Presentation # 167

Attenuation, Near Resolution, and Prevention of Pruritus in Patients With Primary Biliary Cholangitis Treated With Seladelpar: A Secondary Analysis of Patterns of Pruritus Change in the RESPONSE Trial

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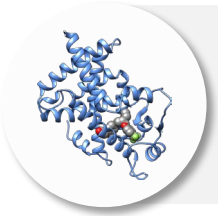
Primary Biliary Cholangitis

- Primary biliary cholangitis (PBC) is a chronic, progressive, autoimmune, **cholestatic liver disease** that affects approximately 1 in 1000 women over 40 years of age[1]
- **Cholestatic pruritus** can occur in **up to 80%** of patients with PBC, is frequently debilitating, and can greatly **reduce the quality of life (QoL)** of patients[2,3]
- **Off-label drug options** for cholestatic pruritus, such as rifampicin and fibrates, have **limitations**[4]
- In the **most severe cases of cholestatic pruritus**, it can become an **indication for liver transplantation** even in the absence of liver failure[4]
- Until recently, approved **PBC therapies** that improve biochemical markers of disease have either not improved or have worsened pruritus**,** and there is **a high unmet need for therapies that improve both pruritus** and **PBC activity**[3-5]

1. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-72. 2. Bowlus CL, et al. *J Hepatol*. 2022;77:353-64. 3. Kremer AE, et al. *Dig Dis*. 2015;33:164-75. 4. Düll MM, Kremer AE. *Curr Hepatol Rep*. 2020;19:86-95. 5. Hirschfield GM, et al. *New Engl J Med*. 2024;390:783-94.

Seladelpar: PPARδ Agonist



- **Seladelpar** is a first-in-class **delpar (selective PPARδ agonist)** targeting multiple cell types and processes in PBC[1]
- In August 2024, seladelpar was granted **accelerated approval** in the United States for the treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as a monotherapy in patients unable to tolerate UDCA[2]

Hepatocytes & Cholangiocytes	Macrophages & Kupffer Cells	Hepatocytes	Hepatocytes
Improves cholestasis	**Reduces inflammation**	**Reduces pruritus**	**Increases lipid metabolism**
↓ Bile acid synthesis[3-6]	↓ Inflammatory cytokines[6]	↓ Bile acids[4]	↓ Total cholesterol, LDL, triglycerides[3,6,9]
↓ ALP[3]	↓ Inflammatory lipid mediators[7]	↓ IL-31[8,a]	↑ Fatty acid oxidation[6,7]
↓ GGT[3]	↓ ALT[3]		

Seladelpar is a selective PPARδ agonist with anticholestatic, anti-inflammatory, and antipruritic effects[1-10]

Seladelpar X-ray crystal structure adapted from Choi Y, et al. 2021.[6] [a]Although the mechanism of pruritus in PBC is yet to be fully elucidated, reductions in IL-31 may be related to pruritus improvement, which was observed in the ENHANCE study.[8]
ALP, alkaline phosphatase; **ALT**, alanine aminotransferase; **GGT**, gamma-glutamyl transferase; **IL-31**, interleukin-31; **LDL**, low-density lipoprotein; **PBC**, primary biliary cholangitis; **PPARδ**, peroxisome proliferator–activated receptor delta; **UDCA**, ursodeoxycholic acid.
1. Hirschfield GM, et al. *N Engl J Med.* 2024;390:783-94. 2. Livdelzi (seladelpar). Prescribing information. Gilead Sciences, Inc.; 2024. 3. Hirschfield GM, et al. *Hepatology.* 2023;78(2):397-415. 4. Kremer AE, et al. *Liver Int.* 2022;42(1):112-23.
5. Kouno T, et al. *J Biol Chem.* 2022;298(7):102056. 6. Choi Y, et al. Discovery on Target 2021. Oral presentation. 7. Choi Y, et al. AASLD 2022. Poster 4731. 8. Kremer AE, et al. *Hepatology.* 2024;80(1):27-37. 9. Bowlus C, et al. AASLD 2022. Poster 4759.
10. Hirschfield G, et al. AASLD 2023. Oral presentation 5002.

