Biochemical response is associated with liver stiffness stability in patients with primary biliary cholangitis treated with seladelpar for up to 3 years in the ongoing open-label ASSURE study

THU-270

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Rare liver diseases (including paediatric and genetic) – Clinical

Conclusions

- Biochemical response with seladelpar at 12 months was associated with liver stiffness measurement (LSM) stability or improvement through 3 years in ASSURE
- ALP normalisation at 12 months led to 4–6 times higher chances of maintaining or improving LSM at 3 years
- These findings support the potential for seladelpar to positively influence fibrosis and ultimately the disease course of primary biliary cholangitis (PBC)
- Further analysis with longer follow-up time is warranted to confirm these findings, especially for long-term clinical outcomes in patients with PBC

Plain Language Summary

- A positive biochemical response is linked to stable or better liver stiffness measurements over time
- Alkaline phosphatase levels returning to normal has the stongest association with stable or better liver stiffness measurements over time
- By achieving biochemical response and keeping liver stiffness meaurements stable, seladelpar may help slow the worsening of primary biliary cholangitis

†DATA FOOTNOTE

- The original abstract presented interim analyses; this poster reports updated analyses that excluded four patients whose liver stiffness was not measured using an Echosens FibroScan instrument

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Introduction

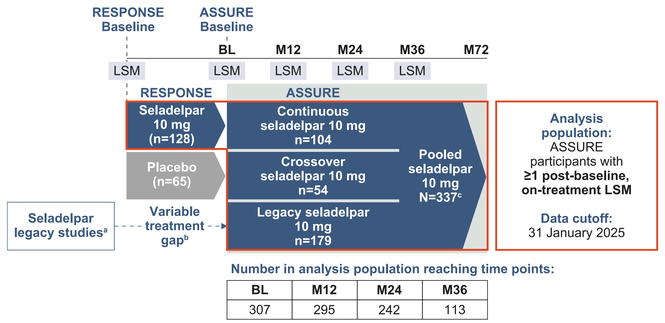
- Liver stiffness measurement (LSM) predicts clinical outcomes in patients with primary biliary cholangitis (PBC),[1,2] with progressive increases over time associated with ongoing disease activity[3,4]
- Seladelpar is a first-in-class delpar (selective peroxisome proliferator-activated receptor delta [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 who are unable to tolerate UDCA[5–8]
- In the pivotal Phase 3 RESPONSE study (NCT04620733)[9] and ongoing, open-label Phase 3 ASSURE study (NCT03301506),[10,11] seladelpar treatment led to the majority of patients achieving the composite biochemical response that was the primary endpoint in RESPONSE, and one third of patients achieving alkaline phosphatase (ALP) normalisation up to Month 36
- We previously reported that seladelpar treatment led to stable liver stiffness over time, with 85% of patients demonstrating stable or improved liver stiffness at 36 months in the interim ASSURE analysis[12]
- Here, we evaluated the association of biochemical response at Month 12 with LSM changes at 36 months of seladelpar treatment in the ongoing ASSURE study

Objective

- To assess the association between biochemical response at Month 12 and long-term LSM trends

Methods

Figure 1. Study Design



[a]Legacy studies include the Phase 2 dose-ranging study (NCT02955602), Phase 3 long-term safety study (NCT03301506), Phase 3 ENHANCE study (NCT03602560) and Phase 1b hepatic impairment study (NCT04950764). The Phase 2 and 3 parent studies required an inadequate response or intolerance to first-line UDCA. [b]Treatment gaps between legacy studies and ASSURE ranged from 4 weeks (Phase 1b impairment study) to 212 weeks (Phase 3 ENHANCE study). [c]In ASSURE, 2 patients initiated seladelpar at 5 mg and were excluded from the analysis.
AE, adverse event; BL, baseline; LSM, liver stiffness measurement; M, month; UDCA, ursodeoxycholic acid.

- Patients from RESPONSE and legacy seladelpar studies enrolled in ASSURE and received open-label seladelpar 10 mg once daily (**Figure 1**)
- Liver stiffness was assessed as an exploratory endpoint and measured annually using vibration-controlled transient elastography (VCTE; FibroScan via Echosens)
  - LSM values with confirmed interquartile range/LSM ratio ≥30% were excluded
- Data for this interim analysis included all patients in ASSURE with ≥1 post-baseline (BL) LSM; BL was defined as seladelpar initiation (cutoff: 31 January 2025)
- LSM changes by composite biochemical response (CBR) status at Month 12 were assessed through Month 36
  - CBR was defined as ALP <1.67 × upper limit of normal (ULN), ≥15% reduction in ALP from BL and total bilirubin ≤ULN
  - CBR was assessed among evaluable patients at Month 12
- Clinically meaningful LSM change was defined by ≥30% threshold; additional analyses were performed using ≥20% and >0% (any change) thresholds
- BL characteristics and on-treatment biochemical response were compared in a univariate analysis, and multivariate analysis was used to identify factors associated with stable/improved LSM vs worsening LSM (≥30%, ≥20%, or any change) at Month 36
- Odds of LSM stability or improvement at Month 36 were compared between patients achieving ALP normalisation or CBR with ALP >ULN at Month 12 and those not achieving CBR at Month 12

