Seladelpar Leads to Sustained Reduction in Cholestatic Markers With Consistent Safety Profile in Patients With Primary Biliary Cholangitis up to 48 Months

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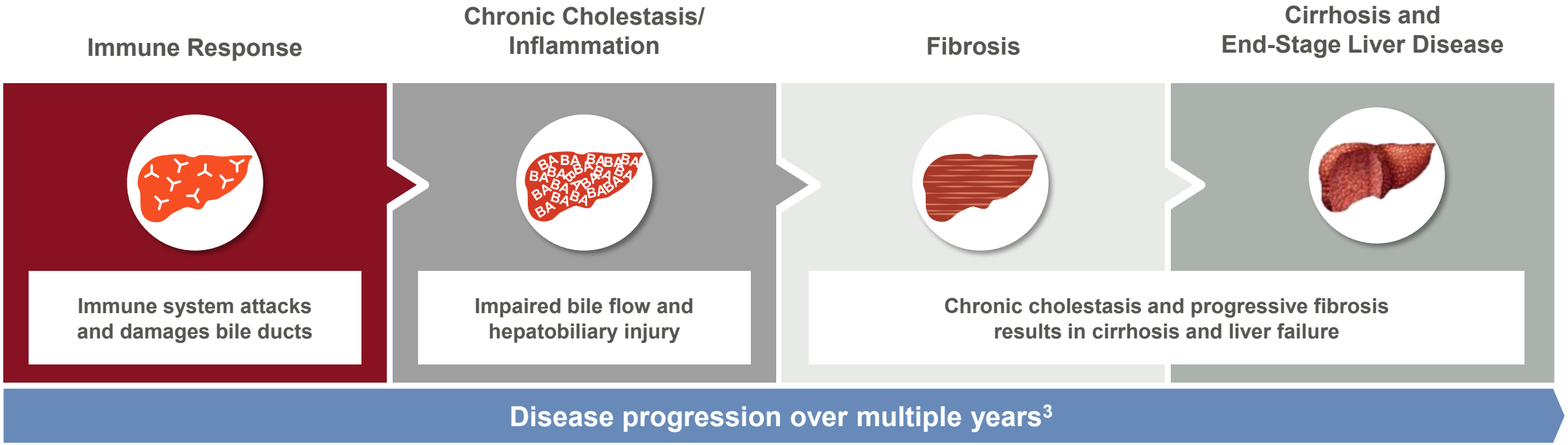
Primary Biliary Cholangitis

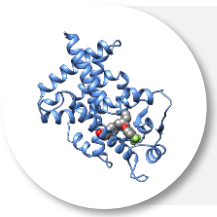
- PBC is a chronic, progressive, autoimmune, cholestatic liver disease that affects approximately 1 in 1000 women over 40 years of age[1]
- PBC can result in hepatocellular injury, fibrosis, and eventual progression to cirrhosis[2]
- The first-line treatment is ursodeoxycholic acid (UDCA), but many patients do not achieve an adequate ALP response or normalization with UDCA alone[1,2]



ALP, alkaline phosphatase; **BA**, bile acids; **PBC**, primary biliary cholangitis; **UDCA**, ursodeoxycholic acid.

1. European Association for the Study of the Liver. *J Hepatol.* 2017;67(1):145-72. **2.** American Association for the Study of Liver Diseases. *Hepatology*. 2018;0(0):1-260.**3.** Selmi C, et al. *Lancet*. 2011;377(9777):1600-9.

Seladelpar: PPARδ Agonist



- **Seladelpar** is a first-in-class **delpar (selective peroxisome proliferator–activated receptor delta [PPARδ] agonist)** indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as a monotherapy in patients who are unable to tolerate UDCA[1–4]

Hepatocytes & Cholangiocytes	Macrophages & Kupffer Cells	Hepatocytes	Hepatocytes
Improves cholestasis	**Reduces inflammation**	**Reduces pruritus**	**Increases lipid metabolism**
↓ Bile acid synthesis[5–8]	↓ Inflammatory cytokines[8]	↓ Bile acids[6]	↓ Total cholesterol, LDL, triglycerides[5,8,11]
↓ ALP[5]	↓ Inflammatory lipid mediators[9]	↓ IL-31[10,a]	↑ Fatty acid oxidation[8,9]
↓ GGT[5]	↓ ALT[5]		

Seladelpar is a selective PPARδ agonist with anticholestatic, anti-inflammatory, and antipruritic effects[1-12]

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. US prescribing information. Gilead Sciences, Inc.; 2024. **3.** Livdelzi. UK summary of product characteristics. Gilead Sciences, Inc.; 2024. **4.** Lyvdelzi. EMA prescribing information. Gilead Sciences, Inc. 2025. **5.** Hirschfield GM, et al. *Hepatology*. 2023;78(2):397-415. **6.** Kremer AE, et al. *Liver Int*. 2022;42(1):112-23. **7.** Kouno T, et al. *J Biol Chem*. 2022;298(7):102056. **8.** Choi Y, et al. Discovery on Target 2021. Oral presentation. **9.** Choi Y, et al. AASLD 2022. Poster 4731. **10.** Kremer AE, et al. *Hepatology*. 2024;80(1):27-37. **11.** Bowlus C, et al. AASLD 2022. Poster 4759. **12.** Hirschfield G, et al. AASLD 2023. Oral presentation 5002.

Study Background and Objective

Pivotal Phase 3 RESPONSE[1] Trial

A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis

G.M. Hirschfield, C.L. Bowlus, M.J. Mayo, A.E. Kremer, J.M. Vierling, K.V. Kowdley, C. Levy, A. Villamil, A.L. Ladrón de Guevara Cetina, E. Janczewska, E. Zigmond, S.-H. Jeong, Y. Yilmaz, Y. Kallis, C. Corpechot, P. Buggisch, P. Invernizzi, M.C. Londoño Hurtado, S. Bergheanu, K. Yang, Y.-J. Choi, D.B. Crittenden, and C.A. McWherter, for the RESPONSE Study Group*

12 months of seladelpar treatment led to:

- Statistically significant improvement in cholestatic biomarkers and pruritus
- Overall safe and well tolerated

Open-Label Safety ASSURE[2] Trial

Long-Term Efficacy and Safety of Selective PPARδ Agonist Seladelpar in Primary Biliary Cholangitis: ASSURE Interim Study Results

Cynthia Levy, MD[1], Palak J. Trivedi, MD[2,3], Kris V. Kowdley, MD, FACG[4], Stuart C. Gordon, MD[5], Christopher L. Bowlus, MD[6], Maria Carlota Londoño, MD[7], Gideon M. Hirschfield, PhD[8], Aliya Gulamhusein, MD[8], Eric J. Lawitz, MD[9], John M. Vierling, MD[10], Marlyn J. Mayo, MD[11], Ira M. Jacobson, MD, FACG[12], Andreas E. Kremer, MD, PhD[13], Christophe Corpechot, MD[14], David Jones, MD[15], Peter Buggisch, MD[16], Shuqiong Zhuo, MS[17], Sarah Proehl, MD[18], Carrie Heusner, PhD[17], Charles A. McWherter, PhD[17,*] and Daria B. Crittenden, MD[18,*], on behalf of the ASSURE Investigators

Continued seladelpar treatment led to:

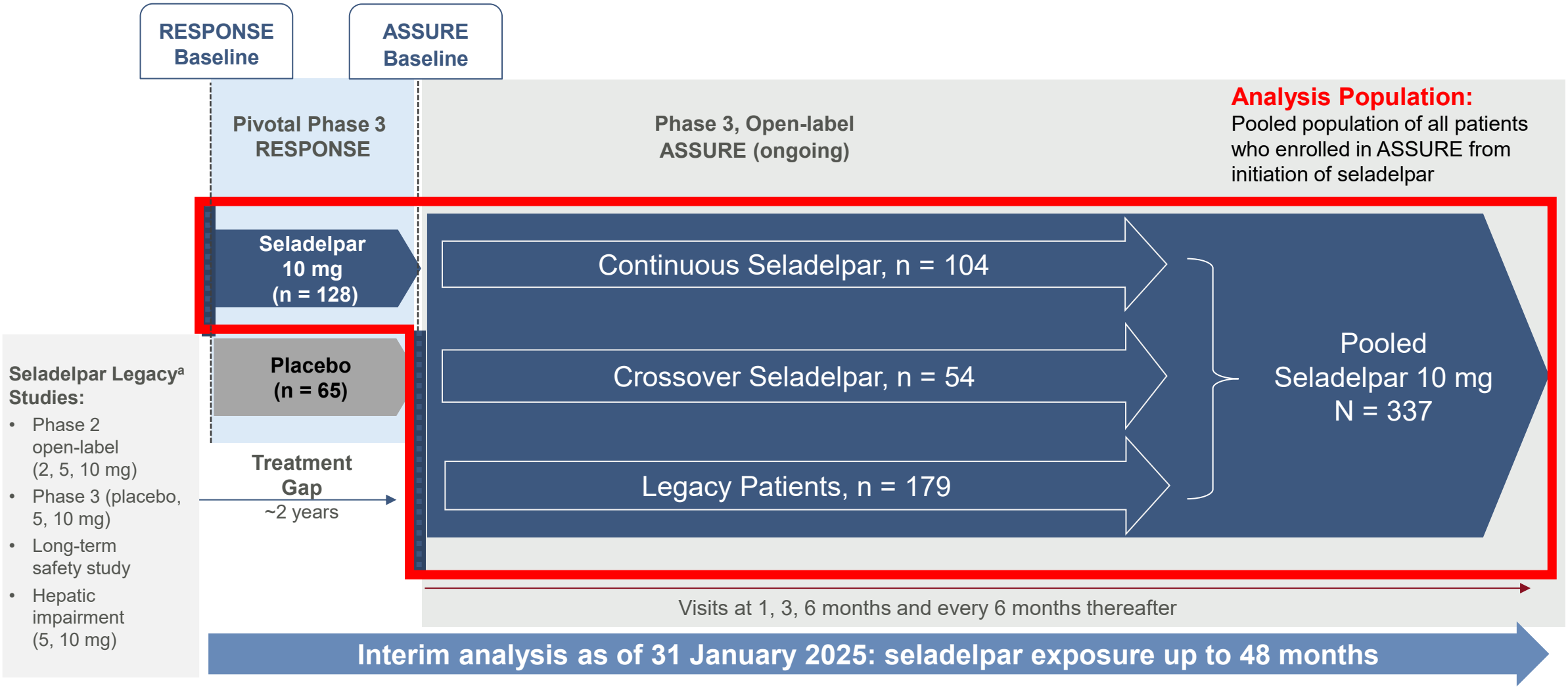
- Consistent efficacy up to 24 months, and a consistent safety profile up to 36 months

Objective: To evaluate biochemical efficacy and safety outcomes of long-term seladelpar treatment (up to 48 months) in the ongoing ASSURE study

ALP, alkaline phosphatase; **PPARδ**, peroxisome proliferator–activated receptor delta; **ULN**, upper limit of normal.

1. Hirschfield GM, et al. *N Engl J Med.* 2024;390:783-94. **2.** Levy C, et al. *Am J Gastroenterol.* 2025;1-14.

Study Schema: Pooled Interim Analysis of ASSURE



[a]Legacy studies include the Phase 2 dose-ranging study (NCT02955602), Phase 3 long-term safety study (NCT03301506), Phase 3 ENHANCE study (NCT03602560), Phase 1b hepatic impairment study (NCT04950764), Phase 3 placebo-controlled RESPONSE study (NCT04620733), and Phase 3, open-label ASSURE study (NCT03301506). The Phase 2 and 3 parent studies required an inadequate response or intolerance to first-line UDCA. Data cutoff: January 31, 2025. Data from the RESPONSE study were added to the ASSURE data for patients who received seladelpar in response. In ASSURE, 2 patients initiated seladelpar at 5 mg and were excluded from the analysis.
UDCA, ursodeoxycholic acid.

Analyses

- Data cut off : Jan 31st 2025
- Efficacy assessments included composite biochemical response, normalization of ALP and total bilirubin, and percent change from baseline in ALP and total bilirubin.
- Efficacy data are presented through 36 months secondary to small sample sizes after 36 months
- Safety assessments included laboratory assessments and collection of AEs; safety was assessed through 48 months

AE, adverse event; **ALP,** alkaline phosphatase; **UDCA**, ursodeoxycholic acid.

1. Levy C, et al. *Am J Gastroenterol*. 2025; 1-14.

Baseline Characteristics at Seladelpar Initiation

	Seladelpar 10 mg N = 337
Age, years, mean (SD)	58.1 (9.7)
Female sex, n (%)	318 (94)
Race, n (%)	
American Indian or Alaska Native	11 (3)
Asian	24 (7)
Black or African American	7 (2)
White	289 (86)
Other	0
BMI, kg/m^2, mean (SD)	27.3 (5.8)
ALP, U/L, mean (SD)[b]	287.5 (128.4)
ALT, U/L, mean (SD)[c]	43.0 (23.0)
AST, U/L, mean (SD)[d]	38.0 (16.3)
Total bilirubin, mg/dL, mean (SD)[e]	0.8 (0.3)
Patients with cirrhosis at baseline, n (%)	53 (16)
Child-Pugh class A[a]	49 (92)
Child-Pugh class B[a]	4 (8)
Portal hypertension[a]	9 (17)
MELD score ≥12, n (%)	2 (0.6)
Pruritus NRS, mean (SD)	2.7 (2.8)
Pruritus NRS ≥4, n(%)	107 (32)

