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Livdelzi® (seladelpar) Pruritus Data

This document is in response to your request for information regarding Livdelzi® (seladelpar [SEL]) and data on pruritus during clinical studies.

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Summary

Clinical Study Data on SEL and Pruritus

In the phase 3 RESPONSE study, among participants with moderate to severe pruritus (NRS score ≥4), the reduction in pruritus NRS scores from BL to Month 6 was significantly greater in participants who received SEL 10 mg than in participants who received placebo (LSM difference, -1.5; 95% CI: -2.5 to -0.5; *P*=0.005).[1] Among participants with NRS score ≥4 or severe pruritus at BL, near resolution of symptoms at Month 12 was seen in 26.5% and 18.8% of participants in the SEL arm, respectively, compared with 0% in the placebo arm.[2] Pruritus was one of the most common AEs reported in the SEL 10 mg and placebo arms, at 4.7% and 15.4%, respectively.[1]

- In a subanalysis of participants with an NRS score ≥4, participants treated with SEL had significantly greater improvements from BL through Month 12 in scores for the 5-D Itch disability domains for leisure/social, housework/errands, and work/school items compared with participants in the placebo arm (*P*<0.005 or *P*<0.05). Greater improvements in pruritus distribution and duration of itch were also observed in participants treated with SEL than in participants who received placebo.[3]

In the open-label ASSURE study, among participants with NRS scores ≥4 who entered the study from the RESPONSE study, sustained and clinically meaningful improvements in NRS scores were observed through Month 30 in participants who continued treatment with SEL. Rapid improvements from ASSURE BL were observed in participants who switched from placebo to SEL; these improvements were sustained and clinically meaningful with up to 18 months of exposure. Sustained improvements in 5-D Itch and PBC-40 itch scores were also observed in the continuous SEL group, and new improvements from ASSURE BL were observed in the crossover group.[4]

In the phase 3 ENHANCE study, among participants in the prespecified subgroup with moderate-to-severe pruritus at BL who were evaluable at Month 3, those in the SEL 10 mg arm had significant decreases in mean pruritus NRS score compared with those in the placebo arm (-3.14 vs -1.55; *P*=0.02), but not when compared with those in the SEL 5 mg arm (-2.01; *P*=0.48). Pruritus was reported by 11.2%, 3.4%, and 12.6% of participants in the SEL 10 mg, SEL 5 mg, and placebo arms, respectively.[5]

- In another analysis of ENHANCE, compared with matched healthy volunteers, participants with PBC had 31-fold higher serum concentrations of IL-31 at BL, which was closely correlated with pruritus NRS score. The correlation was maintained throughout the study with significant decreases from BL to Month 3 in mean IL-31 levels occurring among participants in the SEL 10 mg and 5 mg arms who had improvements in pruritus NRS score itch intensity. Similar results were demonstrated in a confirmatory phase 2 study, with a correlation between IL-31 levels and pruritus symptoms as measured by VAS.[6]

Pruritus-related data from the RESPONSE and ENHANCE studies were pooled and showed that the use of SEL 10 mg was associated with consistent improvements from BL to Month 6 in pruritus across several measures (pruritus NRS, PBC-40 itch domain, and 5-D Itch total score) in participants with moderate to severe pruritus at BL. Participants in the SEL arms had greater improvements in sleep disturbance scores than participants in the placebo arm through Month 6. Fewer pruritus AEs were noted with SEL than with placebo (8% vs 14%, respectively).[7]

An open-label, LTE study evaluated the efficacy and safety of SEL 10 mg and 5 mg in those who completed participation in a lead-in study (the phase 3 ENHANCE study and an open-label phase 2 study). Over the 2-year treatment period, pruritus was reported as an AE in 24.5% of participants; the incidence decreased from 22.6% during Year 1 to 2.8% during Year 2.[8,9]

Clinical Study Data on SEL and Pruritus

RESPONSE Study

Study design and select demographics[1]

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. Randomization was stratified according to BL ALP levels (<350 U/L vs ≥350 U/L) and BL pruritus NRS scores (<4 vs ≥4). SEL was administered as add-on therapy to standard of care UDCA treatment or as monotherapy in participants who experienced intolerance of UDCA.

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 at Month 12. Key secondary endpoints included ALP normalization (≤1 × ULN) at Month 12 and the change from BL to Month 6 in weekly mean participant-reported pruritus NRS score (ranges from 0 [“no itch”] to 10 [“worst itch imaginable”]) in those with moderate to severe pruritus (ie, NRS score ≥4) at BL. Other secondary endpoints assessed in the overall population and in those with moderate-to-severe pruritus included changes in the total score and itch domain score of the PBC-40 QOL questionnaire and the 5-D Itch Scale (assesses degree, duration, direction [ie, worsening or improvement], disability, and distribution of itching; scale ranges from 5 to 25, with higher scores indicating worse itch-related QOL).

BL pruritus intensity via the pruritus NRS and QOL 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. In the SEL and placebo arms, 71.1% and 73.8% of participants, respectively, had a history of pruritus, and 38.3% (n=49; mean NRS score: 6.1) and 35.4% (n=23; mean NRS score: 6.6) of participants, respectively, had moderate-to-severe pruritus at BL, with an overall mean BL NRS score of 6.3 (mean ± SD scores: SEL, 3±2.8; placebo, 3±3).

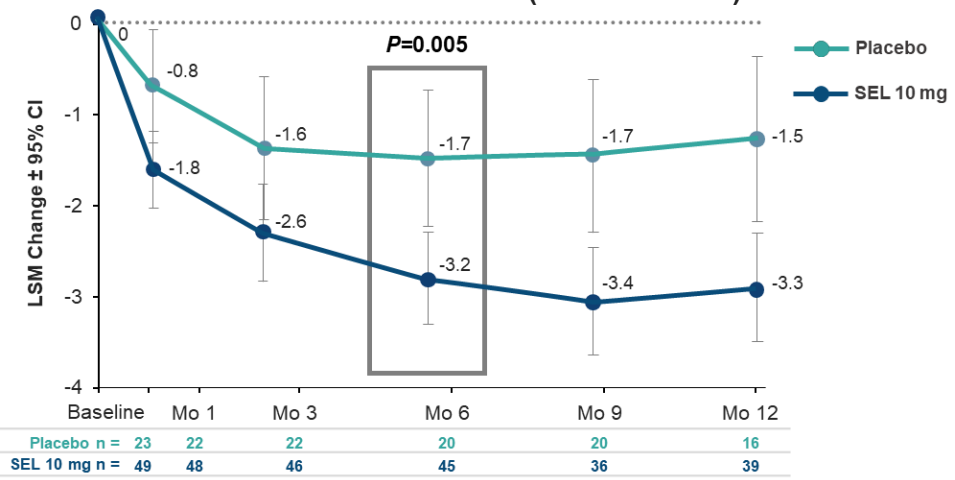
Pruritus-related results

Change in Pruritus NRS from BL to Month 12

In terms of achieving the primary composite endpoint and the key secondary endpoint of ALP normalization, there was no significant difference between those with BL pruritus NRS scores <4 and those with scores ≥4.[1,10]

In participants with NRS score ≥4, the reduction in the pruritus NRS score from BL to Month 6 was significantly greater in SEL-treated participants than in participants assigned to receive placebo (-3.2 and -1.7, respectively; LSM difference, -1.5; 95% CI: -2.5 to -0.5; *P*=0.005; Figure 1). In the overall population, the SEL-treated arm experienced a decrease from BL to Month 6 in pruritus NRS scores of -1.3, while the placebo arm had a decrease of -0.4 (LSM difference, -0.9; 95% CI: -1.4 to -0.5).[1]

Figure 1. RESPONSE: Change in Pruritus NRS Over Time in Participants With PBC and Moderate-to-Severe Pruritus (NRS Score ≥4) at BL[1]



Note: After 6 months, pruritus was evaluated on a monthly basis through Month 12 using the pruritus NRS for 7 consecutive days each month. The change from BL in weekly averaged pruritus NRS scores at Month 6 was analyzed using a mixed-effects model for repeated measures.

