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Livdelzi® (seladelpar) Use in Patients With MASLD

This document is in response to your request for information regarding the safety and efficacy of Livdelzi® (seladelpar [SEL]) as treatment for primary biliary cholangitis (PBC) in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

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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

Clinical Data on SEL Use in Participants With PBC and MASLD

RESPONSE was a phase 3, multicenter, placebo-controlled study that evaluated SEL 10 mg ± UDCA in participants with PBC with an inadequate response to or intolerance of UDCA.[1]

- In a post hoc subgroup analysis that evaluated outcomes according to metabolic syndrome status, 42 participants (22%) had PBC and metabolic syndrome. Among these participants, the rate of composite biochemical response was higher in the SEL arm than in the placebo arm through Month 12. Of the participants in the SEL arm, rates of composite biochemical response were lower in participants with metabolic syndrome than in those without metabolic syndrome at all assessed time points through Month 12.[2]
- Changes from BL to Month 12 in laboratory parameters and the incidences of AEs and liver-related laboratory abnormalities were similar among participants with and without metabolic syndrome.[2]

Real-World Data on SEL Use in Patients With PBC and MASLD

In a retrospective cohort study of patients with PBC who received SEL, a subgroup of 381 patients had PBC and MASLD. At 6 months, biochemical response was achieved by 64.2% of patients and ALP normalization at 6 months was achieved by 38.4% of patients. No patients at 6 months had an ALT level >5 × ULN, and no cases of drug-induced liver injury or renal or muscle safety concerns were observed.[3]

Clinical Data on SEL Use in Participants With PBC and MASLD

RESPONSE Study

Study design and demographics

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. Participants were eligible if they had PBC, were aged 18 to 75 years, had received UDCA for ≥12 months or had an intolerance of UDCA (last dose >3 months from screening), and had an ALP level ≥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 (eg, albumin level < lower limit of normal and TB level > ULN), hepatic decompensation, or other chronic liver disease were excluded.[1]

The primary composite endpoint was the proportion of participants who achieved a biochemical response, which was 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 (eg, moderate-to-severe pruritus) at BL.[1]

SEL or placebo was administered in combination with UDCA in 93.8% of participants and as monotherapy in 6.2% of participants who were unable to tolerate UDCA.[1] A total of 118 participants completed 1 year of treatment with SEL 10 mg.[4]

Post hoc subgroup analysis: concurrent metabolic syndrome[2]

A post hoc subgroup analysis was conducted to evaluate the efficacy and safety of SEL in participants with PBC and concurrent metabolic syndrome, defined as meeting three of the criteria in Table 1. Efficacy endpoints included composite biochemical response, ALP normalization, and changes in laboratory parameters (ie, ALP, TB, GGT, ALT, and AST) from BL to Month 12. Overall, 42 of the 193 enrolled participants (22%) had evidence of metabolic syndrome at BL (Table 2).

Table 1. RESPONSE Post Hoc Subgroup Analysis: Metabolic Syndrome Criteria Met in SEL and Placebo Groups[2]

Metabolic Syndrome Criteria Met,[a] n (%)	Metabolic Syndrome (n=42)	
	SEL 10 mg (n=24)	Placebo (n=18)
Diabetes mellitus[b]	21 (88)	16 (89)
Hypertension[c]	21 (88)	14 (78)
BMI >27.6 kg/m^2	20 (83)	15 (83)
Triglycerides ≥150 mg/dL	11 (46)	11 (61)
Low HDL[d]	8 (33)	4 (22)

[a]Participants had to meet three criteria to be included in the analysis; criteria were not mutually exclusive.
[b]Defined as blood glucose ≥100 mg/dL or a medical history of diabetes and concomitant medication for hyperglycemia.
[c]Defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or a medical history of hypertension and concurrent antihypertensive medication at study entry.
[d]Defined as HDL <40 mg/dL in males or <50 mg/dL in females.

Table 2. RESPONSE Post Hoc Subgroup Analysis: BL Demographics and Disease Characteristics by Metabolic Syndrome Status[2]

Key Demographics and Characteristics	Metabolic Syndrome (n=42)		No Metabolic Syndrome (n=151)	
	SEL 10 mg (n=24)	Placebo (n=18)	SEL 10 mg (n=104)	Placebo (n=47)
Age, mean ± SD, years	57±10.1	59±8.3	57±10	56±9.4
Female, n (%)	24 (100)	14 (78)	99 (95)	46 (98)
BMI, mean ± SD, kg/m^2	30.6±4.51	30.3±4.4	26.4±5.52	25.5±4.27
Cirrhosis,[a] n (%)	6 (25)	4 (22)	12 (12)	5 (11)
Liver stiffness, mean ± SD, kPa	12.5±8.91	10.2±5.73	9.2±5.18	8.2±3.43
ALP, mean ± SD, U/L	341.9±162.52	301.2±123.55	308.2±111.93	318.7±116.36
ALT, mean ± SD, U/L	48.7±26.04	45.9±19.84	47.2±22.97	49.2±24.01
AST, mean ± SD, U/L	40.4±17.4	38.9±15.11	39.4±15.92	42.7±16.4
GGT, mean ± SD, U/L	338.4±333.95	351.7±325.56	253±211.57	262.9±212.72
TB, mean ± SD, mg/dL	0.8±0.31	0.8±0.47	0.8±0.32	0.7±0.22

[a]All participants with cirrhosis had Child-Pugh Class A.

