Seladelpar Treatment of Patients With Primary Biliary Cholangitis Improves the GLOBE Score and Predicts Improved Transplant-Free Survival

THU-286

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Conclusions

- In the Phase 3, placebo-controlled RESPONSE trial, seladelpar treatment resulted in an early decrease in GLOBE score for patients with primary biliary cholangitis (PBC), which was maintained for up to 24 months in the long-term open-label ASSURE trial
- The early and sustained decrease in GLOBE score was associated with improved predicted transplant-free survival

Plain Language Summary

- The GLOBE score can be calculated for people with primary biliary cholangitis (PBC) and is based on their age and 4 markers of liver health
- People with PBC who have lower GLOBE scores have better outcomes, such as longer survival without needing a liver transplant
- This analysis showed that people with PBC who were treated with seladelpar, a second-line treatment for PBC, had lower GLOBE scores and better predicted outcomes than people who were taking a placebo pill

References: **1.** European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-72. **2.** Hirschfield GM, et al. *N Eng J Med*. 2024;290(9):783-94. **3.** Livdelzi. US prescribing information. Gilead Sciences, Inc.; 2024. **4.** Livdelzi. UK summary of product characteristics. Gilead Sciences, Inc.; 2025. **5.** Seladelpar Gilead. EMA prescribing information. Gilead Sciences, Inc.; 2025. **6.** Lawitz E, et al. AASLD. 2024. Poster 5044. **7.** Sohal A, et al. *Hepat Med*. 2023;15:63-77.

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Introduction

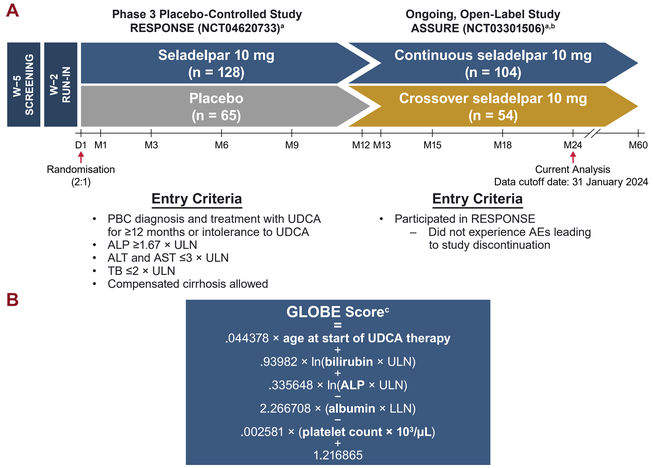
- PBC is a chronic, progressive, autoimmune cholestatic liver disease which requires long-term treatment to prevent progressive liver injury and potentially the need for liver transplantation[1]
- Seladelpar is a first-in-class delpar (selective peroxisome proliferator–activated receptor delta [PPARδ] agonist) indicated for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as a monotherapy in patients unable to tolerate UDCA[2-5]
- In the Phase 3, placebo-controlled RESPONSE study (NCT04620733), patients with PBC who had an inadequate response or intolerance to UDCA who received seladelpar 10 mg demonstrated significant improvements in biochemical markers of cholestasis and pruritus compared with placebo; similar results have been reported in an interim analysis from the ongoing, open-label extension ASSURE study (NCT03301506)[2,6]
- The GLOBE score is a validated risk assessment tool that provides an estimate of transplant-free survival for patients with PBC based on age and liver biochemistry[7]

Objectives

- To evaluate the change in GLOBE score and its components in patients with PBC who received seladelpar 10 mg or placebo in the pivotal, placebo-controlled, Phase 3 RESPONSE study and seladelpar 10 mg in the subsequent open-label extension ASSURE study over 24 months
- To explore improvements in predicted transplant-free survival over 2 years of seladelpar treatment

Methods

Figure 1. RESPONSE to ASSURE Rollover Study Design (A) and GLOBE Score Criteria (B)



[a]Study drug administered orally once daily as an add-on to UDCA, or as monotherapy in patients intolerant to UDCA.
[b]The ongoing open-label ASSURE study includes patients previously enrolled in RESPONSE (shown here) and legacy seladelpar studies (not shown).
[c]A higher GLOBE score indicates a worse prognosis.
AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, day; LLN, lower limit of normal; M, month; PBC, primary biliary cholangitis; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; W, week.