In the prespecified subgroup of participants with moderate-to-severe pruritus at BL and in the overall population, reductions in most measures of itch from BL to Month 12 were greater in SEL-treated participants than in those who received placebo as measured by the 5-D Itch Scale (in all domains except direction) and by the PBC-40 QOL questionnaire.[1]

Pruritus was one of the most common AEs reported in the SEL 10 mg and placebo arms (4.7% and 15.4%, respectively). Among those with cirrhosis at BL, the incidence of pruritus in the SEL 10 mg and placebo arms was 11.1% (2/18) and 22.2% (2/9), respectively; in those without cirrhosis at BL, the incidence rate was 3.6% (4/110) and 14.3% (8/56), respectively.[1,10]

Changes in NRS and PBC-40 QOL scores from BL to Month 12[2]

An analysis was conducted to assess changes from BL to Month 12 in pruritus NRS and PBC-40 QOL scores. In 49 participants with moderate-to-severe pruritus (NRS score ≥4) at BL, treatment with SEL reduced the mean itch intensity score from moderate (NRS score ≥4 to <7) to mild (NRS score >0 to <4), with a ≥4-point decline in NRS score from BL to Month 12 in 30.6% of participants (15/49). Among participants in the SEL arm with moderate-to-severe pruritus (n=49) or severe pruritus (NRS score ≥7; n=16) at BL, near resolution of symptoms (NRS score of 0 or 1) at Month 12 was seen in 26.5% and 18.8% of participants, respectively, compared with 0% in the placebo arm. Among participants with no pruritus (NRS score of 0) at BL, no participants in the SEL arm and 26.7% of participants in the placebo arm developed pruritus at Month 12. According to PBC-40 scores, participants in the SEL arm with severe pruritus at BL reported improvements in QOL, including decreases in itch, sleep disturbance, and fatigue from BL to Month 12.

Overall, reports of AEs were similar among the SEL and placebo arm regardless of itch severity at BL (Table 1).

Table 1. RESPONSE: Overall Safety by Pruritus NRS Score of Mild (NRS <4) or Moderate to Severe (NRS ≥4) at BL[2]

Safety Parameter, n (%)	NRS <4 at BL		NRS ≥4 at BL	
	SEL 10 mg (n=79)	Placebo (n=42)	SEL 10 mg (n=49)	Placebo (n=23)
Any AE	68 (86.1)	34 (81)	43 (87.8)	21 (91.3)
Grade ≥3 AEs[a]	9 (11.4)	2 (4.8)	5 (10.2)	3 (13)
SAEs[b]	5 (6.3)	3 (7.1)	4 (8.2)	1 (4.3)
Treatment-related SAEs	0	0	0	0
AEs that led to treatment DC	1 (1.3)	1 (2.4)	3 (6.1)	2 (8.7)
AEs that led to study DC	0	1 (2.4)	3 (6.1)	2 (8.7)
AEs that led to death	0	0	0	0

Abbreviations: DC=discontinuation; SAE=serious adverse event.
[a]Grade ≥3 AEs were categorized per the Common Terminology Criteria for Adverse Events.
[b]In participants with an NRS score ≥4 at BL, the following SAEs were reported in the SEL arm: papillary thyroid cancer, duodenal obstruction and chronic obstructive pulmonary disease, COVID-19 infection, and rotator cuff syndrome (each, n=1). In the placebo arm, 1 participant experienced an SAE of suicide attempt, which was unrelated to pruritus.

Clinically meaningful changes in pruritus NRS scores to Month 12[11]

Using data from RESPONSE, study investigators sought to determine the threshold for clinically MWPC through Month 6 in symptoms of pruritus, using the pruritus NRS score, among participants with moderate-to-severe pruritus at BL (NRS score ≥4). Out of the 193 participants within the study, changes in the pruritus NRS scores of 72 participants (SEL, n=49; placebo, n=23) were correlated with PGI-S and PGI-C assessments as anchors, and estimates of meaningful changes were developed using eCDF curves. The PGI-S instrument instructs participants to reflect on the previous 7 days, and results were collected at run-in, Day 1, Month 1, and every 3 months until Month 12. The PGI-C instrument evaluates experiences from the beginning of the study, and results were collected at Month 1 and every 3 months until Month 12. Further, 12 participants underwent qualitative interviews before the study; using feedback from these interviews, investigators developed estimates of MWPC in pruritus NRS scores.

A ≥3-point decrease in the pruritus NRS score was associated with clinically meaningful improvement of pruritus based on cumulative results from anchor-based (PGI-S and PGI-C)

and distribution-based analyses (eCDF curve), as shown in Table 2. Half of the interviewed participants indicated that a ≥3-point decrease in pruritus NRS correlated with a clinically meaningful change.

Table 2. RESPONSE: Evaluation of Pruritus Anchor Measures and Corresponding Changes in Pruritus NRS Scores[11]

Pruritus Anchors and Measures	Change in Anchor	Corresponding Change in Pruritus NRS, Mean (Median)
PGI-S	No change	-2.01 (-1.96)
	1-point improvement	-2.98 (-2.93)
	2-point improvement	-4.8 (-5.21)
PGI-C	No change	-1.18 (-1.67)
	"A little bit better"	-2.04 (-1.68)
	"Moderately better"	-2.44 (-2.46)
eCDF curve	Clinically meaningful threshold range: PGI-S, 2.9-point to ≥4.1-point decrease in NRS; PGI-C, 2.9-point to ≥4.6-point decrease in NRS	

Effect on itch-associated disability and pruritus distribution to Month 12[3]

Study design and select demographics[1]

The effects of treatment with SEL vs placebo on pruritus-related disability and distribution of pruritus were evaluated in a subanalysis of participants enrolled in the RESPONSE study. Outcomes were measured using the 5-D Itch Scale domains for degree (severity of itch), direction (improvement or worsening of itch), disability (effect of itch on leisure/social, housework/errands, and work/school), distribution (itch affecting the abdomen, back, buttocks, chest, contact with clothing, face, forearms, groin, head/scalp, lower legs, palms, soles, thighs, tops of feet/toes, tops of hands/fingers, and upper arms), and duration (hours spent itching per day). At BL, 5-D Itch Scale disability and distribution domain scores were similar between the SEL and placebo arms in both the NRS ≥4 and overall populations. However, participants with BL NRS ≥4 had overall higher scores across domains than participants in the overall population (Table 3).

