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GILEAD | Medical Information

Livdelzi® (seladelpar) Impact on Fibrosis

This document is in response to your request for information regarding Livdelzi® (seladelpar [SEL]) for the treatment of primary biliary cholangitis (PBC) and its impact on fibrosis.

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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]

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

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).

Impact of SEL on Fibrosis

In the multicenter, placebo-controlled, phase 3 RESPONSE study that evaluated SEL 10 mg ± UDCA in participants with PBC who had inadequate response to or intolerance of UDCA, no meaningful changes from baseline to Month 12 in LSMs or ELF scores were observed.[2]

- In a post hoc analysis that compared the efficacy and safety of SEL in subgroups of participants by age (<45 years vs >45 years) and baseline LSM (≥10 kPa vs <10 kPa), participants who received SEL were more likely to achieve composite biochemical response regardless of age ($P \leq 0.0066$) or baseline LSM ($P \leq 0.0273$) than were participants who received placebo.[3]

In an interim analysis of the ongoing, open-label, phase 3 ASSURE study that evaluated the long-term efficacy and safety of SEL 10 mg in participants with PBC, including some with cirrhosis,[5] who entered the study from the RESPONSE study and several legacy studies (N=337), LSMs were generally stable through Month 36 of treatment.[6]

- Participants within the subgroup of the highest LSMs (≥16.9 kPa) at baseline tended to show an improvement in LSMs at Month 36, whereas those in subgroups with the lowest

(<10.7 kPa) and mid-range (≥10.7 and <16.9 kPa) LSMs at baseline had stable LSMs at Month 36.[6]
- Most of the participants (85%; 97/114) who had LSM assessments available at baseline and Month 36 remained in the same subgroup category or had an improvement in subgroup category.[6]
- In a subanalysis of the relationship between biochemical response at Month 12 and LSM at Month 36, results of a multivariate analysis showed that composite biochemical response at Month 12 was associated with stable or improved LSM at Month 36 using the ≥30% change threshold for clinically meaningful change (OR, 5.13; *P*<0.05).[7]

Product Labeling[1]

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 baseline 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, total bilirubin, 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.

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 portal hypertension, SEL exposures (C_{max} and AUC) were 1.7 to 1.8-fold higher in PBC patients with mild hepatic impairment with portal hypertension and 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 <1.2-fold in PBC patients with mild hepatic impairment with portal hypertension and PBC patients with moderate hepatic impairment following 10 mg SEL once daily dosing for 28 days.

Impact of SEL on Fibrosis

RESPONSE Study

Study design

RESPONSE was a phase 3, international, randomized, placebo-controlled study that evaluated the safety and efficacy of SEL 10 mg in participants with PBC and 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.[2]

Biopsy was one of three inclusion criteria that confirmed a diagnosis of PBC (only two criteria were required for the diagnosis). Cirrhosis at baseline was documented if participants met ≥1 of the following criteria[8]:

- Prior liver biopsy that showed cirrhosis (eg, Ludwig Stage 4 or Ishak Stage 5);
- History of or current decompensated liver disease, which included ascites, hepatic encephalopathy, esophageal varices, or other clinical conditions that were consistent with liver cirrhosis, portal hypertension, or both;
- Liver stiffness measurement of >16.9 kPa by FibroScan at screening;
- Platelet count <140 × 10^3 cells/cc^3 and a serum albumin level <3.5 g/dL, an INR >1.3 (not due to antithrombotic agent use), a total bilirubin level >1 × ULN;
- Radiologic evidence of cirrhosis (ie, a nodular liver) with concurrent splenomegaly; or
- By clinical determination by the investigator.

There is currently no information regarding the appearance of participant biopsy results.

