Presentation #164

Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis and Compensated Cirrhosis in the Phase 3 Placebo-Controlled RESPONSE Trial

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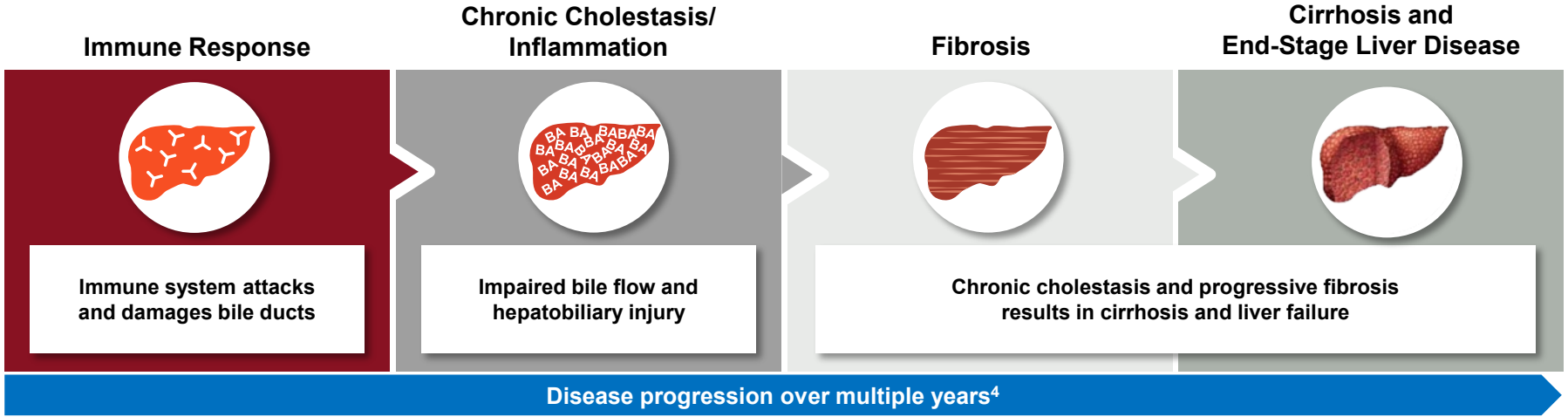
Primary Biliary Cholangitis

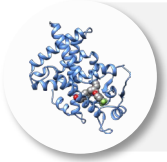
- PBC is a chronic, progressive, autoimmune, cholestatic liver disease that affects approximately 1 in 1000 women over 40 years of age[1]
- PBC can result in hepatocellular injury, fibrosis, and eventual progression to cirrhosis[2]
- There is a need for safe and efficacious second-line treatment options for patients with PBC who have progressed to cirrhosis[3]



BA, bile acids; **PBC**, primary biliary cholangitis.

1. European Association for the Study of the Liver. *J Hepatol.* 2017;67(1):145-72. 2. Cai S-Y, Boyer JL. *Ann Transl Med.* 2021;9(8):737. 3. Lindor KD, et al. *Hepatology.* 2019;69(1):394-419. 4. Selmi C, et al. *Lancet.* 2011;377(9777):1600-9.

Seladelpar: PPARδ Agonist



- **Seladelpar** is a first-in-class **delpar (selective PPARδ agonist)** targeting multiple cell types and processes in PBC[1]
- In August 2024, seladelpar was granted **accelerated approval** in the United States for the treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as a monotherapy in patients unable to tolerate UDCA[2]

Hepatocytes & Cholangiocytes	Macrophages & Kupffer Cells	Hepatocytes	Hepatocytes
Improves cholestasis	**Reduces inflammation**	**Reduces pruritus**	**Increases lipid metabolism**
↓ Bile acid synthesis[3-6]	↓ Inflammatory cytokines[6]	↓ Bile acids[4]	↓ Total cholesterol, LDL, triglycerides[3,6,9]
↓ ALP[3]	↓ Inflammatory lipid mediators[7]	↓ IL-31[8,a]	↑ Fatty acid oxidation[6,7]
↓ GGT[3]	↓ ALT[3]		

Seladelpar is a selective PPARδ agonist with anticholestatic, anti-inflammatory, and antipruritic effects[1-10]

