Efficacy and Safety of Seladelpar vs Placebo in Patients With Primary Biliary Cholangitis and Metabolic Syndrome in the Pivotal Phase 3 RESPONSE Study

SAT-362

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Immune-Mediated and Cholestatic Disease: Clinical Aspects

Conclusions

- Metabolic syndrome was a frequently observed comorbidity (22%) in patients with primary biliary cholangitis (PBC) enrolled in the RESPONSE study
- The efficacy and safety profile of seladelpar appeared similar in patients with and without metabolic syndrome
- Further studies are needed to better understand the efficacy and safety of seladelpar and other PBC treatment options in patients with PBC and coexisting metabolic syndrome or hepatic steatosis, as well as the impact of these conditions on the management of PBC

Plain Language Summary

- Primary biliary cholangitis (PBC) is a long-term liver disease that gets worse over time
- Many people with PBC also have metabolic syndrome—a group of conditions that increase the risk of heart disease, liver disease due to excess fat buildup in the liver, and other serious health problems and which may be associated with more severe PBC
- Seladelpar is a drug used to treat people with PBC
- This analysis looked at how well seladelpar worked and how safe it was in people with PBC based on whether they also had metabolic syndrome at the beginning of the study
- Seladelpar helped to improve markers of liver disease in people with PBC with and without metabolic syndrome
- Overall, seladelpar appeared safe in patients with and without metabolic syndrome

References: **1.** European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-72. **2.** Lindor KD, et al. *Hepatology*. 2019;69(1):394-419. **3.** Floreani A, et al. *J Clin Gastroenterol*. 2015;49(1):57-60. **4.** Tanaka A, et al. *Lancet*. 2024;404:1053-66. **5.** Hérnandez-Pérez M, et al. *Aliment Pharmacol Ther*. 2024;60:613-9. **6.** Rinella ME, et al. *Hepatology*. 2023;78:1966-86. **7.** Livdelzi. US prescribing information. Gilead Sciences, Inc.; 2025. **8.** Livdelzi. UK summary of product characteristics. Gilead Sciences, Inc.; 2024. **9.** Lyvdelzi. EMA prescribing information. Gilead Sciences, Inc.; 2025. **10.** Hirschfield GM, et al. *N Engl J Med*. 2024;390(9):783-94. **11.** National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation*. 2002;106(25):3143.

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Introduction

- Primary biliary cholangitis (PBC) is a chronic, autoimmune, cholestatic liver disease associated with progressive liver injury and significant symptom burden[1,2]
- Metabolic-associated steatotic liver disease (MASLD), which is diagnosed based on the presence of hepatic steatosis plus any of the criteria for metabolic syndrome, is associated with poorer prognosis in patients with PBC[3,4]
- The true prevalence of MASLD in patients with PBC is unknown
  - PBC diagnosis is often based on abnormal liver biochemical test results and does not require biopsy, and MASLD has historically been underdiagnosed due to heterogenous presentation[2-5]
- Approximately 20% to 30% of patients with PBC have concomitant metabolic syndrome and are therefore at risk for MASLD[5,6]
- 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[7-9]
- In the pivotal Phase 3, placebo-controlled RESPONSE study (NCT04620733), seladelpar significantly improved biomarkers of cholestasis and pruritus compared with placebo in patients with PBC over 12 months[10]

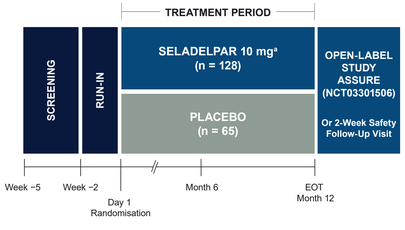
Objective

- To evaluate the efficacy and safety of seladelpar in patients with PBC and evidence of concurrent metabolic syndrome, which reflects clinical risk factors commonly associated with MASLD, in the RESPONSE study

