.2)	57.1 (9.1)	57.6 (9.1)
Female, n (%)	35 (97)	13 (81)	76 (96)	45 (98)
Patients with cirrhosis at BL, n (%)	16 (44)	7 (44)	1 (1)	2 (4)
Child-Pugh Class A, n (%) of patients with cirrhosis	16 (100)	7 (100)	1 (100)	2 (100)
LSM, kPa, mean (SD)[a]	16.6 (6.9)	14.6 (3.7)	6.8 (1.8)	6.7 (1.6)
ALP, U/L, mean (SD)[b]	338.3 (143.1)	374.9 (135.7)	304.1 (112.9)	292.2 (108.2)
ALP ≥350 U/L, n (%)	11 (31)	8 (50)	19 (24)	10 (22)
ALT, U/L, mean (SD)[c]	53.2 (25.4)	55.3 (22.1)	45.3 (22.6)	45.4 (23.1)
AST, U/L, mean (SD)[d]	46.9 (17.8)	48.6 (14.9)	36.5 (14.7)	38.5 (14.9)
GGT, U/L, mean (SD)[e]	298.2 (173.0)	394.0 (277.1)	240.6 (238.3)	240.7 (208.1)
Total bilirubin, mg/dL, mean (SD)	0.87 (0.28)	0.90 (0.33)	0.69 (0.27)	0.68 (0.29)
Pruritus NRS, mean (SD)	4.3 (3.1)	3.5 (2.9)	2.5 (2.6)	2.9 (3.0)
Pruritus NRS level ≥4, n (%)	19 (53)	7 (44)	24 (30)	15 (33)

BL was defined as the last nonmissing assessment evaluated prior to the first administration of the study drug.
Among all patients, panel B includes the patient characteristics in 177 patients with LSM collected at baseline
[a]Scores range from 1.5 to 75 (measured in kPa) with higher scores indicating greater liver stiffness. [b]The ULN is 116 U/L. [c]The ULN is 41 U/L. [d]The ULN is 32 U/L in men and 38 U/L in women. [e]The ULN is 110 mg/dL.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; Dx, diagnosis; GGT, gamma-glutamyl transferase; LSM, liver stiffness measurement; NRS, numerical rating scale; PBC, primary biliary cholangitis; ULN, upper limit of normal.

- Seladelpar led to a composite biochemical response in a substantial proportion of patients with PBC regardless of their age at Dx (**Figure 2A**)
  - In both the younger and older age at PBC Dx subgroups, the risk difference (95% CI) of composite biochemical response at Month 12 favoured seladelpar over placebo at 33% (6, 52; *P* = .0066) and 44% (25, 60; *P* <.0001)
- Seladelpar led to a composite biochemical response in a substantial proportion of patients with PBC regardless of baseline LSM (**Figure 2B**)
  - In both the higher and lower LSM at baseline subgroups, the risk difference (95% CI) of composite biochemical response at Month 12 favoured seladelpar over placebo at 35% (2, 56; *P* = .0273) and 43% (25, 58; *P* <.0001)

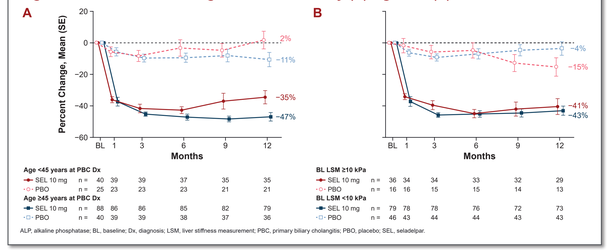
Figure 2. Composite Biochemical Response by (A) Age and (B) LSM



CIs per treatment and group were calculated using Clopper-Pearson method.
Risk difference CIs were based on the exact method; *P*-values were calculated using the Fisher's exact test.
BL, baseline; Dx, diagnosis; LSM, liver stiffness measurement; PBC, primary biliary cholangitis; PBO, placebo; SEL, seladelpar.

- Seladelpar led to a significant decline in ALP in patients with PBC regardless of their age at Dx or baseline LSM compared to placebo (**Figure 3**)

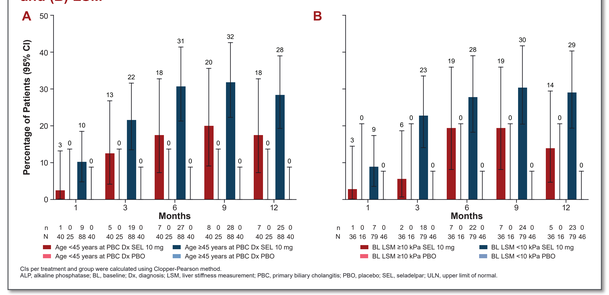
Figure 3. ALP Percent Change From Baseline by (A) Age and (B) LSM



ALP, alkaline phosphatase; BL, baseline; Dx, diagnosis; LSM, liver stiffness measurement; PBC, primary biliary cholangitis; PBO, placebo; SEL, seladelpar.