According to the Supplementary Appendix for the RESPONSE study, “liver histology changes based on pathology review of biopsy tissues” was listed as an exploratory endpoint not reported in the study because they were considered exploratory data that did not impact the overall interpretation of the study results.[8]

Exploratory endpoints that were reported in the study included changes in markers of fibrosis through Month 12. Fibrosis was measured non-invasively via liver stiffness by TE and via the ELF score.[2]

Liver fibrosis results

At Month 12, no meaningful changes from baseline in LSMs or ELF scores were observed (exploratory endpoints; Table 1).[2]

Table 1. RESPONSE: Liver Stiffness and ELF Score at Month 12[8]

		n	SEL 10 mg	n	Placebo
Liver stiffness by TE[a]	Baseline, mean ± SD, kPa	115	9.84±6.16	62	8.74±4.18
	At Month 12, mean ± SD, kPa	99	9.76±8	55	9.84±10
	Change from baseline, mean ± SD, kPa	96	0.24±4.39	55	1.34±7.56
	Change from baseline, mean ± SD, %	96	4.58±37.56	55	9.87±42.93
ELF score[b]	Baseline, mean ± SD	128	10.16±1.03	65	10.23±0.85
	At Month 12, mean ± SD	113	10.14±1.07	57	10.21±0.99
	Change from baseline, mean ± SD	113	0.06±0.6	57	-0.002±0.56
	Change from baseline, mean ± SD, %	113	0.74±6	57	0.007±5.36

[a]Score range is 1.5 to 75 kPa; higher scores indicate more severe liver stiffness. Liver stiffness was categorized into F0, F1, F2, F3, and F4, where the cutoff values were 7.1, 8.8, 10.7, and 16.9 kPa, respectively.
[b]ELF score is based on three laboratory parameters (ie, hyaluronic acid, Type III procollagen peptide, and tissue inhibitor of metalloproteinase 1) that reflect the status of liver fibrosis. Higher scores indicate greater fibrosis.

Safety[2]

Safety profiles were similar between participants with and those without cirrhosis at baseline (Table 2). One participant in the SEL arm who had cirrhosis at baseline experienced variceal bleeding after completion of the treatment period; this was the only AE that was deemed related to PBC.

Table 2. RESPONSE: Incidence of AEs Occurring in ≥2 Participants With Cirrhosis in Any Treatment Arm by Presence of Cirrhosis[2]

AEs, n (%)	Participants With Cirrhosis		Participants Without Cirrhosis	
	SEL 10 mg (n=18)	Placebo (n=9)	SEL 10 mg (n=110)	Placebo (n=56)
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

Post hoc analysis in two high-risk subgroups[3]

A post hoc analysis compared the efficacy and safety of SEL in participants aged <45 years with those of participants aged >45 years at PBC diagnosis, as well as in participants with LSM ≥10 kPa with those of participants with LSM <10 kPa at study entry. Efficacy endpoints at Month 12 included composite biochemical response (ALP <1.67 × ULN or an ALP reduction ≥15% from baseline and total bilirubin ≤ ULN), ALP normalization, deep response (ALP ≤ ULN and total bilirubin ≤ ULN), and mean percent changes in parameters of interest (ie, ALP, total bilirubin, ALT, and GGT levels).

At Month 12, a composite biochemical response was more likely to be achieved with SEL treatment than with placebo in both the subgroup of participants aged <45 years (risk difference, 33%; 95% CI: 6–52%; *P*=0.0066) and the subgroup of participants aged >45 years (risk difference, 44%; 95% CI: 25–60%; *P*<0.0001). In addition, a composite biochemical response was more likely to be achieved with SEL treatment than with placebo in both the subgroup of participants with baseline LSM ≥10 kPa (risk difference, 35%; 95% CI: 2–56%; *P*=0.0273) and the subgroup with baseline LSM <10 kPa (risk difference, 43%; 95% CI: 25–58%; *P*<0.0001).

Compared with placebo, SEL treatment led to a greater decline in ALP, GGT, and ALT levels across all subgroups of participants, and total bilirubin and AST levels remained stable through Month 12. Treatment with SEL led to marked and sustained deep response across all subgroups of patients up to Month 12.

The incidences of hepatic, muscle, or renal AEs were similar between participants who received SEL and placebo, regardless of subgroup. There were no treatment-related SAEs.

ASSURE Study

Study design and demographics

The ongoing, nonrandomized, open-label, phase 3 ASSURE study (NCT03301506) is evaluating the long-term efficacy and safety of SEL 10 mg in participants with PBC. 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).[5]

Cirrhosis was defined using the same criteria noted in the RESPONSE study design summary above, and criteria included having a prior liver biopsy that showed cirrhosis (eg, Ludwig Stage 4 or Ishak Stage 5).[6]

An interim analysis evaluated trends in LSMs through 3 years of treatment with SEL 10 mg and included all participants (N=311) who had ≥1 post-baseline LSM assessment (assessed via TE using FibroScan; assessed locally every 12 months). Results were assessed in subgroups established post hoc using three 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).[6]

Table 3. ASSURE: Baseline Demographics and Disease Characteristics in Overall LSM Study Population and by Baseline LSM Subgroup[6]

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 baseline, 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)

[a]Data are from participants with cirrhosis.

