Sustained Efficacy and Safety of Seladelpar for up to 36 Months in Patients With Primary Biliary Cholangitis From the Placebo-Controlled RESPONSE Study to the Open-Label ASSURE Study

#4434

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Conclusions

- A rapid and sustained biochemical response was shown from the randomized, placebo-controlled Phase 3 RESPONSE study, continuing into the open-label ASSURE study with efficacy data up to 3 years of treatment
- For patients starting seladelpar in ASSURE who rolled over from RESPONSE, a similar trend of rapid and sustained biochemical response was shown in ASSURE
- Seladelpar continued to appear safe and well tolerated through 3 years of exposure, with no increase in the frequency of adverse events over time and no new safety signals identified with ongoing exposure

Plain Language Summary

- Primary biliary cholangitis (PBC) is a long-term liver disease that gets worse over time
- Seladelpar is a drug used to treat people with PBC
- ASSURE (NCT03301506) is an ongoing study that includes patients who participated in the Phase 3 RESPONSE study (NCT04620733) and prior seladelpar trials
- This study showed that seladelpar helped to improve measures of liver disease in patients with PBC who rolled over from RESPONSE into ASSURE
- These changes happened shortly after starting treatment with seladelpar and continued throughout treatment
- Seladelpar also appeared to be safe and well tolerated in patients with PBC who were treated with the drug for up to 3 years

References: **1.** European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-72. **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. *N Engl J Med*. 2024;390:783-94. **6.** Levy C, et al. *Am J Gastroenterol*. 2025. **7.** Hirschfield GM, et al. Presented at: AASLD, The Liver Meeting; November 7–11, 2025. Presentation 5015.

Acknowledgments: This study was funded by Gilead Sciences, Inc. Medical writing and editorial support were provided by Sefa Basci, PharmD, of Red Nucleus, and funded by Gilead Sciences, Inc.

Disclosures: Conflict of interest disclosures may be viewed using the QR code at the top right.