Seladelpar X-ray crystal structure adapted from Choi Y, et al. 2021.[6] [a]Although the mechanism of pruritus in PBC is yet to be fully elucidated, reductions in IL-31 may be related to pruritus improvement, which was observed in the ENHANCE study.[8]
ALP, alkaline phosphatase; **ALT**, alanine aminotransferase; **GGT**, gamma-glutamyl transferase; **IL-31**, interleukin-31; **LDL**, low-density lipoprotein; **PBC**, primary biliary cholangitis; **PPARδ**, peroxisome proliferator–activated receptor delta; **UDCA**, ursodeoxycholic acid.
1. Hirschfield GM, et al. *N Engl J Med.* 2024;390:783-94. 2. Livdelzi (seladelpar). Prescribing information. Gilead Sciences, Inc.; 2024. 3. Hirschfield GM, et al. *Hepatology.* 2023;78(2):397-415. 4. Kremer AE, et al. *Liver Int.* 2022;42(1):112-23.
5. Kouno T, et al. *J Biol Chem.* 2022;298(7):102056. 6. Choi Y, et al. Discovery on Target 2021. Oral presentation. 7. Choi Y, et al. AASLD 2022. Poster 4731. 8. Kremer AE, et al. *Hepatology.* 2024;80(1):27-37. 9. Bowlus C, et al. AASLD 2022. Poster 4759.
10. Hirschfield G, et al. AASLD 2023. Oral presentation 5002.

Background

- In the Phase 3, placebo-controlled RESPONSE study (NCT04620733), seladelpar significantly improved ALP and pruritus in patients with PBC[1]
  - The primary endpoint of composite biochemical response[a] was met in 62% of patients treated with seladelpar vs 20% of patients treated with placebo (*P* <.0001)[1,2]
- In a predefined subgroup analysis, a higher percentage of patients with cirrhosis reached the composite biochemical response criteria at month 12 in the seladelpar arm (39%) than in the placebo arm (22%)[3]
  - Patients with cirrhosis represented approximately 14% of the RESPONSE study population[1]
- Here, we report additional analyses of patients with and without cirrhosis in the RESPONSE study

[a]The primary endpoint was a composite biochemical response, including ALP <1.67 × ULN, ALP decrease ≥15%, and total bilirubin ≤1 × ULN at month 12.
ALP, alkaline phosphatase; **PBC**, primary biliary cholangitis; **ULN**, upper limit of normal.
1. Hirschfield GM, et al. *New Engl J Med*. 2024;390:783-94. 2. Data on file. Gilead Sciences, Inc.; 2024. 3. Hirschfield GM, et al. *New Engl J Med*. 2024;390:783-94. Supplementary Appendix.

Study Design

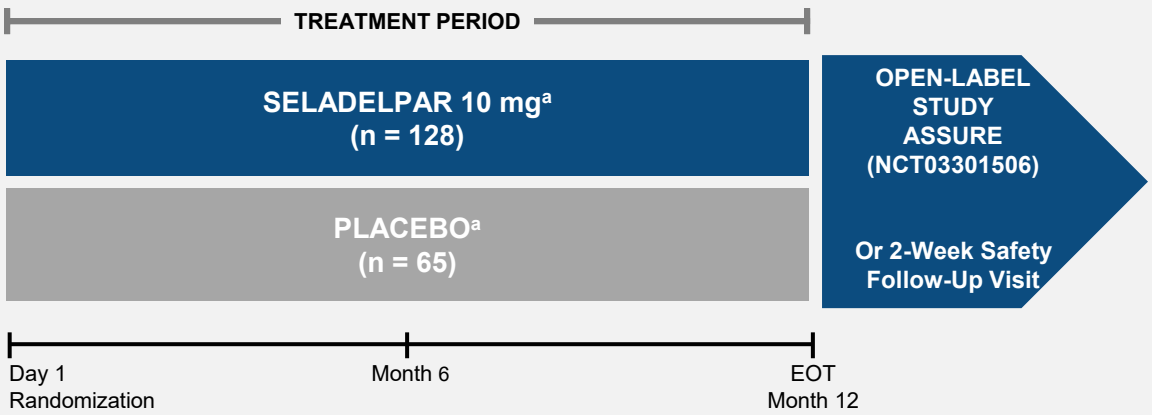
RESPONSE (NCT04620733): Phase 3 Study in Patients With PBC