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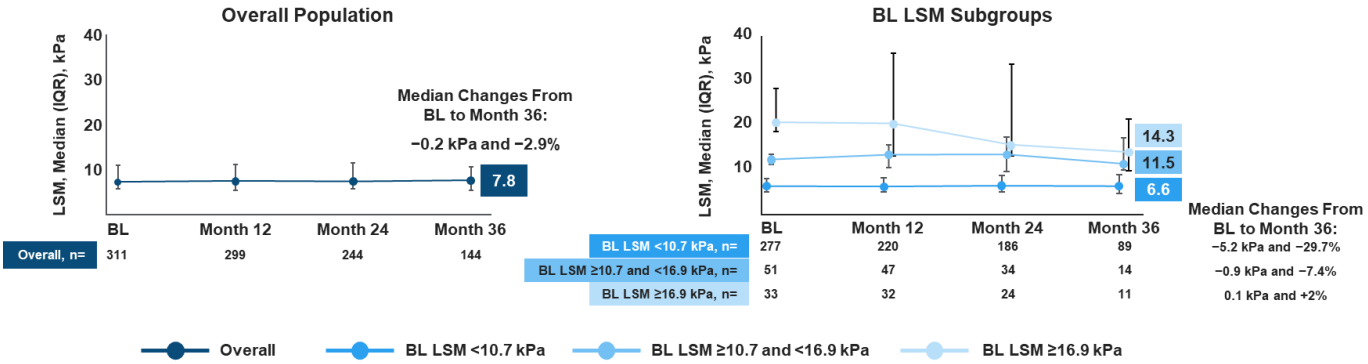
Liver fibrosis results[6]

Through up to 36 months of treatment, LSMs were stable over time in the overall LSM study population: median change from baseline, -0.2 kPa; median percent change from baseline, -2.9%. LSMs tended to improve in the subgroup of participants with the highest baseline LSMs (≥16.9 kPa) and remained stable in the subgroups with the lowest and mid-range baseline LSMs (Figure 1).

Figure 1. ASSURE: Changes in LSMs Overall and by Baseline LSM Subgroup[6]



Abbreviation: BL=baseline.

Most of the participants (85%; 97/114) who had LSM assessments available at baseline and Month 36 remained in the same subgroup category or had an improvement in subgroup category (Table 4).

Table 4. ASSURE: Shifts in LSM Categories at Month 36 Relative to Baseline LSM Categories[6]

LSM Category at Baseline	LSM 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: Cells with bolded text denote stable or improved LSM category.

Of the 25 participants who had >30% worsening in LSMs from baseline at Month 36, 20 participants (80%) were among those in the lowest baseline LSM subgroup (<10.7 kPa), and 10 of these maintained that status at Month 36. Conversely, of the 19 participants who had >30% improvement in LSMs from baseline, 11 were among those in the lowest baseline LSM subgroup, and 17/19 participants (89%) had LSMs <10.7 kPa at Month 36.

Younger age at initiation of SEL (*P*=0.0275) and higher ALP level at baseline (*P*=0.0122) were among the baseline characteristics that were significantly associated with a worsening of LSMs by >30% from baseline at Month 36.

Safety[5]

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 5). 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 (Table 5).

Table 5. ASSURE: Safety Overview[5]

		SEL 10 mg			
		Overall (N=337)	Month 12 (N=337)	Month 24 (N=280);	Month 36 (N=124)
Exposure, years		575.7	313.7	214.4	47.6
Participants with exposure-adjusted TEAEs per 100 PY					
≥1 TEAE		50.2	85.8	70	63
SAE		6.9	7.7	6.5	6.3
Grade ≥3 TEAE		8.3	9.6	8.4	8.4
TEAE that led to study drug DC		2.4	2.2	3.3	0
TEAE that led to study DC		1.6	1.6	1.9	0
TEAE that led to death		0.2	0	0.5	0
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

Abbreviations: DC=discontinuation; PY=patient-year(s).