- In RESPONSE, patients with PBC were randomised 2:1 to receive seladelpar 10 mg or placebo orally once daily for 12 months
- After 12 months, patients were eligible for ASSURE (**Figure 1A**)
  - Patients receiving placebo in RESPONSE started receiving seladelpar 10 mg in ASSURE (crossover seladelpar), and patients receiving seladelpar in RESPONSE continued their seladelpar treatment in ASSURE (continuous seladelpar)
- GLOBE scores were calculated for each follow-up visit for up to 24 months and the change in GLOBE score was assessed from baseline, with higher scores indicating a worse prognosis (**Figure 1B**)
- The contributions of alkaline phosphatase (ALP), total bilirubin (TB), albumin, and platelets to the change in GLOBE score from baseline over time were evaluated
- The predicted transplant-free survival, based on GLOBE scores, was assessed for patients who received placebo for up to 1 year and seladelpar for up to 2 years

Results

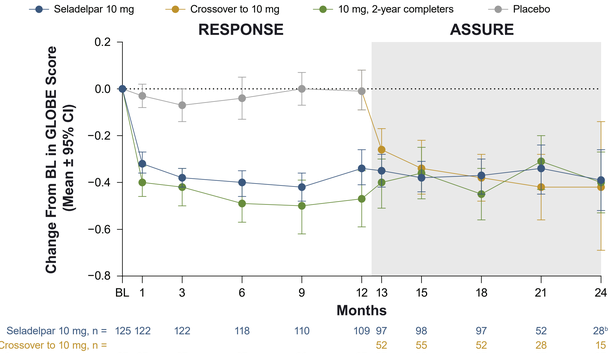
Table 1. Demographics and Clinical Characteristics at Baseline

	Seladelpar 10 mg (n = 128)	Placebo (n = 65)	Seladelpar 10 mg, 2-Year Completers (n = 28)
Age, years, mean (SD)	57 (10.0)	57 (9.2)	57 (9.6)
Female, n (%)	123 (96)	60 (92)	28 (100)
Age at PBC diagnosis, years, mean (SD)	49 (9.9)	49 (10.9)	49 (7.8)
Duration of PBC, years, mean (SD)	8 (6.7)	9 (6.5)	9 (7.1)
UDCA intolerance, n (%)	8 (6)	4 (6)	3 (11)
Daily UDCA dose, mg/kg, mean (SD)	15.0 (3.1)	14.8 (3.3)	14.7 (2.7)
ALP, U/L, mean (SD)	315 (123.0)	314 (117.7)	284 (89.5)
TB, mg/dL, mean (SD)	0.77 (0.31)	0.74 (0.31)	0.73 (0.33)
Albumin, g/dL, mean (SD)	4.2 (0.3)	4.1 (0.2)	4.2 (0.2)
Platelets, 10^3/μL, mean (SD)	242 (78.9)[a]	242 (84.5)	272 (80.1)[a]
GLOBE score, mean (SD)	0.31 (0.66)[a]	0.33 (0.71)	0.15 (0.69)[a]
Cirrhosis, n (%)	18 (14)	9 (14)	3 (11)
AMA positive, n (%)	106 (83)	55 (85)	18 (64)

[a]n = 125 for the seladelpar 10 mg arm and n = 27 for the 2-year completers arm; 3 patients in the seladelpar 10 mg group and 1 patient in the 2-year completers group did not have baseline platelets data or a baseline GLOBE score.
ALP, alkaline phosphatase; AMA, anti-mitochondrial antibodies; PBC, primary biliary cholangitis; TB, total bilirubin; UDCA, ursodeoxycholic acid.

- Overall, baseline characteristics were balanced between the seladelpar and placebo groups (**Table 1**)
- The baseline GLOBE score was similar between patients in the seladelpar 10 mg and placebo arms (mean 0.31 [SD 0.66] vs mean 0.33 [SD 0.71]), as were the GLOBE score components
- The 2-year completers group had a lower baseline GLOBE score than the seladelpar 10 mg and placebo groups, primarily due to lower baseline ALP levels
- Across the RESPONSE and ASSURE studies, 28 patients in the seladelpar 10 mg arm completed 2 years of treatment; however, one lacked a baseline GLOBE score, so the analysis included data from 27 patients