Study Design

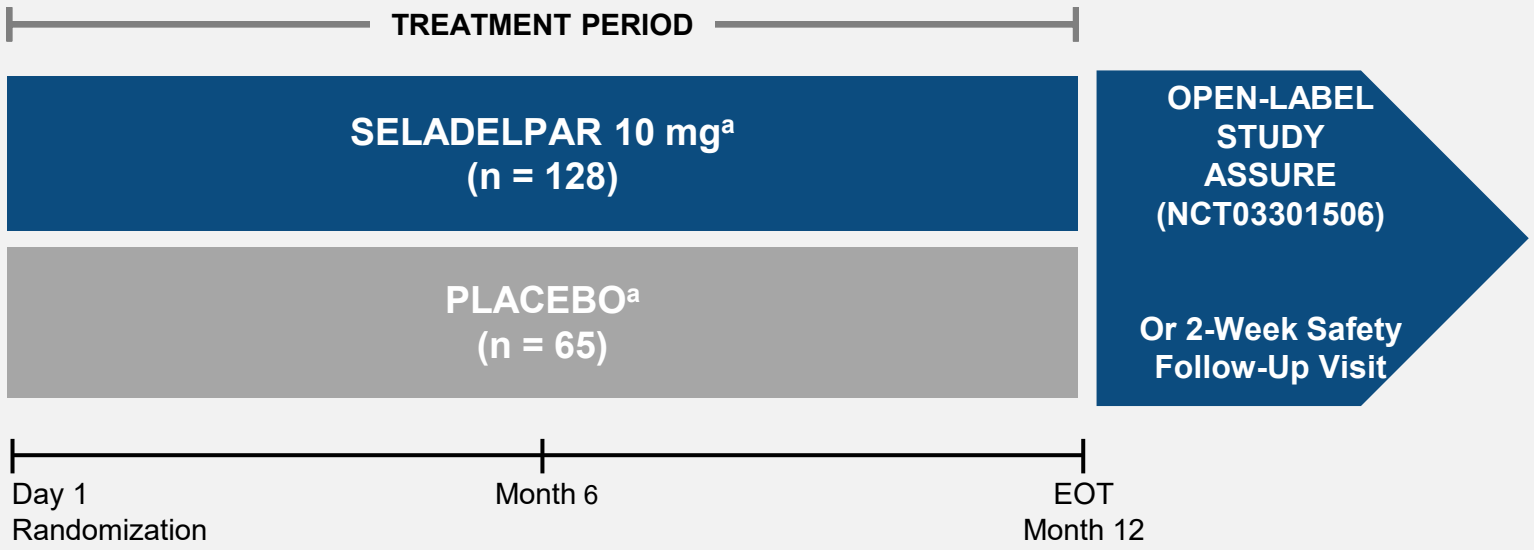
RESPONSE (NCT04620733): Phase 3 Study in Patients With PBC

Entry Criteria

- PBC and inadequate response or intolerance to UDCA
- ALP ≥1.67 × ULN
- ALT/AST ≤3 × ULN
- TB ≤2 × ULN
- Compensated cirrhosis allowed

Stratification

- ALP <350 U/L vs ALP ≥350 U/L
- Pruritus NRS <4 vs NRS ≥4



Primary Endpoint – Composite Biochemical Response Rate at Month 12

- ALP <1.67 × ULN; ALP decrease ≥15%; TB ≤1 × ULN

Key Secondary Endpoints

- ALP normalization rate (ALP ≤1 × ULN) at month 12
- Change in pruritus NRS at month 6 in patients with baseline NRS ≥4[b]

Seladelpar was administered orally once daily.
[a]Study drug given as an add-on to UDCA in patients on UDCA for at least 12 months, or as monotherapy in patients intolerant to UDCA. [b]Pruritus data collected daily through the first 6 months, then monthly for 7 consecutive days each month until EOT.
ALP, alkaline phosphatase; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **EOT**, end of treatment; **NRS**, numerical rating scale; **PBC**, primary biliary cholangitis; **TB**, total bilirubin; **UDCA**, ursodeoxycholic acid; **ULN**, upper limit of normal.

Background and Objective

- In the Phase 3, placebo-controlled RESPONSE study (NCT04620733), seladelpar improved pruritus in patients with PBC
  - **Seladelpar significantly reduced** itch as measured by the **pruritus numerical rating scale (NRS)** compared with placebo at month 6 in patients with NRS ≥4 at baseline
    - This effect was **sustained through month 12**
    - The PBC-40 Itch domain and 5-D Itch scale (secondary and exploratory endpoints, respectively) also **demonstrated similar effects** on pruritus with seladelpar
- Here, we report detailed **pruritus and QoL outcomes** in patients on seladelpar in the RESPONSE study

PBC, primary biliary cholangitis; **QoL**, quality of life.
Hirschfield GM, et al. *New Engl J Med*. 2024;390:783-94.