Table 3. RESPONSE: BL Demographics and Disease Characteristics in the BL NRS ≥4 and Overall Populations[3]

Key Demographics and Characteristics	NRS ≥4 Population		Overall Population	
	SEL 10 mg (n=49)	Placebo (n=23)	SEL (n=128)	Placebo (n=65)
Age, years, mean ± SD	53±10.7	55±10.3	57±10	57±9.2
Female, n (%)	48 (98)	22 (96)	123 (96)	60 (92)
NRS score,[a] mean ± SD	6.1±1.4	6.6±1.4	3±2.8	3±3
Any pruritus medication at BL,[b] n (%)	11 (22)	5 (22)	18 (14)	11 (17)
5-D Itch Scale disability domain score, mean ± SD	3.5±1.1	3.5±0.8	2.3±1.4	2.2±1.2
Leisure/social item	3±1.2	3±1	2±1.3	2±1.2
Housework/errands item	3±1.1	3±1	2±1.2	2±1.1
Work/school item	2±1.3	2±1.4	1±1.2	1±1.2
5-D Itch Scale distribution domain score,[c] mean ± SD	3.1±1.2	3.1±1.1	2.2±1.3	2.1±1.2
5-D Itch Scale duration domain score, mean ± SD	2.4±1.4	2.4±1.4	1.6±1.1	1.6±1.1

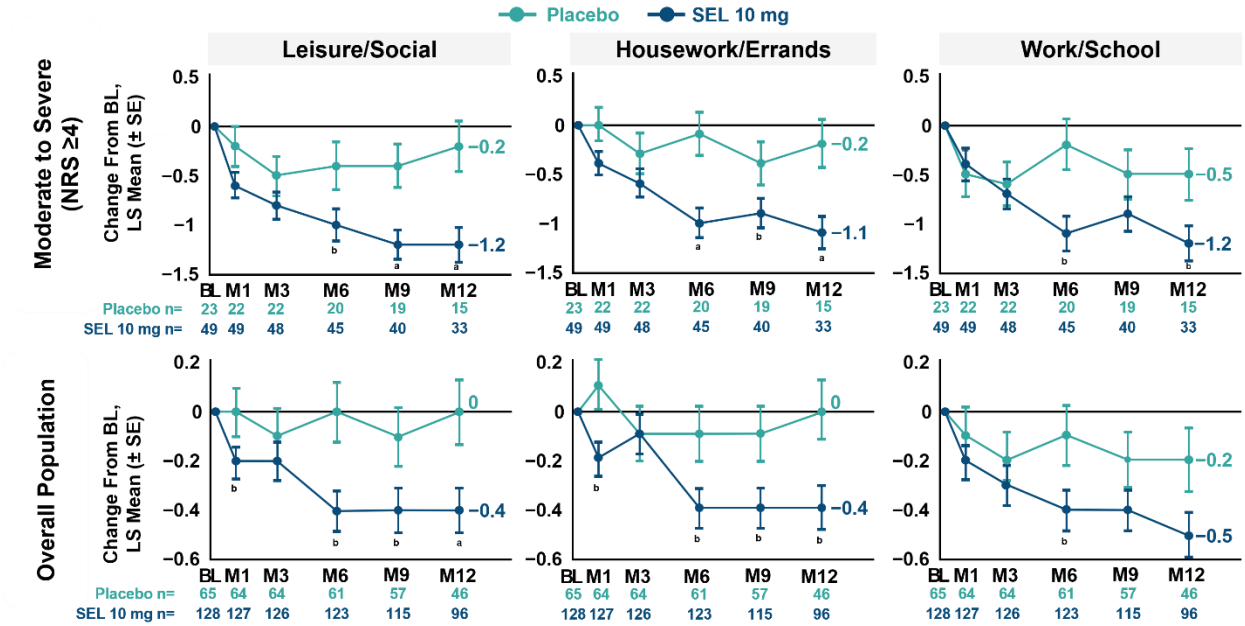
Key Demographics and Characteristics	NRS ≥4 Population		Overall Population	
	SEL 10 mg (n=49)	Placebo (n=23)	SEL (n=128)	Placebo (n=65)
Number of itchy body regions,[d] mean	8.94	9.3	5.11	4.78

[a]Based on worst itch in the past 24 hours (0 ["no itch"] to 10 ["worst itch imaginable"]).
[b]Including cholestyramine, colestipol, rifampicin, gabapentin, and sertraline.
[c]Presence of itch across body regions, evaluated by scoring the total number of affected parts based on 5 bins: 1=0–2 parts; 2=3–5 parts; 3=6–10 parts; 4=11–13 parts; 5=14–16 parts.
[d]Means were calculated by the total number of itchy body regions at the time point divided by the number of participants with data available.

Change from BL in 5-D Itch disability domain scores

Significant improvements from BL to Month 12 were observed in the NRS ≥4 population and in the overall population treated with SEL vs placebo for most 5-D Itch Scale disability domain items (Figure 2).

Figure 2. RESPONSE: 5-D Itch Scale Disability Domain Item Changes From BL to Month 12[3]



Abbreviation: M=month.
[a]*P*<0.005 vs placebo. [b]*P*<0.05 vs placebo.

Change from BL in 5-D Itch Scale distribution domain scores

Among participants with BL NRS ≥4 for whom data were available, a greater improvement from BL in the mean number of itchy body regions was observed at Month 12 with SEL vs placebo (38% decrease [Month 12 value, 5.52] vs 15% decrease [7.87], respectively; treatment difference in number of itchy body regions: -2.35).

Among participants in the overall population with data available, a greater improvement from BL in the average number of itchy body regions was observed at Month 12 with SEL vs placebo (38% decrease [Month 12 value, 3.19] vs 19% decrease [3.85], respectively; treatment difference in number of itchy body regions: -0.66).

Change in 5-D Itch Scale duration domain scores

Among participants with BL NRS ≥4 and in the overall population with data available, a greater decrease in 5-D Itch Scale duration domain scores from BL to Month 12 was observed with SEL compared with participants who received placebo; in participants who received placebo, daily duration of itch at Month 12 remained similar to BL (Table 4).

Table 4. RESPONSE: 5-D Itch Scale Distribution Domain Score Change From BL to Month 12[3]

Participants, n (%)	NRS ≥4 Population				Overall Population			
	SEL 10 mg		Placebo		SEL 10 mg		Placebo	
	BL	Month 12	BL	Month 12	BL	Month 12	BL	Month 12
<6 h/day	16 (33)	26 (79)	5 (22)	4 (27)	88 (69)	87 (91)	43 (66)	31 (67)
6–12 h/day	11 (22)	5 (15)	9 (39)	7 (47)	17 (13)	6 (6)	12 (18)	9 (20)
12–18 h/day	9 (18)	1 (3)	3 (13)	3 (20)	10 (8)	1 (1)	4 (6)	4 (9)
18–23 h/day	6 (12)	0	2 (9)	0	6 (5)	1 (1)	2 (3)	0
All day	7 (14)	1 (3)	4 (17)	1 (7)	7 (5)	1 (1)	4 (6)	2 (4)

Clinically meaningful changes in 5-D Itch Scale distribution domain scores to Month 12[12]

Study investigators used data from RESPONSE and the PGI-C and PGI-S pruritus scales to estimate the MWPC threshold on the 5-D Itch total score at Months 6 and 12 in the overall study population (SEL, n=128; placebo, n=65). PGI-C served as the primary anchor, whereas distribution-based analyses (eCDF curves) were used to support anchor-based findings. The proportion of participants reporting a ≥5-point reduction in the 5-D Itch total score was assessed at Months 6 and 12 in both the overall population and the moderate-to-severe pruritus subgroup (n=72). At BL, the mean (±SD) 5-D Itch total score was 11.6 (4.9) in the SEL group and 11.2 (4.7) in the PBO group in the overall population; the corresponding values in the moderate-to-severe pruritus subgroup were 16.2 (3.6) and 16.4 (2.8).