Entry Criteria

- PBC and inadequate response or intolerance to UDCA
- ALP ≥1.67 × ULN
- ALT/AST ≤3 × ULN
- TB ≤2 × ULN
- Compensated cirrhosis allowed

Stratification

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



Primary Endpoint – Composite Biochemical Response Rate at Month 12

- ALP <1.67 × ULN; ALP decrease ≥15%; TB ≤1 × ULN

Key Secondary Endpoints

- ALP normalization rate (ALP ≤1 × ULN) at month 12
- Change in pruritus NRS at month 6 in patients with baseline NRS ≥4[b]

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]Pruritus data collected daily through the first 6 months, then monthly for 7 consecutive days each month until EOT.
ALP, alkaline phosphatase; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **EOT**, end of treatment; **NRS**, numerical rating scale; **PBC**, primary biliary cholangitis; **TB**, total bilirubin; **UDCA**, ursodeoxycholic acid; **ULN**, upper limit of normal.

Cirrhosis Population: Criteria Met

n (%)	Seladelpar 10 mg (n = 128)	Placebo (n = 65)
Patients with cirrhosis at baseline	18 (14)	9 (14)
Criteria met per protocol definition of cirrhosis[a]		
Liver biopsy[b]	7 (39)	2 (22)
Liver stiffness by FibroScan[c]	10 (56)	4 (44)
Radiological evidence	5 (28)	3 (33)
Laboratory findings	2 (11)	1 (11)
Combination of platelets <140 × 10^3 cells/μL with serum albumin <3.5 g/dL	1 (6)	0
Combination of platelets <140 × 10^3 cells/μL with total bilirubin >1.0 × ULN	1 (6)	1 (11)
Clinical determination by the investigator	10 (56)	5 (56)

60% of patients met ≥2 criteria for cirrhosis
No patients met cirrhosis criteria due to laboratory findings alone

Percentages add up to >100% as patients may have met >1 criteria. The percentage of patients with each criterium met are reported with the number of patients with cirrhosis at baseline as the denominator.
[a]"Current or decompensated liver disease" was another category for meeting cirrhosis criteria, but it was exclusionary, and no patients met this category. This category included ascites, hepatic encephalopathy, esophageal varices, or other clinical conditions consistent with liver cirrhosis, portal hypertension, or both. Patients with a prior PBC clinical outcome or acute liver decompensation were excluded. [b]For example, Ludwig stage 4 or Ishak stage 5. [c]Greater than 16.9 kPa at screening.
PBC, primary biliary cholangitis; **ULN**, upper limit of normal.

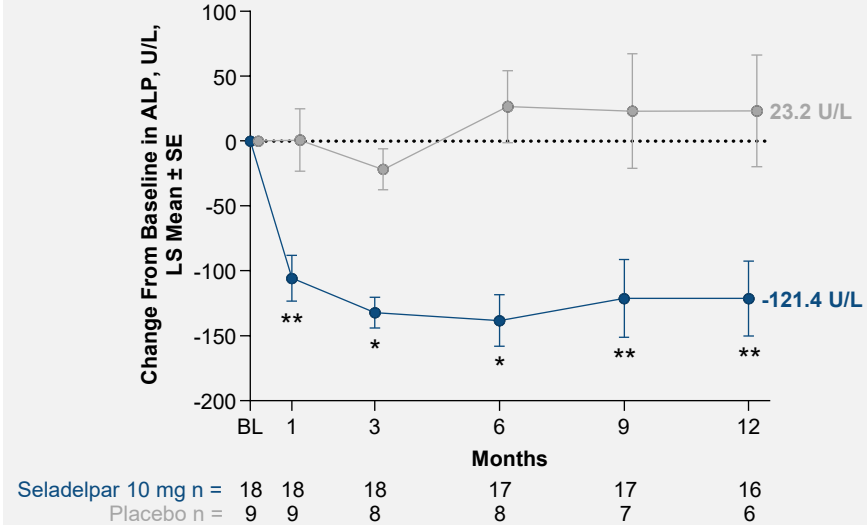
Demographics and Baseline Characteristics