Methods

- Patients with PBC who had an inadequate response or intolerance to UDCA were randomised 2:1 to receive daily oral seladelpar 10 mg or placebo for 12 months (**Figure 1**)
  - Key entry criteria: alkaline phosphatase (ALP) ≥1.67 × the upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN, and total bilirubin ≤2 × ULN
- Medical history was collected at baseline
  - Patients with confirmed metabolic dysfunction-associated steatohepatitis (MASH) were excluded; MASLD was not exclusionary; presence or absence of hepatic steatosis was not formally collected at study entry
- In this post hoc subgroup analysis, patients were classified as having metabolic syndrome at baseline if they met 3 of the following criteria (adapted from the National Cholesterol Education Program Adult Treatment Panel III guidelines):[11]
  - Body mass index (BMI) >27.6 kg/m^2
  - Triglycerides ≥150 mg/dL
  - High-density lipoprotein <40 mg/dL in males or <50 mg/dL in females
  - Elevated blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic) or current treatment for hypertension
  - Fasting glucose ≥100 mg/dL or current treatment for diabetes
- Efficacy endpoints included composite biochemical response (ALP <1.67 × ULN, total bilirubin ≤ ULN, and ALP reduction ≥15% from baseline), ALP normalisation, and changes from baseline in laboratory parameters (ALP, total bilirubin, gamma-glutamyl transferase [GGT], ALT, and AST) at Month 12
- Safety was assessed by the incidence and severity of adverse events (AEs) and by changes in laboratory parameters

Figure 1. RESPONSE Study Design



Primary Endpoint:

Composite response at Month 12 (ALP <1.67 × ULN, ALP reduction ≥15% from baseline, and total bilirubin ≤ ULN)

Key Secondary Endpoints:

- ALP normalisation at month 12[b]
- Change from baseline in pruritus NRS at 6 months in patients with baseline NRS ≥4[c]

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 normalisation was defined as ALP ≤1.0 × 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; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Results

- Of 193 patients enrolled, 42 (22%) had evidence of metabolic syndrome at baseline (**Table 1**)

Table 1. Patients With PBC and Metabolic Syndrome in the RESPONSE Study

Metabolic Syndrome Criteria Met,[a] n (%)	Metabolic Syndrome (n = 42)	
	Seladelpar 10 mg (n = 24)	Placebo (n = 18)
BMI >27.6 kg/m^2	20 (83)	15 (83)
Triglycerides ≥150 mg/dL	11 (46)	11 (61)
Low HDL[b]	8 (33)	4 (22)
Hypertension[c]	21 (88)	14 (78)
Diabetes mellitus[d]	21 (88)	16 (89)

[a]Patients must meet 3 criteria to be included, and criteria were not mutually exclusive; percentages are calculated based on which criteria each patient met. [b]Defined as <40 mg/dL in males or <50 mg/dL in females. [c]Defined as systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or medical history of hypertension and use of concomitant antihypertensive medication at study entry. [d]Defined as baseline blood glucose ≥100 mg/dL or a medical history of diabetes and concomitant medication for hyperglycaemia.
BMI, body mass index; HDL, high-density lipoprotein; PBC, primary biliary cholangitis.

- At baseline, patients with metabolic syndrome vs patients without had higher mean BMI (30.4 kg/m^2 vs 26.2 kg/m^2), ALP (324.5 U/L vs 311.5 U/L), and liver stiffness (11.5 kPa vs 8.9 kPa), and were more likely to have cirrhosis (10/42 [24%] vs 17/151 [11%]; **Table 2**)

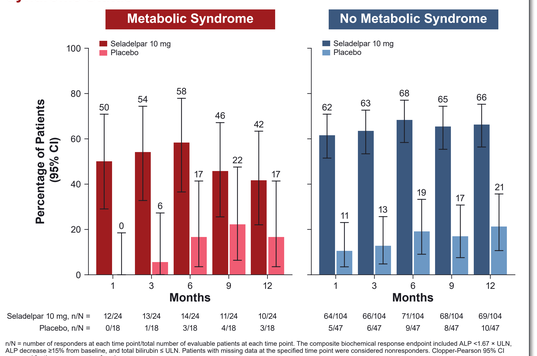
Table 2. Demographics and Baseline Characteristics by Metabolic Syndrome Status