Methods

Itch and QoL Scales in RESPONSE

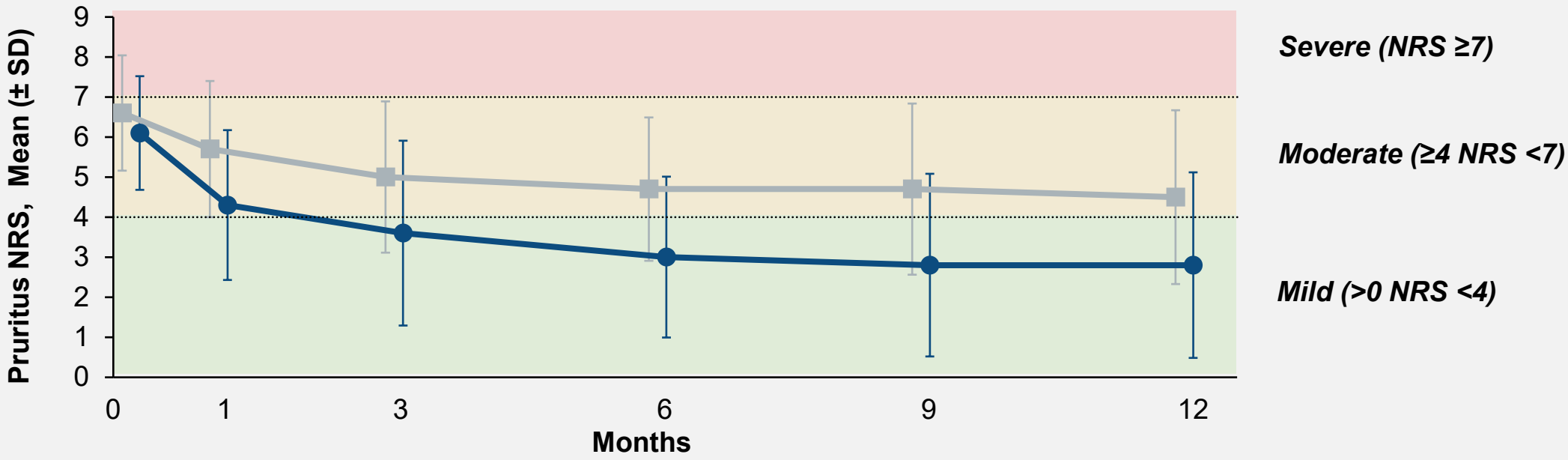
- **Scores on the pruritus NRS** ranged from **0 to 10**, with higher scores indicating worse itch[1]
  - **Moderate to severe pruritus** was defined by an **NRS ≥4 score**[1]
  - **Severe pruritus** was defined by an **NRS ≥7 score**[1]
  - For the present **analysis, near resolution of pruritus** was defined as **NRS ≤1**
- Pruritus symptoms were assessed using the **PBC-40 Itch domain** using a scale of **0 to 15**, with higher scores indicating poorer QoL[2,3]
  - **Clinically significant pruritus** is defined as a PBC-40 Itch domain **≥7 score**[3]

NRS, numerical rating scale; **PBC,** primary biliary cholangitis; **QoL**, quality of life.

1. von Maltzahn R, et al. *J Patient Rep Outcomes.* 2024;8(1):60. 2. [adapted from] Jacoby A, et al. *Gut.* 2005; 54(11):1622-9. 3. Mayo M, et al. *Dig Dis Sci.* 2023;68(3):995-1005.

Mean Pruritus NRS Over Time in Patients With Moderate to Severe Pruritus at Baseline

NRS ≥4 at Baseline



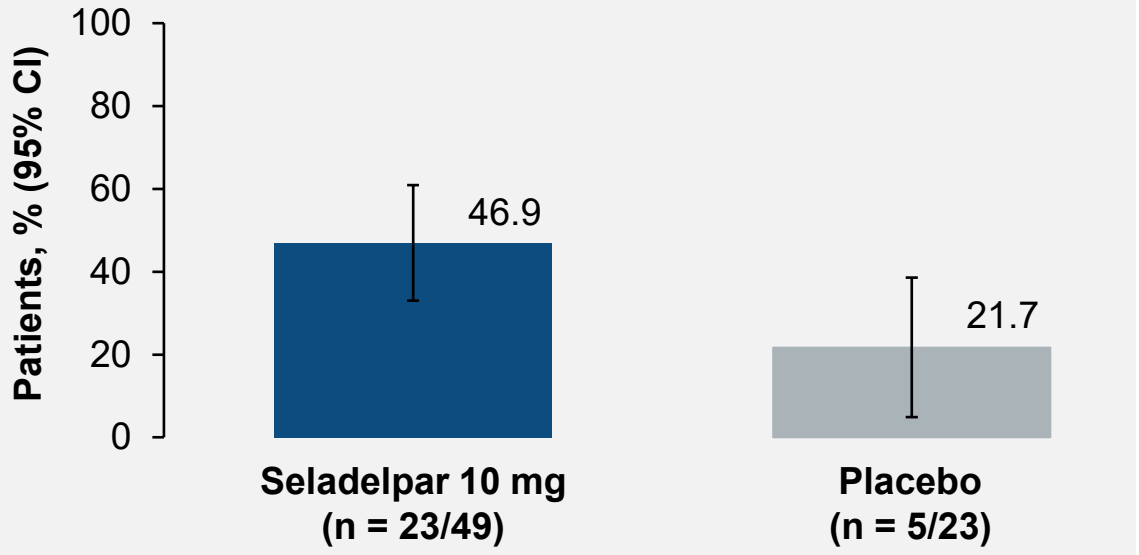
Seladelpar reduced the mean itch intensity from moderate to mild by month 12

