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Livdelzi® (seladelpar) Use in Hepatic Impairment

This document is in response to your request for information regarding Livdelzi® (seladelpar [SEL]) for the treatment of primary biliary cholangitis (PBC) and its use in patients with hepatic impairment.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/pbc/livdelzi/livdelzi_pi.

Summary

Product Labeling[1]

SEL has been associated with dose-related increases in serum transaminase (AST and ALT) levels >3 × ULN in PBC patients receiving 50 mg once daily (5 × higher than the recommended dosage) and 200 mg (20 × higher than the recommended dosage) once daily. Transaminase levels returned to pretreatment levels upon SEL discontinuation. SEL 10 mg once daily did not show a similar pattern for increases in transaminase levels.

Obtain BL clinical and laboratory assessments at treatment initiation with SEL and monitor thereafter according to routine patient management. Interrupt SEL treatment if the liver tests (ALT, AST, TB, and/or ALP) worsen, or the patient develops signs and symptoms consistent with clinical hepatitis (eg, jaundice, right upper quadrant pain, eosinophilia). Consider permanent discontinuation if liver tests worsen after restarting SEL.

Avoid use of SEL in patients with complete biliary obstruction. If biliary obstruction is suspected, interrupt SEL and treat as clinically indicated.

Clinical Data on SEL Use in Hepatic Impairment

RESPONSE was a phase 3, placebo-controlled study that evaluated SEL 10 mg in 193 participants with PBC with an inadequate response or intolerance to UDCA. The primary composite endpoint was defined as an ALP level <1.67 × ULN, an ALP level decrease by ≥15%, and a TB level ≤1 × ULN.[2]

- Among participants with cirrhosis, 38.9% and 22.2% of participants in the SEL and placebo arms, respectively, achieved the composite biochemical response at Month 12, with a difference of 16.7% (95% CI: -22.7 to 47.1).[3]
- Regardless of BL cirrhosis status, participants in the SEL arm had greater reductions in ALP, ALT, and GGT levels from BL to Month 12 than did participants in the placebo arm.[4]
- SAEs experienced by participants with and without cirrhosis were similar.[3,4]

Pooled analyses of an open-label, phase 2 study and the phase 3 ENHANCE study were conducted to assess outcomes in participants with PBC with and without compensated

cirrhosis[5] and in participants with compensated cirrhosis and PHT.[6] The composite efficacy endpoint was identical to that of the RESPONSE study.[5,6]

- Efficacy appeared comparable in participants with PBC with and without cirrhosis. Among those with cirrhosis, significantly more participants in the SEL 10 mg arm than in the placebo arm achieved the composite endpoint (63% vs 0%; *P*=0.0351); the rate in the SEL 5 mg arm did not reach significance (50%). SEL was well tolerated in participants with and without cirrhosis.[5]
- In participants with cirrhosis and PHT, improvements in biomarkers of cholestasis and hepatocellular injury were achieved. SEL was also well tolerated in these participants.[6]

The ongoing, open-label, phase 3 ASSURE study evaluated participants who entered the study from the RESPONSE study and several legacy studies.[7]

- In an interim analysis of participants with cirrhosis who entered the study from legacy studies (n=35), there was a durable improvement (for up to 2 years) in cholestasis markers. Overall, AEs were reported by 28 participants (80%) with cirrhosis, and 8 participants (22.9%) reported liver-related AEs.[8]
- In a pooled interim analysis of participants with cirrhosis ± PHT from the legacy and RESPONSE studies (n=53), 49% of participants achieved a composite biochemical response at Month 12, which was sustained in 47% through Month 36, and 29% achieved ALP normalization at Month 12, which was maintained in 16% at Month 36. GGT, ALT, TB, and AST levels remained generally stable through Month 36. With up to 4 years of follow-up, 4 liver-related events led to treatment discontinuation. No SAEs were considered treatment-related.[9]
- In an interim analysis that evaluated trends in LSM through 3 years of treatment with SEL 10 mg and included all participants (N=311) who had ≥1 post-BL LSM assessment, LSM tended to improve in the subgroup of participants with the highest BL LSM (≥16.9 kPa): LSM change from BL, +0.1 kPa; LSM percent change from BL, +2%. The presence of cirrhosis at BL was not associated with a worsening of LSM by 30% from BL to Month 36.[10]
- Overall, there was no increase in the frequency of exposure-adjusted TEAEs through Month 36 in participants from the RESPONSE study and several legacy studies. Rates of liver-related AEs were stable or decreased over the study period, and most were Grade 1 or 2.[7]

Product Labeling[1]

Indications and Usage

Limitations of Use: Use of SEL is not recommended in patients who have or develop decompensated cirrhosis (eg, ascites, variceal bleeding, hepatic encephalopathy).

Warnings and Precautions

Liver test abnormalities

SEL has been associated with dose-related increases in serum transaminase (AST and ALT) levels >3 × ULN in PBC patients receiving 50 mg once daily (5 × higher than the recommended dosage) and 200 mg (20 × higher than the recommended dosage) once daily.

Transaminase levels returned to pretreatment levels upon SEL discontinuation. SEL 10 mg once daily did not show a similar pattern for increases in transaminase levels.

Obtain BL clinical and laboratory assessments at treatment initiation with SEL and monitor thereafter according to routine patient management. Interrupt SEL treatment if the liver tests (ALT, AST, TB, and/or ALP) worsen, or the patient develops signs and symptoms consistent with clinical hepatitis (eg, jaundice, right upper quadrant pain, eosinophilia). Consider permanent discontinuation if liver tests worsen after restarting SEL.

Biliary obstruction

Avoid use of SEL in patients with complete biliary obstruction. If biliary obstruction is suspected, interrupt SEL and treat as clinically indicated.

Use in Specific Populations

Hepatic impairment

No dosage adjustment is recommended for PBC patients with mild hepatic impairment (Child-Pugh A).

The safety and efficacy of SEL in patients with decompensated cirrhosis have not been established. Use of SEL is not recommended in patients who have or develop decompensated cirrhosis (eg, ascites, variceal bleeding, hepatic encephalopathy).

Monitor patients with cirrhosis for evidence of decompensation. Consider discontinuing SEL if the patient progresses to moderate or severe hepatic impairment (Child-Pugh B or C).

Clinical Pharmacology

Pharmacokinetics: patients with hepatic impairment

Hepatic impairment of various etiologies

Following a single oral dose of 10 mg SEL, SEL AUC increased 1.1-fold in subjects with mild (Child-Pugh A), 2.5-fold in moderate (Child-Pugh B), and 2.1-fold in severe (Child-Pugh C) hepatic impairment. SEL C_{max} increased 1.3-fold in subjects with mild (Child-Pugh A), 5.2-fold in moderate (Child-Pugh B), and 5-fold in severe (Child-Pugh C) hepatic impairment.

Hepatic impairment in patients with PBC

Compared to PBC patients with mild hepatic impairment (Child-Pugh A) without PHT, SEL exposures (C_{max}, AUC) were 1.7 to 1.8-fold higher in PBC patients with mild hepatic impairment with PHT, 1.6 to 1.9-fold higher in PBC patients with moderate hepatic impairment (Child-Pugh B), and 2.1 to 2.5-fold higher in PBC patients with severe hepatic impairment (Child-Pugh C) after a single oral dose of 10 mg SEL.

Accumulation ratios were less than 1.2-fold in PBC patients with mild hepatic impairment with PHT and PBC patients with moderate hepatic impairment following 10 mg SEL once daily dosing for 28 days.