Subanalysis of biochemical response at Month 12 and LSM trends[7]

A subanalysis evaluated the association between biochemical response at Month 12 and LSM changes at Month 36 among participants with ≥1 post-baseline LSM at data cutoff (January 31, 2025). LSM changes by biochemical response (ALP <1.67 × ULN, ≥15% reduction in ALP from baseline, and total bilirubin ≤ ULN) were assessed among evaluable participants at Month 12 and through Month 36 (N=307). A clinically meaningful change in LSM was defined by a ≥30% threshold; additional analyses used ≥20% and >0% (any change) as thresholds. The odds of achieving LSM stability or improvement at Month 36 were assessed by comparing participants with and without composite biochemical response and ALP normalization at Month 12.

At Month 12, 68.7% of evaluable participants (211/307) achieved a composite biochemical response. Among these participants, LSM remained stable, with a median change of -7% at Month 36; 18.7% improved by ≥30%, 65.9% remained stable, and 15.4% worsened by ≥30%. Among participants who did not achieve a composite biochemical response at Month 12, LSM increased, with a median change of +23.6% at Month 36; 9.1% improved by ≥30%, 45.4% remained stable, and 45.5% worsened by ≥30%.

In a univariate analysis of participants with an LSM change from baseline of ≥30%, older age at baseline, lower ALP level at baseline, achievement of composite biochemical response, ALP level <1.67 × ULN, ≥15% ALP reduction, total bilirubin ≤ ULN, or ALP <1.5 × ULN at Month 12 were each associated with LSM stability or improvement at Month 36 (each, $P<0.05$). A multivariate analysis showed that composite biochemical

response at Month 12 was associated with stable or improved LSM at Month 36 using the ≥30% change threshold (OR, 5.13; *P*<0.05).

References

1. Enclosed. LIVDELZI® (seladelpar) capsules, for oral use. US Prescribing Information. Foster City, CA.
2. Hirschfield GM, Bowlus CL, Mayo MJ, et al. A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis. *N Engl J Med.* 2024;390(9):783-794.
3. Mayo MJ, Hirschfield GM, Galambos M, et al. Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis and Risk Factors for Progression Including Younger Age at Diagnosis or Higher Liver Stiffness in the Pivotal RESPONSE Study [Poster SAT-363]. Paper presented at: European Association for the Study of the Liver (EASL) Congress 2026; May 27-30, 2026; Barcelona, Spain.
4. Trauner M, Liang Y, Ravichandar D, et al. Seladelpar Downregulates Inflammatory and Fibrotic Pathways: Insights From Serum Proteomic Analysis [Poster 1164]. Paper presented at: The Liver Meeting, American Association for the Study of Liver Diseases (AASLD); November 5-9, 2026; Denver, CO.
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6. Bowlus CL, Hirschfield GM, Villamil AM, et al. 36 Months of Treatment With Seladelpar Is Associated With Stable or Improved Liver Stiffness in Patients With Primary Biliary Cholangitis. [Poster #5031]. Paper presented at: The Liver Meeting, American Association for the Study of Liver Diseases; November 7–11, 2025; Washington, DC.
7. Hirschfield GM, Bowlus CL, Corpechot C, et al. 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 [Poster THU-270]. Paper presented at: European Association for the Study of the Liver (EASL) Congress 2026; 27-30 May, 2026; Barcelona, Spain.
8. Hirschfield GM, Bowlus CL, Mayo MJ, et al. A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis.[Supplementary Appendix]. *N Engl J Med.* 2024;390(9):783-794.

Abbreviations

AE=adverse event
ALP=alkaline phosphatase
ELF=Enhanced Liver Fibrosis
GGT=γ-glutamyltransferase
LSM=liver stiffness measurement
OR=odds ratio
PBC=primary biliary cirrhosis
SAE=serious adverse event
SEL=seladelpar
TE=transient elastography
TEAE=treatment-emergent adverse event
UDCA=ursodeoxycholic acid
ULN=upper limit of normal

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Livdelzi US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/pbc/livdelzi/livdelzi_pi.

Follow-Up

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