Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis in the RESPONSE Trial:
A Phase 3 International, Randomized, Placebo-Controlled Study

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Sponsor: CymaBay Therapeutics, Inc.

Presented by Gideon Hirschfield, FRCP, PhD

Toronto Centre for Liver Disease
University of Toronto

AASLD The Liver Meeting®
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- Professor of Medicine, University of Toronto

- I disclose the following financial relationship(s) with a commercial interest:

Consulting

- CymaBay Therapeutics
- Escient
- Gilead
- GlaxoSmithKline
- Intercept/Advanz
- Ipsen
- Kowa
- Mirum
- Pliant

Lectures, presentations, speaker bureaus, manuscript writing, or educational events

- GlaxoSmithKline
- Intercept
- Ipsen

Primary Biliary Cholangitis (PBC)

Approximately 1 in 1000 women over 40 years of age live with PBC

- Chronic, progressive, autoimmune, cholestatic liver disease
- Serum markers of cholestasis are prognostic
  - Alkaline phosphatase (ALP)
  - Total bilirubin (TB)
- Frequently symptomatic
  - Pruritus
  - Fatigue

Patient Priorities

Disease control

Symptom control

Potent, safe, and tolerable therapy

1. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172. 2. American Liver Foundation. Primary biliary cholangitis (PBC). Updated September 7, 2023. Accessed October 31, 2023. https://liverfoundation.org/liver-diseases/autoimmune-liver-diseases/primary-biliary-cholangitis-pbc/ 3. Mayo Clinic. Primary biliary cholangitis. June 21, 2023. Accessed August 3, 2023. https://www.mayoclinic.org/diseases-conditions/primary-biliary-cholangitis/symptoms-causes/syc-20376874 4. Levy C, et al. *Clin Gastroenterol Hepatol.* 2023;21(8):2076-2087.

Seladelpar

First-in-Class, Potent, Selective Delpar (PPARδ Agonist) Targeting Multiple Cell Types and Processes in PBC

Improves Cholestasis

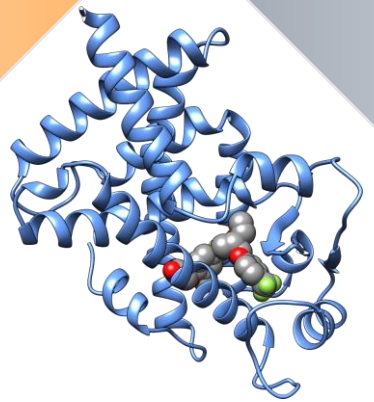
- ⇩ Bile acid synthesis
- ⇩ ALP
- ⇩ GGT

Hepatocytes and Cholangiocytes

Reduces Markers of Inflammation

- ⇩ Inflammatory cytokines
- ⇩ Inflammatory lipid mediators
- ⇩ ALT

Macrophages and Kupffer Cells



Seladelpar

Potent PPARδ engagement

Reduces Pruritus

- ⇩ Bile acids
- ⇩ Serum IL-31*

Hepatocytes

Increases Lipid Metabolism

- ⇩ Cholesterol/LDL-C/triglycerides
- ⇧ Fatty acid oxidation

Hepatocytes

EMA, European Medicines Agency; FDA, Food and Drug Administration; IL-31, interleukin-31; LDL-C, low-density lipoprotein cholesterol; PPARδ, peroxisome proliferator-activated receptor delta.
*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.

1. CymaBay Therapeutics, Inc. Seladelpar granted revised breakthrough therapy designation for the treatment of primary biliary cholangitis including pruritus in patients without cirrhosis or with compensated cirrhosis. October 23, 2023. Accessed October 28, 2023. https://www.cymabay.com/investors-media/news-events/press-releases/detail/577/seladelpar-granted-revised-breakthrough-therapy-designation 2. Hirschfield GM, et al. *Hepatology*. 2023;78(2):397-415. 3. Kremer AE, et al. *Liver Int*. 2022;42(1):112-123. 4. Kremer AE, et al. Presented at: ACG 2023 Annual Meeting; October 20-25, 2023; Vancouver, Canada. 5. Kuono T, et al. *J Biol Chem*. 2022;298(7):102056. 6. Choi Y, et al. Presented at: Discovery on Target; September 27-30, 2021; Boston, MA. 7. Choi Y, et al. Poster presented at: AASLD: The Liver Meeting; November 4-8, 2022; Washington, DC. Poster 4731. 8. Bowlus C, et al. Poster presented at: AASLD: The Liver Meeting; November 4-8, 2022; Washington, DC. Poster 4759.