Among participants who reported feeling "moderately better" on the PGI-C or who had a 1-point improvement on the PGI-S, anchor-based estimates ranged from a median 2.5- to 5-point decrease on the 5-D Itch score, with a distribution-based estimate of 2.39 points (0.5 × SD; Table 5). These analyses supported a 3- to 5.5-point decrease on the 5-D Itch scale as the MWPC threshold. This threshold aligned with patient-reported improvement based on eCDF curves and resulted in <20% of non-improved participants being misclassified as improved.

Table 5. Within-Patient Anchor-Based Analyses of 5-D Itch Total Score Change by PGI-C Response and PGI-S Change[12]

Pruritus Anchors		n	5-D Itch Change at Month 6		n	5-D Itch Change at Month 12	
			Mean (SD)	Median		Mean (SD)	Median
PGI-C response	“Very much better”	37	-3.87 (3.72)	-3.75	38	-3.9 (4.27)	-4
	“Moderately better”	24	-3.49 (4.38)	-2.5	24	-2.38 (3.94)	-3.5
	“A little better”	31	-1.64 (3.38)	-1	19	-2.94 (3.75)	-3
	“No change”	58	0.22 (2.33)	0	58	-0.18 (2.66)	0
	“A little worse”	4	2.12 (5.56)	4	5	3.23 (5.73)	1.67
	“Moderately worse”	3	-0.83 (6.33)	1.5	0	NE	NE
	“Very much worse”	0	NE	NE	1	-11.5 (NE)	-11.5

Pruritus Anchors		n	5-D Itch Change at Month 6		n	5-D Itch Change at Month 12	
			Mean (SD)	Median		Mean (SD)	Median
PGI-S change	3-point improved	1	-15.5 (NE)	-15.5	2	-12.25 (4.6)	-12.25
	2-point improved	10	-6.19 (2.11)	-6.5	8	-6.19 (2.91)	-6.5
	1-point improved	41	-4.21 (3.64)	-5	41	-3.7 (3.47)	-5
	No change	88	-0.44 (2.74)	0	82	-0.81 (2.99)	0
	1-point worsening	22	0.8 (3.32)	1	9	2.9 (3.25)	2.5
	2-point worsening	0	NE	NE	2	6.75 (8.13)	6.75
	3-point worsening	0	NE	NE	0	NE	NE

Abbreviation: NE=not estimable.
Note: Several worsening categories contained few or no patients; therefore, thresholds were NE.

At Months 6 and 12, a greater proportion of the patients treated with SEL than of those who received placebo achieved a clinically meaningful ≥5-point reduction in 5-D Itch total score in both the overall population (SEL, 24.2% [n/N=31/128] vs placebo, 13.8% [n/N=9/65] at Month 6 and 23.4% [n/N=30/128] vs 9.2% [n/N=6/65], respectively, at Month 12) and the moderate-to-severe pruritus subgroup (44.9% [n/N=22/49] vs 26.1% [n/N=6/23] at Month 6 and 42.9% [n/N=21/49] vs 17.4% [n/N=4/23], at Month 12, respectively).

ASSURE Study

Study design

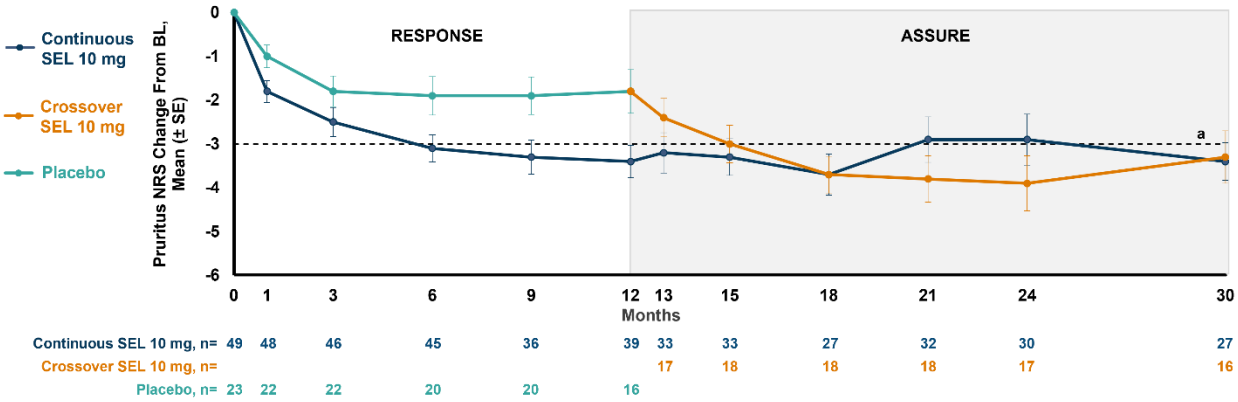
The ongoing, non-randomized, open-label, phase 3 ASSURE study (NCT03301506) is evaluating the long-term efficacy and safety of SEL 10 mg in participants with PBC. Participants who had completed the RESPONSE study or other legacy studies were eligible for inclusion.[13] The current interim analysis evaluated pruritus outcomes (NRS, 5-D Itch Scale, and PBC-40 itch domain) up to a data cutoff date of January 31, 2025, in participants who rolled over from the RESPONSE study and had BL pruritus NRS scores ≥4 who had received up to 30 months of exposure to SEL (continuous SEL group) or had crossed over from placebo to receive SEL in ASSURE and had up to 18 months of exposure (crossover SEL group).[4]

Results[4]

Change in NRS scores from BL to Month 30

Sustained reductions in NRS scores were observed through Month 30 in the continuous SEL group, while new and rapid reductions in the NRS score from ASSURE BL were observed in the crossover SEL group, with results sustained with up to 18 months of exposure. In both groups, clinically meaningful reductions from BL were observed at Month 30 (Figure 3).

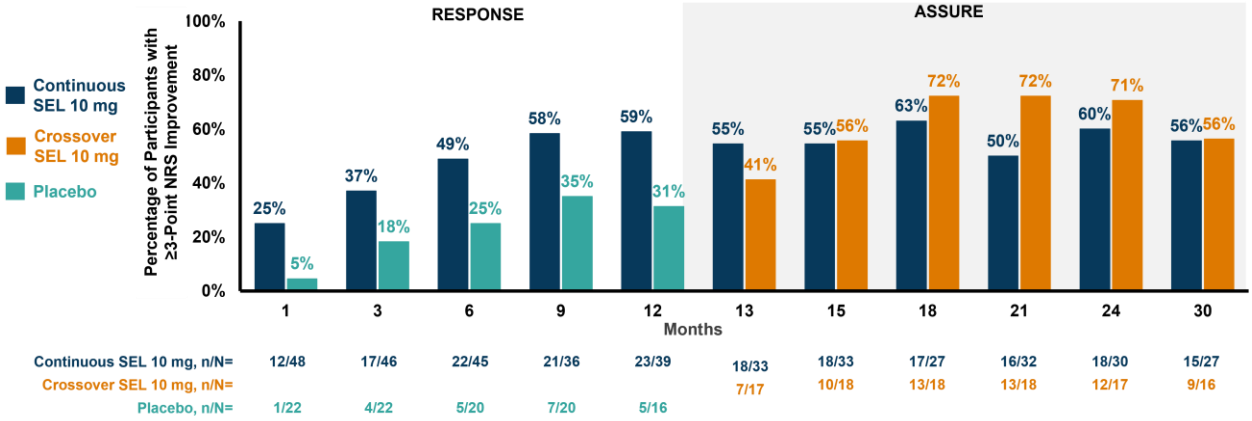
Figure 3. ASSURE: Mean Change in NRS Score in Patients With BL Pruritus NRS Score ≥4[4]



[a]Dashed line represents the clinically meaningful threshold.