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Clinical Data on SEL Use in Hepatic Impairment

RESPONSE Study

Study design and demographics[2]

RESPONSE was a phase 3, international, randomized, placebo-controlled study that evaluated SEL 10 mg in participants with PBC and an inadequate response to or intolerance of first-line treatment with UDCA. Participants (N=193) were randomly assigned 2:1 to receive either SEL 10 mg (n=128) or placebo (n=65) once daily for 12 months. Eligibility criteria included participants with PBC aged 18 to 75 years who had received UDCA for ≥12 months or had an intolerance of UDCA (last dose >3 months from screening) and had an ALP ≥1.67 × ULN, an AST/ALT level ≤3 × ULN, a TB level ≤2 × ULN, an eGFR >45 mL/min/1.73 m^2, an INR <1.1 × ULN, and a platelet count ≥100,000/mm^3. Those with advanced PBC (ie, albumin level <LLN and TB level >ULN), hepatic decompensation, or other chronic liver disease were excluded.

The primary composite endpoint was the proportion of participants who achieved a biochemical response, defined as an ALP level <1.67 × ULN, an ALP level decrease by ≥15%, and a TB level ≤1 × ULN. Key secondary endpoints included ALP normalization (≤1 × ULN) at Month 12 and change from BL to Month 6 in weekly mean pruritus NRS score in those with an NRS score ≥4 (ie, moderate-to-severe pruritus) at BL.

Overall, 14% of participants (27/193) had cirrhosis at BL (Table 1).

Table 1. RESPONSE: BL Demographics and Disease Characteristics (ITT)[2]

Key Demographics and Characteristics		SEL 10 mg (n=128)	Placebo (n=65)
Age, mean ± SD, years		56.6±10	57±9.2
Female, n (%)		123 (96.1)	60 (92.3)
Race or ethnicity, White/Asian/American Indian or Alaska Native/Black/Hispanic or Latinx, %		89.1/5.5/2.3/1.6/22.7	86.2/6.2/4.6/3.1/41.5
Duration of disease, mean ± SD, years		8.2±6.7	8.6±6.5
Cirrhosis,[a] n (%)		18 (14.1)	9 (13.8)
Liver stiffness, mean ± SD, kPa		9.8±6.2	8.7±4.2
History of pruritus, n (%)		91 (71.1)	48 (73.8)
Pruritus NRS score,[b] mean ± SD		3±2.8	3±3
Score ≥4, n (%)		49 (38.3)	23 (35.4)
Laboratory values, mean ± SD	ALP,[c] U/L	314.6±123	313.8±117.7
	TB, mg/dL	0.77±0.3	0.74±0.3
	AST/ALT,[d] U/L	39.6±16.1/47.4±23.5	41.7±16/48.2±22.8
	GGT,[e] U/L	269±240	287.5±249.6
	Albumin, g/dL	4.2±0.3	4.1±0.2
	Platelet count,[f] ×10^3/mm^3	241.7±78.9	241.9±84.5

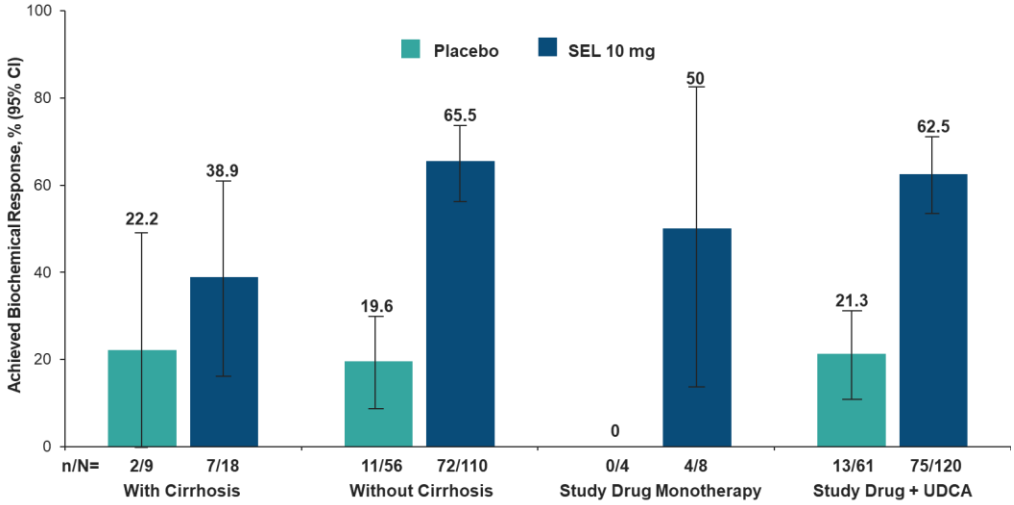
[a]No participants in the SEL arm and 3 (4.6%) participants in the placebo arm had PHT. [b]NRS scores range from 0 (no itch) to 10 (worst itch imaginable). [c]ULN: 116 U/L. [d]ULN: 34/41 U/L. [e]ULN: 52 and 38 U/L in men and women, respectively. [f]Data were missing for 3 participants in the SEL 10 mg arm.

Efficacy

At Month 12, 38.9% (7 out of 18) and 22.2% (2 out of 9) of SEL-treated participants and placebo-treated participants with cirrhosis, respectively, had achieved the composite biochemical response (difference: 16.7%; 95% CI: -22.7 to 47.1).[2,3]

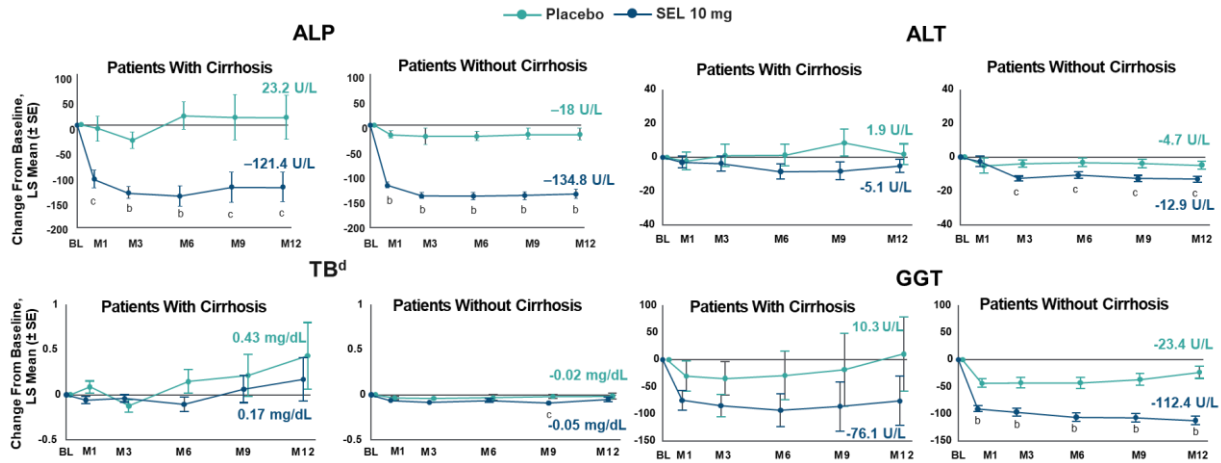
These results were considered generally consistent with those observed in participants without cirrhosis, with the difference in response between those with and without cirrhosis deemed not clinically meaningful by the investigators.[2,3]

Figure 1. RESPONSE: Biochemical Response[2]



Regardless of their BL cirrhosis status, participants in the SEL arm had greater reductions in ALP, ALT, and GGT levels from BL to Month 12 than did participants in the placebo arm (Figure 2). In both the SEL and placebo arms, TB levels remained stable in participants with and those without cirrhosis. In the SEL arm, mean INR and MELD scores were similar between participants with and those without cirrhosis. In participants with BL cirrhosis, liver stiffness generally remained stable over 12 months in both the SEL and placebo arms.[4]

Figure 2. RESPONSE: Cholestatic and Liver Injury Markers[4a]



Abbreviation: LS=least squares.
[a]Participants with cirrhosis: placebo, n=9; SEL 10 mg, n=18; participants without cirrhosis: placebo, n=56; SEL 10 mg, n=110. [b]*P*<0.001. [c]*P*<0.05. [d]Mean TB levels were normal at BL.