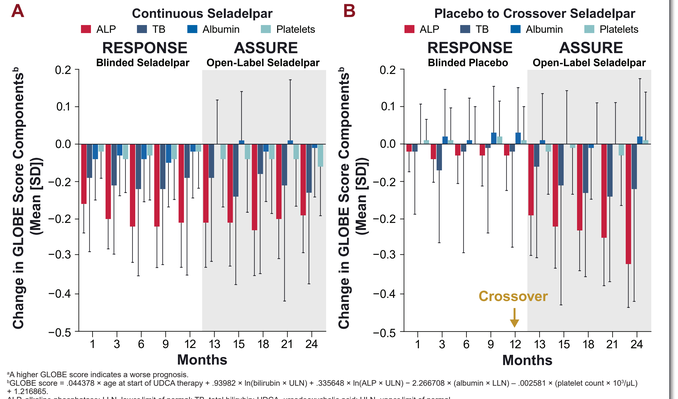
Figure 2. Mean Change in GLOBE Score[a]



n = number of evaluable patients at each time point.
[a]A higher GLOBE score indicates a worse prognosis.
[b]One patient had their month 24 visit early and is not represented in the 2-year completers arm.
BL, baseline.

- For patients in the continuous seladelpar group, the GLOBE score decreased early in the study, and lower GLOBE scores were maintained through 2 years of treatment (**Figure 2**)
  - At 1 month, the mean GLOBE score decrease was −0.32 (95% CI, −0.36 to −0.27)
  - At 12 months, the mean GLOBE score decrease was −0.34 (95% CI, −0.41 to −0.26)
  - At 24 months, the mean GLOBE score decrease was −0.39 (95% CI, −0.52 to −0.26)
- For patients in the crossover seladelpar group, a similar decrease in GLOBE score was observed
  - At 13 months, after 1 month of treatment with seladelpar in ASSURE, the mean GLOBE score decrease was −0.26 (95% CI, −0.35 to −0.17)
  - At 24 months, after 12 months of treatment with seladelpar in ASSURE, the mean GLOBE score decrease was −0.42 (95% CI, −0.69 to −0.14)

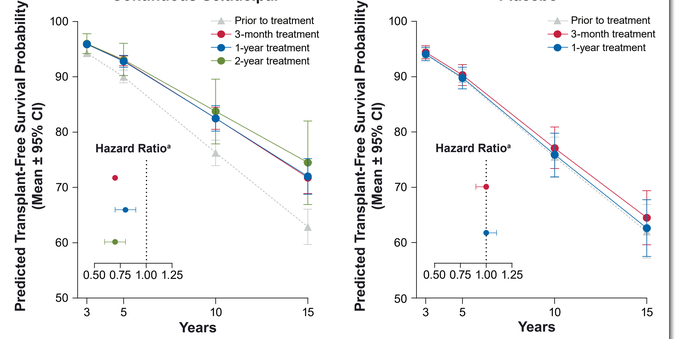
Figure 3. Mean Change in GLOBE Score[a] Components



[a]A higher GLOBE score indicates a worse prognosis.
[b]GLOBE score = .044378 × age at start of UDCA therapy + .93982 × ln(bilirubin × ULN) + .335648 × ln(ALP × ULN) − 2.266708 × (albumin × LLN) − .002581 × (platelet count × 10^3/μL) + 1.216865.
ALP, alkaline phosphatase; LLN, lower limit of normal; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

- For patients receiving continuous seladelpar, the greatest changes in GLOBE score were attributable to the ALP component followed by the TB component (**Figure 3A**)
- A similar trend was seen in patients originally treated with placebo after crossing over to seladelpar (**Figure 3B**)

Figure 4. Predicted Transplant-Free Survival



[a]Hazard ratios were calculated with survival estimates.

- In the continuous seladelpar group, an improvement in predicted transplant-free survival was observed as early as 3 months into treatment, and the greatest improvement was observed after 2 years of treatment (**Figure 4**)
  - Hazard ratios (95% CIs) for transplant-free survival with continuous seladelpar treatment compared with prior to treatment were:
    - 3 months: 0.7 (0.7–0.7)
    - 1 year: 0.8 (0.7–0.9)
    - 2 years: 0.7 (0.6–0.8)
  - Hazard ratios (95% CIs) for transplant-free survival with placebo compared with prior to treatment were:
    - 3 months: 1.0 (0.9–1.0)
    - 1 year: 1.0 (1.0–1.1)