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Livdelzi® (seladelpar) Switching From Fibrates

This document is in response to your request for information regarding switching from fibrates to Livdelzi® (seladelpar [SEL]) for the treatment of primary biliary cholangitis (PBC).

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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 Studies on Switching From Fibrates to SEL

In a phase 3 study and its ongoing, open-label extension, prior use of fibrates did not impact the biochemical response to SEL compared to placebo through 12 months of treatment.[1,2]

- Regardless of prior fibrate use, biochemical response was sustained through 18 months of treatment in participants who received SEL and improved in participants who switched from placebo to SEL at Month 12.[3]
- The incidence of overall AEs and liver-related AEs were similar between the prior fibrates and/or OCA use group and the no prior fibrates and/or OCA use group.[3]

Clinical Studies on Switching From Fibrates to SEL

Currently, there is no specific guidance on switching from fibrates to SEL.

RESPONSE and ASSURE Studies

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 ursodeoxycholic acid. 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.[1] The use of fibrates before screening was an exclusion criterion and a washout period of 6 weeks was required prior to enrollment.[3] At completion of the RESPONSE study, participants were eligible to enroll in the ongoing phase 3, long-term, open-label study, ASSURE, in which participants either continued treatment with SEL 10 mg (n=104) or switched from placebo to SEL 10 mg (n=54).[3]

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]

Pruritus intensity, assessed using pruritus NRS data, were collected daily via the use of an electronic diary during the run-in period and through Month 6 and then for 7 consecutive days each month through to the end of the treatment period.[3]

In the SEL 10 mg and placebo groups, fibrates were previously used in 5.5% (n=7) and 7.7% (n=5) of participants, respectively, and fibrates and/or OCA were previously used in 15.6% (n=20) and 20% (n=13) of participants, respectively.[3] Of the 33 participants who had prior fibrate and/or OCA use in the RESPONSE study, 27 enrolled in the ASSURE study.[3]

Table 1. RESPONSE: BL Demographics and Disease Characteristics[3]

Key Demographics and Characteristics	Prior Treatment With Fibrates/OCA		No Prior Treatment With Fibrates/OCA	
	SEL 10 mg (n=20)	Placebo (n=13)	SEL 10 mg (n=108)	Placebo (n=52)
Age, mean ± SD, years	55.8±9.3	55.4±11.1	56.7±10.2	57.4±8.7
Female, n (%)	18 (90)	12 (92)	105 (97)	48 (92)
Duration of PBC, mean ± SD, years	9.5±6.3	12.3±7.9	7.9±6.8	7.7±5.8
Prior use of fibrates	7 (35)	5 (38)	–	–
Duration of fibrate/OCA treatment, mean ± SD, years	2.7±2.4	2.0±1.4	–	–
Duration of fibrate/OCA washout prior to study, mean ± SD, years	0.9±0.8	0.8±0.8	–	–
Cirrhosis at baseline,[a] n (%)	2 (10)	0	16 (15)	9 (17)
ALP, mean ± SD, U/L	371.0±145.0	348.6±141.9	304.1±116.2	305.1±110.7
TB, mean ± SD, mg/dL	0.8±0.2	0.6±0.2	0.8±0.3	0.8±0.3

[a]All participants with cirrhosis at baseline were Child-Pugh Class A.

Efficacy

The primary composite endpoint was achieved by more participants in the SEL arm than in the placebo arm (responder rate [95% CI]: 61.7% [53.3–70.1%] vs 20% [10.3–29.7%]).[1] Prior use of fibrates did not impact the response to SEL compared to placebo in regard to the primary endpoint (Table 2) or the key secondary endpoint of change from BL to Month 6 in weekly mean pruritus NRS scores among participants with a pruritus NRS score >4 at BL (Figure 1).[1,2] Fewer participants with prior fibrates and/or OCA use than those with no prior use achieved the key secondary endpoint of ALP normalization at Month 12 (Table 2), although the ALP percent change from BL was similar.[3] Declines in ALT and GGT were similar between the prior fibrates and/or OCA use and no the prior fibrates and/or OCA use groups, and the TB percent change was generally stable, with some variation.