	With Cirrhosis (n = 27)		Without Cirrhosis (n = 166)	
	Seladelpar 10 mg (n = 18)	Placebo (n = 9)	Seladelpar 10 mg (n = 110)	Placebo (n = 56)
Female, n (%)	18 (100)	7 (78)	105 (95)	53 (95)
Age, years, mean (SD)	59.5 (12.3)	55.6 (9.9)	56.1 (9.6)	57.2 (9.1)
UDCA intolerance, n (%)	0	1 (11)	8 (7)	3 (5)
Child-Pugh score, mean (SD)	5.1 (0.3)	5.0 (0)	N/A	N/A
Child-Pugh score 6, n (%)	2 (11)	0	N/A	N/A
Liver stiffness, kPa, mean (SD)	20.3 (8.8)	15.9 (5.0)	8.0 (3.1)	7.5 (2.5)
ALP, U/L, mean (SD)	344.0 (143.5)	349.3 (160.0)	309.7 (119.3)	308.1 (110.2)
TB, mg/dL, mean (SD)	1.0 (0.3)	1.0 (0.4)	0.7 (0.3)	0.7 (0.3)
ALT, U/L, mean (SD)	45.6 (18.9)	52.6 (13.0)	47.8 (24.2)	47.5 (24.0)
AST, U/L, mean (SD)	46.5 (14.7)	46.6 (14.2)	38.5 (16.1)	40.9 (16.3)
GGT, U/L, mean (SD)	241.2 (145.5)	461.9 (339.1)	273.6 (252.4)	259.5 (223.6)
Platelets, 10^3 cells/μL, mean (SD)	186.9 (68.6)	178.1 (68.4)	249.7 (77.3)	252.1 (82.8)

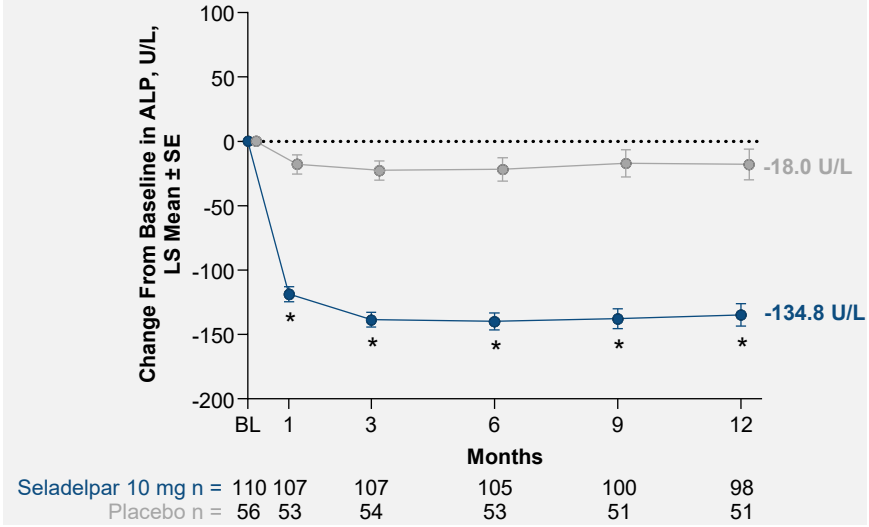
ALP, alkaline phosphatase; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **GGT**, gamma-glutamyl transferase; **N/A**, not applicable; **TB**, total bilirubin; **UDCA**, ursodeoxycholic acid.