	Metabolic Syndrome (n = 42)		No Metabolic Syndrome (n = 151)	
	Seladelpar 10 mg (n = 24)	Placebo (n = 18)	Seladelpar 10 mg (n = 104)	Placebo (n = 47)
Age, years, mean (SD)	57 (10.1)	59 (8.3)	57 (10.0)	56 (9.4)
Female, n (%)	24 (100)	14 (78)	99 (95)	46 (98)
BMI, kg/m^2, mean (SD)	30.6 (4.51)	30.3 (4.40)	26.4 (5.52)	25.5 (4.27)
Patients with cirrhosis at baseline,[a] n (%)	6 (25)	4 (22)	12 (12)	5 (11)
Child-Pugh Class A, n (%)[b]	6 (100)	4 (100)	12 (100)	5 (100)
Liver stiffness, kPa, mean (SD)	12.5 (8.91)	10.2 (5.73)	9.2 (5.18)	8.2 (3.43)
ALP, U/L, mean (SD)	341.9 (162.52)	301.2 (123.55)	308.2 (111.93)	318.7 (116.36)
ALT, U/L, mean (SD)	48.7 (26.04)	45.9 (19.84)	47.2 (22.97)	49.2 (24.01)
AST, U/L, mean (SD)	40.4 (17.40)	38.9 (15.11)	39.4 (15.92)	42.7 (16.40)
GGT, U/L, mean (SD)	338.4 (333.95)	351.7 (325.56)	253.0 (211.57)	262.9 (212.72)
Total bilirubin, mg/dL, mean (SD)	0.8 (0.31)	0.8 (0.47)	0.8 (0.32)	0.7 (0.22)

[a]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 × 10^3 cells/µL with a serum albumin level <3.5 g/dL, or an international normalised ratio >1.3 (not due to antithrombotic agent use), or a total bilirubin level >1 × upper limit of normal; 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.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase.

- Seladelpar resulted in a higher rate of the composite biochemical response endpoint than placebo, regardless of the presence of metabolic syndrome (**Figure 2**)

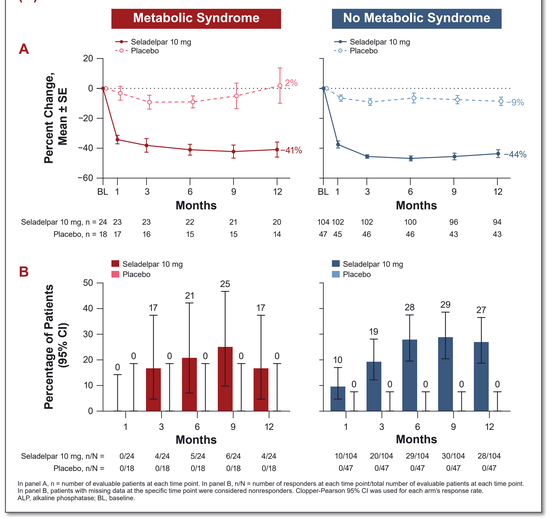
Figure 2. Composite Biochemical Response Rate by Metabolic Syndrome Status



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 specified time point were considered nonresponders. Clopper-Pearson 95% CI was used for the response rate of each arm.
ALP, alkaline phosphatase; ULN, upper limit of normal.

- At month 12, the mean percent change from baseline in ALP with seladelpar treatment was similar regardless of metabolic syndrome status (metabolic syndrome: −41%; no metabolic syndrome: −44%; **Figure 3A**); minimal change was observed in patients who received placebo
- Treatment with seladelpar resulted in generally similar rates of ALP normalisation at Month 12, regardless of metabolic syndrome status (noting 95% CIs for subgroups overlapped; **Figure 3B**)
  - No patients in the placebo arm achieved ALP normalisation at Month 12

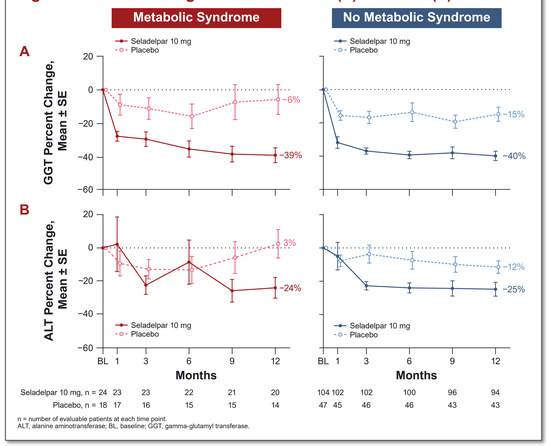
Figure 3. ALP (A) Percent Change From Baseline and (B) Normalisation Rate



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. Clopper-Pearson 95% CI was used for each arm's response rate.
ALP, alkaline phosphatase; BL, baseline.