- Across different criteria of high risk, seladelpar led to marked and sustained deep response up to Month 12 (**Figure 4**)

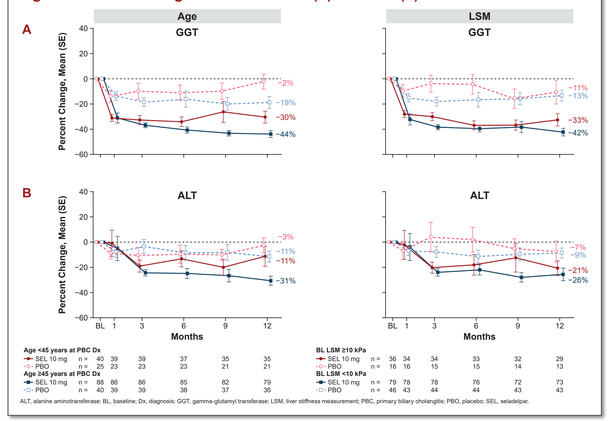
Figure 4. Deep Response (ALP and Total Bilirubin Normalisation) by (A) Age and (B) LSM



CIs per treatment and group were calculated using Clopper-Pearson method.
ALP, alkaline phosphatase; BL, baseline; Dx, diagnosis; LSM, liver stiffness measurement; PBC, primary biliary cholangitis; PBO, placebo; SEL, seladelpar; ULN, upper limit of normal.

- Seladelpar treatment led to a greater decrease in GGT and ALT across subgroups; total bilirubin and AST remained stable through Month 12 (**Figure 5**)

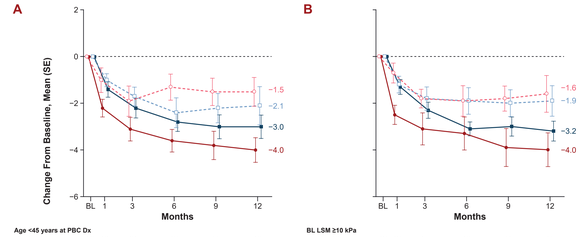
Figure 5. Percent Change From Baseline in (A) GGT and (B) ALT



ALT, alanine aminotransferase; BL, baseline; Dx, diagnosis; GGT, gamma-glutamyl transferase; LSM, liver stiffness measurement; PBC, primary biliary cholangitis; PBO, placebo; SEL, seladelpar.

- Seladelpar led to a greater reduction in pruritus NRS in patients with moderate to severe pruritus (NRS ≥4 at baseline) regardless of their age at Dx or baseline LSM compared with placebo (**Figure 6**)

Figure 6. Change From Baseline in Pruritus NRS Weekly Averages in Patients With Moderate to Severe Pruritus (NRS ≥4 at Baseline) by (A) Age and (B) LSM



BL, baseline; Dx, diagnosis; LSM, liver stiffness measurement; NRS, numerical rating scale; PBC, primary biliary cholangitis; PBO, placebo; SEL, seladelpar.

- No treatment-related serious adverse events (AEs) were reported in any patients; incidence of liver-, muscle-, and renal-related AEs (per a pre-defined search algorithm) were similar or lower with seladelpar vs placebo regardless of subgroup evaluated (**Table 2**)

Table 2. Overall Safety by (A) Age and (B) LSM

A

	Younger Age (<45 years) at PBC Dx (N = 65)		Older Age (≥45 years) at PBC Dx (N = 128)	
Patient Incidence, n (%)	Seladelpar 10 mg (n = 40)	Placebo (n = 25)	Seladelpar 10 mg (n = 88)	Placebo (n = 40)
Any AE	36 (90)	24 (96)	75 (85)	31 (78)
Grade ≥3 AEs (per CTCAE)	3 (8)	2 (8)	11 (13)	3 (8)
SAEs	2 (5)	2 (8)	7 (8)	2 (5)
Treatment-related SAEs	0	0	0	0
AEs leading to treatment discontinuation	3 (8)	2 (8)	1 (1)	1 (3)
AEs leading to death	0	0	0	0
AEs of Interest				
Liver-related AEs	3 (8)	2 (8)	5 (6)	4 (10)
Muscle-related AEs	3 (8)	2 (8)	5 (6)	3 (8)
Renal-related AEs	0	0	0	0

B

	Higher LSM (≥10 kPa) at Baseline (N = 52)		Lower LSM (<10 kPa) at Baseline (N = 125)	
Patient Incidence, n (%)	Seladelpar 10 mg (n = 36)	Placebo (n = 16)	Seladelpar 10 mg (n = 79)	Placebo (n = 46)
Any AE	32 (89)	14 (88)	69 (87)	38 (83)
Grade ≥3 AEs (per CTCAE)	3 (8)	2 (13)	7 (9)	3 (7)
SAEs	3 (8)	1 (6)	4 (5)	2 (4)
Treatment-related SAEs	0	0	0	0
AEs leading to treatment discontinuation	1 (3)	2 (13)	2 (3)	1 (2)
AEs leading to death	0	0	0	0
AEs of Interest				
Liver-related AEs	3 (8)	4 (25)	5 (6)	1 (2)
Muscle-related AEs	2 (6)	2 (13)	5 (6)	3 (7)
Renal-related AEs	0	0	0	0

All AEs listed were treatment emergent unless otherwise stated. AEs of interest determined by a pre-defined search strategy.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; Dx, diagnosis; LSM, liver stiffness measurement; PBC, primary biliary cholangitis; SAE, serious AE.

Limitations

- This was a post hoc analysis and was not designed or powered to compare subgroups with limited sample size
- Liver stiffness measurements were collected through local read as an exploratory endpoint
- Follow-up was limited up to 1 year