Results†

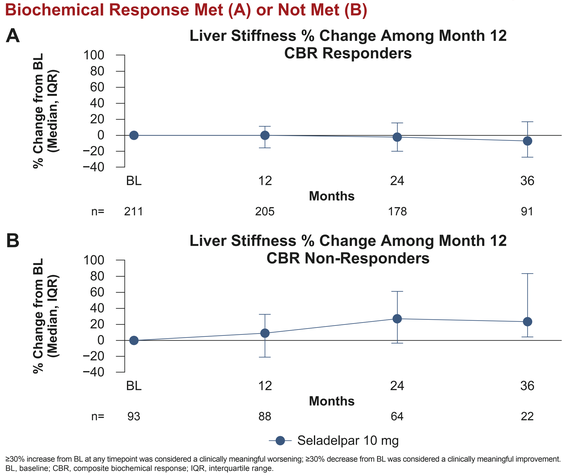
Table 1. Demographics and Baseline Characteristics

	Seladelpar 10 mg (N=307)
Age, years, mean (SD)	58.5 (9.6)
Female sex, n (%)	290 (94.5)
BMI ≥30, n (%)	85 (27.7)
LSM, kPa, mean (SD)	9.8 (7.4)
ELF score, mean (SD)	10.0 (1.0)
ALP, U/L,[a] mean (SD)	288.0 (128.5)
AST, U/L,[a] mean (SD)	37.9 (16.5)
ALT, U/L,[a] mean (SD)	42.8 (23.4)
GGT, U/L,[a] mean (SD)	227.9 (198.0)
TB, mg/dL,[a] mean (SD)	0.7 (0.3)
Cirrhosis, n (%)	49 (16.0)
Child-Pugh A, n (%)[b]	46 (93.9)
Child-Pugh B, n (%)[b]	3 (6.1)
Child-Pugh score, mean (SD)	5.2 (0.5)

[a]ALP ULN=116 U/L; AST ULN=34 U/L; ALT ULN=41 U/L; GGT ULN=52 U/L for male patients, 38 U/L for female patients; TB ULN=1.10 mg/dL.
[b]Percentage of patients with cirrhosis.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ELF, Enhanced Liver Fibrosis; GGT, gamma-glutamyl transferase; LSM, liver stiffness measurement; SD, standard deviation; TB, total bilirubin; ULN, upper limit of normal.

- Among 307 patients with ≥1 post-BL LSM enrolled in ASSURE, 36.8% (113/307) of patients had available Month 36 LSM values as of the data cut (**Table 1**)
  - At BL, mean (standard deviation) LSM was 9.8 (7.4) kPa, and 16.0% (49/307) of patients had cirrhosis
- With seladelpar treatment, 68.7% (211/307) of evaluable patients achieved CBR at Month 12
  - At BL (all mean), in patients with CBR at Month 12, age was 59.3 years, ALP 244.2 U/L, and LSM 8.9 kPa; in patients without CBR at Month 12, age was 56.5 years, ALP 386.2 U/L, and LSM 12.1 kPa

Figure 2. Liver Stiffness Changes Over Time per Month 12 Composite Biochemical Response Met (A) or Not Met (B)



≥30% increase from BL at any timepoint was considered a clinically meaningful worsening; ≥30% decrease from BL was considered a clinically meaningful improvement.
BL, baseline; CBR, composite biochemical response; IQR, interquartile range.