NRS, numerical rating scale.

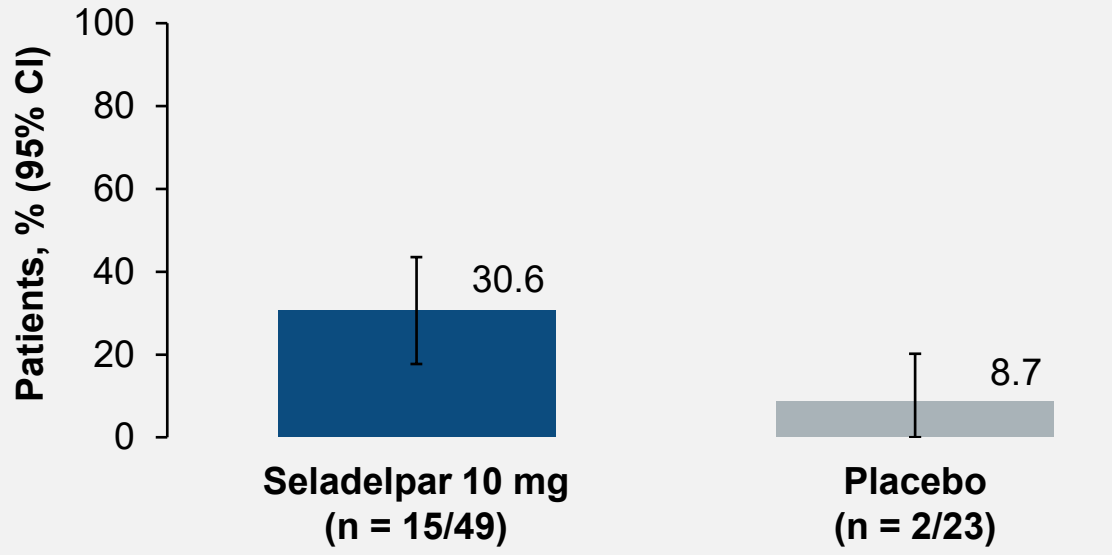
Pruritus NRS Response Rates at Month 12 in Patients With Moderate to Severe Pruritus at Baseline

NRS ≥4 at Baseline

Patients With a ≥3-Point Decline in Pruritus NRS at Month 12



Patients With a ≥4-Point Decline in Pruritus NRS at Month 12



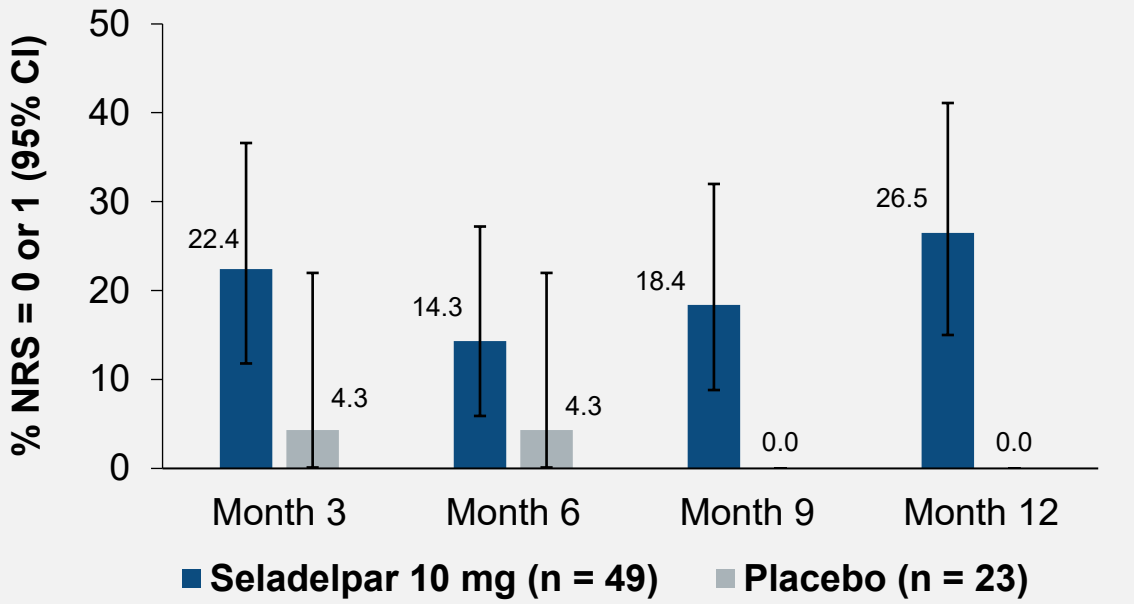
A higher percentage of patients receiving seladelpar had a ≥3-point or ≥4-point decline in pruritus NRS at month 12