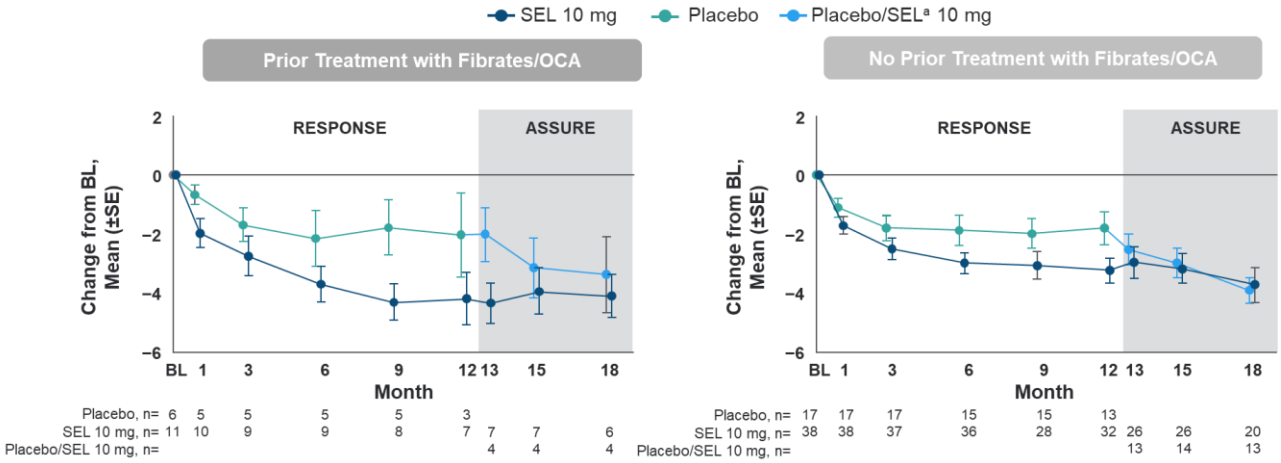
Table 2. RESPONSE and ASSURE: Primary Composite[a] and Key Secondary Endpoints According to Prior OCA and/or Fibrates Use[3]

Outcome, n/N (%)		Month 12 (RESPONSE)		Month 18 (ASSURE)	
		SEL 10 mg	Placebo	SEL 10 mg	Placebo/SEL[b]
Composite biochemical response	Prior treatment with fibrates/OCA	9/20 (45)	1/13 (8)	9/15 (60)	7/11 (64)
	No prior treatment with Fibrates/OCA	70/108 (65)	12/52 (23)	54/87(62)	32/41 (78)

Outcome, n/N (%)		Month 12 (RESPONSE)		Month 18 (ASSURE)	
		SEL 10 mg	Placebo	SEL 10 mg	Placebo/SEL[b]
ALP normalization	Prior treatment with fibrates/OCA	2/20 (10)	0/13 (0)	2/15 (13)	1/11 (9)
	No prior treatment with fibrates/OCA	30/108 (28)	0/52 (0)	32/87(37)	13/41 (32)

[a]Defined as an ALP level <1.67 × ULN, an ALP level decrease by ≥15%, and a TB level ≤1 × ULN.
[b]Includes participants who received placebo in RESPONSE and were switched to SEL 10 mg at ASSURE enrollment.

Figure 1. RESPONSE and ASSURE: Change in Pruritus NRS Score Among Participants With BL Pruritus NRS Score >4 According to Prior OCA and/or Fibrates Use[3]



[a]Includes participants who received placebo in RESPONSE and were switched to SEL 10 mg at ASSURE enrollment.