Introduction

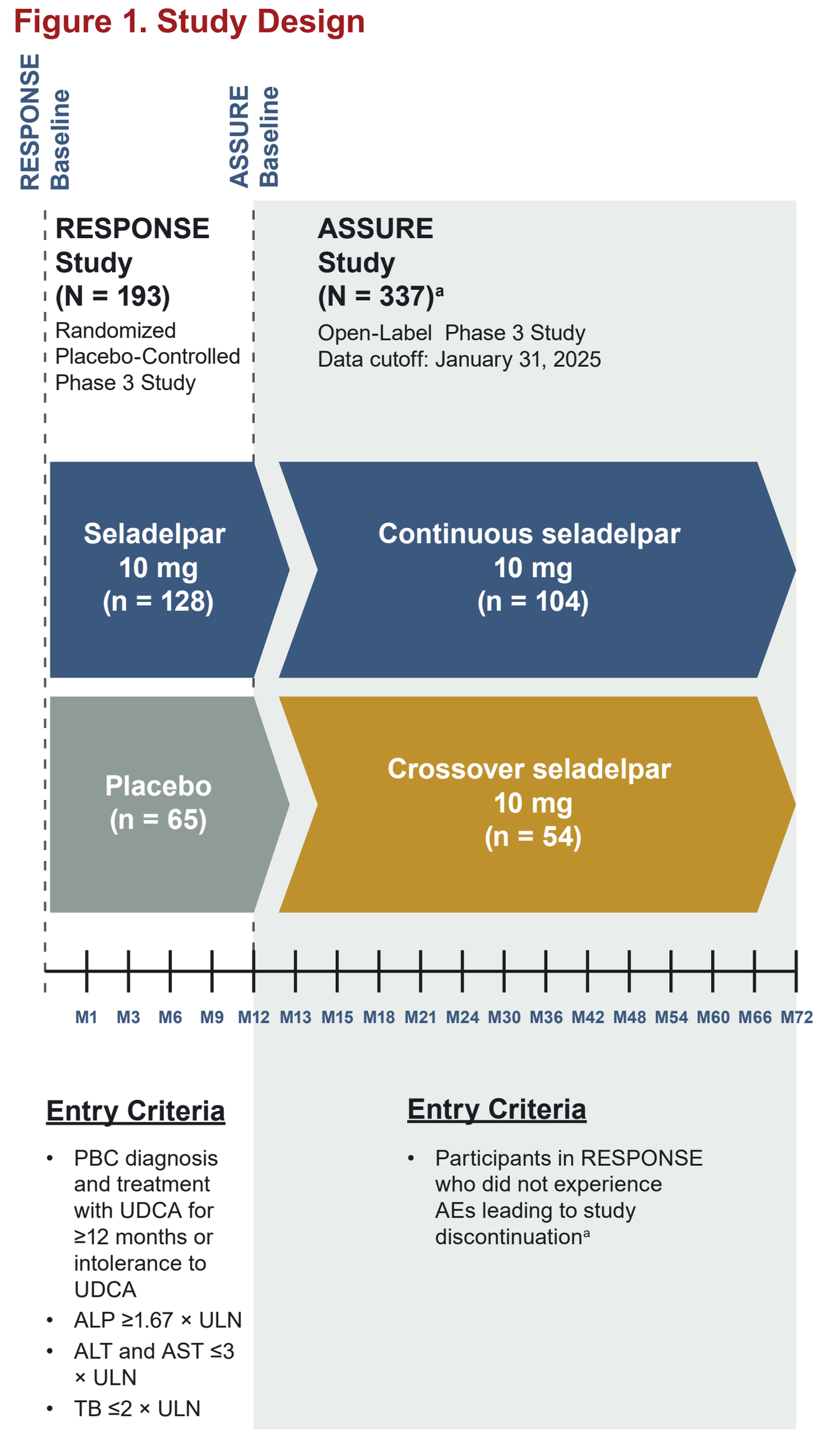
- Primary biliary cholangitis (PBC) is a chronic, autoimmune, cholestatic liver disease that is associated with progressive liver injury and significant symptom burden[1]
- Seladelpar is a first-in-class delpar (selective peroxisome proliferator–activated receptor delta [PPARδ] agonist) indicated for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients who are unable to tolerate UDCA[2-4]
- In the Phase 3, randomized, placebo-controlled RESPONSE study (NCT04620733), seladelpar significantly improved biochemical markers of cholestasis and pruritus vs placebo at 12 months in patients with PBC[5]
- After completing RESPONSE, patients were eligible to enroll in ASSURE (NCT03301506), an ongoing, open-label, Phase 3 trial[6]

Objectives

- This analysis was conducted to report updated long-term efficacy and safety data for seladelpar in patients who rolled over into ASSURE after completion of RESPONSE, with an interim analysis of ASSURE as of 31 January 2025 (seladelpar exposure up to 3 years).[6]

Methods

Figure 1. Study Design



The current interim analysis data cutoff date was January 31, 2025.
Study drug administered orally once daily as an add-on to UDCA or as monotherapy in patients intolerant to UDCA.