Safety

The safety profiles of participants with and without cirrhosis at BL were similar (Table 2).[2-4]

Table 2. RESPONSE: AEs in Participants in Any Treatment Arm by Presence of Cirrhosis[2-4]

AEs, n (%)		Participants With Cirrhosis		Participants Without Cirrhosis	
		SEL 10 mg (n=18)	Placebo (n=9)	SEL 10 mg (n=110)	Placebo (n=56)
Overall safety	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)[a]	1 (11)	7 (6)	3 (5)
	Treatment-related SAEs	0	0	0	0
	AE that led to drug discontinuation	0	2 (22)	4 (4)	1 (2)
	AE that led to death	0	0	0	0
Liver-related AE		2 (11)[b]	2 (22)	6 (5)	4 (7)
AEs that occurred in ≥2 participants with cirrhosis in either treatment group	COVID-19	3 (16.7)	2 (22.2)	20 (18.2)	8 (14.3)
	Pruritus	2 (11.1)	2 (22.2)	4 (3.6)	8 (14.3)
	Nausea	2 (11.1)	1 (11.1)	6 (5.5)	2 (3.6)
	Abdominal pain	2 (11.1)	0	7 (6.4)	1 (1.8)
	Vitamin D deficiency	2 (11.1)	0	4 (3.6)	2 (3.6)
	Pharyngitis	2 (11.1)	0	2 (1.8)	5 (8.9)
	Diabetes mellitus	2 (11.1)	0	1 (0.9)	0
	Leukopenia	2 (11.1)	0	0	1 (1.8)
	Thrombocytopenia	2 (11.1)	0	0	0
	Dry eye	1 (5.6)	2 (22.2)	0	0
	Dry mouth	0	2 (22.2)	1 (0.9)	0
Laboratory parameters of interest	ALT or AST ≥3 × ULN	1 (6)	2 (22)	8 (7)	5 (9)
	TB >2 × ULN	1 (6)	2 (22)	2 (2)	1 (2)
	Creatine kinase >3 × ULN	0	0	2 (2)	1 (2)
	Cr ≥1.5 × BL	0	0	1(1)	0

[a]One participant who had a history of osteoporosis had a femur fracture, and 1 participant who had a history of coronary artery disease had coronary artery disease, dyspnea exertional, and esophageal varices hemorrhage.
[b]One participant experienced ascites (Grade 1) and then experienced an SAE of esophageal varices hemorrhage (Grade 3), and 1 participant experienced hepatomegaly (Grade 1).

Pooled Analyses From the Dose-Ranging and ENHANCE Studies: Participants With and Without Compensated Cirrhosis

Study design and BL demographics

This pooled analysis of an open-label, phase 2 study (SEL 10 mg and 5 mg)[11] and the phase 3 ENHANCE study[12] evaluated the efficacy and safety of SEL in participants with and without compensated cirrhosis. Eligibility criteria included a PBC diagnosis, ALP levels ≥1.67 × ULN, and UDCA use for the past 12 months or intolerance of UDCA treatment. Diagnoses of cirrhosis were confirmed by liver biopsy, liver elastography, or imaging. PHT diagnosis was based on the presence of thrombocytopenia, splenomegaly, or gastroesophageal varices, or from the medical record. The efficacy endpoints included the following: a composite endpoint (defined as an ALP level <1.67 × ULN, ≥15% ALP decrease

from BL, and a TB level ≤ULN), % change in ALP level, the proportion of participants achieving an ALP level ≤ULN, and changes in liver biochemistry.[5]

Fifty-three participants (phase 2 study, n=24; ENHANCE study, n=29; all were Child-Pugh A) had cirrhosis at BL, which included 20 participants identified by imaging (ultrasound, CT, or MRI), 19 identified by a liver biopsy, and 14 identified by liver elastography (FibroScan or magnetic resonance elastography). One participant had a history of hepatic encephalopathy.[5]

Table 3. Pooled Study in Participants With and Without Cirrhosis: BL Demographics and Disease Characteristics[5]

Key Demographics and Characteristics		Participants With Cirrhosis (n=53)			Participants Without Cirrhosis (n=313)		
		SEL 10 mg (n=24)	SEL 5 mg (n=22)	Placebo (n=7)	SEL 10 mg (n=117)	SEL 5 mg (n=116)	Placebo (n=80)
Female/male, n		21/3	21/1	7/0	110/7	109/7	78/2
Age, mean ± SD, years		59±9	57±8	56±12	56±9	56±9	56±8
Duration of PBC, mean ± SD, years		10±5	10±8	9±9	9±7	9±6	8±6
AMA positive, n (%)		23 (96)	21 (96)	6 (86)	104 (89)	104 (90)	69 (86)
BMI, mean ± SD, kg/m^2		27±5	26±5	26±5	28±6	27±6	28±6
History of pruritus, n (%)		20 (83)	19 (86)	6 (86)	81 (69)	83 (72)	51 (64)
MELD score, mean ± SD		7.6±1.6	7.6±1.6	7±1.2	6.7±0.8	6.7±0.8	6.6±0.7
UDCA dose, mean ± SD, mg/kg/day		17±4	15±5	15±4	15±4	16±4	15±2
UDCA intolerant, n (%)		2 (8)	1 (5)	0	9 (8)	9 (8)	2 (3)
Mean ± SD	Normal range						
ALP	37–116 U/L	299±103	278±121	278±68	294±124	319±148	295±109
ALT	6–41 U/L	57±24	43±25	46±18	44±20	48±22	44±21
TB	0.1–1.1 mg/dL	0.9±0.4	0.9±0.4	0.9±0.6	0.7±0.3	0.7±0.3	0.7±0.3
DB	0–0.2 mg/dL	0.3±0.2	0.3±0.2	0.3±0.3	0.2±0.1	0.2±0.2	0.2±0.1
GGT	7–38 U/L	226±134	232±238	219±165	245±229	236±183	230±196
AST	9–34 U/L	55±20	44±20	41±12	39±14	40±16	37±17
Platelets	140–400 × 10^9/L	206±73	161±90	279±72	258±73	243±70	265±77
INR	0.8–1.2	1.1±0.1	1.1±0.1	1±0.1	1±0.1	1±0.1	1±0.1
Albumin	3.5–5.5 g/dL	4±0.4	3.9±0.4	4.1±0.2	4.1±0.3	4.1±0.3	4.2±0.2

Efficacy[5]

The efficacy of SEL appeared to be comparable between cirrhotic and noncirrhotic participants with PBC (Figure 3).