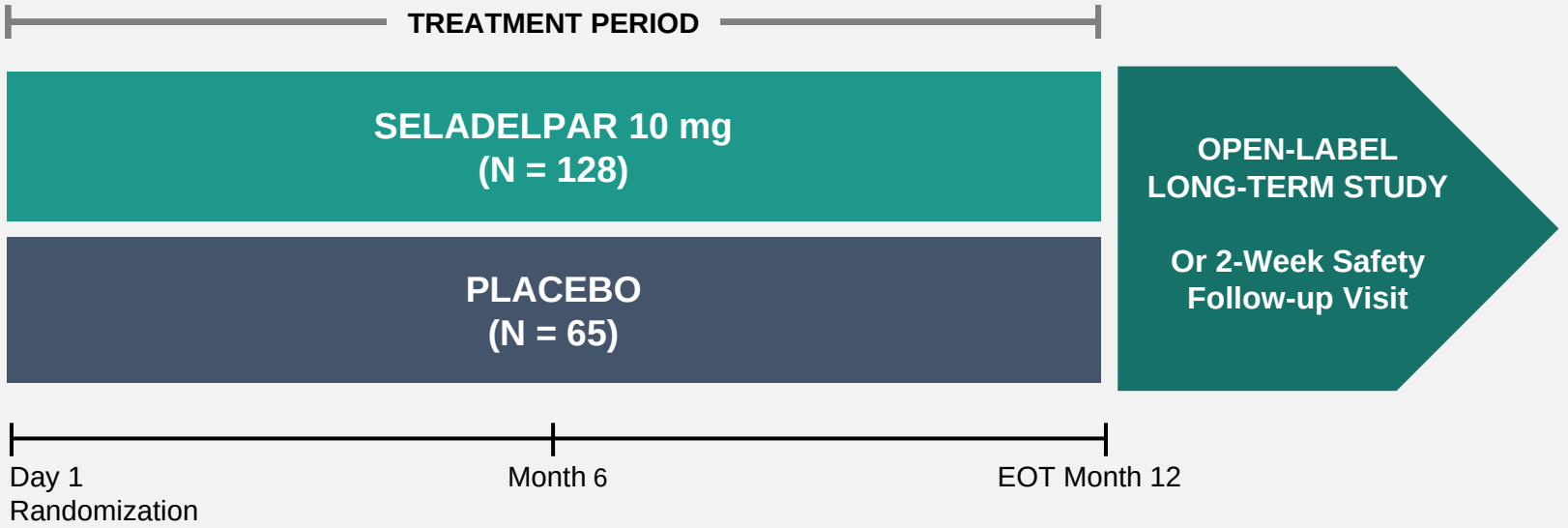
RESPONSE: Phase 3 Study Design

Entry Criteria

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

Stratification

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



PRIMARY ENDPOINT – COMPOSITE RESPONDER RATE AT MONTH 12

ALP < 1.67 × ULN; ALP decrease ≥ 15%; total bilirubin ≤ 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

Seladelpar was administered orally once daily.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; EOT, end of treatment; NRS, Numerical Rating Scale; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

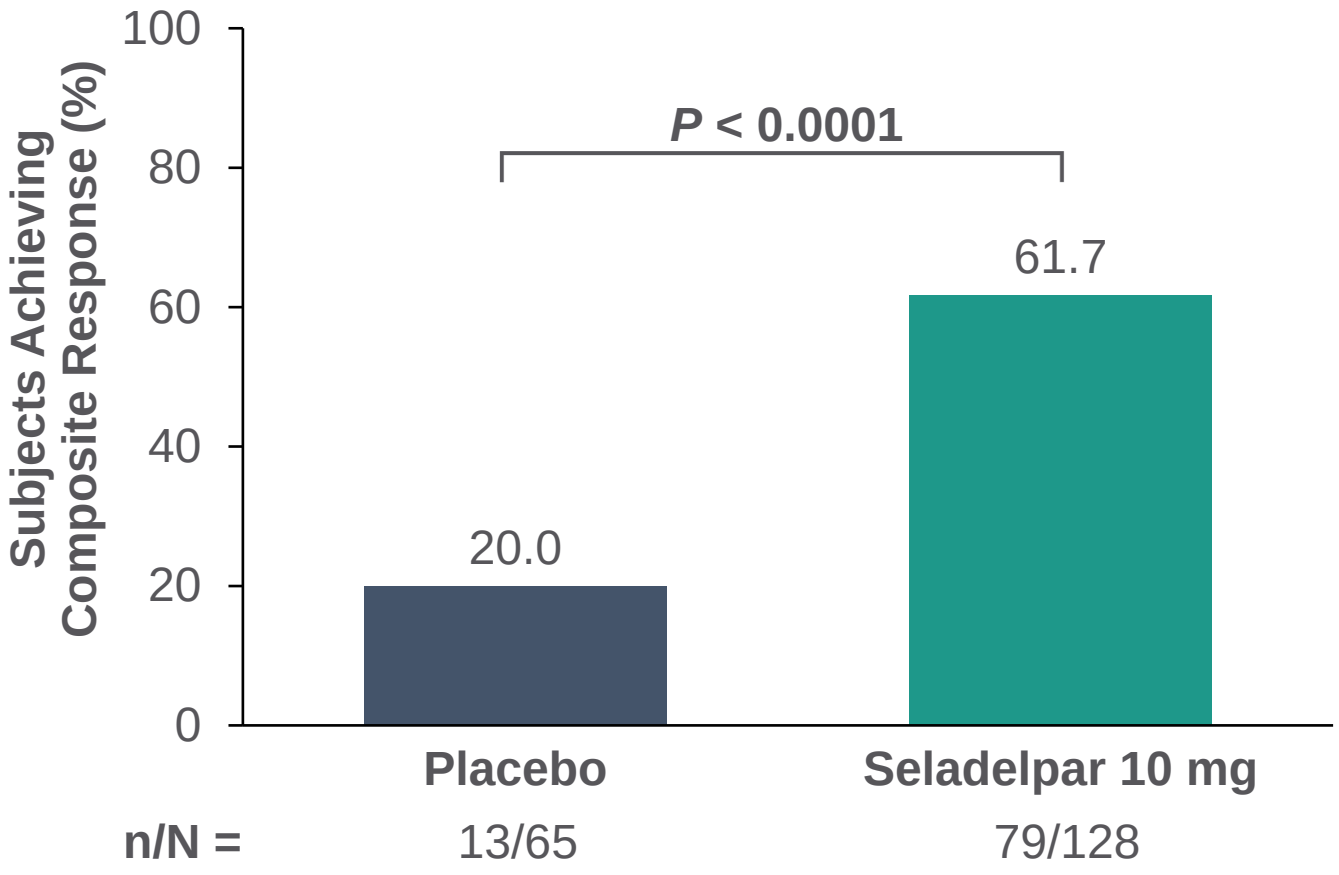
Demographic and Baseline Characteristics