Patients with missing data at the specific time point were considered nonresponders.
NRS, numerical rating scale.

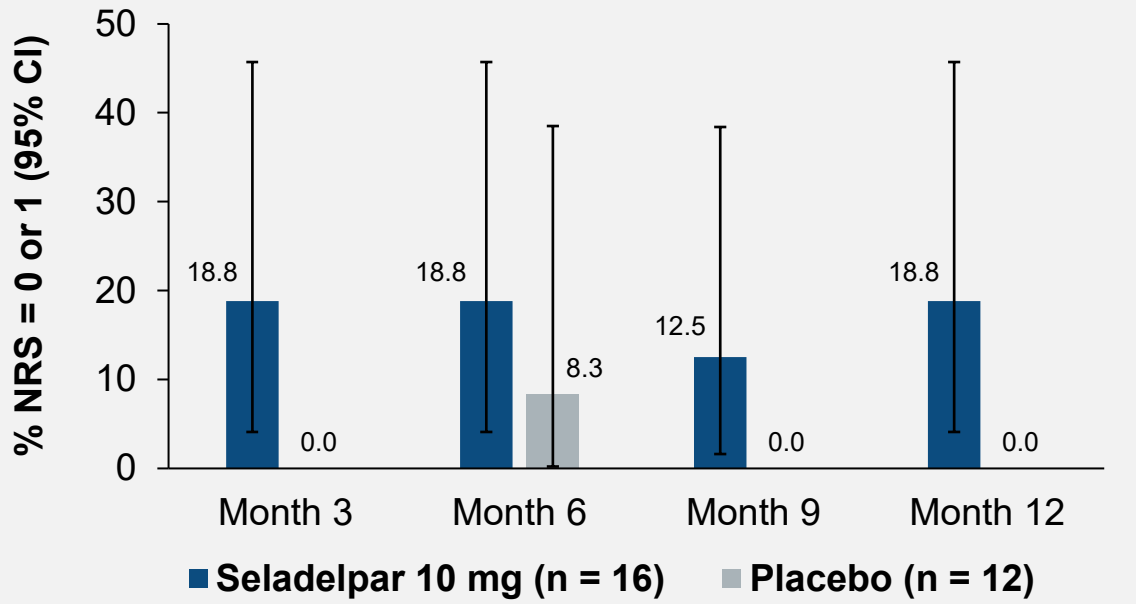
Near Pruritus Resolution (NRS 0 or 1) in Patients With Moderate to Severe and Severe Pruritus at Baseline

NRS ≥4 or ≥7 at Baseline

Percentage of Patients With Baseline NRS ≥4



Percentage of Patients With Baseline NRS ≥7



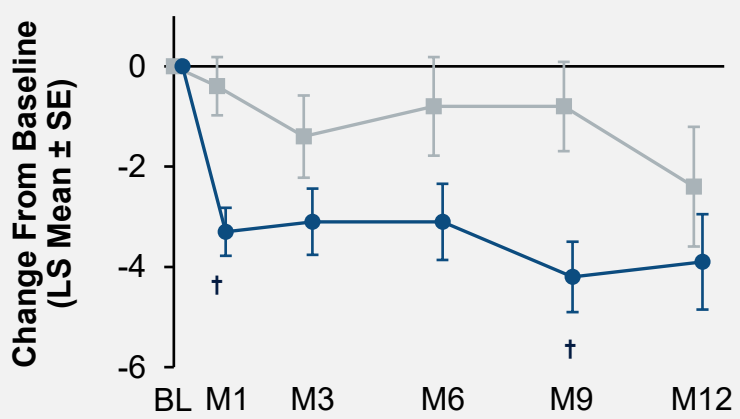
Over a quarter of patients with moderate to severe pruritus and nearly 20% of patients with severe pruritus at baseline experienced near resolution of itch at month 12 vs 0% of patients on placebo

Patients with missing data at the specified time point were considered nonresponders.
NRS, numerical rating scale.