Figure 3. Pooled Study in Participants With and Without Cirrhosis: Composite Endpoint and ALP Normalization[5]

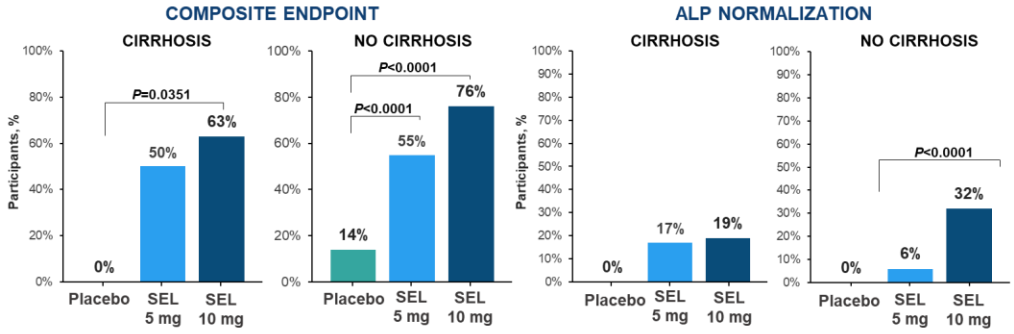
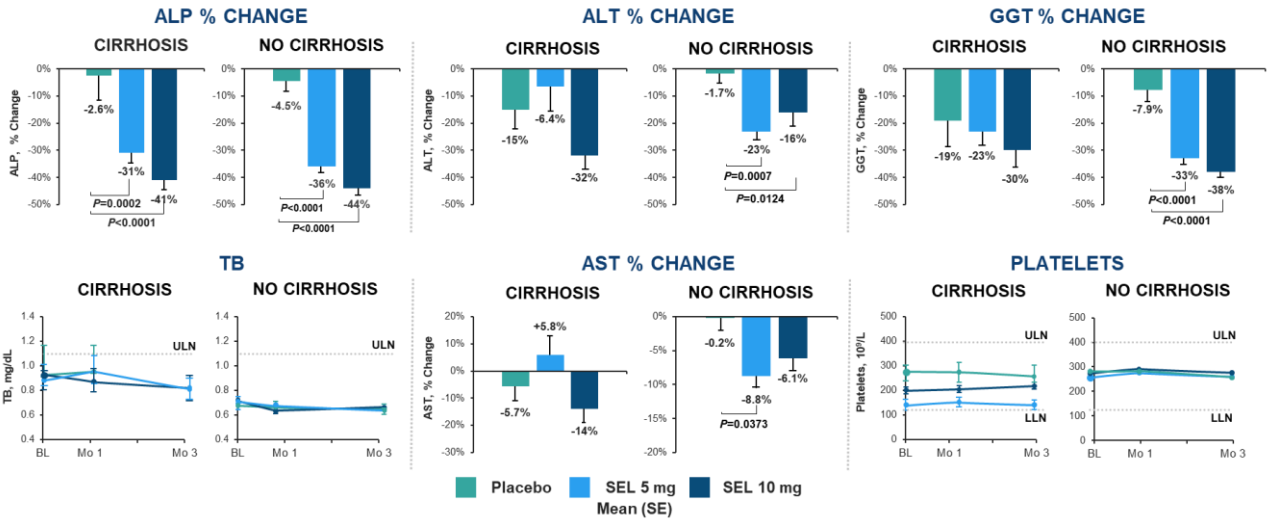


Figure 4. Pooled Study in Participants With and Without Cirrhosis: Change in ALP, ALT, TB, GGT, AST, and Platelets[5]



Safety[5]

SEL appeared to be well tolerated in participants with and without cirrhosis (Table 4). No AEs that resulted in death, treatment-related Grade ≥3 AEs (CTCAE), or treatment-related SAEs were reported.

Table 4. Pooled Study in Participants With and Without Cirrhosis: AEs[5]

AEs, n (%)	Participants With Cirrhosis (n=53)			Participants Without Cirrhosis (n=313)		
	SEL 10 mg (n=24)	SEL 5 mg (n=22)	Placebo (n=7)	SEL 10 mg (n=117)	SEL 5 mg (n=116)	Placebo (n=80)
Participant with ≥1 AE	15 (63)	17 (77)	6 (86)	76 (65)	75 (65)	48 (60)
Any TRAE	3 (13)	8 (36)	3 (43)	22 (19)	27 (23)	6 (8)
Any SAE	1 (4)[a]	2 (9)[b]	0	2 (2)[c]	2 (2)[d]	2 (3)[e]
Any AE that led to discontinuation of SEL	1 (4)[f]	0	0	1 (1)[g]	2 (2)[h]	-

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AEs, n (%)		Participants With Cirrhosis (n=53)			Participants Without Cirrhosis (n=313)		
		SEL 10 mg (n=24)	SEL 5 mg (n=22)	Placebo (n=7)	SEL 10 mg (n=117)	SEL 5 mg (n=116)	Placebo (n=80)
Most common AEs	Dry mouth	4 (17)	1 (5)	0	0	6 (5)	0
	Pruritus	3 (13)	2 (9)	0	12 (10)	7 (6)	6 (8)
	Headache	3 (13)	1 (5)	0	6 (5)	7 (6)	0
	Nausea	3 (13)	1 (5)	0	4 (3)	8 (7)	2 (3)
	Fatigue	3 (13)	0	1 (14)	4 (3)	6 (5)	2 (3)

[a]Angina pectoris. [b]Febrile neutropenia and procedural pain. [c]Supraventricular tachycardia and cellulitis. [d]Atrial fibrillation and cognitive disorder. [e]Rectal polyp and pyelonephritis acute. [f]Discontinuation due to pruritus. [g]Discontinuation due to insomnia and pruritus. [h]Discontinuations due to gastroesophageal reflux disease and pruritus.

Pooled Analyses From the Dose-Ranging and ENHANCE Studies: Participants With Cirrhosis ± PHT

Study design and BL demographics

Another pooled analysis of the open-label, phase 2 study (SEL 10 mg and 5 mg)[11] and the phase 3 ENHANCE study[12] evaluated the efficacy and safety of SEL in participants with compensated cirrhosis and evidence of PHT. Eligibility criteria and cirrhosis diagnosis were identical to those in the previous pooled analysis. The efficacy endpoints included the following: a composite endpoint (defined as an ALP level <1.67 × ULN, a ≥15% ALP decrease from BL, and a TB level ≤ULN), % change in ALP level, the proportion of participants achieving ALP normalization, and changes in liver biochemistry.[6]

Of the 53 participants with cirrhosis at BL, 22 participants (phase 2 study, n=15; ENHANCE study, n=7) also had PHT. No participants in the placebo group had cirrhosis and PHT.[6]

Table 5. Pooled Study in Participants With Cirrhosis: BL Demographics and Disease Characteristics by PHT Status[6]

Key Demographics and Characteristics		PHT (n=22)		Without PHT (n=31)		
		SEL 10 mg (n=9)	SEL 5 mg (n=13)	SEL 10 mg (n=15)	SEL 5 mg (n=9)	Placebo (n=7)
Female, n (%)		8 (89)	12 (92)	13 (87)	9 (100)	7 (100)
Age, mean ± SD, years		57±8	55±8	60±9	60±8	56±12
At PBC diagnosis, mean ± SD, years		48±7	44±8	50±10	49±9	47±10
AMA positive, n (%)		9 (100)	12 (92)	14 (93)	9 (100)	6 (86)
MELD score, mean ± SD		8±1.3	8±1.8	7±1.7	7±0.7	7±1.2
UDCA dose, mean ± SD, mg/kg/day		16±2	16±6	17±4	13±3	15±4
Concomitant UDCA, n (%)		8 (89)	12 (92)	13 (87)	9 (100)	7 (100)
Mean ± SD	Normal range					
ALP	37–116 U/L	284±77	273±117	308±118	285±134	278±68
ALT	6–41 U/L	47±22	46±29	62±24	40±20	46±18
TB	0.1–1.1 mg/dL	1±0.45	1±0.45	0.9±0.35	0.7±0.28	0.9±0.61
DB	0–0.2 mg/dL	0.4±0.27	0.4±0.23	0.3±0.17	0.2±0.13	0.3±0.29
GGT	7–38 U/L	207±136	196±126	237±137	285±346	219±165
AST	9–34 U/L	61±25	46±21	51±16	42±18	41±12
Platelets	140–400 × 10^9/L	152±72	96±27	231±60	255±57	279±72
INR	0.8–1.2	1.1±0.1	1.1±0.1	1±0.1	1±0.1	1±0.1
Albumin	3.5–5.5 g/dL	3.7±0.43	3.9±0.35	4.1±0.22	3.9±0.38	4.1±0.16