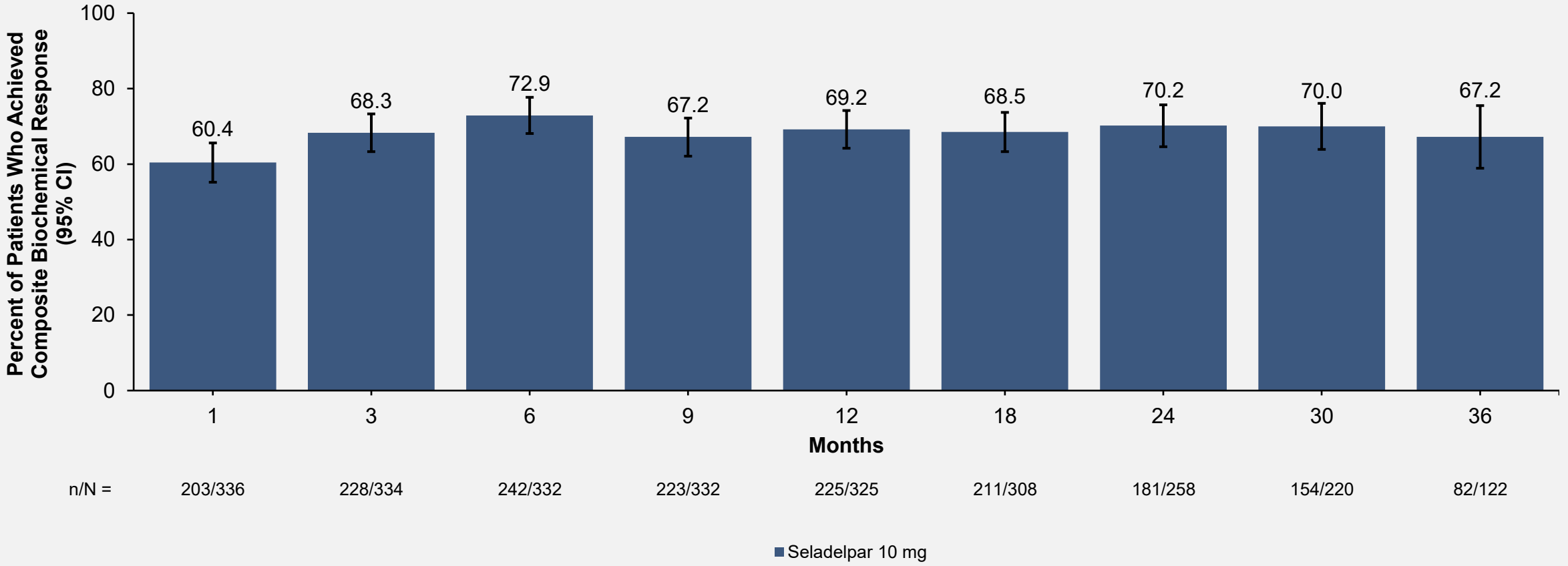
Seladelpar Exposure in ASSURE

	Seladelpar 10 mg (N = 337)	
Treatment Duration	**Number of Patients**	**Percent**
≥1 year	325	96.4
≥2 years	258	76.6
>3 years	117	34.7
>3.5 years	33	9.8

Baseline defined at seladelpar initiation. For patients who rolled over from the CB8025-32048 seladelpar arm, baseline starts from RESPONSE. For all other patients, baseline starts from ASSURE.
[a]Percentage based on patients with cirrhosis at baseline. [b]The ULN is 116 U/L. [c]The ULN is 41 U/L. [d]The ULN is 34 U/L. [e]The ULN is 1.10 mg/dL.
ALP, alkaline phosphatase; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **BMI**, body mass index; **MELD**, Model for End-Stage Liver Disease; **NRS,** numeric rating scale; **ULN**, upper limit of normal.

Composite Biochemical Response

ALP <1.67 × ULN, ALP decrease ≥15% from baseline, and total bilirubin normalization

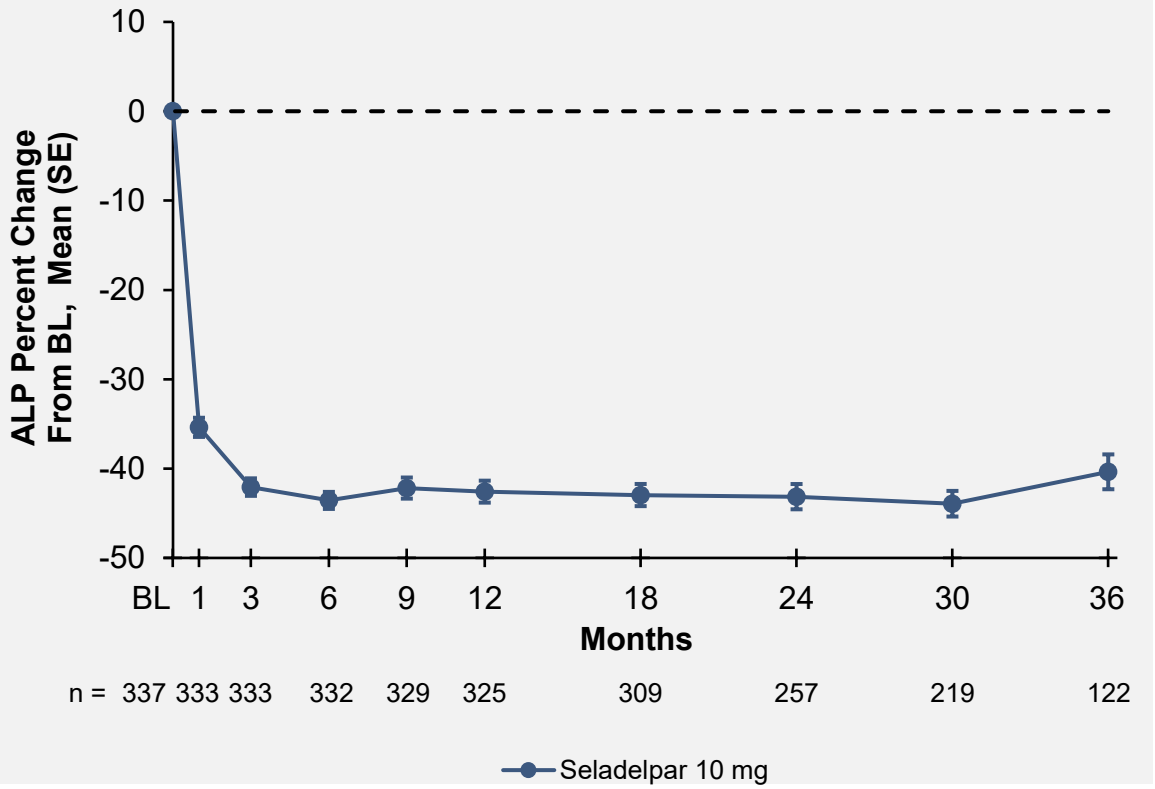


The majority of patients on seladelpar achieved a composite biochemical response at each time point

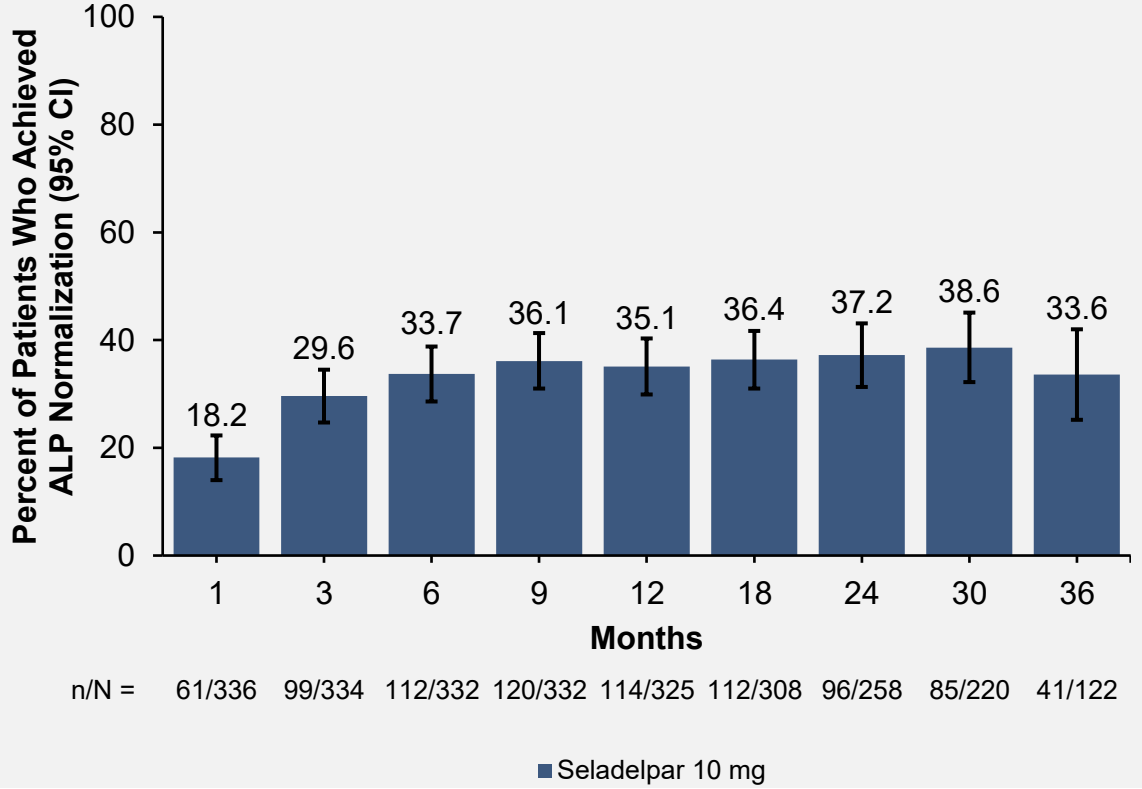
n/N = number of responders at each time point/total number of evaluable patients at each time point.
Baseline was defined at seladelpar initiation.
ALP, alkaline phosphatase; **ULN**, upper limit of normal.