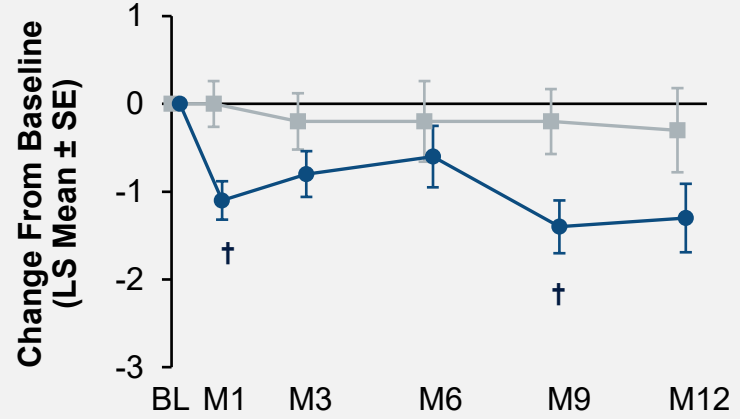
QoL Measures in Patients With Severe Pruritus at Baseline

NRS ≥7 at Baseline

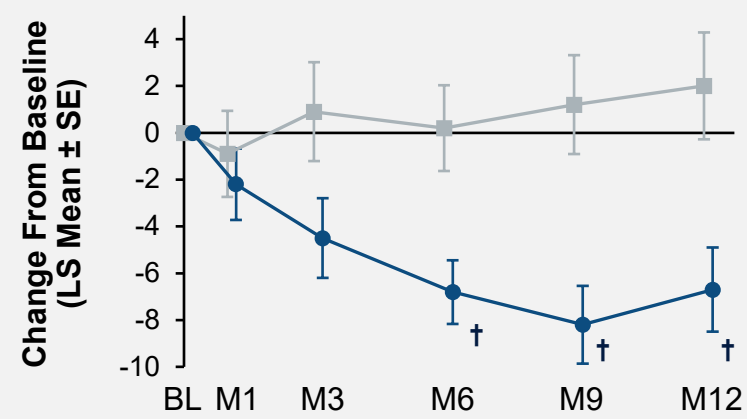
PBC-40 Itch



PBC-40 Sleep Disturbance



PBC-40 Fatigue



Seladelpar 10 mg (n = 16) Placebo (n = 12)

Decreases in itch, sleep disturbance, and fatigue as measured by the PBC-40 were observed in patients with severe itch at baseline

Change from baseline is estimated by a mixed-effects model for repeated measures. n = the number of subjects who had both a baseline value and a value at that time point. For PBC-40, score ranges were as follows: 0–15 for itch, 11–55 for fatigue, and 0–5 for sleep disturbance. Sleep disturbance data are based on the sleep disturbance question within the Itch domain of PBC-40.

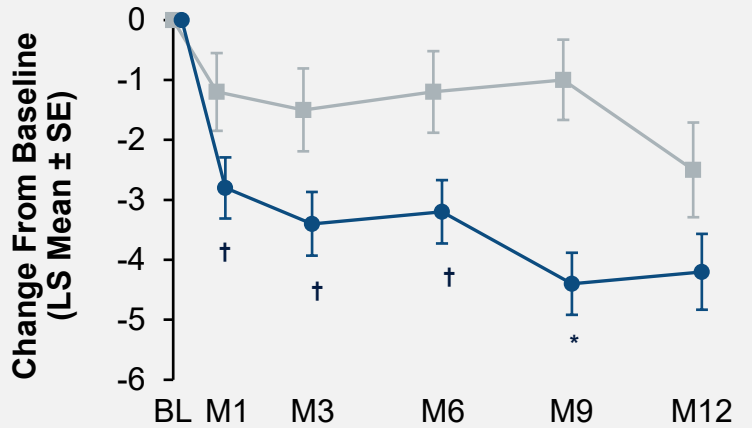
†*P* <.05 vs placebo.

BL, baseline; **LS**, least squares; **M**, month; **NRS**, numerical rating scale; **PBC**, primary biliary cholangitis; **QoL**, quality of life.