[a]Patients could enroll in ASSURE by rolling over from the RESPONSE study, or after earlier participation in legacy seladelpar studies[6]
AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; M, month; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; TB, total bilirubin.

- This analysis included data from RESPONSE and an interim analysis of ASSURE up to January 31, 2025 (Figure 1)
- Patients who completed RESPONSE were allowed to roll over into ASSURE
- In RESPONSE, patients with PBC with an inadequate response or intolerance to UDCA and alkaline phosphatase (ALP) ≥1.67 × the upper limit of normal (ULN) received blinded, daily oral seladelpar 10 mg or placebo; patients who enrolled in ASSURE received open-label, daily oral seladelpar 10 mg
- Patients were analyzed by treatment assignment in RESPONSE, corresponding to continuous seladelpar and crossover seladelpar in ASSURE, respectively. Baseline was defined as the entry into RESPONSE
- Efficacy endpoints included:
  - Composite biochemical response (ALP <1.67 × ULN, ALP decrease ≥15% from baseline, and total bilirubin ≤ULN)
  - ALP normalization
  - Percent change from baseline through 36 months in ALP, gamma-glutamyl transferase (GGT), alkaline aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin
- Safety was assessed through overall incidence and exposure-adjusted patient incidence of adverse events (AEs) in RESPONSE and ASSURE