Change From Baseline in ALP

Patients With Cirrhosis



Patients Without Cirrhosis



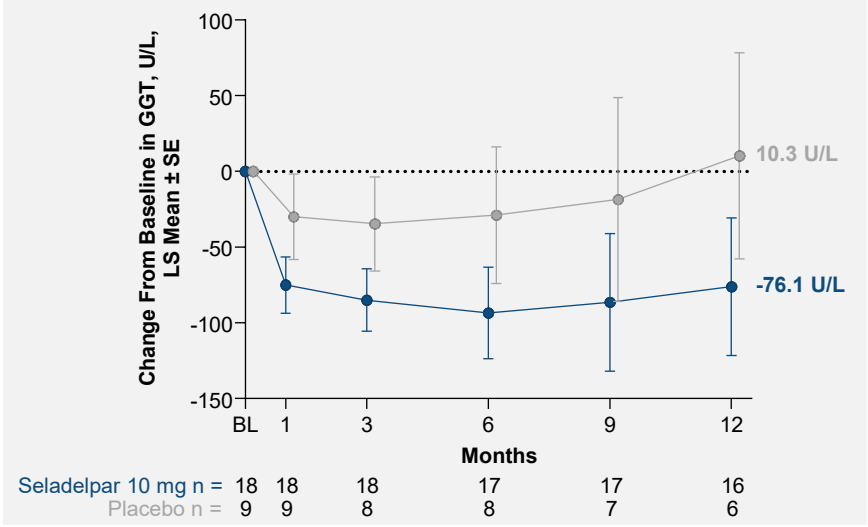
Seladelpar 10 mg Placebo

Rapid and sustained ALP reductions occurred with seladelpar vs placebo in patients with and without cirrhosis

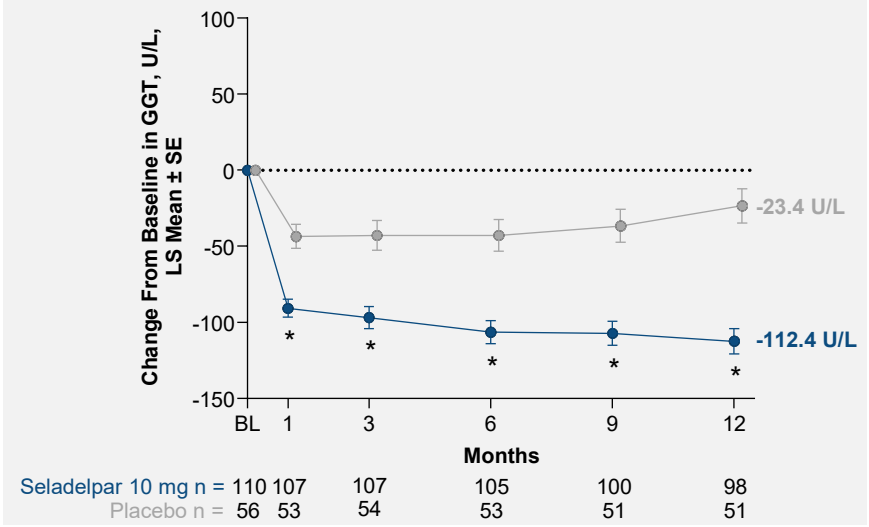
*P <.0001. **P <.05.
ALP, alkaline phosphatase; **BL**, baseline; **LS**, least squares.

Change From Baseline in GGT

Patients With Cirrhosis



Patients Without Cirrhosis



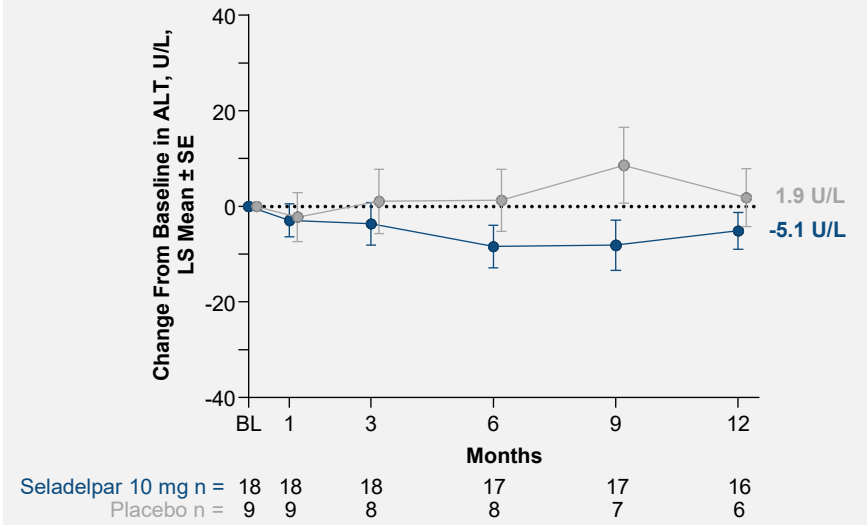
Seladelpar 10 mg Placebo

Rapid and sustained reductions in GGT occurred with seladelpar vs placebo in patients with and without cirrhosis