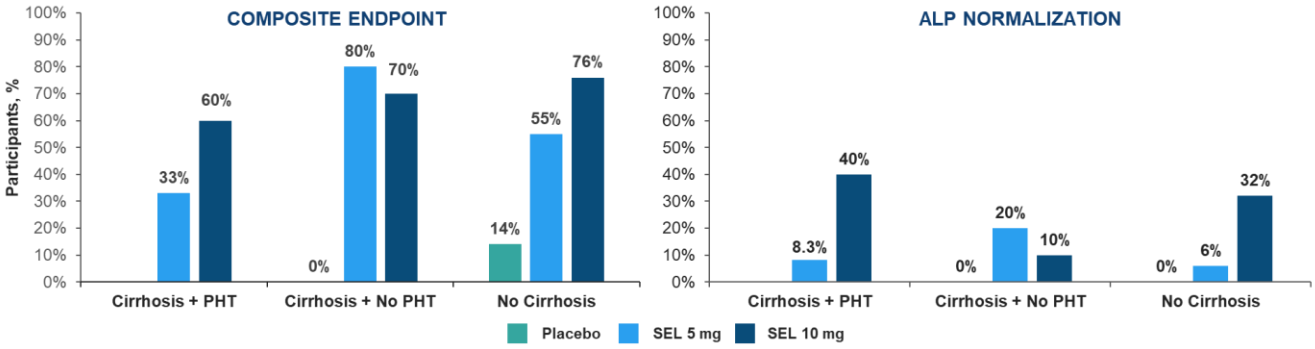
Note: Please refer to Table 3 for BL demographics and disease characteristics for participants without cirrhosis.

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Efficacy[6]

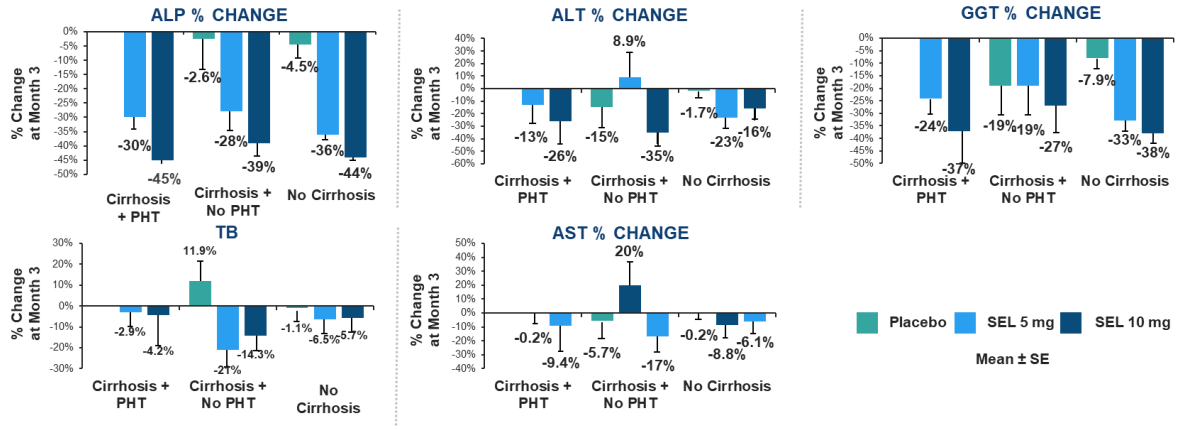
SEL treatment in participants with compensated cirrhosis and PHT resulted in improvements in biomarkers of cholestasis and hepatocellular injury (Figure 5).

Figure 5. Pooled Study in Participants With Cirrhosis: Composite Endpoint and ALP Normalization by PHT Status[6]



SEL treatment in participants with compensated cirrhosis and PHT resulted in improvements in biomarkers of cholestasis and hepatocellular injury (Figure 6).

Figure 6. Pooled Study in Participants With Cirrhosis: Percent Change From BL at Month 3 in ALP, ALT, GGT, TB, and AST Levels by PHT Status[6]



Safety[6]

Within Year 1, SEL was well-tolerated in participants with cirrhosis and PHT. No TRAEs of Grade ≥3 (CTCAE), liver-related SAEs, treatment-related SAEs, or SAEs with an outcome of death were reported in any group (Table 6).

Table 6. Pooled Study in Participants With Cirrhosis: Safety Outcomes Within Year 1[6]

Safety Outcome, n (%)	PHT (n=22)		Without PHT (n=31)		
	SEL 10 mg (n=9)	SEL 5 mg (n=13)	SEL 10 mg (n=15)	SEL 5 mg (n=9)	Placebo (n=7)
Participant with ≥1 AE	7 (78)	10 (77)	10 (67)	7 (78)	7 (100)
TRAE	1 (11)	6 (46)	2 (13)	4 (44)	4 (57)
AE that led to discontinuation of SEL	2 (22)	1 (8)	0	1 (11)	1 (14)
Any SAE	1 (11)	3 (23)	0	2 (22)	0

Safety Outcome, n (%)		PHT (n=22)		Without PHT (n=31)		
		SEL 10 mg (n=9)	SEL 5 mg (n=13)	SEL 10 mg (n=15)	SEL 5 mg (n=9)	Placebo (n=7)
AEs that occurred in ≥8% of SEL-treated participants overall	Diarrhea	3 (33)	2 (15)	0	0	1 (14)
	Urinary tract infection	2 (22)	1 (8)	0	0	0
	Nausea	1 (11)	3 (23)	2 (13)	0	0
	Pruritus	1 (11)	2 (15)	3 (20)	0	1 (14)
	Abdominal pain upper	0	4 (31)	2 (13)	1 (11)	0

ASSURE: Open-Label, Long-Term, Phase 3 Study

Study design and BL demographics[8]

The nonrandomized, parallel, open-label, phase 3 ASSURE study (NCT03301506) is evaluating the long-term efficacy and safety of SEL 10 mg in participants with PBC (N=337). Eligible participants included those from the RESPONSE study (n=158; includes those who continued on SEL 10 mg [continuous SEL, n=104] and those who switched from placebo to SEL [crossover to SEL, n=54]) and the following legacy studies: the phase 3 ENHANCE study; a phase 2, dose-ranging study; a long-term, phase 3 safety study; and a phase 1b hepatic impairment study (overall for legacy studies, n=179). Efficacy endpoints include composite biochemical response (defined as an ALP level <1.67 × ULN, an ALP level decrease by ≥15%, and a TB level ≤1 × ULN), ALP normalization, changes in liver enzymes (eg, ALP, TB, GGT, and ALT), and changes in pruritus NRS score for participants with a BL score ≥4.

Interim data analysis was performed and included all data through January 31, 2024. Analyses of overall study endpoints were performed for participants from the RESPONSE and legacy study groups; data for participants with cirrhosis (n=35; mean ± SD liver stiffness, 19.9±13.9 kPa) are from the legacy study group. Data from participants who received ≥1 dose of SEL 10 mg were analyzed.