Results

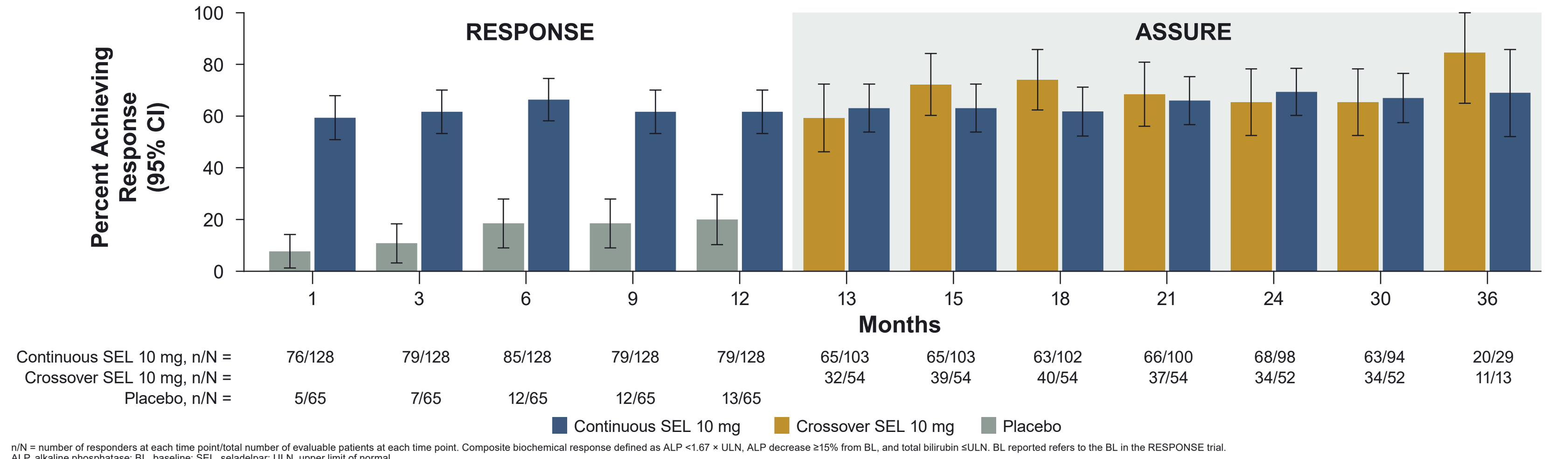
Table 1. Demographics and Baseline Characteristics at Entry Into RESPONSE and ASSURE

	RESPONSE[a]		ASSURE[b]	
	SEL 10 mg n = 128	Placebo n = 65	Continuous SEL n = 104	Crossover SEL n = 54
Age, years, mean (SD)	56.6 (10.0)	57.0 (9.2)	58.0 (10.1)	57.9 (9.3)
Female sex, n (%)	123 (96.1)	60 (92.3)	99 (95)	50 (93)
Race, n (%)				
American Indian or Alaska Native	3 (2)	3 (5)	2 (2)	3 (6)
Asian	7 (5)	4 (6)	6 (6)	4 (7)
Black or African American	2 (2)	2 (3)	2 (2)	2 (4)
White	114 (89)	56 (86)	92 (88)	43 (80)
Other	0	0	0	0
BMI, kg/m², mean (SD)	27.2 (5.6)	26.8 (4.8)	27.8 (6.1)	26.9 (5.1)
Patients with cirrhosis at baseline, n (%)	18 (14)	9 (14)	16 (15)	6 (11)
Child-Pugh class A, n (%)[c]	18 (100)	9 (100)	15 (94)	6 (100)
Child-Pugh class B, n (%)[c]	0	0	1 (6)	0
MELD score ≥12, n (%)	0	0	2 (2)	0
ALP, U/L, mean (SD)[d]	314.6 (123.0)	313.8 (117.7)	183.3 (111.5)	288.7 (125.5)
ALT, U/L, mean (SD)[e]	47.4 (23.5)	48.2 (22.8)	36.0 (25.2)	41.4 (21.3)
AST, U/L, mean (SD)[f]	39.6 (16.1)	41.7 (16.0)	37.2 (20.6)	37.0 (14.3)
GGT, U/L, mean (SD)[g]	269.0 (240.0)	287.5 (249.6)	174.8 (164.4)	232.8 (209.3)
Total bilirubin, mg/dL, mean (SD)[h]	0.8 (0.3)	0.7 (0.3)	0.7 (0.5)	0.7 (0.3)

