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Livdelzi® (seladelpar) Switching From Obeticholic Acid

This document is in response to your request for information regarding switching from obeticholic acid (OCA) 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 Data on Switching From OCA to SEL

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

- Regardless of prior OCA use, biochemical response was sustained through 18 months of treatment in participants who received continuous SEL and improved in participants who switched from placebo to SEL at Month 12.[2]
- The incidences of overall AEs and liver-related AEs were similar between the prior OCA and/or fibrates use group and the no prior OCA and/or fibrates use group.[2]

In a real-world study that analyzed outcomes in participants who switched from OCA to SEL (mean ± SD interval between OCA and SEL, 8±18 days)[3]:

- Compared to BL values, more participants who switched from OCA to SEL achieved ALP response, ALP normalization, and reduction in ALP levels over time. No notable changes were observed for other parameters assessed (TB, ALT, and AST levels). However, a greater increase from BL in mean GGT levels was observed after switching to SEL.
- There were no safety concerns regarding increased ALT/AST levels, eGFR, or CK levels.

Clinical Studies on Switching From OCA to SEL

Currently, there is no specific guidance on switching from OCA 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 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. The use of OCA before screening was an exclusion criterion, and a washout period of 6 weeks was required prior to enrollment.[4] 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).[2]

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, was collected daily via 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.[4]

In the SEL 10 mg and placebo groups, OCA was previously used in 11.7% (n=15) and 15.4% (n=10) of participants, respectively, and OCA and/or fibrates were previously used in 15.6% (n=20) and 20% (n=13) of participants, respectively (Table 1).[4] Of the 33 participants who had prior OCA and/or fibrate use in the RESPONSE study, 27 enrolled in the ASSURE study.[2]

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

Key Demographics and Characteristics	Prior Treatment With OCA/Fibrates		No Prior Treatment With OCA/Fibrates	
	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 OCA	15 (75)	10 (77)	–	–
Duration of OCA/fibrate treatment, mean ± SD, years	2.7±2.4	2.0±1.4	–	–
Duration of OCA/fibrate washout prior to study, mean ± SD, years	0.9±0.8	0.8±0.8	–	–
Cirrhosis at BL[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 BL were Child-Pugh Class A.

Efficacy

The primary composite endpoint was achieved in 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 OCA and/or fibrates did not impact 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 OCA and/or fibrate use than 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.[2] Declines in ALT and GGT

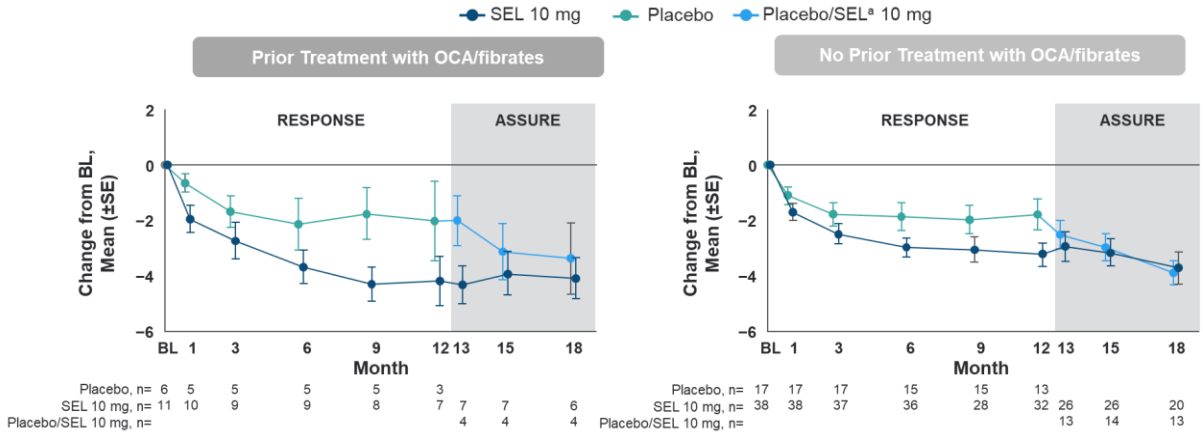
were similar between the prior OCA and/or fibrate use and no the prior OCA and/or fibrate use groups, and the TB percent change was generally stable, with some variation.

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

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 OCA/fibrates	9/20 (45)	1/13 (8)	9/15 (60)	7/11 (64)
	No prior treatment with OCA/fibrates	70/108 (65)	12/52 (23)	54/87(62)	32/41 (78)
ALP normalization	Prior treatment with OCA/fibrates	2/20 (10)	0/13 (0)	2/15 (13)	1/11 (9)
	No prior treatment with OCA/fibrates	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[2]



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

Safety[2]

Incidences of overall AEs and liver-related AEs were similar between the prior OCA and/or fibrates 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[2]

AEs, n (%)	Prior Treatment With OCA/Fibrates		No Prior Treatment With OCA/Fibrates	
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)

AEs, n (%)		Prior Treatment With OCA/Fibrates		No Prior Treatment With OCA/Fibrates	
RESPONSE Study (Month 12)		**SEL 10 mg (n=20)**	**Placebo (n=13)**	**SEL 10 mg (n=108)**	**Placebo (n=52)**
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)
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.