Table 7. ASSURE: BL Demographics and Disease Characteristics in Legacy Study Participants With Cirrhosis[8]

Key Demographics and Characteristics	Participants With Cirrhosis[a] (n=35)
Age, mean ± SD, years	60.8±7.2
Female, n (%)	32 (91.4)
Race or ethnicity, White/Asian/American Indian or Alaska Native/Black or African American/Hispanic or Latinx, n (%)	25 (71.4)/6 (17.1)/3 (8.6)/1 (2.9)/4 (11.4)
BMI, mean ± SD, kg/m^2	27.2±5.6
Cirrhosis at BL, n (%)	35 (100)
Child-Pugh class, A/B, n (%)	31 (88.6)/4 (11.4)
Cirrhosis and PHT at BL, n (%[b])	8 (22.9)
ALP level,[c] mean ± SD, U/L	245.4±99.2[d]
TB level, mean ± SD, mg/dL	0.995±0.49[e]
GGT, mean ± SD, U/L	216.1±223
ALT, mean ± SD, U/L	36.6±15.5

[a]Five participants (14.3%) reported prior obeticholic acid and/or fibrates use, and 1 participant (2.9%) reported UDCA intolerance.
[b]Percentage calculated from the number of participants with cirrhosis.
[c]Mean ALP values are from ASSURE entry. At RESPONSE entry, the mean ± SD ALP levels were 314.6±123 U/L and 313.8±117.7 U/L in the SEL (n=128) and placebo arms (n=65), respectively.
[d]ALP level <350 U/L, n=29 (82.9%).
[e]TB level ≤ULN, n=24 (68.6%).

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Interim analysis in legacy study participants with cirrhosis[8]

Efficacy

There was a rapid and durable improvement (for up to 2 years) in cholestasis markers in participants with cirrhosis in the legacy studies.

Figure 7. ASSURE: Composite Biochemical Response in Legacy Study Participants With Cirrhosis[8]

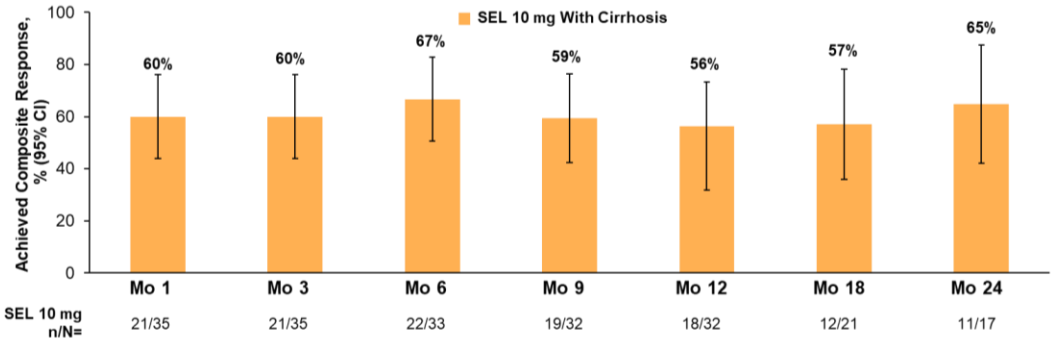


Figure 8. ASSURE: ALP Normalization in Legacy Study Participants With Cirrhosis[8]

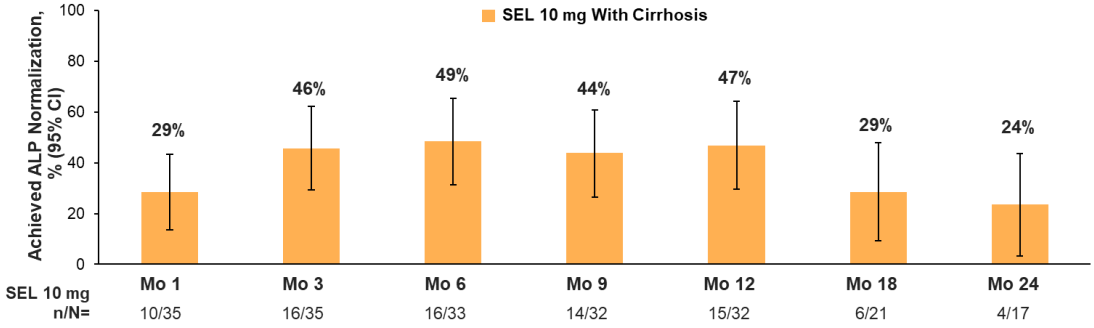


Figure 9. ASSURE: Change From BL in ALP and TB Levels in Legacy Study Participants With Cirrhosis[8]

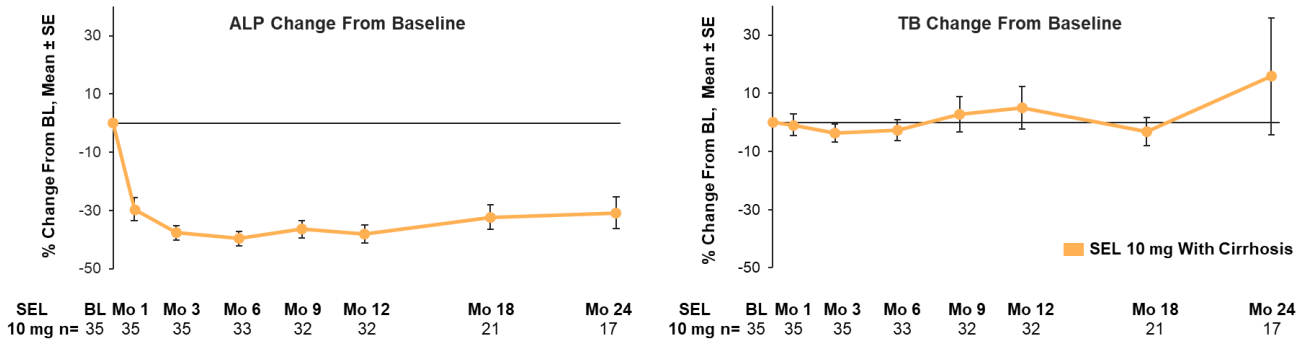
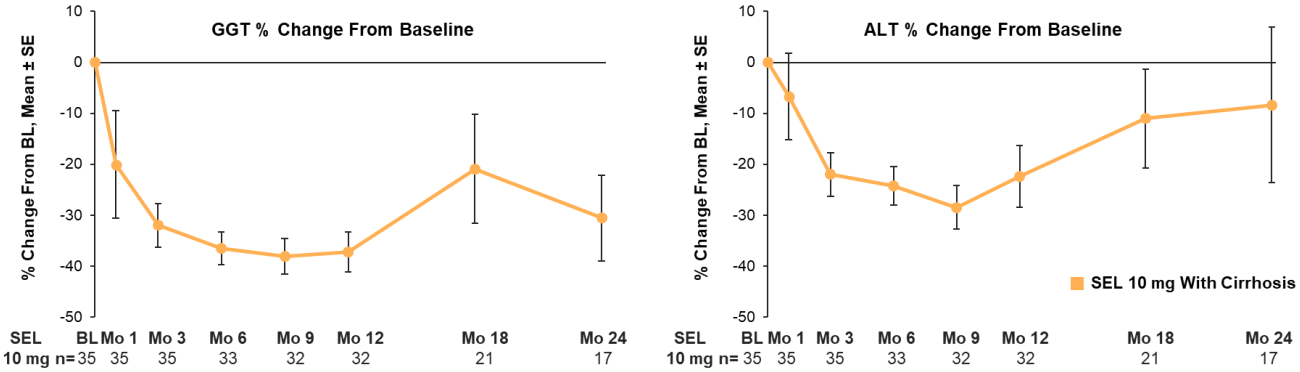


Figure 10. ASSURE: Percent Change From BL in GGT and ALT Levels in Legacy Study Participants With Cirrhosis[8]



Safety

Overall, AEs were reported in 80% of participants with cirrhosis (Table 8). Of the 7 participants who experienced SAEs, no SAEs were treatment related. Each SAE was observed in individual participants, without a particular pattern.