ALP Percent Change and Normalization

ALP Percent Change



ALP Normalization

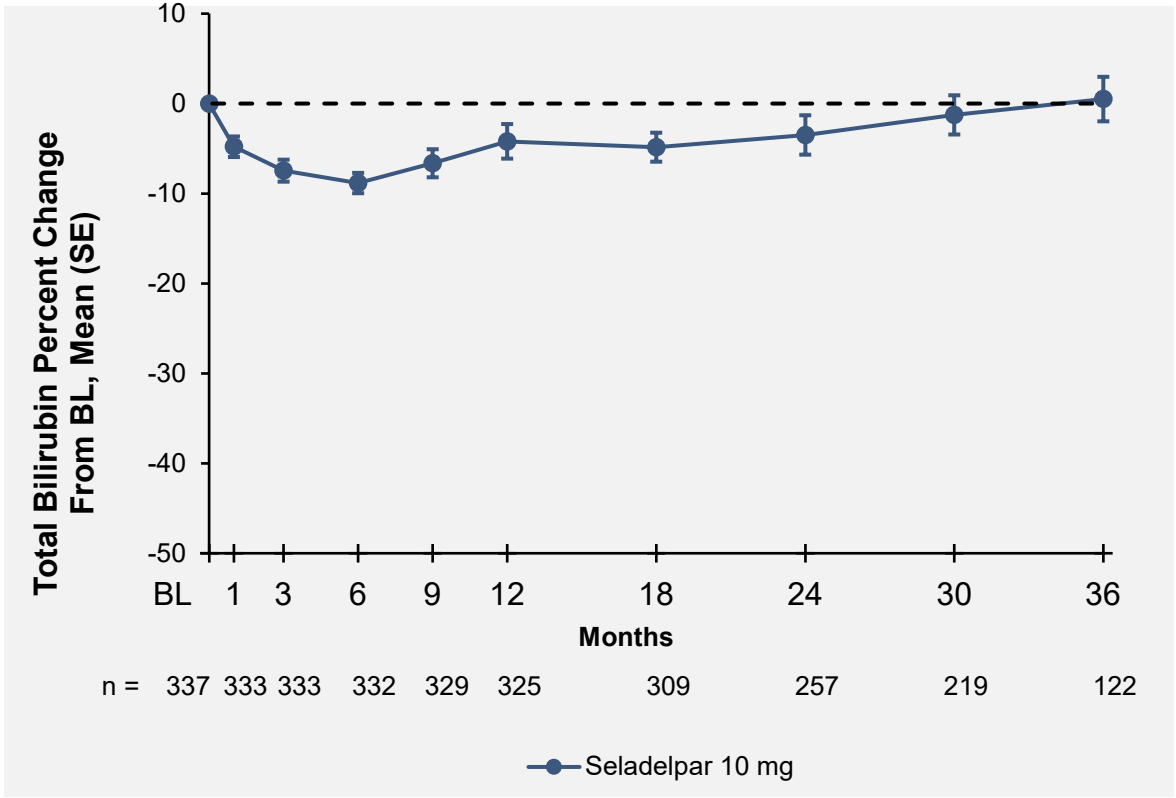


Seladelpar treatment led to rapid and sustained normalization and reductions in ALP. Approximately one-third of patients achieved ALP normalization at each time point

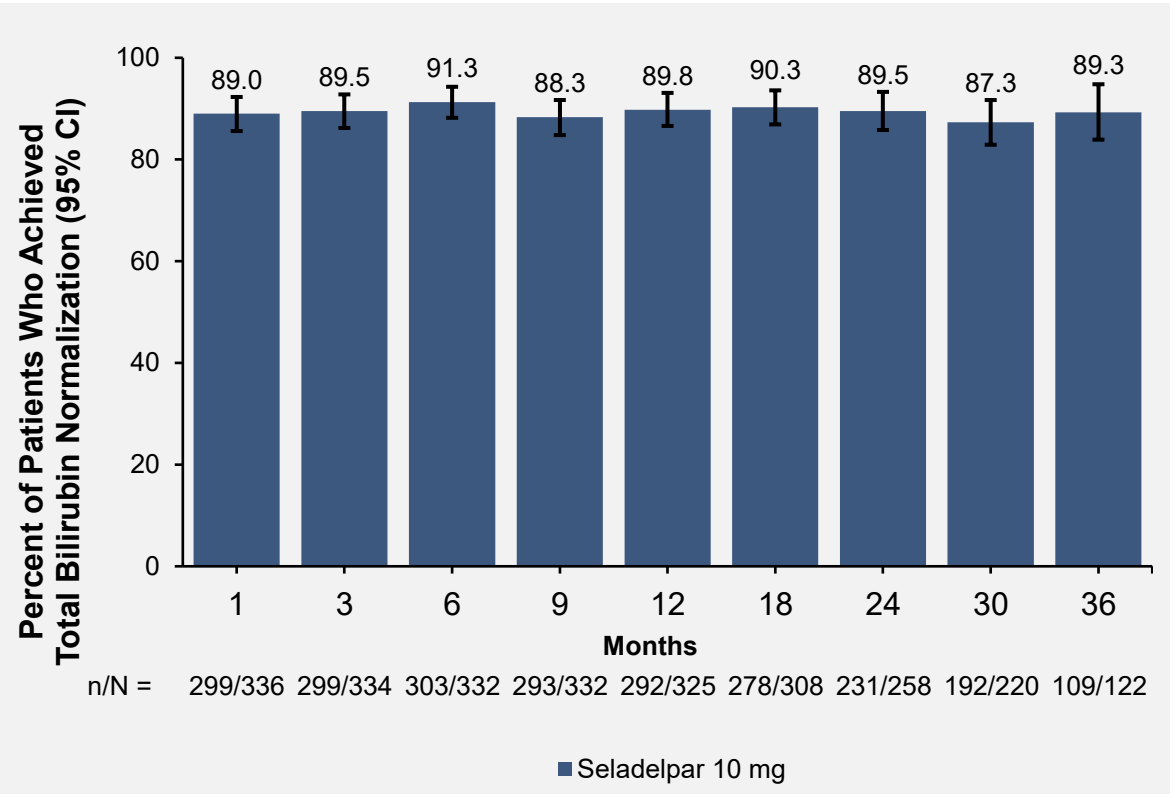
n = number of evaluable patients at each time point.
n/N = number of responders at each time point/total number of evaluable patients at each time point.
BL was defined at seladelpar initiation.
ALP, alkaline phosphatase; **BL**, baseline.