Real-World Study[3]

Study design and demographics

The real-world experience of participants with PBC who switched from OCA to SEL was evaluated in a longitudinal observational cohort study. The OCA to SEL analysis group included 130 participants who switched from OCA within 3 months, without use of other second-line treatments, and who had received ≥30 days of treatment with SEL. Outcomes included biochemical response rates (defined as ALP <1.67 × ULN; or TB, ALT, AST, and GGT levels ≤1 × ULN) from BL. Mean changes from BL in laboratory parameters and laboratory safety (ALT, AST, eGFR, and CK) were also evaluated. A summary of BL demographics and disease characteristics is provided in Table 4.

Table 4. BL Demographics and Disease Characteristics (Bowlus et al)[3]

Key Demographics and Characteristics	OCA→SEL (N=130)
Age, mean ± SD, years	58.8±11.91
Female, n (%)	114 (87.7)
Duration of PBC, mean ± SD, years	5.6±2.9
Duration of OCA, median (IQR), days	420 (240–1138)
Interval between last OCA treatment and SEL initiation[a], mean ± SD, days	8±18

Key Demographics and Characteristics		OCA→SEL (N=130)
Medical conditions/comorbidities, n (%)	Cirrhosis	15 (11.5)
	AIH	10 (7.7)
	MASH	6 (4.6)
	MASLD	33 (25.4)

Abbreviations: AIH=autoimmune hepatitis; MASH=metabolic dysfunction-associated steatohepatitis; MASLD=metabolic dysfunction–associated steatotic liver disease.
[a]Ninety-eight participants (75%) had no gap between last OCA treatment and SEL initiation.

Efficacy

The mean (SD) duration of treatment with SEL was 119 (68) days, with 93% of participants maintaining continuous treatment with SEL until the end of the observation period. During treatment with SEL, 130 participants (86.9%) received concomitant UDCA and 42 (32.3%) received concomitant statins.

ALP normalization (ALP level ≤1 × ULN) was achieved by 30% of participants with SEL treatment compared with 10% of participants at BL. Compared to BL values, ALP response rates increased in participants who switched from OCA to SEL (Table 5). A slight increase from BL in response rates for ALT and GGT levels was observed with SEL, whereas decreases from BL were observed for AST and TB (Table 5).

Table 5. Biochemical Response Rates Before and After SEL Initiation (Bowlus et al) [3]

Response Rates, n/N (%)[a]	At BL	After SEL Treatment
ALP <1.67 × ULN	23/42 (54.8)	25/30 (83.3)
TB ≤1 × ULN	38/39 (97.4)	29/30 (96.7)
ALT ≤1 × ULN	17/39 (43.6)	15/30 (50)
AST ≤1 × ULN	23/39 (59)	14/30 (46.7)
GGT ≤1 × ULN	6/14 (42.9)	5/11 (45.5)

Mean levels of ALP decreased from BL with SEL (Table 6). Slight reductions were observed in ALT levels, and no changes were observed in TB levels; increases were observed in levels of AST and GGT (Table 6).

Table 6. Change From BL in Laboratory Parameters (Bowlus et al)[3]

Parameter	n	At BL, Mean	n	After SEL Treatment, Mean
ALP, U/L	42	234.9	30	171
TB, mg/dL	39	0.6	30	0.6
ALT, U/L	39	46.3	30	44.3
AST, U/L	39	39.3	30	43.1
GGT, U/L	14	98.8	11	121.5

Safety

Laboratory safety remained generally similar before and after initiation of SEL (Table 7). No additional safety outcomes were reported.

Table 7. Laboratory Safety Results (Bowlus et al)[3]

Laboratory Safety[a]	OCA→SEL (N=130)	
	Before SEL	After SEL Treatment
ALT or AST >3 × ULN, n (%)	2 (1.5)	2 (1.5)
eGFR (mL/min/1.73 m^2), mean ± SD	90.6±18.6	89±20.2
CK >1 × ULN, n (%)	1 (0.8)	0

[a]In participants with data available.

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. Bowlus CL, Gordon SC, Beltran T, et al. Real-World Experience of Seladelpar Among Patients With Primary Biliary Cholangitis Including Patients Who Switched From Obeticholic Acid. [Poster #5037]. Paper presented at: The Liver Meeting, American Association for the Study of Liver Diseases; November 7–11, 2025; Washington, DC.
4. 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
CK=creatine kinase
GGT=γ-glutamyl transferase
NRS=numerical rating scale
OCA=obeticholic acid
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:

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Adverse Event Reporting

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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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