Table 8. ASSURE: AEs in Legacy Study Participants With Cirrhosis[8]

Safety Outcomes, n (%)	Legacy Study Participants With Cirrhosis (n=35)
AEs	28 (80)
Grade 3 AEs	5 (14.3)
AEs that led to treatment discontinuation	2 (5.7)
Liver-related AEs	8 (22.9)
Muscle-related AEs	3 (8.6)
SAEs	7 (20)

Eight participants experienced liver-related AEs, as presented in Table 9. Of the 5 Grade 3 AEs, 3 were liver-related: 1 was anorectal varices, another was an increase in blood bilirubin (also an SAE but the participant remained in the study), and the third was hepatorenal syndrome that was considered a protocol-defined PBC clinical outcome of ascites (also an SAE and led to discontinuation of treatment). The second AE that led to treatment discontinuation was an increase in blood bilirubin. A separate AE of increase in blood bilirubin led to treatment interruption.

Table 9. ASSURE: Liver-Related AEs in Legacy Study Participants With Cirrhosis[8]

AE, n (%)	Participants With Cirrhosis (n=35)
Liver-related AEs	8 (22.9)
Blood bilirubin increased	3 (8.6)
Ascites	2 (5.7)
ALT increased	2 (5.7)
AST increased	2 (5.7)
Anorectal varices	1 (2.8)
GGT increased	1 (2.8)
Hepatic cyst	1 (2.8)
Hepatic lesion	1 (2.8)
Hepatorenal syndrome	1 (2.8)
Ocular icterus	1 (2.8)
Varices esophageal	1 (2.8)
Portal hypertensive colopathy	1 (2.8)

Interim analysis in legacy and RESPONSE studies in participants with cirrhosis ± PHT through Year 4[9]

A pooled interim efficacy and safety analysis was conducted in 53 participants with cirrhosis at BL, including those with PHT, who enrolled in ASSURE following initiation of SEL in the legacy or RESPONSE studies (data cutoff: January 31, 2025; up to 48 months of exposure). BL was defined as SEL initiation in RESPONSE or ASSURE. Efficacy outcomes through Month 36 were as follows: composite biochemical response, ALP normalization, and changes in ALT, AST, GGT, and TB levels. Safety was evaluated for up to 4 years, and PBC clinical outcomes were adjudicated by an independent external committee. Overall, 29 participants had ≥1 BL feature consistent with PHT (platelets <140 × 10^3/mcL, albumin <1 × LLN, TB >1 × ULN, ascites, or history of varices or PHT; Table 10).

Table 10. ASSURE: BL Demographics and Disease Characteristics in Legacy and RESPONSE Studies in Participants With Cirrhosis ± PHT[9]

Key Demographics and Characteristics	Participants With Cirrhosis ± PHT (n=53)
Age, mean ± SD, years	60.4±9.07
Female, n (%)	48 (91)
BMI, mean ± SD, kg/m^2	27.2±5.47
Child-Pugh class, A/B, n (%)	49 (92)/4 (8)
Liver stiffness, mean ± SD, kPa	20.6±14.66
≥1 clinical sign of PHT at BL, n (%)	29 (55)
ALP, mean ± SD, U/L	267.5±113.69
TB, mean ± SD, mg/dL	0.98±0.449
GGT, mean ± SD, U/L	242.1±222.28
ALT, mean ± SD, U/L	39.6±17.17

Efficacy

Among evaluable participants, 49% achieved a composite biochemical response at Month 12, which was maintained through Month 36; 29% achieved ALP normalization at Month 12, and among those with available data at Month 36, 16% had normal ALP levels (Table 11).

Table 11. ASSURE: Composite Biochemical Response and ALP Normalization in Legacy and RESPONSE Studies in Participants With Cirrhosis ± PHT Through Month 36[9]

Timepoint	Composite Biochemical Response, n/N (%)	ALP Normalization, n/N (%)
Month 12	25/51 (49)	15/51 (29)
Month 18	22/47 (47)	15/47 (32)
Month 24	23/39 (59)	13/39 (33)
Month 30	13/29 (45)	8/29 (28)
Month 36	9/19 (47)	3/19 (16)

Mean percent change from BL was -35% for ALP level at Month 12 and -28% at Month 36, whereas mean percent changes from BL to Month 36 were -9% for GGT level and -29% for ALT level. TB and AST levels remained generally stable through Month 36, with mean values of 0.969 mg/dL and 39.6 U/L, respectively, at Month 36.

Safety

TEAEs were reported in the majority of participants with up to 4 years of follow-up (Table 12). No SAEs were considered treatment-related, and no consistent pattern of SAEs was observed. Four participants experienced protocol-defined PBC clinical outcomes at the data cutoff, of which none were considered treatment-related; 1 participant developed ascites requiring treatment at ~24 months, 1 had MELD scores ≥15 at 2 consecutive visits after 18 months, and 2 participants met criteria for both events after ~12 months of treatment.

Table 12. ASSURE: AEs in Legacy and RESPONSE Study Participants With Cirrhosis ± PHT Through 4 Years[9]

Safety Outcomes, n (%)	RESPONSE and Legacy Study Participants With Cirrhosis ± PHT (n=53)
Any AEs	50 (94)
Grade ≥3 AEs[a]	21 (40)
SAEs[b]	17 (32)
Treatment-related SAEs	0
AEs that led to treatment discontinuation[c,d]	8 (15)
AEs that led to death	0

[a]Per CTCAE.
[b]Three SAEs were associated with protocol-defined PBC clinical outcomes that were not attributed to SEL.
[c]Four discontinuations were due to liver-related events (disease progression [n=1], hepatorenal syndrome [n=1], and increased blood bilirubin [n=2]), all of which were assessed as unlikely to be related or unrelated to SEL.
[d]Time to discontinuation ranged from ~12 months to 3 years.

The exposure-adjusted incidence of liver-related AEs remained stable through Month 48 (15 per 100 PY) and was comparable to that observed in the placebo arm of the RESPONSE trial over 1 year (17 per 100 PY).

Interim analysis of LSM trends through Year 3

An interim analysis evaluated trends in LSM through 3 years of treatment with SEL 10 mg and included all participants (N=311) who had ≥1 post-BL LSM assessment (assessed via transient elastography using FibroScan; assessed locally every 12 months). Results were assessed in subgroups established post hoc using 3 LSM categories, which were based on established diagnostic thresholds for PBC: <10.7 kPa (F0–F2); ≥10.7 and <16.9 kPa (F3); and ≥16.9 kPa (F4).[10]

Table 13. ASSURE: BL Demographics and Disease Characteristics in Overall LSM Study Population and by BL LSM Subgroup[10]