In the continuous SEL group, clinically meaningful improvements in NRS (defined as an improvement in NRS score of ≥3 points) observed during RESPONSE were maintained during ASSURE (Figure 4). In the SEL crossover group, ≥41% of participants achieved a clinically meaningful reduction in NRS from ASSURE BL to any time point (Figure 4).

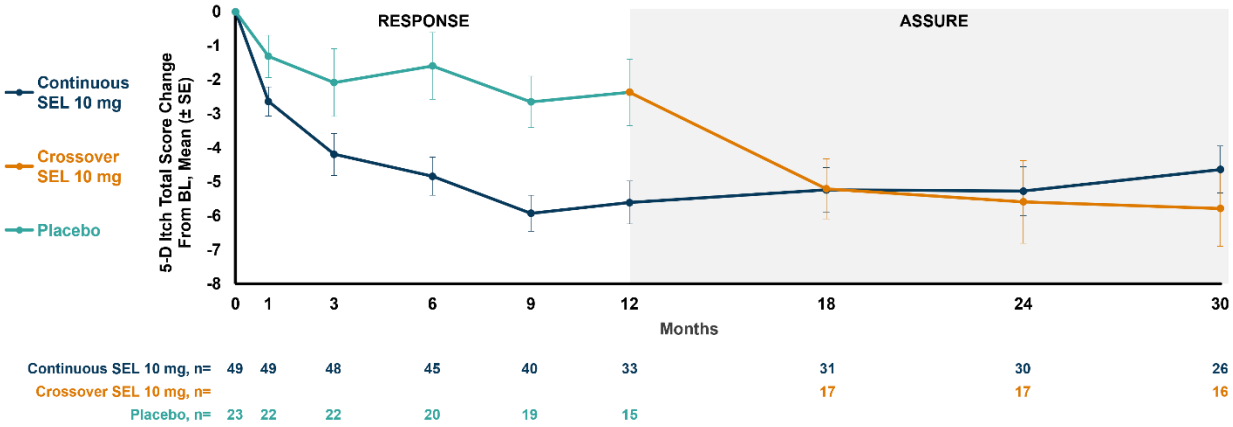
Figure 4. ASSURE: Clinically Meaningful Change in NRS Score in Participants With NRS Score ≥4[4]



Change in 5-D Itch Scale scores from BL to Month 30

Improvements in 5-D Itch Scale scores were maintained in the continuous SEL group through 30 months of treatment exposure (Figure 5). In the crossover SEL group, 5-D Itch Scale scores rapidly reduced from ASSURE BL, remained stable over time, and were similar to those observed in the continuous SEL group during ASSURE (Figure 5).

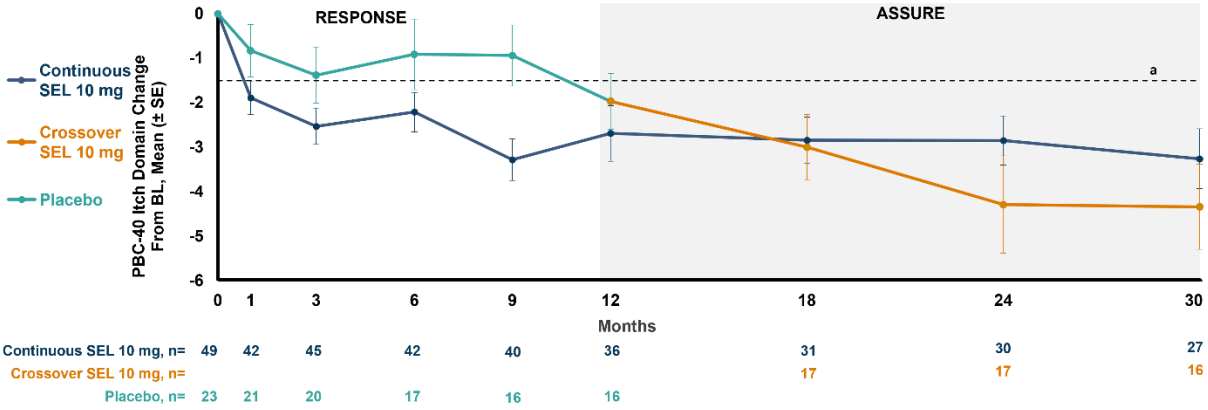
Figure 5. ASSURE: Mean Change in 5-D Itch Scale Total Score in Participants With NRS Score ≥4[4]



Change in PBC-40 scores from BL to Month 30

Improvements in PBC-40 itch scores were maintained in the continuous SEL group through 30 months of treatment (Figure 6). In the crossover SEL group, PBC-40 itch scores rapidly reduced from ASSURE BL within 6 months and continued to improve over time (Figure 6). In both groups, the changes in scores remained below the threshold for a clinically meaningful change during the ASSURE study (Figure 6).

Figure 6. ASSURE: Mean Change in PBC-40 Itch Score in Participants With NRS Score ≥4[4]



[a]Dashed line represents the clinically meaningful threshold.

Safety[4]

Safety outcomes were not reported.

ENHANCE Study

Study design and select demographics[5]

ENHANCE was a multicenter, randomized, double-blind, placebo-controlled, phase 3 study that was designed to compare safety outcomes after 12 months of SEL (5 or 10 mg daily) or placebo in adult participants with PBC who were at high risk for disease progression. SEL

was administered as add-on therapy to standard of care UDCA treatment or as monotherapy in participants who experienced intolerance of UDCA.

The study was terminated early due to unexpected histological findings that were later determined to be preexisting in the nonalcoholic steatohepatitis SEL program. At the time of study termination, the study was fully enrolled, and 265 participants were randomly assigned (1:1:1; stratified by ALP level [<350 or ≥350 U/L] and pruritus NRS score [<4 or ≥4]) to receive placebo (n=87), SEL 5 mg (n=89), or SEL 10 mg (n=89). Participants in the 5 mg SEL arm could have their dose increased to 10 mg if the primary composite endpoint was not met at Month 6. The primary endpoint was a composite biochemical response, which was defined as an ALP level <1.67 × ULN, an ALP level decrease by ≥15%, and a TB level ≤1 × ULN at Month 3. Key secondary endpoints included the rate of ALP normalization (level ≤1 × ULN) and the change in pruritus NRS scores from BL to Month 3 in participants with an NRS score ≥4 at Month 3.