Baseline defined as the baseline during entry into the trial.
[a]RESPONSE data have been previously reported.[5] [b]ASSURE data have been previously reported.[6] [c]Of patients with cirrhosis. [d]The ULN is 116 U/L. [e]The ULN is 41 U/L. [f]The ULN is 34 U/L. [g]The ULN is 52 U/L in men and 38 in women. [h]The ULN is 1.10 mg/dL.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; MELD, model for end-stage liver disease; SEL, seladelpar; ULN, upper limit of normal.

- Of 193 patients enrolled in RESPONSE (seladelpar, n = 128; placebo, n = 65), 158 patients (seladelpar, n = 104; placebo, n = 54) enrolled in ASSURE and received seladelpar 10 mg
- As of the data cutoff date (January 31, 2025), 94% of continuous seladelpar patients (98/104) received seladelpar for ≥2 years, and 27% (28/104) received seladelpar for ≥3 years; 24% of crossover seladelpar patients (13/54) received seladelpar for ≥2 years
- Baseline characteristics were generally comparable between the arms in RESPONSE and ASSURE, except that at ASSURE baseline, ALP levels were lower in the continuous seladelpar group following 12 months of seladelpar treatment in RESPONSE (Table 1)

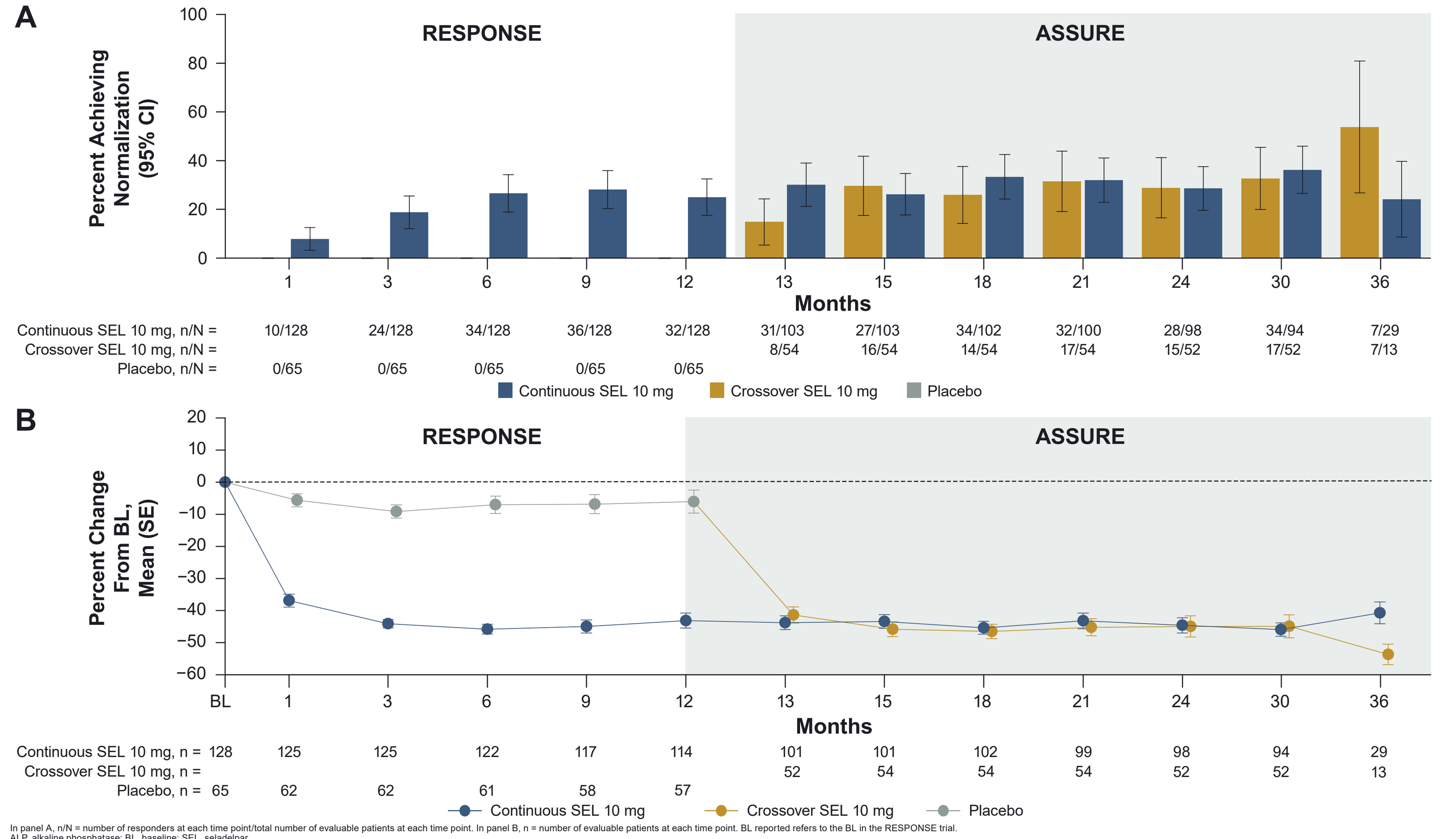
Figure 2. Composite Biochemical Response Rates Through 36 Months of Seladelpar Treatment