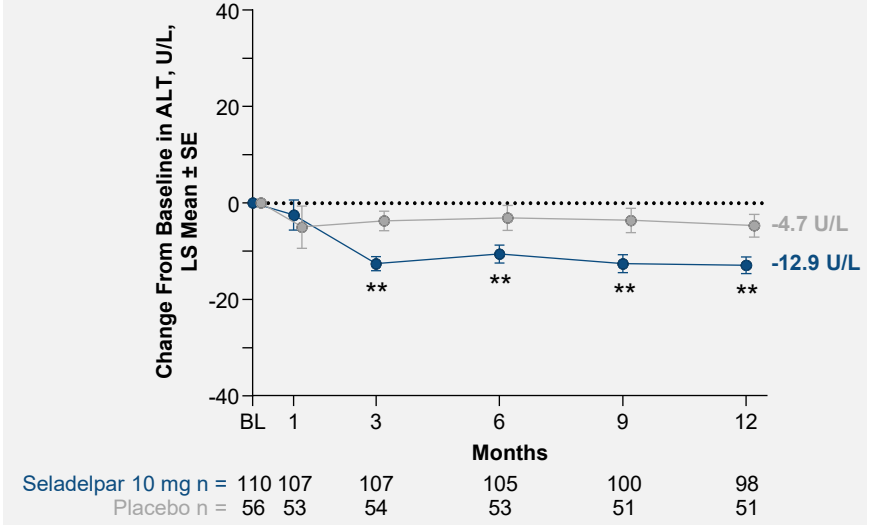
*P <.0001.
BL, baseline; **GGT**, gamma-glutamyl transferase; **LS**, least squares.

Change From Baseline in ALT

Patients With Cirrhosis



Patients Without Cirrhosis



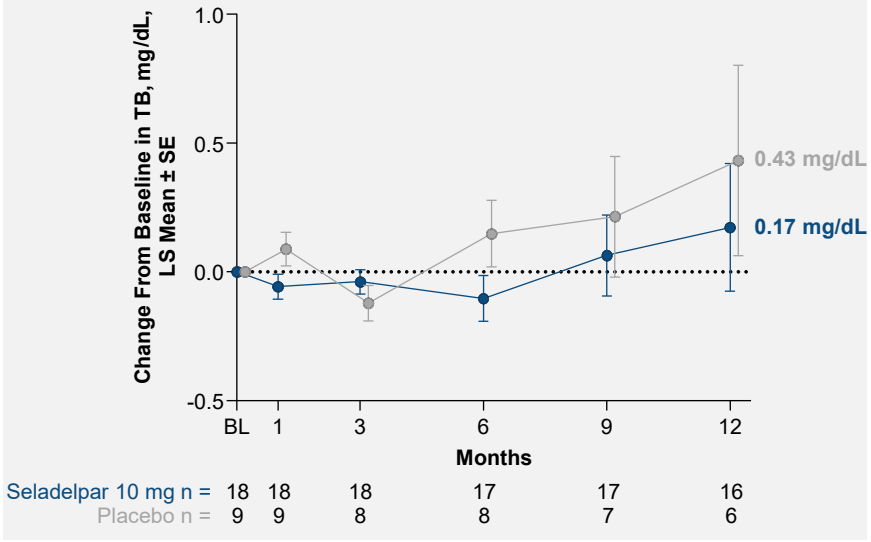
Seladelpar 10 mg Placebo

Sustained reductions in ALT occurred with seladelpar vs placebo in patients with and without cirrhosis

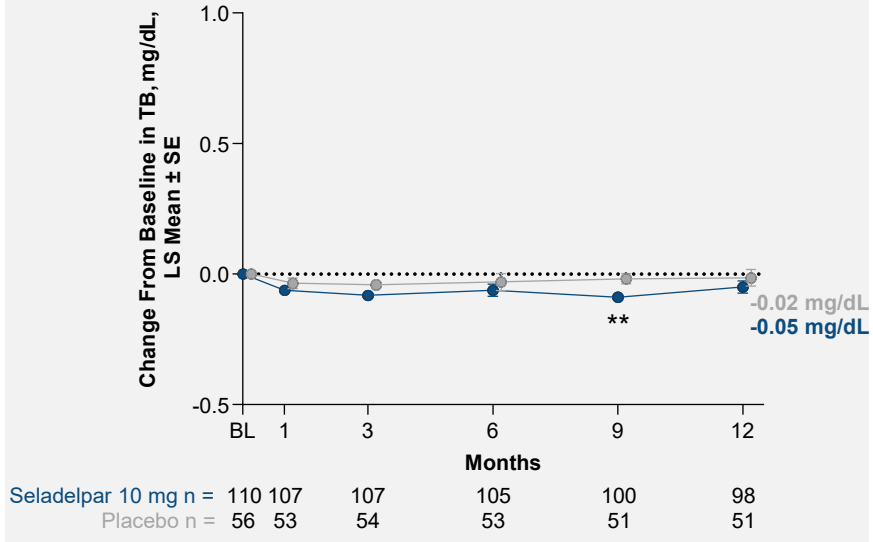
**P <.05.
ALT, alanine aminotransferase; **BL**, baseline; **LS**, least squares.