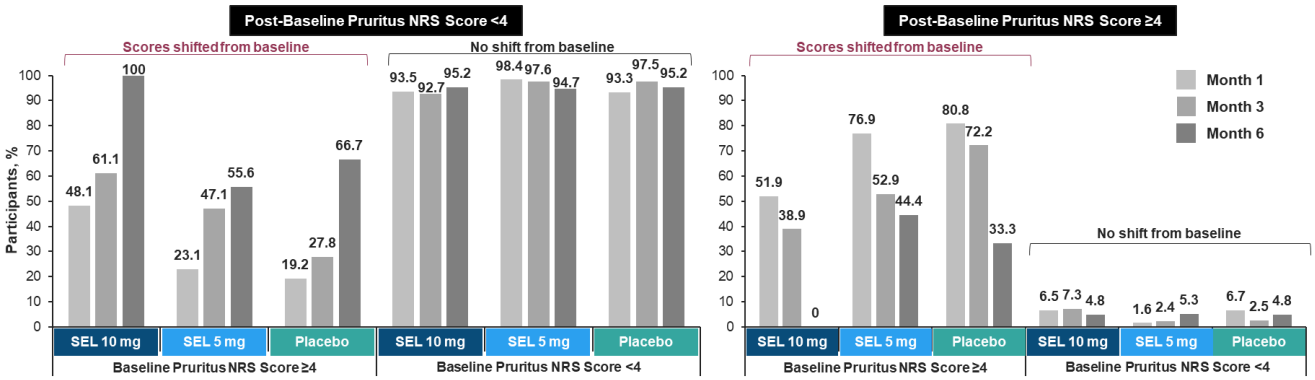
At BL, 73%, 74%, and 66% of participants in the SEL 10 mg, SEL 5 mg, and placebo arms had a history of pruritus, and 30%, 30%, and 31% of participants had moderate-to-severe pruritus (NRS score ≥4), respectively. Among participants with a BL pruritus NRS score ≥4, the mean ± SD scores were 6.2±1.4, 6.1±1.4, and 6.1±1.2 in the SEL 10 mg, SEL 5 mg, and placebo arms, respectively.

Overall pruritus-related study results

Among participants with moderate-to-severe pruritus at BL who were evaluable at Month 3, those in the SEL 10 mg arm had significant decreases in mean pruritus NRS score compared with those in the placebo arm (-3.14 vs -1.55; *P*=0.02), but not with those in the SEL 5 mg arm (-2.01; *P*=0.48).[5]

A post hoc analysis demonstrated shifts in NRS scores of ≥4 at BL to scores of <4 at Month 3, and vice versa (from <4 to ≥4; Figure 7) [5,14]

Figure 7. ENHANCE: Participants with Pruritus NRS Scores ≥4 or <4 at BL and Post-BL Time Points[5,14]



A ≥4-point reduction from BL to Month 3 in pruritus NRS score was achieved by 36.8% of participants in the SEL 10 mg arm, compared with 5.6% of those in the placebo arm. There were significant differences between the placebo and SEL 10 mg arms in the proportion of participants who achieved ≥2-point (*P*=0.04) and ≥4-point (*P*=0.02) NRS score reductions. Nonsignificant differences between the SEL 5 mg and placebo arms were observed for the ≥2-point (50% vs 33.3%, respectively; *P*=0.32) and ≥4-point (22.2% vs 5.6%; *P*=0.14) NRS score reductions.[5]

Among participants with moderate-to-severe pruritus at BL, greater changes in the total and individual domains of the 5-D Itch Scale scores were observed in the SEL arms than in the placebo arm at Months 1 and 3, and both SEL arms showed greater decreases from BL to Month 3 in the PBC-40 itch domain score than did the placebo arm.[5]

Pruritus-related safety data are summarized below (Table 6). Two participants in the SEL 10 mg arm discontinued treatment due to pruritus, insomnia, and rheumatoid arthritis.[5]

Table 6. ENHANCE: Pruritus-Related Safety Outcomes by Study Arm[5,14]

Safety Parameters, n (%) or %	SEL 10 mg (n=89)	SEL 5 mg (n=89)	Placebo (n=87)
≥1 TEAE	58 (65.2)	56 (62.9)	64 (73.6)
Pruritus (qualitative)	10 (11.2)[a]	3 (3.4)[b]	11 (12.6)[c]
≥1 treatment-related TEAE[d]	15 (16.9)	25 (28.1)	16 (18.4)
Treatment-related pruritus	3.4	2.2	5.7

Abbreviation: TEAE=treatment-emergent adverse event.
[a]Among those with and without cirrhosis, the incidence of pruritus was 15% (2/13) and 11% (8/76), respectively.
[b]Among those with and without cirrhosis, the incidence of pruritus was 0% (0/9) and 4% (3/80), respectively.
[c]Among those with and without cirrhosis, the incidence of pruritus was 14% (1/7) and 13% (10/80), respectively.
[d]All were Grade 1 or 2.

Effect of SEL on IL-31 levels and association with pruritus NRS scores[6]

Study design and demographics

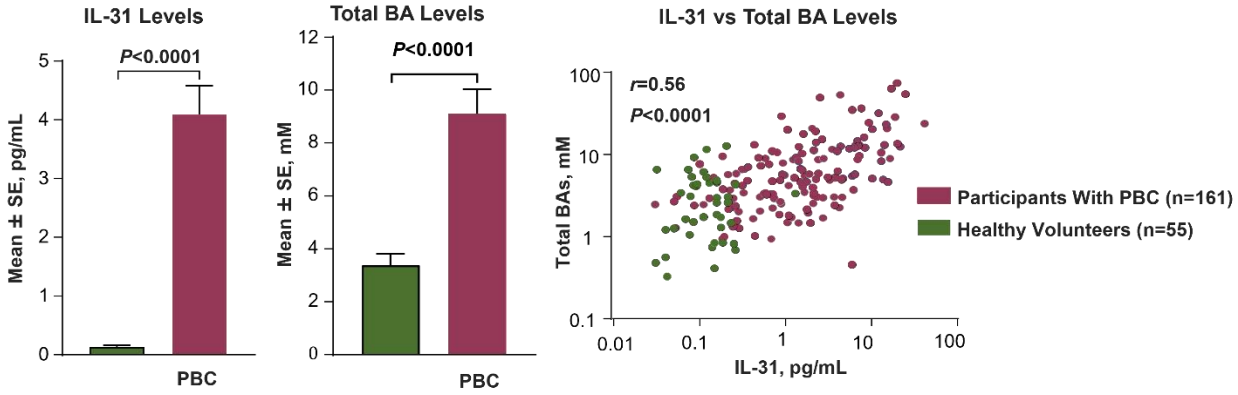
An additional analysis of the ENHANCE study evaluated the treatment effects of SEL on IL-31 levels and the association of IL-31 levels with pruritus NRS scores, BA levels, and other laboratory measures at BL and at Month 3. A total of 161 participants with serum IL-31 samples available were eligible for this analysis (SEL 10 mg, n=53; SEL 5 mg, n=53; placebo, n=55). BL IL-31 and BA levels from this analysis were compared with those of healthy volunteers (n=55) who were matched for age, sex, and BMI to those in the ENHANCE study. A clinically meaningful improvement in pruritus NRS scores was defined as a decrease of ≥2. BA levels were collected at BL and at Month 3.

At BL, 26%, 29%, and 28% of participants in the SEL 10 mg, SEL 5 mg, and placebo arms, respectively, had a pruritus NRS score ≥4; across these arms, the mean ± SD pruritus NRS scores were 6±1.4, 6.3±1.5, and 6.1±1.3.