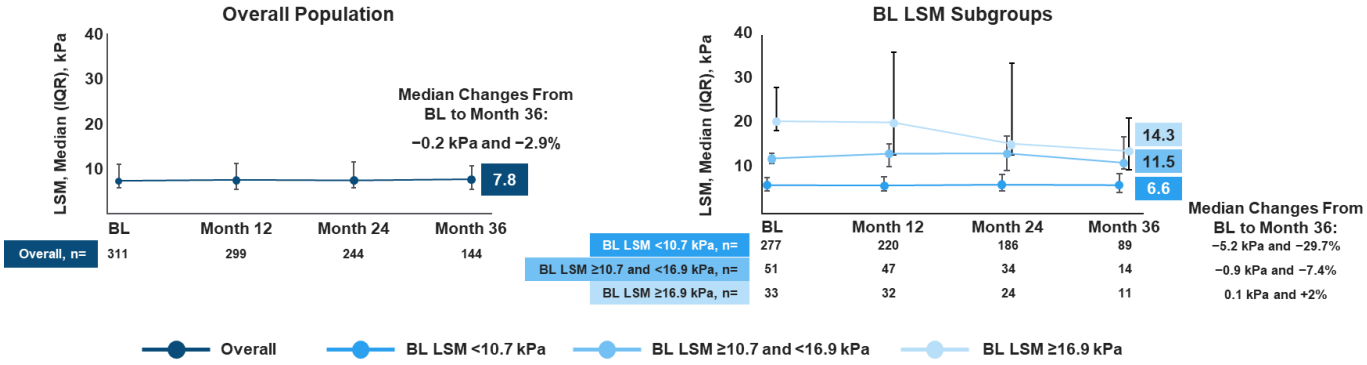
Key Demographics and Characteristics	Total (N=311)	LSM <10.7 kPa (n=227)	LSM ≥10.7 and <16.9 kPa (n=51)	LSM ≥16.9 kPa (n=33)
Age at enrollment, mean ± SD, years	58±9.6	58±9.3	58±11.7	60±8.1
Female, n (%)	294 (95)	217 (96)	50 (98)	27 (82)
LSM, median (IQR), kPa	7.5 (5.9–11.1)	6.6 (5.5–8)	12.6 (11.6–13.6)	21.1 (18.9–28.4)
ELF, mean ± SD	10±1.03	9.7±0.85	10.7±0.86	11±1.19
Cirrhosis at BL, n (%)	49 (16)	9 (4)	14 (27)	26 (79)
Child-Pugh class,[a] A/B, n (%)	46 (94)/3 (6)	9 (100)/0	14 (100)/0	23 (88)/3 (12)

Abbreviation: ELF=Enhanced Liver Fibrosis.
[a]Data are from participants with cirrhosis.

Liver fibrosis results[10]

Through up to 36 months of treatment, LSM remained stable over time in the overall LSM study population: median change from BL, -0.2 kPa; median percent change from BL, -2.9%. LSM tended to improve in the subgroup of participants with the highest BL LSM (≥16.9 kPa; Figure 11).

Figure 11. ASSURE: Changes in LSM Overall and by BL LSM Subgroup[10]



Most participants (85%; 97/114) who had LSM assessments available at BL and Month 36 remained in the same category or had an improvement in category; most participants in the highest LSM category at BL experienced improvement (Table 14).

Table 14. ASSURE: Shifts in LSM Categories at Month 36 Relative to BL LSM Categories[10]

LSM Category at BL	Category at Month 36, n/N (%)		
	<10.7 kPa	≥10.7 and <16.9 kPa	≥16.9 kPa
<10.7 kPa (n=89)	**76/89 (85)**	11/89 (12)	2/89 (2)
≥10.7 and <16.9 kPa (n=14)	**5/14 (36)**	**5/14 (36)**	4/14 (29)
≥16.9 kPa (n=11)	**3/11 (27)**	**4/11 (36)**	**4/11 (36)**

Note: Bolded text denotes stable or improved LSM category.

Of the 25 participants who had >30% worsening in LSM from BL to Month 36, 1 participant was from the highest BL LSM subgroup (≥16.9 kPa), whereas 20 (80%) were from the lowest BL LSM category (<10.7 kPa), and 10 of them remained in the lowest category at Month 36. Conversely, of the 19 participants who had >30% improvement in LSM from BL to Month 36, 5 were from the highest BL LSM subgroup; 2 of these participants improved to

the mid-range LSM subgroup (≥10.7 to <16.9 kPa), and 3 improved to the lowest LSM subgroup (<10.7 kPa) at Month 36.

Being younger at the initiation of SEL (*P*=0.0275) and having a higher ALP level at BL (*P*=0.0122) were significantly associated with a worsening of LSM by >30% from BL at Month 36, whereas the presence of cirrhosis at BL was not associated with a worsening of LSM by >30% from BL to Month 36.

Safety[7]

There was no increase in the frequency of exposure-adjusted TEAEs over the course of the study in participants from the RESPONSE study and several legacy studies (N=337; Table 15). No treatment-related SAEs were reported. One participant died due to autoimmune hemolytic anemia, and the cause was deemed unrelated to SEL.

Rates of liver-, muscle-, and renal-related AEs were stable or decreased over the study period, and most were Grade 1 or 2 in severity (Table 15).

Table 15. ASSURE: Safety Overview[7]

Participants With Exposure-Adjusted TEAEs Per 100 PY		SEL 10 mg			
		Overall (N=337); Exposure: 575.7 Years	Month 12 (N=337); Exposure: 313.7 Years	Month 24 (N=280); Exposure: 214.4 Years	Month 36 (N=124); Exposure: 47.6 Years
≥1 TEAE		50.2	85.8	70	63
Grade ≥3 TEAEs		8.3	9.6	8.4	8.4
TEAEs that led to study drug discontinuation		2.4	2.2	3.3	0
TEAEs that led to study discontinuation		1.6	1.6	1.9	0
TEAEs that led to death		0.2	0	0.5	0
SAEs		6.9	7.7	6.5	6.3
Most common TEAEs (≥3 participants per 100 PY)	COVID-19	11.5	16.3	7	10.5
	Pruritus	6.8	7.3	7.5	4.2
	Nausea	5.2	7	3.3	2.1
	Fatigue	4.9	4.8	6.1	0
	Urinary tract infection	4.7	5.1	5.1	6.3
	Diarrhea	4.5	7	2.3	0
	Headache	4.5	7	2.3	0
	Arthralgia	4	5.1	4.2	0
	Nasopharyngitis	4	5.4	3.7	2.1
	Abdominal pain upper	3.6	4.1	3.3	2.1
	Abdominal pain	3.5	3.8	3.3	2.1
≥1 liver-related TEAE		5	5.7	5.1	2.1
≥1 muscle-related TEAE		4.3	5.4	3.7	0
≥1 renal-related TEAE		0.2	0.3	0	0

Ongoing Studies Evaluating the Safety and Efficacy of SEL for PBC in Participants With Cirrhosis

AFFIRM Trial: Double-Blind, 36-Month, Phase 3 Study in Participants With Compensated Cirrhosis[13]

The randomized, double-blind, placebo-controlled AFFIRM study (NCT06051617) is evaluating the clinical effects of SEL in participants with PBC and compensated cirrhosis. Eligible participants who are aged ≥18 years, have a Child-Pugh score of A or B, have evidence of cirrhosis, and have no history of liver transplantation or active listing for transplant will be assigned to receive SEL (10 mg for Child-Pugh A or 5 mg for Child-Pugh B) or placebo for up to 36 months. The primary outcome measure is event-free survival through Month 36, defined as the time from treatment start to the first of any of the following events: death from any cause, liver transplantation, MELD score ≥15, ascites requiring intervention, or hospitalization for esophageal or gastric varices, hepatic encephalopathy, or spontaneous bacterial peritonitis. The study began in September 2023, is estimated to be completed in August 2030, and has an anticipated enrollment of 318 participants.

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Abbreviations

AE=adverse event
AUC=area under the concentration-time curve
ALP=alkaline phosphatase
AMA=antimitochondrial antibody
BL=baseline
C_{max}=maximum measured concentration
CTCAE=Common Terminology Criteria for Adverse Events
DB=direct bilirubin
GGT=γ-glutamyltransferase
LLN=lower limit of normal
LSM=liver stiffness measurement
MELD=Model for End-Stage Liver Disease
NRS=numeric rating scale
PBC=primary biliary cholangitis
PHT=portal hypertension
PY=patient-year(s)
SAE=serious adverse event
SEL=seladelpar
TB=total bilirubin
TEAE=treatment-emergent adverse event
TRAE=treatment-related adverse event
UDCA=ursodeoxycholic acid
ULN=upper limit of normal

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