n/N = number of responders at each time point/total number of evaluable patients at each time point. Composite biochemical response defined as ALP <1.67 × ULN, ALP decrease ≥15% from BL, and total bilirubin ≤ULN. BL reported refers to the BL in the RESPONSE trial.
ALP, alkaline phosphatase; BL, baseline; SEL, seladelpar; ULN, upper limit of normal.

- For patients who started seladelpar in RESPONSE, composite biochemical response with seladelpar at year 1 (62%) was maintained after 36 months of exposure (69% at ASSURE year 2; Figure 2)
- The RESPONSE group had 20% composite biochemical response at the end of RESPONSE. Following seladelpar treatment in ASSURE, 65% achieved of patients achieve composite biochemical response at year 1 and 85% at year 2

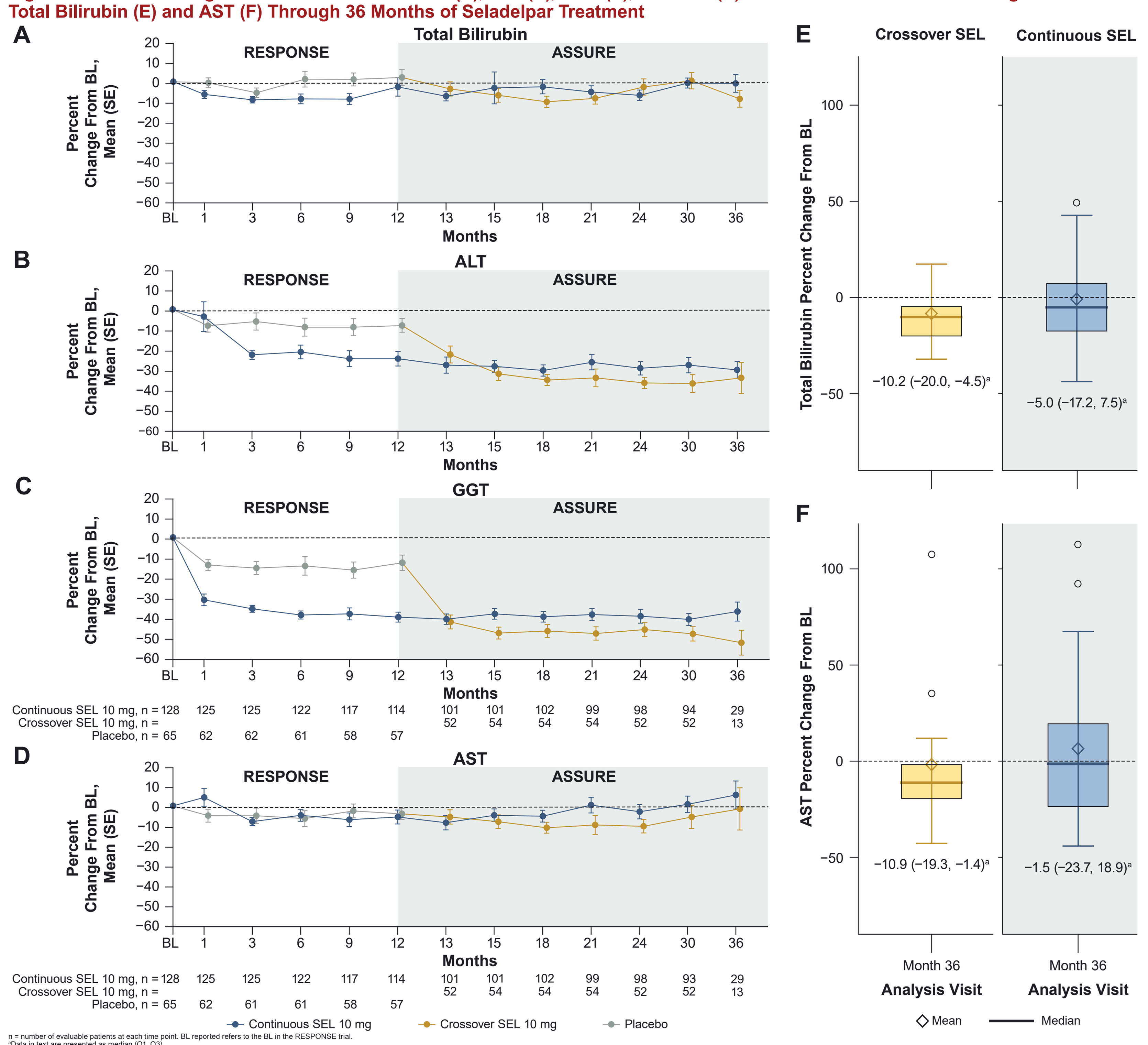
Figure 3. ALP Normalization (A) and ALP Percent Change From BL (B) Through 36 Months of Seladelpar Treatment



In panel A, n/N = number of responders at each time point/total number of evaluable patients at each time point. In panel B, n = number of evaluable patients at each time point. BL reported refers to the BL in the RESPONSE trial.
ALP, alkaline phosphatase; BL, baseline; SEL, seladelpar.

- For patients who started seladelpar in RESPONSE, ALP normalization achieved with seladelpar at year 1 (25%) was maintained after 36 months of exposure (24% at ASSURE year 2; Figure 3A)
- The RESPONSE placebo group had 0% of patients achieve ALP normalization at the end of RESPONSE. Following seladelpar treatment in ASSURE, 29% achieved ALP normalization at year 1 and 54% at year 2
- Seladelpar treatment led to with a rapid and sustained reduction in ALP, which remained consistent for up to 36 months (Figure 3B)