Results

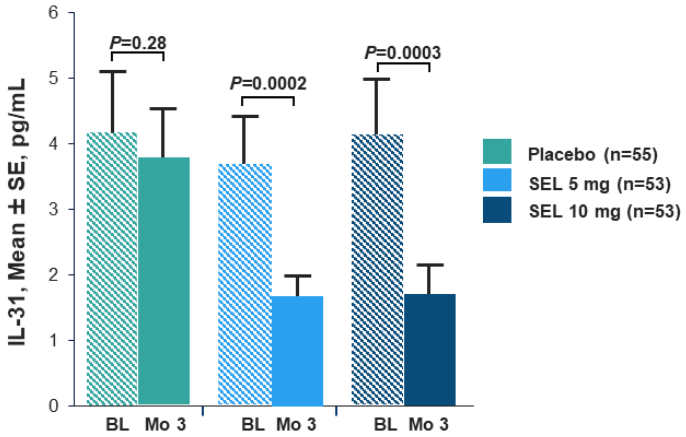
Participants with PBC had 31-fold higher serum concentrations of IL-31 and had elevated serum BA levels at BL compared with healthy volunteers (Figure 8). Serum levels of IL-31 also correlated positively with total BA levels (r=0.56, *P*<0.0001, Figure 8).

Figure 8. ENHANCE: BL IL-31 and Total BA Levels and Correlation Between IL-31 and Total BA Levels in Participants With PBC and Healthy Volunteers[6]



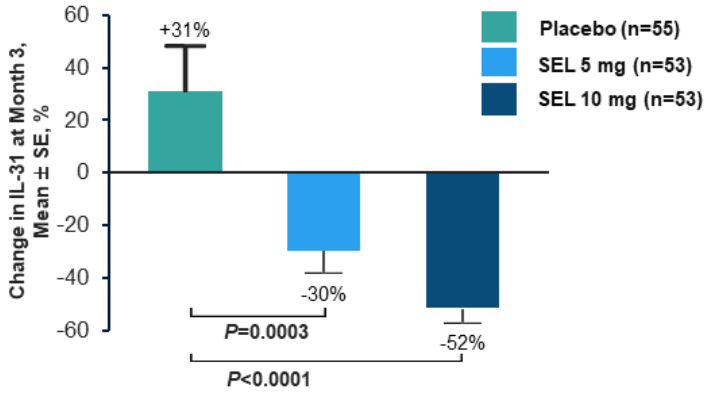
There were significant decreases in mean IL-31 levels in the SEL-treated arms from BL to Month 3: SEL 10 mg arm, 4.2 to 1.7 pg/mL (*P*=0.0003); SEL 5 mg arm, 3.8 to 1.7 pg/mL (*P*=0.0002; Figure 9). Nonsignificant decreases from BL to Month 3 were observed in the placebo arm: 4.3 to 3.9 pg/mL (*P*=0.28).

Figure 9. ENHANCE: Mean Decreases in IL-31 Levels From BL to Month 3[6]



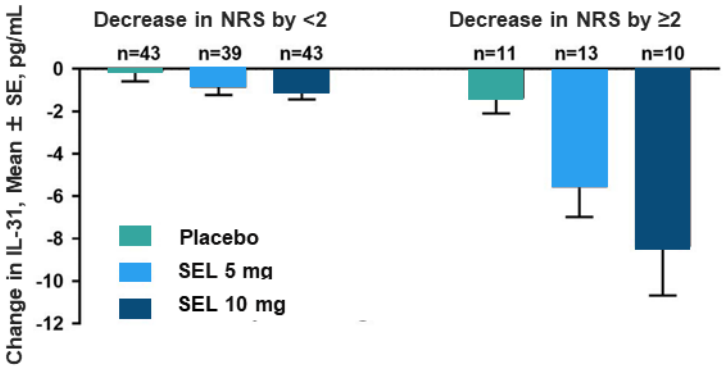
A significant dose-dependent percentage decrease in IL-31 levels was observed in the SEL 5 mg and 10 mg arms compared with the placebo arm (Figure 10). After 3 months, 79% of participants in the SEL 5 mg arm and 91% of those in the SEL 10 mg arm experienced decreases in IL-31 levels, whereas mixed responses were observed in the placebo arm (56% experienced a decrease in levels, and 44% experienced an increase in levels).

Figure 10. ENHANCE: Dose-Dependent Percentage Decrease in IL-31 Levels[6]



There was a correlation of itch intensity and serum IL-31 levels with SEL treatment. At BL, serum IL-31 levels were strongly associated with pruritus NRS (r=0.54, *P*<0.0001). Participants in the SEL and placebo arms experienced significant, dose-ordered associations between changes in IL-31 levels and pruritus NRS: SEL 5 mg, r=0.44 and *P*=0.0011; SEL 10 mg, r=0.54 and *P*<0.0001; and placebo, r=0.36 and *P*=0.008. There were greater dose-dependent reductions in serum IL-31 levels in participants who had a clinically meaningful improvement in pruritus (defined as a decrease in NRS score by ≥2) than in those without pruritus improvement (defined as a decrease in NRS score by <2; Figure 11). Additionally, there was a significant association between changes in IL-31 levels and total BA levels with SEL 10 mg, but not with 5 mg.

Figure 11. ENHANCE: Improvement in NRS Scores[6]



BL IL-31 levels were 2- to 4.7-fold lower in participants without improvement (an NRS score decrease of <2) than in SEL-treated participants who had improvement (Table 7).

Table 7. ENHANCE: Change in IL-31 by Decrease in Pruritus NRS Score[6]

IL-31 Levels, Mean ± SE, pg/mL	NRS Change by <2[a]		NRS Change by ≥2[b]	
	BL	Month 3	BL	Month 3
Placebo	4.2±1.1	4±0.9	4.9±1.9	3.5±1.3
SEL 5 mg	2.3±0.6	1.4±0.3	8.4±2.1	2.8±0.8
SEL 10 mg	2.7±0.7	1.6±0.5	10.9±2.4	2.5±1

[a]No improvement in pruritus was defined by a decrease in NRS score by <2.
[b]Clinically meaningful improvement in pruritus was defined as a decrease in NRS score by ≥2.

To confirm the findings of the ENHANCE study, an open-label, phase 2 study also evaluated the effect of SEL treatment on serum IL-31 levels and pruritus. Similar to results observed in

ENHANCE, serum IL-31 levels were significantly decreased with SEL treatment. In addition, BL serum IL-31 levels and pruritus symptoms, as measured by VAS, were correlated; further, an improvement in pruritus symptoms correlated with a decrease in serum IL-31 levels after 1 year of SEL 10 mg treatment.