Mean (SD)		Placebo (N = 65)	Seladelpar 10 mg (N = 128)
Female, n (%)		60 (92.3%)	123 (96.1%)
Age, years		57.0 (9.2)	56.6 (10.0)
Duration of disease, years		8.6 (6.5)	8.2 (6.7)
On UDCA, n (%)		61 (93.8%)	120 (93.8%)
Pruritus NRS ≥ 4, n (%)		23 (35.4%)	49 (38.3%)
Cirrhosis, n (%)		9 (13.8%)	18 (14.1%)
ALP, U/L	ULN: 116 U/L	313.8 (117.7)	314.6 (123.0)
TB, mg/dL	ULN: 1.1 mg/dL	0.74 (0.3)	0.77 (0.3)
ALT, U/L	ULN: 41 U/L	48.2 (22.8)	47.4 (23.5)
AST, U/L	ULN: 34 U/L	41.7 (16.0)	39.6 (16.1)
GGT, U/L	ULN: 38 U/L	287.5 (249.6)	269.0 (240.0)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; NRS, Numerical Rating Scale; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Primary Endpoint: Month 12 Composite Biochemical Response

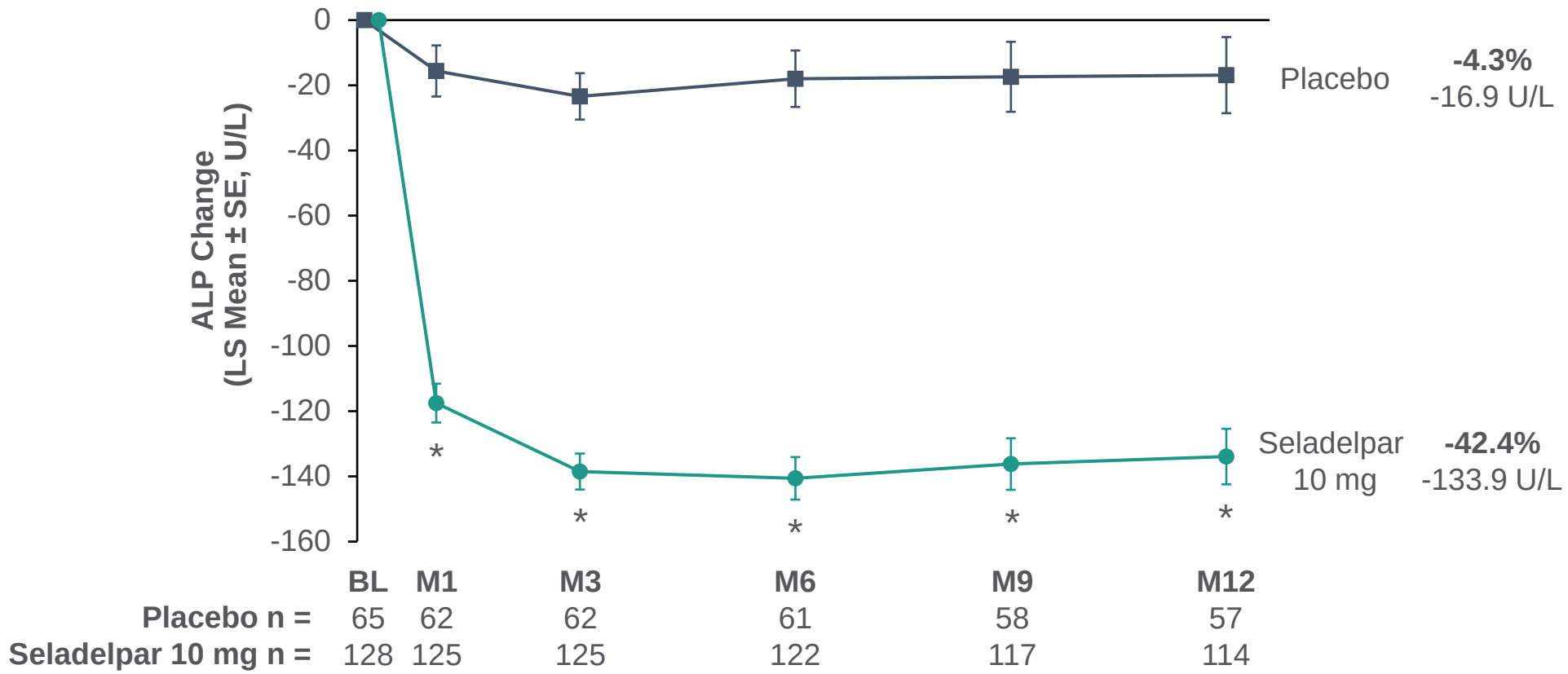
ALP < 1.67 × ULN, ≥ 15% Decrease in ALP, Total Bilirubin ≤ ULN



Approximately 6 in 10 patients achieved the biochemical composite response at Month 12