Total Bilirubin Percent Change and Normalization

Total Bilirubin Percent Change



Total Bilirubin Normalization

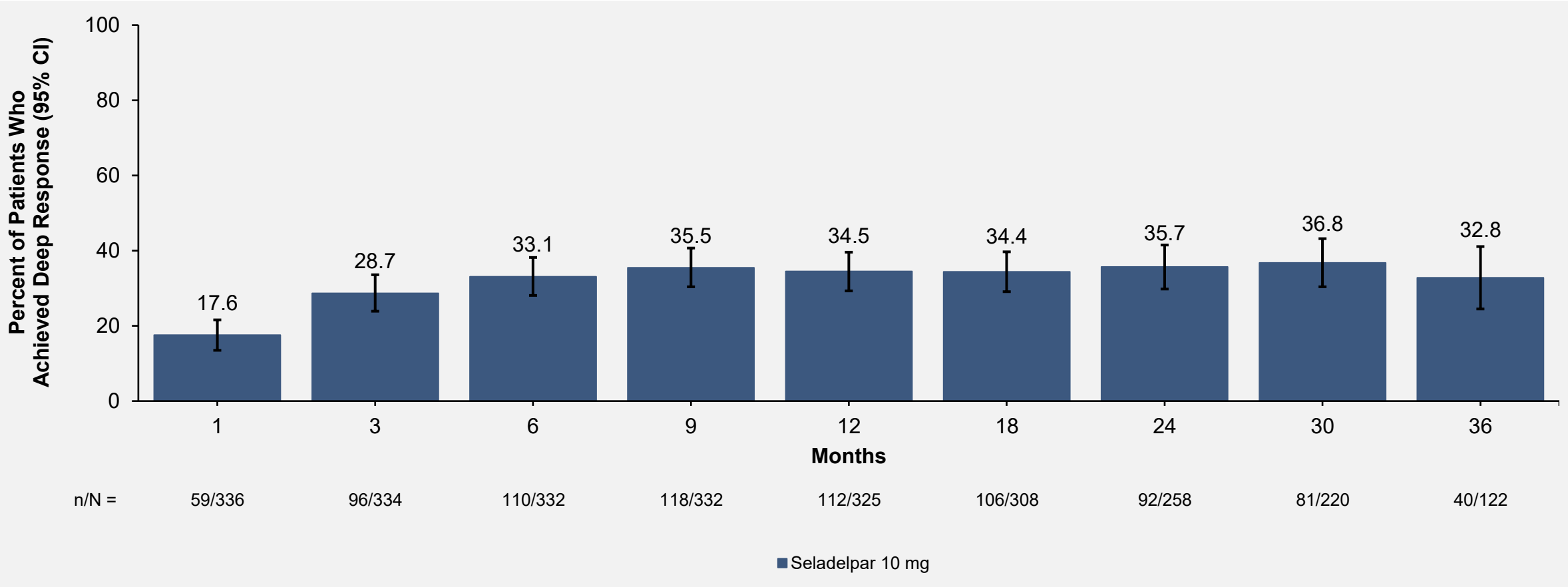


Total bilirubin was overall stable with seladelpar treatment

n/N = number of responders at each time point/total number of evaluable patients at each time point.
The total population denominator represents only those that started with abnormal bilirubin.
BL was defined at seladelpar initiation.
BL, baseline.

Deep Response

Patients Who Achieved Both ALP and Total Bilirubin Normalization

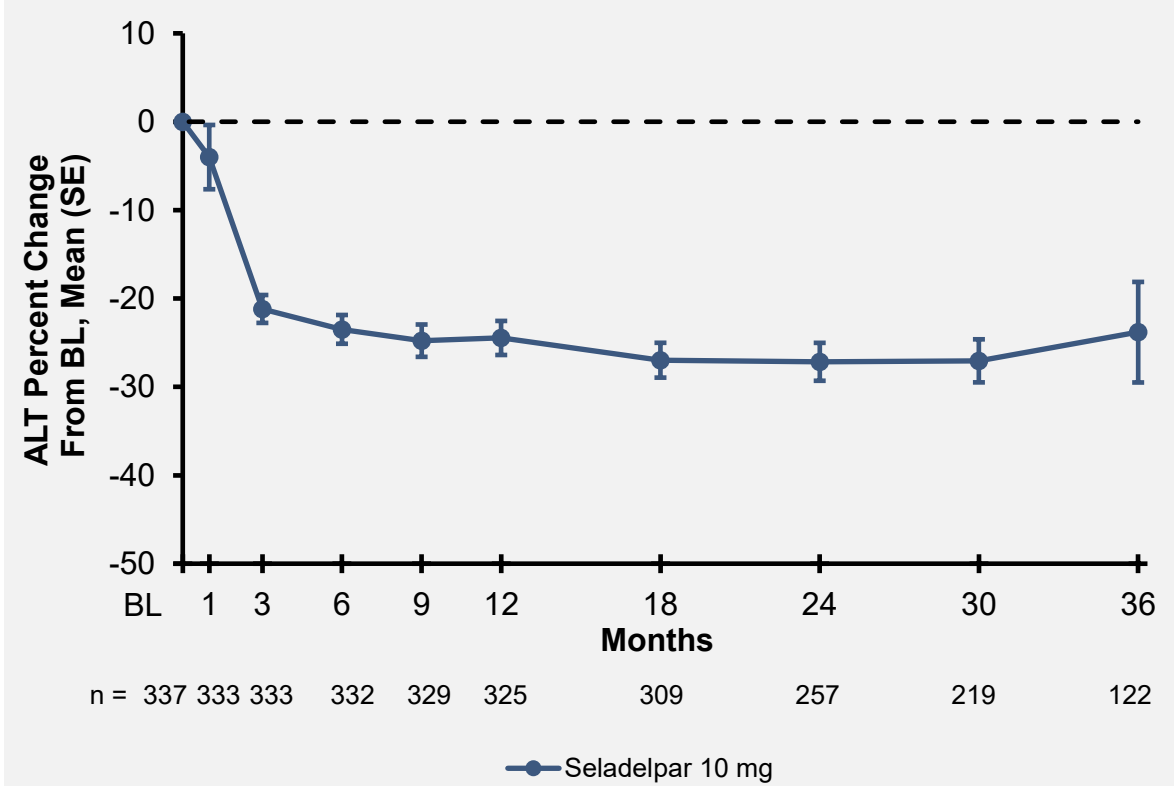


Approximately 1/3 of patients on seladelpar treatment achieved a deep response over time