Among participants with metabolic syndrome, the rate of composite biochemical response was higher in the SEL arm than in the placebo arm through Month 12. Among participants in the SEL arm, rates of composite biochemical response were lower in participants with metabolic syndrome than in participants without metabolic syndrome at Month 1 (50% and 62%, respectively), Month 3 (54% and 63%), Month 6 (58% and 68%), Month 9 (46% and 65%), and Month 12 (42% and 66%).

Among participants who received SEL, changes in laboratory parameters from BL to Month 12 were similar between participants with and without metabolic syndrome (Table 3).

Table 3. RESPONSE Post Hoc Subgroup Analysis: Laboratory Parameters Changes From BL to Month 12 in the SEL Arm by Metabolic Syndrome Status[2]

Laboratory Parameter		SEL	
		Metabolic Syndrome	No Metabolic Syndrome
ALP, mean change from BL, %		-41	-44
ALP normalization, %	Month 1	0	10
	Month 3	17	19
	Month 6	21	28
	Month 9	25	29
	Month 12	17	27
ALT, mean change from BL, %		-24	-25
AST, mean, U/L		36	37
GGT, mean change from BL, %		-39	-40
TB, mean, mg/dL		0.9	0.7

The incidences of AEs and liver-related laboratory abnormalities were generally similar between participants in the SEL and placebo arms, regardless of metabolic syndrome status (Table 4). There were no treatment-related SAEs or AEs that led to death in any group.

Table 4. RESPONSE Post Hoc Subgroup Analysis: AEs and Liver-Related Laboratory Abnormalities by Metabolic Syndrome Status[2]v

Parameter, n (%)		Metabolic Syndrome (n=42)		No Metabolic Syndrome (n=151)	
		SEL 10 mg (n=24)	Placebo (n=18)	SEL 10 mg (n=104)	Placebo (n=47)
Any AE		22 (92)	15 (83)	89 (86)	40 (85)
Grade ≥3 per CTCAE		1 (4)	2 (11)	13 (13)	3 (6)
SAEs		1 (4)	1 (6)	8 (8)	3 (6)
AEs that led to treatment discontinuation		0	1 (6)	4 (4)	2 (4)
AEs of special interest	Liver-related AEs	2 (8)	4 (22)	6 (6)	2 (4)
	Cardiovascular-related AEs	1 (4)	2 (11)	12 (12)	3 (6)
Liver-related laboratory abnormalities	ALT or AST >3 × ULN	1 (4)	1 (6)	8 (8)	6 (13)
	BL ALT and AST >ULN with post-BL ALT or AST >2 × BL	1 (4)	0	2 (2)	4 (9)

Abbreviation: CTCAE=Common Terminology Criteria for Adverse Events.

Real-World Data on SEL Use in Patients With PBC and MASLD

Retrospective Cohort Study[3]

Study design and demographics

A retrospective cohort study evaluated the effectiveness and safety of SEL in various subgroups of patients with PBC and ALP >1.67 × ULN, including patients with MASLD (n=381), using the Epic Cosmos national electronic healthcare database (N=666). The primary endpoint was biochemical response (ALP <1.67 × ULN and ≥15% ALP reduction with normal bilirubin levels) at 6 months. Secondary endpoints included ALP normalization at 3 months and at 6 months and hepatotoxicity (ALT >3 × ULN and >5 × ULN). BL demographics are summarized in Table 5.

Table 5. BL Demographics and Disease Characteristics (Martins et al)[3]

Key Demographics and Characteristics	SEL (n=381)
Age, mean ± SD, years	64.5±10.4
Female, n (%)	339 (89)
White race,[a] n (%)	286 (75.1)
Hispanic/Latinx ethnicity, n (%)	40 (10.5)
Obesity, n (%)	242 (63.5)
Dyslipidemia, n (%)	305 (80.1)
ALP, mean ± SD, U/L	226.5±134.2
ALP >3 × ULN, n (%)	41 (10.8)
Cirrhosis, n (%)	173 (45.4)
History of obeticholic acid use, n (%)	123 (32.3)
History of fibrates use, n (%)	24 (6.3)

[a]Additional race data were not provided.

Results

At 6 months, among patients with both PBC and MASLD, biochemical response was achieved by 64.2% of patients, and ALP normalization was achieved by 38.4%.

Across all assessed subgroups, including those with PBC and MASLD, the proportion of patients with ALT >3 × ULN decreased from 3.5% at BL to 1.1% at 6 months (*P*=0.043), and no patients at 6 months had an ALT level >5 × ULN. No cases of drug-induced liver injury were observed, and there were no renal or muscle safety concerns.

References

1. 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.
2. Mayo MJ, Lawitz EJ, Villamil AM, et al. Efficacy and Safety of Seladelpar vs Placebo in Patients With Primary Biliary Cholangitis and Metabolic Syndrome in the Pivotal Phase 3 RESPONSE Study [POSTER: SAT-362]. European Association for the Study of the Liver; May 27-30, 2026; Barcelona, Spain.
3. Martins A, Levy C. Real-World Effectiveness and Safety of Seladelpar in Primary Biliary Cholangitis: A Nationwide Electronic Health Record-Based Study. [Poster TOP-277-YI]. European Association for the Study of the Liver (EASL) Congress; May 27-30, 2026; Barcelona, Spain.
4. Gilead Sciences Inc. Data on File.

Abbreviations

AE=adverse event
ALP=alkaline phosphatase
BL=baseline
GGT=γ-glutamyltransferase
MASLD=metabolic dysfunction-associated steatotic liver disease
NRS=numerical rating scale
PBC=primary biliary cholangitis
SAE=serious adverse event
SEL=seladelpar
TB=total bilirubin
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

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

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