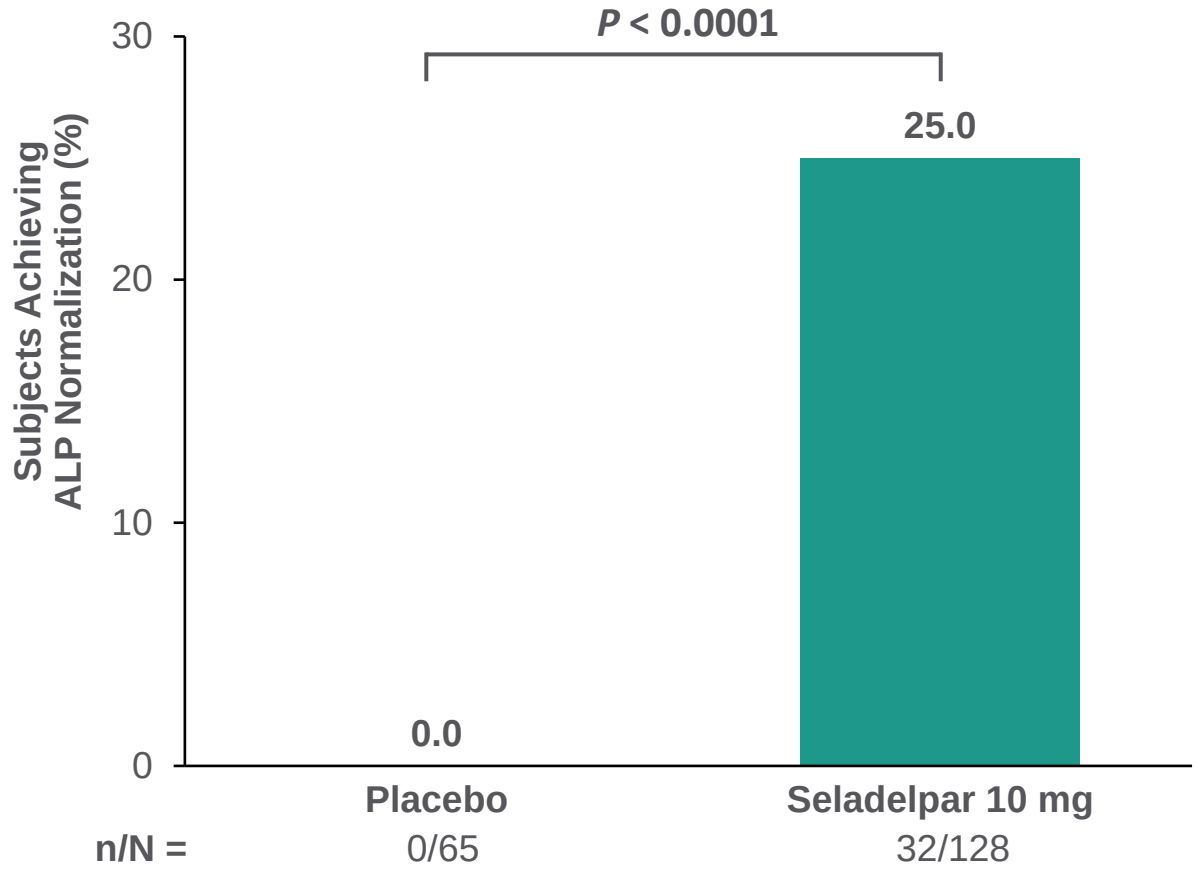
P value by Cochran–Mantel–Haenszel (CMH) test.

ALP Change From Baseline



BL, baseline; LS, least squares; M, month.
*$P < 0.0001$ at all time points.

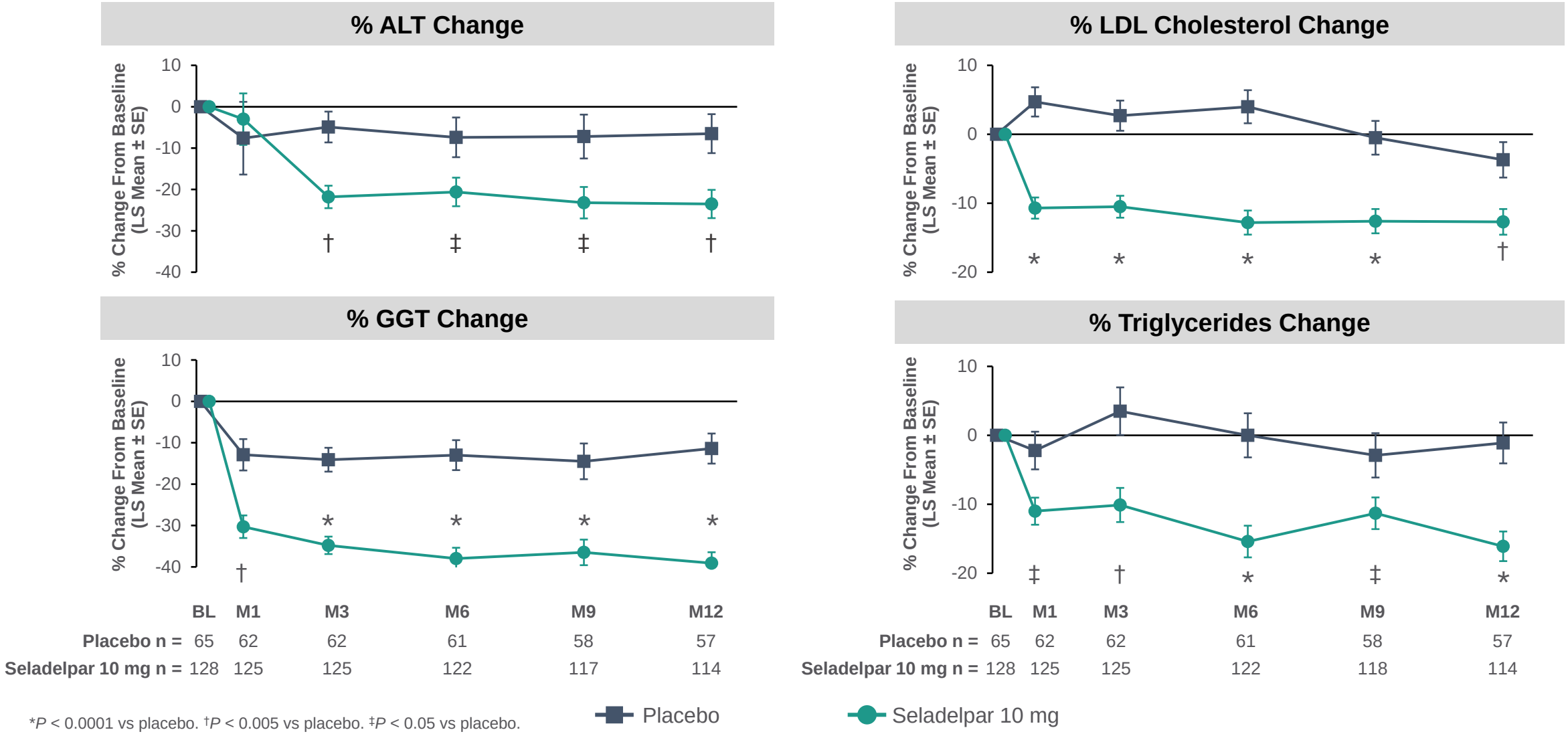
Key Secondary Endpoint: ALP Normalization at Month 12



1 in 4 patients treated with seladelpar normalized ALP

P value by CMH test.