Change in Total Bilirubin and Other Parameters

Patients With Cirrhosis[a]



Patients Without Cirrhosis[a]



Seladelpar 10 mg — Placebo

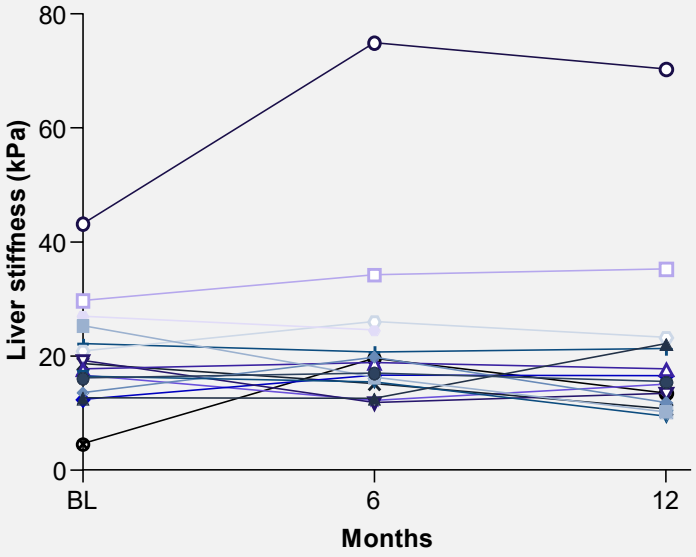
TB remained stable among patients with vs without cirrhosis

Mean INR and MELD score were similar between groups over 12 months

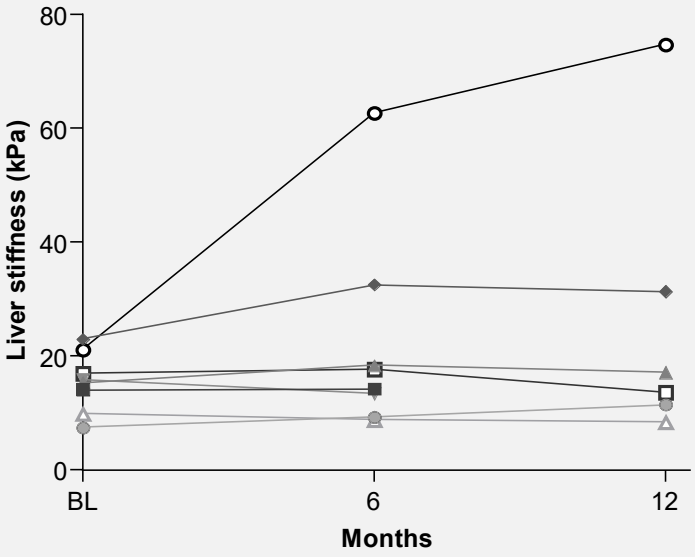
***P* <.05.
[a]Mean TB levels were normal at BL.
BL, baseline; **INR**, international normalized ratio; **LS**, least squares; **MELD**, model for end-stage liver disease; **TB**, total bilirubin.

Transient Elastography in the Cirrhosis Subgroup

Patients Receiving Seladelpar



Patients Receiving Placebo



Liver stiffness generally remained stable over 12 months in patients with cirrhosis in both treatment groups

In patients without cirrhosis, liver stiffness in both treatment groups was also stable

BL, baseline; **kPa**, kilopascal.