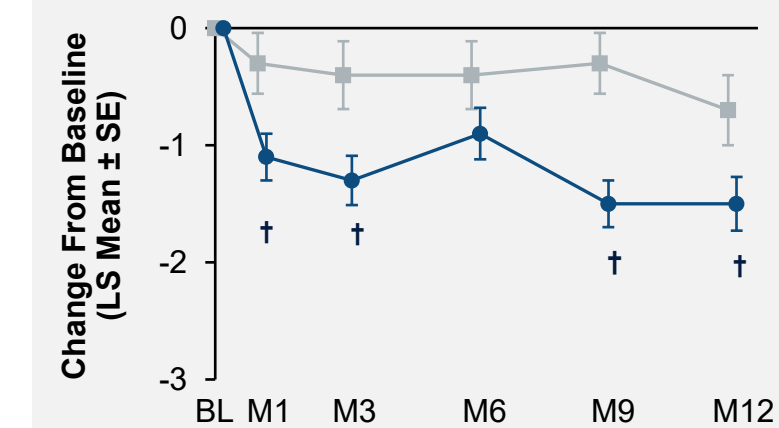
QoL Measures in Patients With Clinically Significant Pruritus at Baseline

PBC-40 ≥7 at Baseline

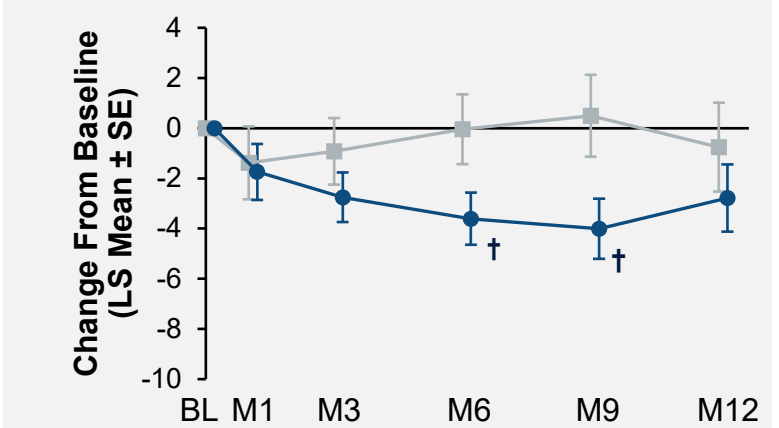
PBC-40 Itch



PBC-40 Sleep Disturbance



PBC-40 Fatigue



Seladelpar 10 mg (n = 45) Placebo (n = 25)

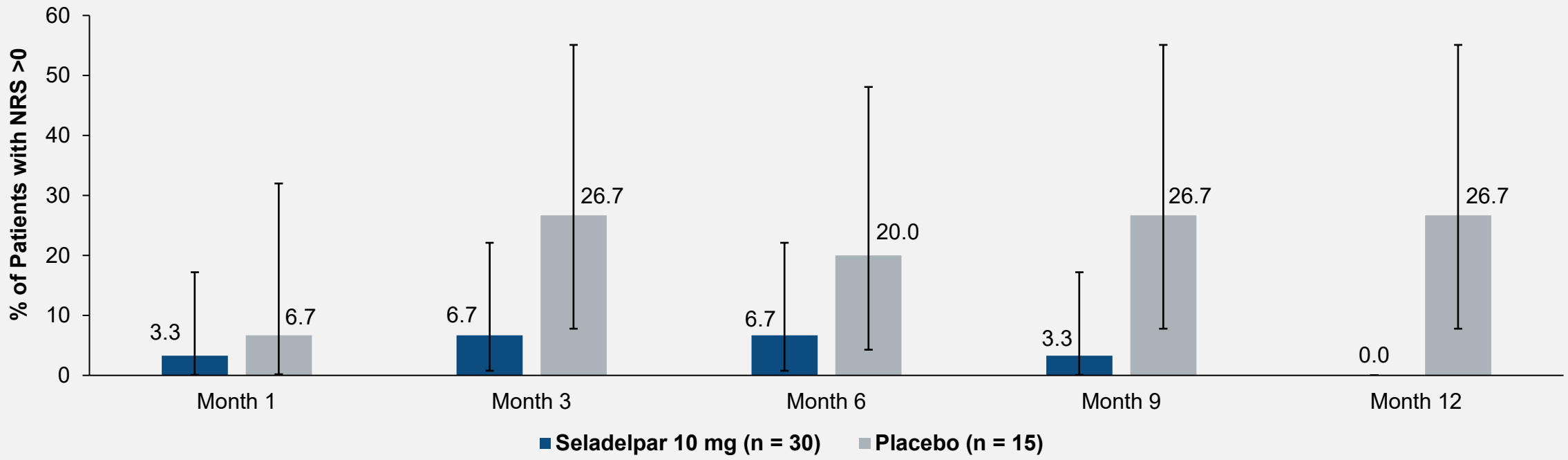
Patients with clinically significant itch at baseline had improvements in itch, sleep, and fatigue with seladelpar