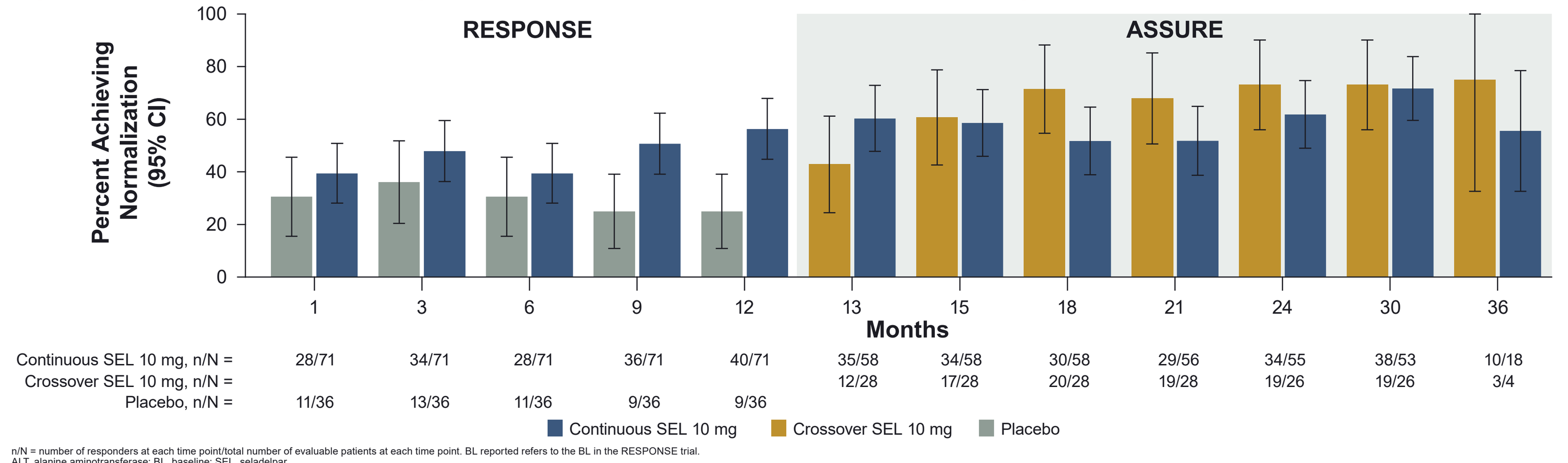
Figure 4. Percent Change From BL in Total Bilirubin (A), ALT (B), GGT (C), and AST (D) and Box Plots of Percent Change From BL in Total Bilirubin (E) and AST (F) Through 36 Months of Seladelpar Treatment



n = number of evaluable patients at each time point. BL reported refers to the BL in the RESPONSE trial.
[a]Data in text are presented as median (Q1, Q3).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; GGT, gamma-glutamyl transferase; SEL, seladelpar.

- In both the seladelpar and placebo arms in RESPONSE, GGT and ALT levels demonstrated consistent reductions sustained through ASSURE year 2 upon seladelpar treatment (Figure 4)
- AST and total bilirubin were overall stable with the median showing a reduction from baseline through ASSURE year 2 in both arms

Figure 5. ALT Normalization Among Those With Elevated ALT at RESPONSE BL Through 36 Months of Seladelpar Treatment



n/N = number of responders at each time point/total number of evaluable patients at each time point. BL reported refers to the BL in the RESPONSE trial.
ALT, alanine aminotransferase; BL, baseline; SEL, seladelpar.

- For patients who started seladelpar in RESPONSE, ALT normalization achieved with seladelpar at year 1 (56%) was maintained after 36 months of exposure (56% at ASSURE year 2; Figure 5)
- The RESPONSE placebo group had 25% of patients achieve ALT normalization at the end of RESPONSE. Following seladelpar treatment in ASSURE, 73% achieved ALT normalization at year 1 and 75% at year 2
- Seladelpar led to sustained, clinically meaningful improvement in pruritus among patients with moderate to severe pruritus in RESPONSE and with up to 30 months of treatment[7]

Table 2. Overall Safety Outcomes in RESPONSE and ASSURE

	RESPONSE[a]		ASSURE[b]	
n (%)	SEL 10 mg n = 128	Placebo n = 65	Continuous SEL n = 104	Crossover SEL n = 54
Any AE (at least one)	111 (87)	55 (85)	92 (88)	48 (89)
SAEs	9 (7)	4 (6)	15 (14)	12 (22)
Treatment-related SAEs	0	0	1[c] (1)	0
Grade ≥3 AEs (per CTCAE)	14 (11)	5 (8)	19 (18)	11 (20)
AEs leading to treatment discontinuation	4 (3)	3 (5)	7[d] (7)	2[e] (4)
AEs leading to death	0	0	0	0
AEs of interest				
Liver-related AEs	8 (6)	6 (9)	17 (16)	8 (15)
Muscle-related AEs	8 (6)	5 (8)	8 (8)	2 (4)
Renal-related AEs	0	0	1 (1)	1 (2)

Data are presented as n (%). n = number of patients in the category. All AEs listed were treatment emergent unless otherwise stated.
[a]Safety data collected in RESPONSE were previously reported.[5] [b]Safety data reported were collected in the ASSURE trial only (only during seladelpar exposure) as of January 31, 2025.[6] [c]One patient initially reported with Grade 3 colitis, likely related to seladelpar, which was reassessed after the data cutoff as Grade 2, unrelated to seladelpar. [d]Preferred terms of AEs leading to treatment discontinuation in ASSURE among the continuous seladelpar group included esophageal varices
hemorrhage, adenocarcinoma of the cervix, ascites, hypervolemia, bipolar I disorder, colon cancer, and hyperbilirubinemia. [e]Preferred terms of AEs leading to treatment discontinuation in ASSURE in the crossover seladelpar group included lymphoma and myalgia.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event; SEL, seladelpar.