Seladelpar Significantly Improved Serum Markers of Liver Injury and Lipid Profile

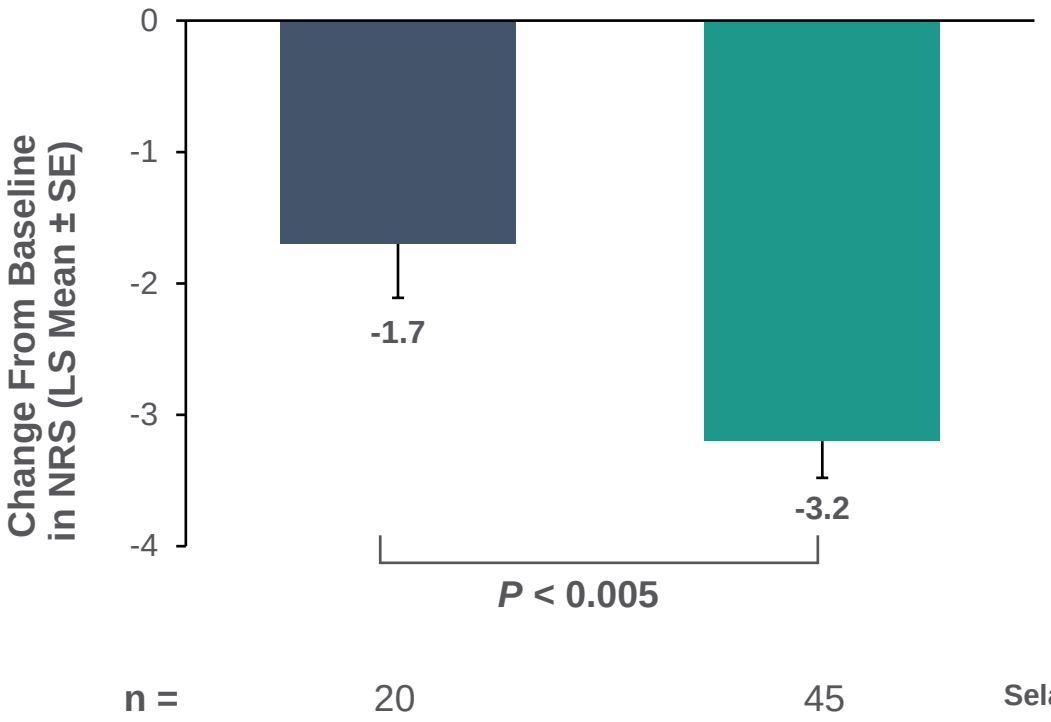


*P < 0.0001 vs placebo. †P < 0.005 vs placebo. ‡P < 0.05 vs placebo.

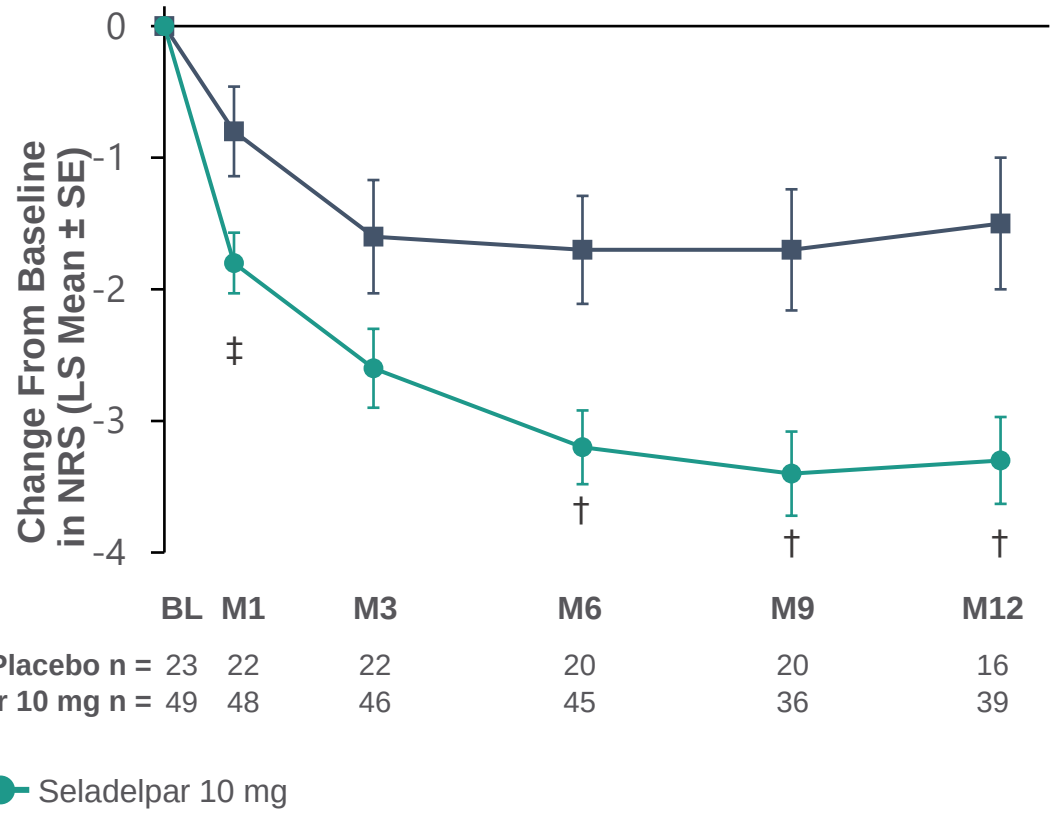
Seladelpar Significantly Improved Pruritus