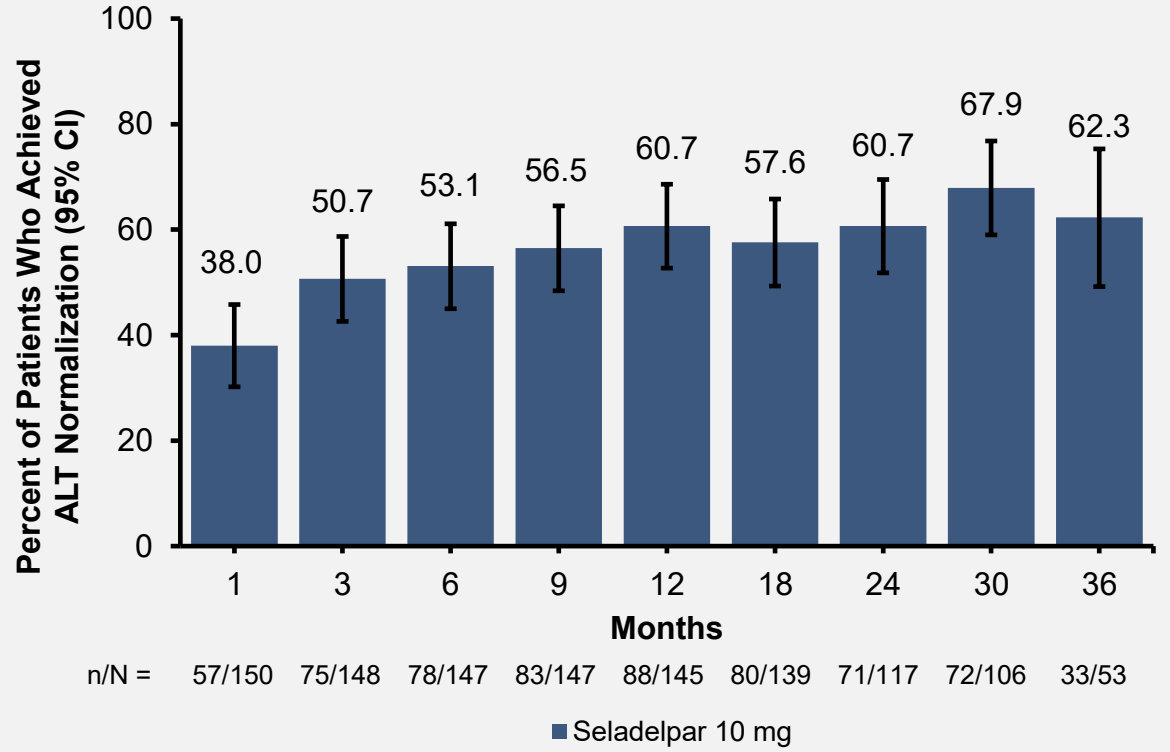
n/N = number of responders at each time point/total number of evaluable patients at each time point.
BL was defined at seladelpar initiation.
ALP, alkaline phosphatase; **BL**, baseline.

ALT Percent Change and Normalization

ALT Percent Change



ALT Normalization in patients with abnormal ALT at baseline



Seladelpar treatment resulted in rapid and sustained reductions in ALT
Among patients with elevated ALT at baseline, 60% of patients normalized with treatment

n = number of evaluable patients at each time point.
n/N = number of responders at each time point/total number of evaluable patients at each time point.
BL was defined at seladelpar initiation.
ALT, alanine aminotransferase; **BL**, baseline.

GLOBE Score

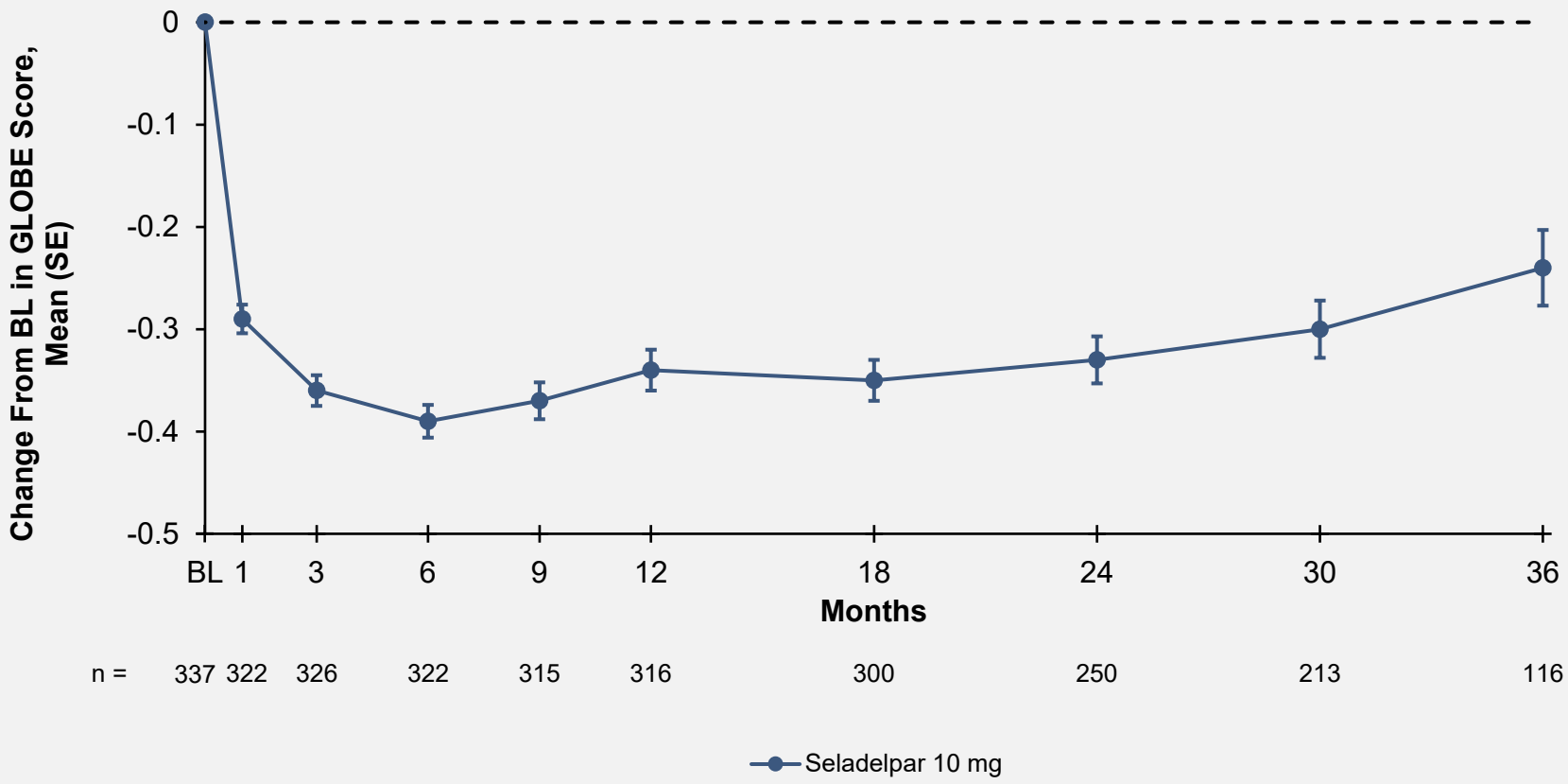
GLOBE Score[a]

A model including:

- Age at UDCA initiation
- Current total bilirubin, ALP, albumin, platelet count

Used to estimate transplant-free survival in an age-, sex-matched population

Higher GLOBE score indicates worse prognosis

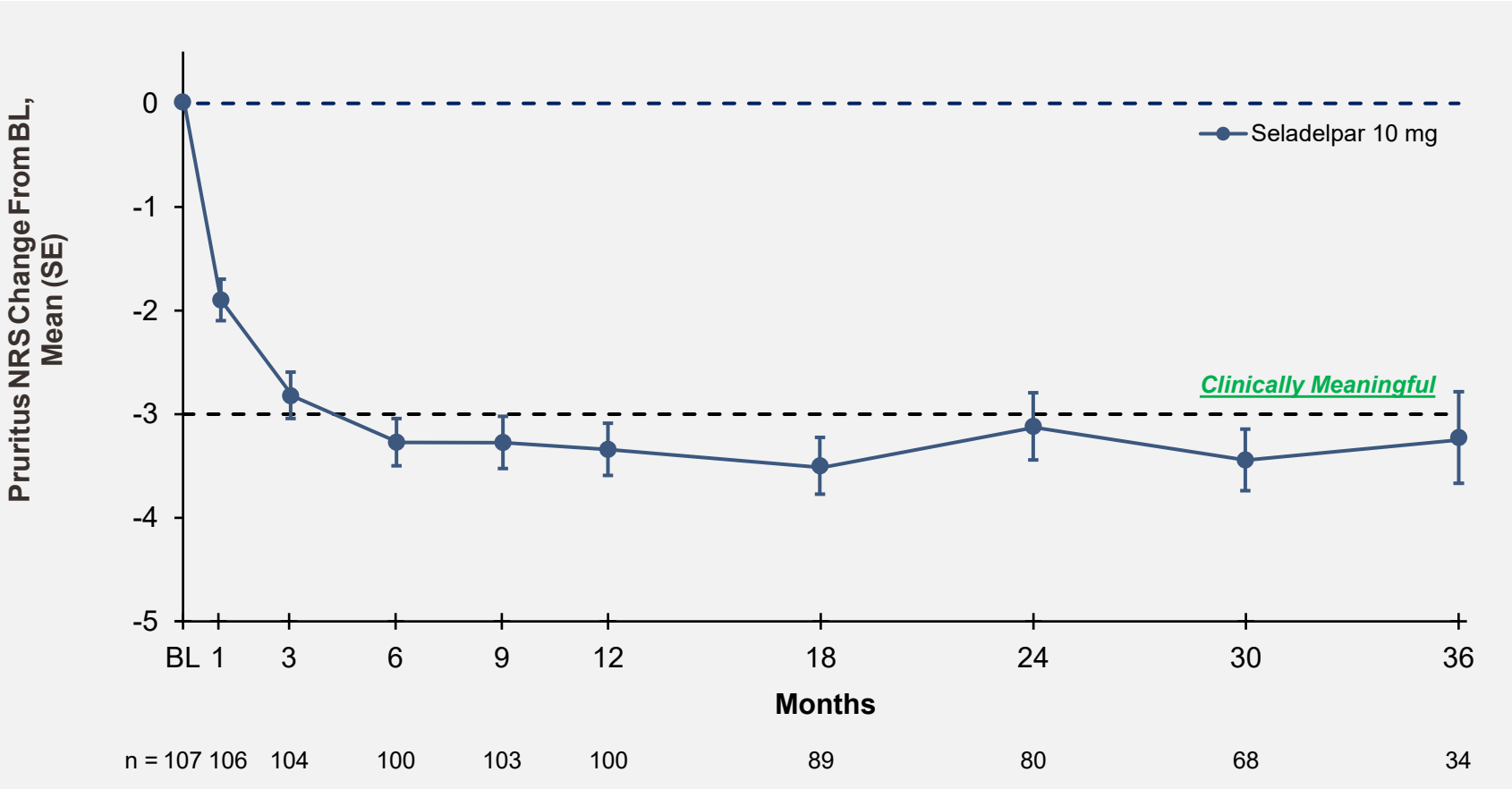


GLOBE scores were improved with seladelpar treatment, suggesting improved prognosis

n = number of evaluable patients at each time point.
BL was defined at seladelpar initiation.
[a]0.044378 × age at start of UDCA therapy + 0.93982 × ln(bilirubin × ULN) + 0.335648 × ln(ALP × ULN)− 2.266708 × (albumin × LLN) − 0.002581 × (platelet count × 10^3/μL) + 1.216865
ALP, alkaline phosphatase; **BL**, baseline; **LLN**, lower limit of normal; **UDCA**, ursodeoxycholic acid; **ULN**, upper limit of normal.

Pruritus Scores in Patients with Moderate to Severe Pruritus at Baseline

Clinically Meaningful Pruritus Improvement as ≥3-Point Improvement[a] in the Pruritus NRS Score



Late-Breaker
Oral 0213

11/10/2025
5:15 pm - 5:30 PM ET

Sustained Improvements of Pruritus in Patients With Primary Biliary Cholangitis Treated With Seladelpar

Seladelpar led to rapid and sustained clinically meaningful pruritus improvement in patients with moderate to severe pruritus

n = number of evaluable patients at each time point. BL was defined at seladelpar initiation. Moderate to severe pruritus was defined as pruritus NRS ≥4 at the time of seladelpar initiation.
[a]A ≥3-point improvement in the pruritus NRS score, shown by the dotted line, previously shown as clinically meaningful in RESPONSE. (Kremer AE, et al. EASL 2025 Poster THU-277).
BL, baseline; **NRS**, numeric rating scale.
1. Levy C, et al. Presented at EASL 2025. Poster THU-291.

Summary of Safety Outcomes in the Pooled Population in ASSURE

n (%)	Seladelpar 10 mg (N = 337)
Any AE (at least one)	297 (88)
SAEs	59 (18)
Treatment-related SAEs	1 (0.3)
Grade ≥3 AEs (per CTCAE)	69 (20)
AEs leading to treatment discontinuation	30 (9)
AEs leading to death	1 (0.3)

Grade 3 colitis updated to Grade 2 and assessed as not related to seladelpar by the investigator after the data cut

Autoimmune hemolytic anemia, assessed as not related to seladelpar by the investigator

Exposure-Adjusted Incidence (*Patients per 100 Patient-Years*)				
	Year 1 N = 337 (E = 330.7 years)	**Year 2 N = 326 (E = 293.4 years)**	**Year 3 N = 259 (E = 201.7 years)**	**Year 4 N = 125 (E = 46.5 years)**
Any AE	83.2	70.9	67.9	62.3

As of the data cutoff (up to 48 months of exposure), no SAEs or fatal events were related to seladelpar and incidence of AEs was stable over time

Data are presented as n (%). n = number of patients in the category. All AEs listed were treatment emergent unless otherwise stated. All AEs listed are results from the ASSURE trial; the RESPONSE seladelpar arm safety data have been presented previously.
AE, adverse event; **CTCAE**, Common Terminology Criteria for Adverse Events; **E** sum of subjects' exposure in years, **SAE**, serious adverse event.

Adverse Events of Interest Leading to Treatment Discontinuation

n (%)	Seladelpar 10 mg (N = 337)
Liver-related AEs	**13 (3.9)**
Elevated bilirubin	7 (2.1)
Ascites	2 (0.6)
Disease progression	1 (0.3)
Esophageal varices hemorrhage	1 (0.3)
Hepatorenal syndrome	1 (0.3)
Autoimmune hepatitis	1 (0.3)
Muscle-related AEs	**1 (0.3)**
Myalgia	1 (0.3)
Renal-related AEs	0

6 among the 13 patients had a PBC clinical outcome[a,b]

No events were adjudicated as drug-induced liver injury[c] related to seladelpar

The overall incidence of AEs leading to treatment discontinuation was low

n, number of patients in the category; [a]PBC clinical outcomes defined as: overall death, liver transplantation, MELD score ≥15 for at least 2 consecutive visits, ascites requiring treatment, and/or hospitalization for new onset or recurrence of any of the following: variceal bleeding, hepatic encephalopathy (as defined by a West Haven score ≥2), spontaneous bacterial peritonitis (confirmed by culture from diagnostic paracentesis). [b]One patient had PBC clinical outcome of ascites requiring treatment and MELD score above 15 for 2 consecutive visits. [c] Events were adjudicated by the CERC for drug-induced liver injury if they met laboratory safety monitoring criteria necessitating permanent withdrawal of study drug. AEs of interest were identified by pre-defined search strategy.
AE, adverse event; **CERC**, critical event review committee; **MELD**, Model for End-Stage Liver Disease; **PBC**, primary biliary cholangitis.