Pooled Analysis of RESPONSE and ENHANCE Studies[7]

Study design and demographics

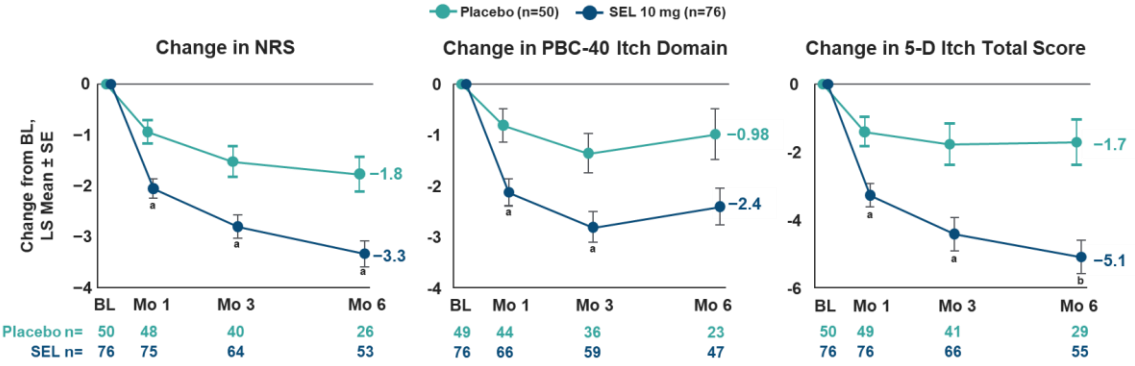
Pooled data from the first 6 months of the RESPONSE and ENHANCE studies evaluated pruritus outcomes in participants (SEL 10 mg, n=76; placebo, n=50) with moderate-to-severe pruritus at BL. Changes from BL to Month 6 in NRS scores, PBC-40 itch domain scores, and 5-D Itch Scale scores were assessed; disturbances in sleep were assessed via the relevant questions within the PBC-40 itch domain and the 5-D Itch Scale disability domain.

At BL in the SEL 10 mg and placebo arms, the mean ± SD NRS scores were 6.2±1.4 and 6.3±1.4, respectively; 33% and 36% had an NRS score ≥7; the mean ± SD PBC-40 itch domain scores were 8.8±2.8 and 9.3±2.9; and the mean ± SD 5-D Itch Scale total scores were 16.1±3.5 and 15.9±3.6.

Pruritus-related results

From BL to Month 6, SEL 10 mg resulted in improvements in pruritus across several measures; decreases were observed with placebo, though differences from BL were not significant (Figure 12). The decreases from BL to Month 6 in NRS (*P*=0.0004), PBC-40 itch domain (*P*=0.023), and 5-D Itch Scale total (*P*<0.0001) scores were significantly greater with SEL 10 mg than with placebo.

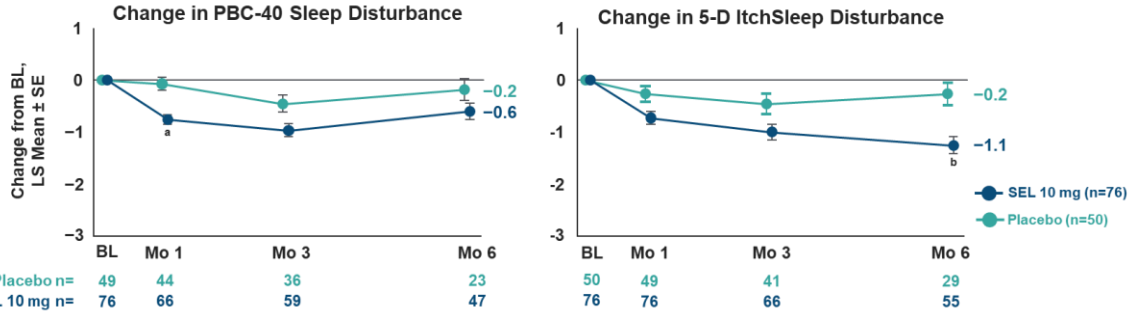
Figure 12. Pooled Analysis of RESPONSE and ENHANCE Studies: Changes in Pruritus NRS, PBC-40 Itch Domain, and 5-D Itch Scale Total Scores[7]



[a]*P*<0.01 vs placebo. [b]*P*<0.0001 vs placebo.

Measures of sleep disturbance were improved through Month 6 to a greater extent with SEL than with placebo. The reduction from BL to Month 6 in the PBC-40 sleep disturbance item score was greater with SEL than with placebo; however, the difference between groups was not significant (*P*=0.114; Figure 13). The improvement from BL to Month 6 in the 5-D Itch Scale sleep disturbance item score was significantly greater with SEL than with placebo (*P*=0.0004; Figure 13).

Figure 13. Pooled Analysis of the RESPONSE and ENHANCE Studies: Changes in PBC-40 and 5-D Itch Scale Sleep Disturbance Items[7]



[a]*P*<0.0001 vs placebo. [b]*P*<0.01 vs placebo.

Safety outcomes were generally similar between the SEL and placebo arms: any AE, 75% (n=57) vs 80% (n=40), respectively; serious AEs (none were treatment-related), 5% (n=4) vs 4% (n=2); pruritus-related AEs, 8% (n=6; pruritus, n=5; vulvovaginal pruritus, n=1) vs 14% (n=7; pruritus, n=7).

Open-Label LTE Safety Study

Study design and demographics[8]

An open-label, partially randomized, uncontrolled, multicenter, LTE study evaluated the safety and efficacy of SEL 10 mg and 5 mg for 2 years. Those who completed participation (12 months) in a lead-in study (phase 3 ENHANCE study and an open-label, phase 2 study) were eligible for inclusion in the LTE study if they did not have an interruption in treatment for ≥4 weeks and did not discontinue treatment due to safety or tolerability issues. Participants continued their prior daily dose of SEL (2, 5, or 10 mg) used during the lead-in studies; doses could be adjusted based on investigator judgement (after Week 12 in the phase 2 study and after Week 26 in ENHANCE). SEL was administered as add-on therapy to standard of care UDCA treatment or as monotherapy in participants who experienced intolerance of UDCA.

In total, the 104 participants enrolled from the open-label phase 2 study and the 2 participants who finished the 12-month ENHANCE study entered the LTE study: SEL 2 mg, n=1; 5 mg, n=18; and 10 mg, n=87. The safety population consisted of 106 participants evaluable for the 2-year period (SEL 10 mg, n=50; 5 mg, n=46; and 2 mg, n=10). The mean ± SD (range) duration of time in the study was 24±6.5 (12–36) months.

At BL, 70% (35/50), 73.9% (34/46), and 60% (6/10) of participants in the SEL 10 mg, SEL 5 mg, and SEL 2 mg arms had a history of pruritus.

Pruritus-related safety results[8,9]

Over the 2-year treatment period, pruritus was reported as an AE in 24.5% of participants; the incidence decreased from 22.6% during Year 1 to 2.8% during Year 2 (Table 8).

Table 8. LTE Study: Treatment-Emergent Pruritus by Year Overall and by Initial Dose[8,9]

Pruritus, n/N (%)	Year 1	Year 2	Year 1 and 2
Overall	24/106 (22.6)	3/106 (2.8)	26/106 (24.5)
10 mg	9/50 (18)	1/50 (2)	10/50 (20)
5 mg	10/46 (21.7)	1/46 (2.2)	11/46 (23.9)
2 mg	5/10 (50)	1/10 (10)	5/10 (50)

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Abbreviations

AE=adverse event
ALP=alkaline phosphatase
BA=bile acids
BL=baseline
eCDF=empirical cumulative distribution function
IL-31=interleukin-31
LSM=least-squares mean
LTE=long-term extension
MWPC=meaningful within-patient change
NRS=numerical rating scale
PBC=primary biliary cholangitis
PBC-40 QOL=Primary Biliary Cholangitis-40 Quality of Life Questionnaire
PGI-C=Patient Global Impression of Change in pruritus
PGI-S=Patient Global Impression of Severity in pruritus
QOL=quality of life
SEL=seladelpar
TB=total bilirubin
UDCA=ursodeoxycholic acid
ULN=upper limit of normal
VAS=visual analog scale

Product Label

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