Subjects With Baseline NRS ≥ 4

Key Secondary Endpoint: Change in Pruritus NRS at Month 6



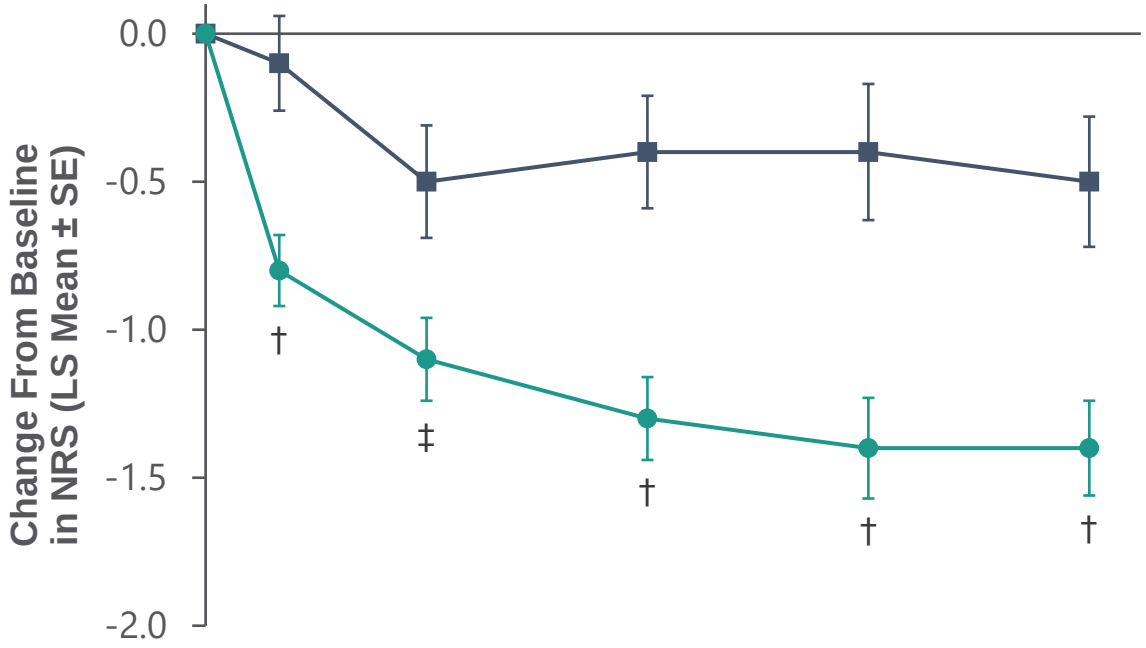
Change in Pruritus NRS Over Time



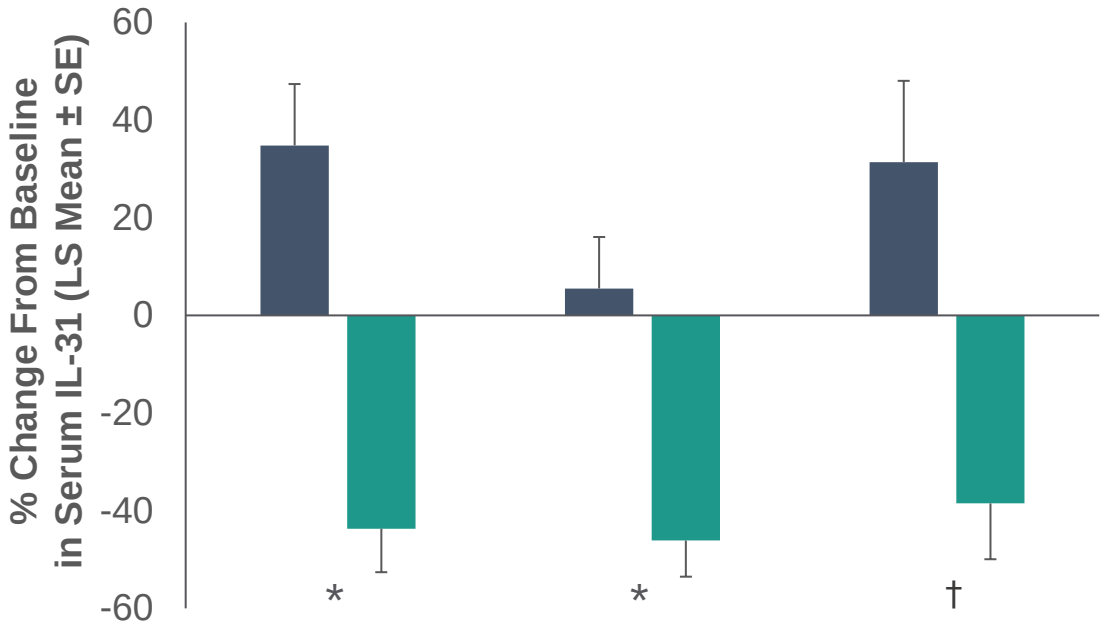
MMRM analysis in subjects with baseline NRS ≥ 4 using weekly averages. Baseline pruritus NRS is defined as the mean of all daily recorded scores during the run-in period and on Day 1. The n values represent the number of subjects with available data at each time point.
MMRM, mixed-effect model for repeated measures.
†$P < 0.005$ vs placebo. ‡$P < 0.05$ vs placebo.

In the Overall Population, Seladelpar Both Had a Durable Effect on Pruritus and Reduced the Pruritogenic Cytokine IL-31

Pruritus NRS



% Serum IL-31 Change



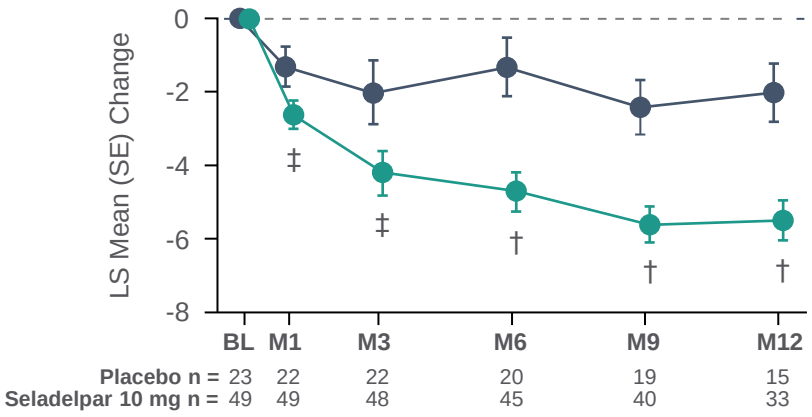
Placebo Seladelpar 10 mg

MMRM analysis in the overall population using weekly averages. Baseline pruritus NRS is defined as the mean of all daily recorded scores during the run-in period and on Day 1. The n values represent the number of subjects with available data at each time point.
*$P < 0.0001$ vs placebo. †$P < 0.005$ vs placebo. ‡$P < 0.05$ vs placebo.