- In patients with CBR at Month 12, LSM remained stable (median change: −7.0%) at Month 36 (**Figure 2A**); 18.7% improved by ≥30%, 65.9% remained stable, and 15.4% worsened by ≥30%
- In patients without CBR at Month 12, LSM increased (median change: +23.6%) at Month 36 (**Figure 2B**); 9.1% improved by ≥30%, 45.4% remained stable, and 45.5% worsened by ≥30%

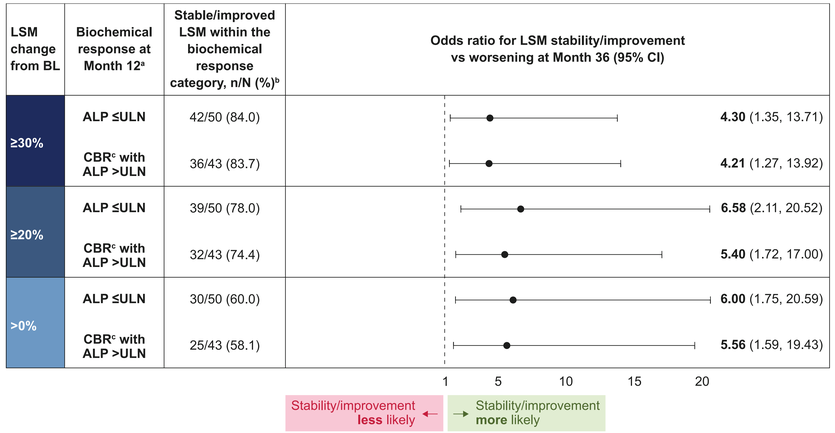
Table 2. Univariate Analysis for Factors Associated With LSM Stability or Improvement at Month 36

	≥30%			≥20%			Any Change		
LSM change from BL	**No worsening (<30%) (N=89)**	**≥30% (N=24)**	**p value**	**No worsening (<20%) (N=78)**	**≥20% (N=35)**	**p value**	**No worsening (0%) (N=59)**	**>0% (N=54)**	**p value**
Baseline characteristics									
Age, years, mean (SD)	60.1 (9.2)	55.7 (9.1)	<0.05	60.0 (9.5)	57.4 (8.8)	0.1876	59.0 (9.6)	59.4 (9.1)	0.9381
ALP <1.5 × ULN, n (%)	17 (19.1)	0	<0.05	16 (20.5)	1 (2.9)	<0.05	13 (22.0)	4 (7.4)	<0.05
On-treatment biochemical response at Month 12, n (%)									
CBR	77 (86.5)	14 (58.3)	<0.05	70 (89.7)	21 (60.0)	<0.05	55 (93.2)	36 (66.7)	<0.05
ALP <1.67 × ULN	79 (88.8)	17 (70.8)	<0.05	72 (92.3)	24 (68.6)	<0.05	55 (93.2)	41 (75.9)	<0.05
≥15% ALP reduction	88 (98.9)	20 (83.3)	<0.05	77 (98.7)	31 (88.6)	<0.05	58 (98.3)	50 (92.6)	0.1420
TB ≤ULN	87 (97.8)	21 (87.5)	<0.05	76 (97.4)	32 (91.4)	0.1529	59 (100)	49 (90.7)	<0.05
ALP <1.5 × ULN	75 (84.3)	15 (62.5)	<0.05	68 (87.2)	22 (62.9)	<0.05	51 (86.4)	39 (72.2)	0.0619
ALP ≤ULN	42 (47.2)	8 (33.3)	0.2272	39 (50.0)	11 (31.4)	0.0673	30 (50.8)	20 (37.0)	0.1416

Statistical differences were assessed using a two-sided Wilcoxon rank-sum test for continuous variables and a Cochran-Mantel-Haenszel test for general association for categorical variables, performed for each factor in each comparison.
ALP, alkaline phosphatase; BL, baseline; CBR, composite biochemical response; LSM, liver stiffness measurement; SD, standard deviation; TB, total bilirubin; ULN, upper limit of normal.

- Older age at BL, lower ALP at BL, and achieving response thresholds at Month 12, including CBR, were significantly associated with LSM stability or improvement at Month 36. These findings were generally consistent across different cutoffs of LSM change (**Table 2**)
  - Power was likely low for ALP ≤ULN due to sample size
  - Multivariate analysis showed CBR at Month 12 was associated with stable/improved LSM at Month 36 (≥30% change threshold; odds ratio 5.13; p<0.05)

Figure 3. Odds of LSM Stability or Improvement at Month 36 by Biochemical Response at Month 12



[a]Compared with CBR non-response reference group using a logistic regression model; [b]n/N = number of patients achieving stability or improvement/number of patients in the corresponding biochemical response category; [c]CBR was defined as ALP <1.67 × ULN, ≥15% reduction in ALP from baseline and total bilirubin ≤ULN.
ALP, alkaline phosphatase; BL, baseline; CBR, composite biochemical response; CI, confidence interval; LSM, liver stiffness measurement; ULN, upper limit of normal.

- When examined by degree of biochemical response, ALP normalisation generally showed the highest odds of achieving stability or improvement across all thresholds of LSM change (**Figure 3**)