Improvements from PBC-40 ≥7 to <7 occurred in 40% and 20% of seladelpar and placebo patients, respectively

Change from baseline is estimated by a mixed-effects model for repeated measures. n = the number of subjects who had both a baseline value and a value at that time point. For PBC-40, score ranges were as follows: 0–15 for itch, 11–55 for fatigue, and 0–5 for sleep disturbance. Sleep disturbance data are based on the sleep disturbance question within the Itch domain of PBC-40.
*P <.0001 vs placebo. †P <.05 vs placebo.
BL, baseline; **LS**, least squares; **M**, month; **NRS**, numerical rating scale; **PBC**, primary biliary cholangitis; **QoL**, quality of life.

Development of Itch in Patients With NRS = 0 at Baseline

Proportion of Patients Who Developed Pruritus Without Itch at Baseline



Among patients without itch at baseline, no patient receiving seladelpar developed itch at month 12

Patients with missing data at the specified time point were considered nonresponders.
NRS, numerical rating scale.

Overall Safety by Pruritus NRS at Baseline

Patient Incidence, n (%)	Patients With NRS <4 at Baseline		Patients With NRS ≥4 at Baseline	
	Seladelpar (n = 79)	Placebo (n = 42)	Seladelpar (n = 49)	Placebo (n = 23)
Any AE	68 (86.1)	34 (81.0)	43 (87.8)	21 (91.3)
Grade ≥3 AEs (per CTCAE)	9 (11.4)	2 (4.8)	5 (10.2)	3 (13.0)
SAEs[a]	5 (6.3)	3 (7.1)	4 (8.2)	1 (4.3)
Treatment-related SAEs	0	0	0	0
AEs leading to treatment discontinuation	1 (1.3)	1 (2.4)	3 (6.1)	2 (8.7)
AEs leading to study discontinuation	0	1 (2.4)	3 (6.1)	2 (8.7)
AEs leading to death	0	0	0	0

- Overall, the proportions of patients with adverse events were similar for seladelpar and placebo regardless of baseline itch severity

All AEs listed are treatment emergent unless otherwise stated.
[a]In the NRS ≥4 group: Seladelpar: One patient experienced an SAE of papillary thyroid cancer; another patient experienced duodenal obstruction and chronic obstructive pulmonary disease; another patient experienced COVID-19 infection; and another patient experienced rotator cuff syndrome. Placebo: One patient receiving placebo experienced an SAE of suicide attempt (not pruritus related).
AE, adverse event; **CTCAE,** Common Terminology Criteria for Adverse Events; **NRS,** numerical rating scale; **SAE,** serious adverse event.

Conclusions

- **Seladelpar reduced pruritus severity** in patients with PBC compared with placebo, leading to clinically meaningful declines in NRS
  - Seladelpar reduced itch **to mild levels** for patients with **moderate to severe pruritus**, with a **higher percentage of patients achieving a 3- or 4-point decline** in NRS at month 12 vs placebo
  - Seladelpar led to **near resolution of itch in almost 20% of patients** and **improvements in sleep and fatigue among** patients with **severe pruritus**
  - Seladelpar reduced itch **to non–clinically significant levels in 2 times as many patients** compared with placebo for patients with **clinically significant itch**, with **improvements in QoL**, including **decreases in fatigue and sleep disturbance**
- **No patient on seladelpar treatment developed pruritus** compared to **27% on placebo at month 12**
- **Seladelpar was overall safe** and **well tolerated** regardless of baseline itch

NRS, numerical rating scale; **PBC**, primary biliary cholangitis; **QoL**, quality of life.

Acknowledgments

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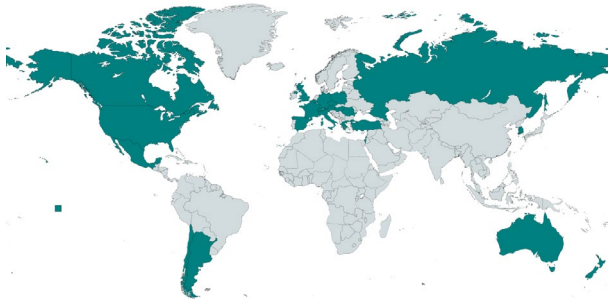

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