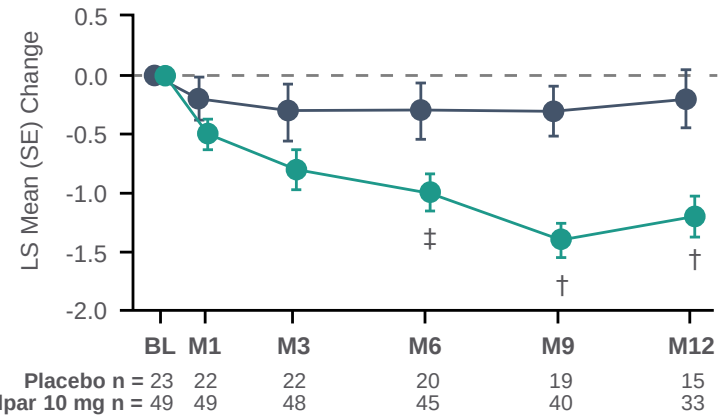
Seladelpar Reductions in Pruritus Were Accompanied by Improvements in Sleep Disturbance

NRS ≥ 4 Population

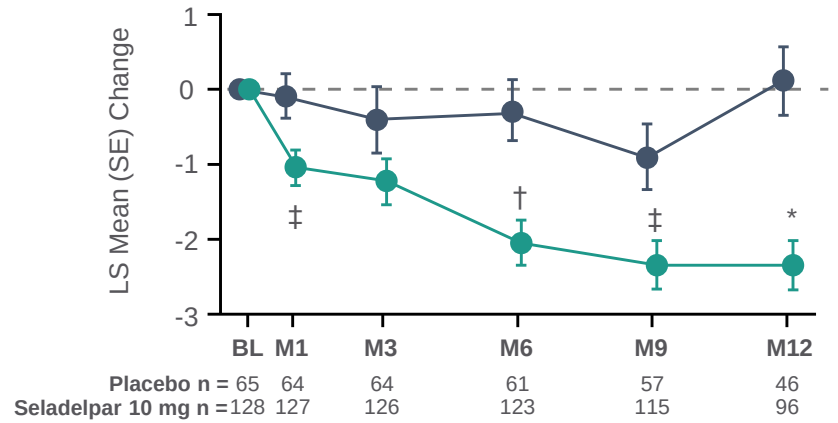
5-D Itch Total

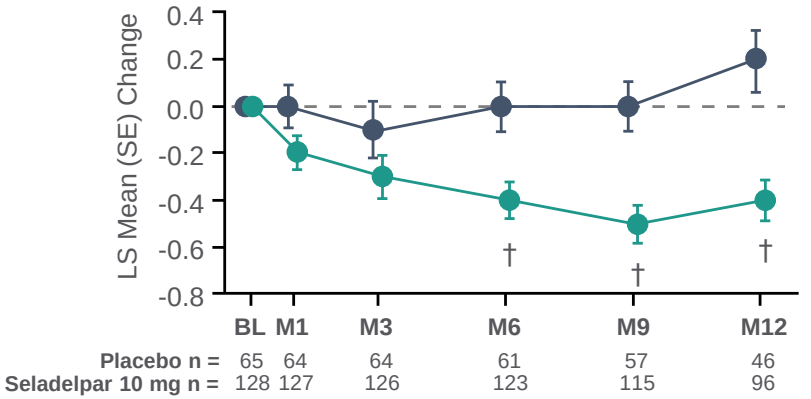


5-D Itch Impact on Sleep



Overall Population





*P < 0.0001 vs placebo. †P < 0.005 vs placebo. ‡P < 0.05 vs placebo.

Placebo Seladelpar 10 mg

Safety Overview: Summary of Adverse Events

No Meaningful Differences Between Placebo and Seladelpar

Safety Population, n (%)	Placebo (N = 65)	Seladelpar 10 mg (N = 128)
Subjects with at least 1 AE	55 (84.6)	111 (86.7)
Any treatment-related AE	8 (12.3)	22 (17.2)
Any treatment-related AE ≥ Grade 3 (CTCAE)	0	0
Any AE with outcome of death	0	0
Any SAE	4 (6.2)	9 (7.0)
Any treatment-related SAE	0	0
Any AE leading to study drug discontinuation	3 (4.6)	4 (3.1)
Liver-related AEs*	6 (9.2)	8 (6.3)
Muscle-related AEs*	5 (7.7)	8 (6.3)

96% of eligible patients completing treatment agreed to enter open-label safety study†

All AEs were treatment emergent. Treatment-related AEs were per investigator assessment.
AE, adverse event; SAE, serious adverse event.
*Liver and muscle AEs were identified by predefined search strategy.
† ASSURE, NCT03301506.

Safety Overview: Summary of Adverse Events

Occurring in ≥ 5% of Patients in Either Arm

Event, n (%)	Placebo (N = 65)	Seladelpar 10 mg (N = 128)
COVID-19	10 (15.4)	23 (18.0)
Pruritus	10 (15.4)	6 (4.7)
Upper respiratory tract infection	6 (9.2)	1 (0.8)
Headache	2 (3.1)	10 (7.8)
Nasopharyngitis	5 (7.7)	7 (5.5)
Pharyngitis	5 (7.7)	4 (3.1)
Abdominal pain	1 (1.5)	9 (7.0)
Arthralgia	4 (6.2)	8 (6.3)
Fatigue	4 (6.2)	8 (6.3)
Nausea	3 (4.6)	8 (6.3)
Abdominal distension	2 (3.1)	8 (6.3)
Asthenia	4 (6.2)	5 (3.9)
Urinary tract infection	4 (6.2)	4 (3.1)
Hypertension	4 (6.2)	4 (3.1)
Vertigo positional	4 (6.2)	1 (0.8)

All AEs were treatment emergent.