Safety[3]

Incidences of overall AEs and liver-related AEs were similar between the prior fibrates and/or OCA use and the no prior use groups (Table 3). The occurrence of ALT or AST >3 × ULN was similar between the SEL and placebo groups in both RESPOSNSE (SEL: prior fibrates/OCA, 20% [4/20]; no prior fibrates/OCA, 5% [5/108]; placebo: prior fibrates/OCA, 15% [2/13]; no prior fibrates/OCA, 10% [5/52]) and ASSURE (SEL: prior fibrates/OCA, 6% [1/16]; no prior fibrates/OCA, 1% [1/88]; placebo/SEL: 0). No drug-related SAEs or fatal AEs were reported.

Table 3. RESPONSE and ASSURE: Safety Overview[3]

AEs, n (%)	Prior Treatment With Fibrates/OCA		No Prior Treatment With Fibrates/OCA	
RESPONSE Study (Month 12)	SEL 10 mg (n=20)	Placebo (n=13)	SEL 10 mg (n=108)	Placebo (n=52)
Any AE	17 (85)	11 (85)	94 (87)	44 (85)
Grade ≥3 AEs	1 (5)	1 (8)	13 (12)	4 (8)
SAEs	1 (5)	1 (8)	8 (7)	3 (6)
AEs that led to treatment withdrawal	1 (5)	1 (8)	3 (3)	2 (4)
AEs that led to study discontinuation	1 (5)	1 (8)	2 (2)	2 (4)
Liver-related AEs	2 (10)	1 (8)	6 (6)	5 (10)

AEs, n (%)		Prior Treatment With Fibrates/OCA		No Prior Treatment With Fibrates/OCA	
RESPONSE Study (Month 12)		**SEL 10 mg (n=20)**	**Placebo (n=13)**	**SEL 10 mg (n=108)**	**Placebo (n=52)**
Most frequently reported AEs (occurred in >10% of participants in any group)	COVID-19	8 (40)	3 (23)	15 (14)	7 (13)
	Pruritus	2 (10)	2 (15)	4 (4)	8 (15)
	Asthenia	0	3 (23)	5 (5)	1 (2)
	Arthralgia	0	2 (15)	8 (7)	2 (4)
	Nasopharyngitis	0	2 (15)	7 (6)	3 (6)
	Hypercholesterolemia	0	2 (15)	1 (1)	0
	Gastroenteritis	0	2 (15)	0	1 (2)
ASSURE Open-Label Extension (Month 12 through Month 18)		**SEL 10 mg (n=16)**	**Placebo/SEL[a] (n=11)**	**SEL 10 mg (n=88)**	**Placebo/SEL[a] (n=43)**
Any AE		12 (75)	8 (73)	59 (67)	31 (72)
Grade ≥3 AEs		2 (13)	1 (9)	6 (7)	2 (5)
SAEs		2 (13)	1 (9)	3 (3)	4 (9)
AEs that led to treatment withdrawal		1 (6)	0	0	0
AEs that led to study discontinuation		0	0	0	0
Liver-related AEs		2 (13)	0	3 (3)	0
Most frequently reported AEs (occurred in >10% of participants in any group)	Pruritus	2 (13)	0	7 (8)	0
	Anemia	2 (13)	0	2 (2)	2 (5)
	Herpes zoster	2 (13)	0	2 (2)	0
	Headache	1 (6)	0	1 (1)	5 (12)
	Diarrhea	0	2 (18)	1 (1)	3 (7)
	Hematuria	0	2 (18)	0	0

[a]Includes participants who received placebo in RESPONSE and were switched to SEL 10 mg at ASSURE enrollment.

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. Villamil A, Pratt D, Kremer AE, et al. Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis Previously Treated With Fibrates or Obeticholic Acid. [Poster #THU-274]. Paper presented at: European Association for the Study of the LiveR; May 7–10 2025; Amsterdam, the Netherlands.
3. 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
BL=baseline
NRS=numerical rating scale
PBC=primary biliary cholangitis
OCA=obeticholic acid
SAE= serious adverse event
SEL=seladelpar
TB=total bilirubin
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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