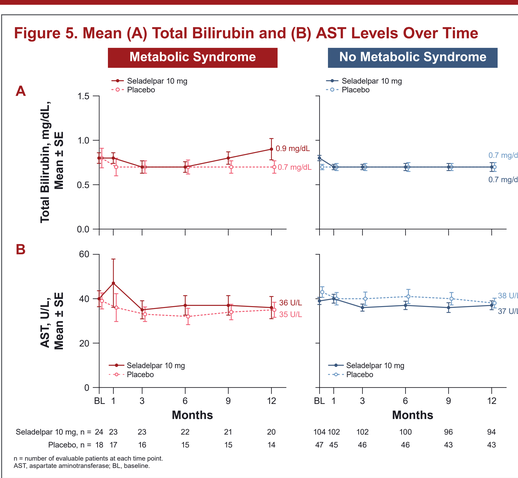
- Decreases in GGT and ALT were observed with seladelpar in patients with and without metabolic syndrome (**Figure 4**)
- Total bilirubin and AST remained overall stable across groups (**Figure 5**)

Figure 4. Percent Change From Baseline in (A) GGT and (B) ALT



n = number of evaluable patients at each time point.
ALT, alanine aminotransferase; BL, baseline; GGT, gamma-glutamyl transferase.

Figure 5. Mean (A) Total Bilirubin and (B) AST Levels Over Time



n = number of evaluable patients at each time point.
AST, aspartate aminotransferase; BL, baseline.

- The incidence of AEs, including cardiovascular and liver-related AEs, was overall similar between the seladelpar and placebo arms irrespective of metabolic syndrome presence (**Table 3**)

Table 3. Overall Safety

Patient Incidence, n (%)	Metabolic Syndrome (n = 42)		No Metabolic Syndrome (n = 151)	
	Seladelpar 10 mg (n = 24)	Placebo (n = 18)	Seladelpar 10 mg (n = 104)	Placebo (n = 47)
Any AE	22 (92)	15 (83)	89 (86)	40 (85)
Grade ≥3 AEs (per CTCAE)	1 (4)	2 (11)	13 (13)	3 (6)
SAEs	1 (4)	1 (6)	8 (8)	3 (6)
Treatment-related SAEs	0	0	0	0
AEs leading to treatment discontinuation	0	1 (6)	4 (4)	2 (4)
AEs leading to death	0	0	0	0
AEs of Interest				
Cardiovascular-related AEs	1 (4)	2 (11)	12 (12)	3 (6)
Liver-related AEs	2 (8)	4 (22)	6 (6)	2 (4)

All AEs listed were treatment emergent unless otherwise stated. AEs of interest were identified based on a prespecified search strategy.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event.

- Liver-related laboratory abnormalities were generally similar across treatment groups, regardless of metabolic syndrome status (**Table 4**)

Table 4. Liver-Related Laboratory Abnormalities

Patient Incidence, n (%)	Metabolic Syndrome (n = 42)		No Metabolic Syndrome (n = 151)	
	Seladelpar 10 mg (n = 24)	Placebo (n = 18)	Seladelpar 10 mg (n = 104)	Placebo (n = 47)
ALT or AST >3 × ULN	1 (4)	1 (6)	8 (8)	6 (13)
BL ALT and AST > ULN with post-BL ALT or AST >2 × BL	1 (4)	0	2 (2)	4 (9)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; ULN, upper limit of normal.

Limitations

- Metabolic syndrome diagnosis and hepatic steatosis data were not collected at baseline
- As there were only 42 patients with metabolic syndrome, this post hoc analysis of the RESPONSE study was not powered for statistical comparisons
- While metabolic syndrome and MASLD frequently co-occur, the diagnostic criteria are not equivalent, thus this analysis may not fully capture the effect of seladelpar in patients with MASLD