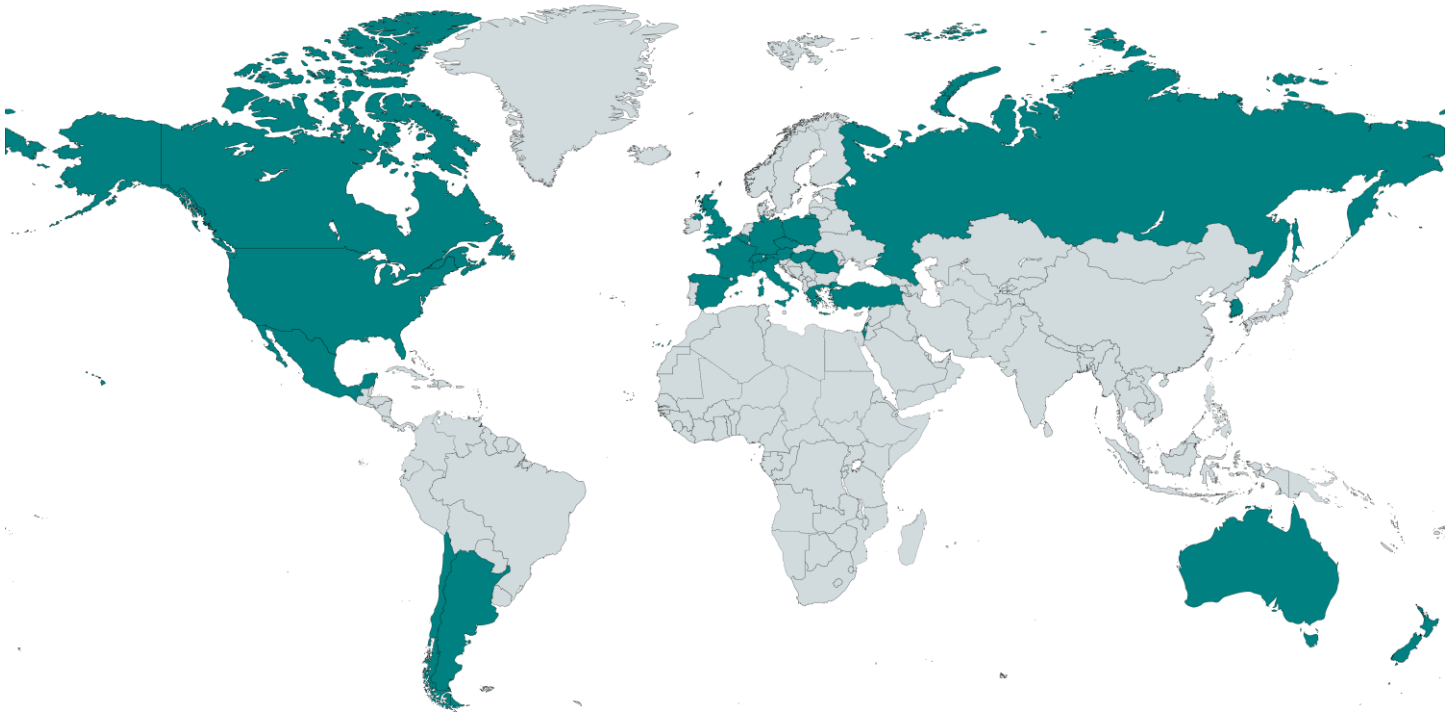
The RESPONSE Phase 3 Study Met Both Primary and Key Secondary Endpoints

Seladelpar Improved Markers of Disease Activity and Pruritus in Patients With PBC

- **Significantly more patients met the composite biochemical endpoint and ALP normalization with seladelpar vs placebo at Month 12**
  - Approximately 6 in 10 patients met the primary composite endpoint
  - Approximately 1 in 4 patients met the key secondary endpoint of ALP normalization
  - Mean reduction in ALP was 42% or 133.9 U/L at Month 12
- **The improvement in pruritus at Month 6 in patients with moderate to severe itch was highly statistically significant**
- **In the overall population, seladelpar reduced pruritus as well as the pruritogenic cytokine IL-31 through Month 12**
- **Treatment with seladelpar decreased ALT, GGT, triglycerides, and LDL cholesterol**
- **Seladelpar appeared safe and well tolerated**

Acknowledgements

We gratefully acknowledge the study patients, investigators, site staff, and the RESPONSE team



Countries involved in the global RESPONSE study:

Argentina	Germany	Poland
Australia	Greece	Romania
Austria	Hungary	Russia
Belgium	Israel	Spain
Canada	Italy	Switzerland
Chile	Republic of Korea	Turkey
Czech Republic	Mexico	UK
France	New Zealand	USA

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Thank you!

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Appendix

RESPONSE Patient Disposition

n (%)	Placebo (N = 65)	Seladelpar 10 mg (N = 128)
Subjects randomized and treated	65 (100.0)	128 (100.0)
Subjects who completed treatment	57 (87.7)	118 (92.2)
Subjects who discontinued treatment	8 (12.3)	10 (7.8)
Primary reason for treatment discontinuation		
Adverse event	4 (6.2)	4 (3.1)
Withdrawal of informed consent	2 (3.1)	4 (3.1)
Significant protocol deviation	1 (1.5)	1 (0.8)
Lost to follow-up	1 (1.5)	1 (0.8)
Eligible subjects who agreed to enter ASSURE*,†	54 (96.4)	106 (96.4)

All randomized subjects analysis set. The N and n values represent the total number of subjects and the number of subjects in each category, respectively.
*Includes subjects who completed RESPONSE, were eligible to enroll in the open-label study ASSURE and agreed to the open-label study; subjects in Russia were not eligible for ASSURE due to operational complexities.
†Percentages based on number of subjects eligible for ASSURE who completed treatment in RESPONSE (56 subjects in placebo, 110 subjects in seladelpar, 166 subjects overall).