Overall Safety

	With Cirrhosis (n = 27)		Without Cirrhosis (n = 166)	
Patient Incidence, n (%)	**Seladelpar 10 mg (n = 18)**	**Placebo (n = 9)**	**Seladelpar 10 mg (n = 110)**	**Placebo (n = 56)**
Any AE	16 (89)	8 (89)	95 (86)	47 (84)
Grade ≥3 AEs (per CTCAE)	2 (11)	2 (22)	12 (11)	3 (5)
SAEs	2 (11)	1 (11)	7 (6)	3 (5)
Treatment-related SAEs	0	0	0	0
AEs leading to treatment discontinuation	0	2 (22)	4 (4)	1 (2)
AEs leading to study discontinuation	0	2 (22)	3 (3)	1 (2)
AEs leading to death	0	0	0	0

- Two patients with cirrhosis treated with seladelpar experienced SAEs; 1 had a femur fracture (with a medical history of osteoporosis), and 1 had coronary artery disease, dyspnea exertional, and esophageal varices hemorrhage (with a medical history of coronary artery disease)

All AEs listed are treatment emergent (began after study drug initiation on Day 1 and up to 30 days after last dose)
AE, adverse event; **CTCAE**, Common Terminology Criteria for Adverse Events; **SAE**, serious adverse event.

AEs of Interest

	With Cirrhosis (n = 27)		Without Cirrhosis (n = 166)	
Patient Incidence, n (%)	**Seladelpar 10 mg (n = 18)**	**Placebo (n = 9)**	**Seladelpar 10 mg (n = 110)**	**Placebo (n = 56)**
Liver-related AEs[a]	2 (11)	2 (22)	6 (5)	4 (7)
Muscle-related AEs[a]	0	1 (11)	8 (7)	4 (7)
Renal-related AEs[a]	0	0	0	0

- Two patients with cirrhosis receiving seladelpar experienced liver-related AEs of hepatomegaly (Grade 1) and ascites (Grade 1), respectively; the patient with ascites then experienced an SAE of esophageal varices hemorrhage (Grade 3)
- All muscle-related AEs occurring in the seladelpar group were Grades 1 or 2 in severity and were not associated with CK changes
- There was no evidence of renal impairment in patients with or without cirrhosis

All AEs listed are treatment emergent (began after study drug initiation on Day 1 and up to 30 days after last dose).
[a]AEs of interest were identified by a predefined search strategy.
AE, adverse event; **CK**, creatine kinase; **SAE**, serious adverse event.

Laboratory Parameters of Interest

	With Cirrhosis (n = 27)		Without Cirrhosis (n = 166)	
Patient Incidence, n (%)	**Seladelpar 10 mg (n = 18)**	**Placebo (n = 9)**	**Seladelpar 10 mg (n = 110)**	**Placebo (n = 56)**
ALT or AST ≥3 × ULN	1 (6)	2 (22)	8 (7)	5 (9)
TB >2 × ULN	1 (6)	2 (22)	2 (2)	1 (2)
CK >3 × ULN	0	0	2 (2)	1 (2)
Creatinine ≥1.5 × baseline	0	0	1 (1)	0

- Elevations in ALT or AST of ≥3 × ULN occurred in 1 patient (6%) with cirrhosis on seladelpar vs 2 patients (22%) on placebo
- Elevations in TB of >2 × ULN occurred in 1 patient (6%) with cirrhosis on seladelpar vs 2 patients (22%) on placebo

All AEs listed are treatment emergent (began after study drug initiation on Day 1 and up to 30 days after last dose).
AE, adverse event; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **CK**, creatine kinase; **TB**, total bilirubin; **ULN**, upper limit of normal.

Conclusions

- In patients with PBC and cirrhosis, seladelpar decreased cholestatic and liver injury markers compared with placebo, similar to effects seen in patients without cirrhosis in the RESPONSE trial
  - Patients treated with seladelpar had greater decreases in ALP, GGT, and ALT levels compared with patients receiving placebo
  - Total bilirubin, INR, and MELD scores remained stable between the treatment groups
- Seladelpar appeared safe and well tolerated in patients with PBC and compensated cirrhosis
  - The AE profile and incidence of liver enzyme elevations with seladelpar were similar to those of placebo in patients with or without compensated cirrhosis

AE, adverse event; **ALP**, alkaline phosphatase; **ALT**, alanine aminotransferase; **GGT**, gamma-glutamyl transferase; **INR**, international normalized ratio; **MELD**, model for end-stage liver disease; **PBC**, primary biliary cholangitis.

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