Conclusions

- ASSURE provides important long-term data on seladelpar in patients with PBC
- The most recent interim analysis from ASSURE continues to demonstrate sustained improvements in biochemical markers of cholestasis in patients with PBC treated with seladelpar
- Seladelpar has shown an overall favorable safety profile in patients with PBC, with no new safety concerns identified with up to 4 years of treatment

PBC, primary biliary cholangitis.

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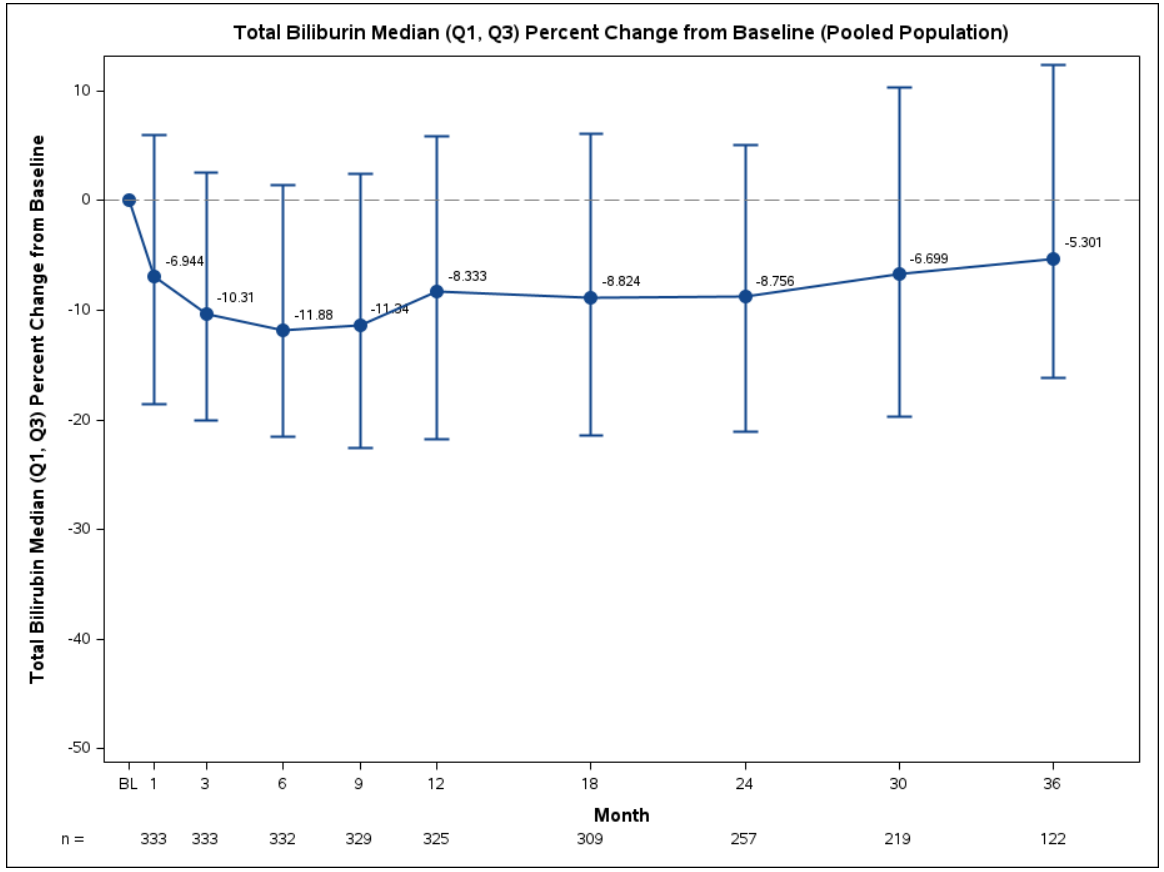
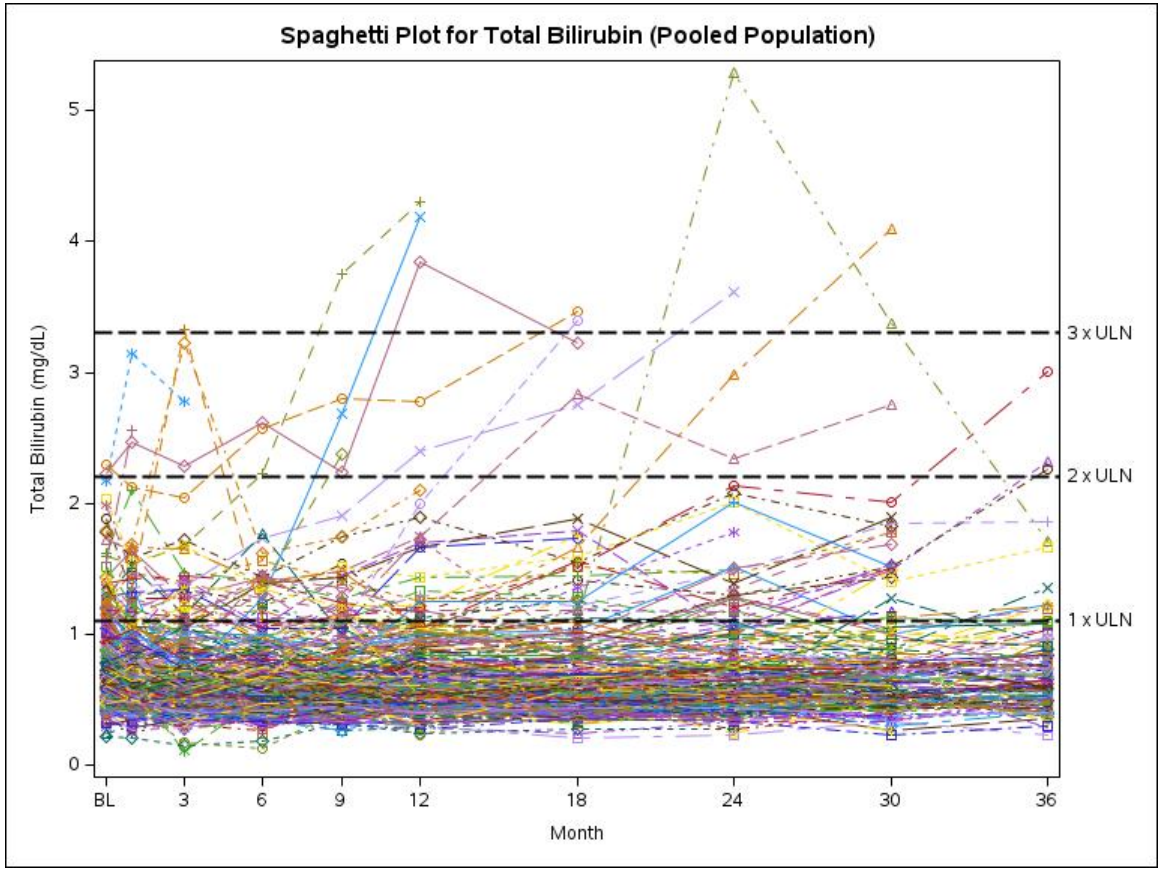
Total bilirubin over time





Total bilirubin was overall stable with seladelpar treatment