- Patient incidence of AEs was similar between seladelpar and placebo in RESPONSE, and overall incidence remained similar in ASSURE
- Per the latest assessment, there were no treatment-related serious AEs and no deaths (Table 2)
- Overall, among the patients who rolled over from RESPONSE, there were 9 patients who discontinued treatment due to an AE, for an overall patient incidence of 6% (9/158)

Table 3. Adverse Events of Interest in ASSURE in Continuous and Crossover Seladelpar Patients

n (%)	Continuous SEL (n = 104)	Crossover SEL (n = 54)
Liver-related AEs[a]	**17 (16)**	**8 (15)**
Ascites	3 (3)	3 (6)
AST increased	2 (2)	1 (2)
ALT increased	2 (2)	1 (2)
Hepatic cirrhosis	3 (3)	2 (4)
Hyperbilirubinemia	3 (3)	0
Varices esophageal	2 (2)	1 (2)
Hepatic enzyme increased	2 (2)	0
Portal hypertension	2 (2)	0
Muscle-related AEs[a]	**8 (8)**	**2 (4)**
Myalgia	2 (2)	2 (4)
Muscle spasms	3 (3)	0
Musculoskeletal chest pain	3 (3)	0
Renal-related AEs[b]	**1 (1)**	**1 (2)**
Acute kidney injury	1 (1)	0
Blood creatinine increased	0	1 (2)
Proteinuria	0	1 (2)

Data are presented as n (%). n = number of patients in the category. All AEs listed were treatment emergent unless otherwise stated. AEs were identified using a prespecified search strategy. Data cutoff: January 31, 2025.
[a]For liver-related and muscle-related AEs, preferred terms reported for AEs occurring in ≥2 patients among the RESPONSE rollover patients in ASSURE are shown on the table. [b]For the renal-related AEs, all preferred terms are shown.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SEL, seladelpar.

- AEs of interest included liver-, muscle-, and renal-related AEs (Table 3)
- Three liver-related AEs led to treatment discontinuation and were consistent with disease progression: Grade 3 hyperbilirubinemia, Grade 4 esophageal varices hemorrhage, and Grade 2 ascites. The latter two events were both adjudicated as PBC clinical outcomes
- All muscle-related AEs were either Grade 1 or 2. One Grade 2 event of myalgia in the crossover group led to treatment discontinuation; there were no associated creatine kinase increases
- All renal-related AEs were Grade 1 or 2, and none led to treatment discontinuation. One patient in the continuous seladelpar arm developed a Grade 2 acute kidney injury in the setting of anemia and hypervolemia, which resolved with supportive care

Table 4. Summary of Exposure-Adjusted Adverse Events

Exposure-Adjusted AEs per 100 Patient-Years	Placebo	Continuous SEL				Crossover SEL		
	RESPONSE (N = 65) (E = 60.2 Y)	RESPONSE[a] (Seladelpar Y1) (N = 128) (E = 122.2 Y)	ASSURE Y1 (Seladelpar Y2) (N = 104) (E = 100.2 Y)	ASSURE Y2 (Seladelpar Y3) (N = 98) (E = 74.5 Y)	ASSURE Y3 (Seladelpar Y4) (N = 32) (E = 8.3 Y)	ASSURE Y1 (Seladelpar Y1) (N = 54) (E = 53.4 Y)	ASSURE Y2 (Seladelpar Y2) (N = 52) (E = 40.2 Y)	ASSURE Y3 (Seladelpar Y3) (N = 14) (E = 2.7 Y)
Any AE	91.4	90.9	83.8	73.8	120.9	84.3	62.2	74.1
SAEs	6.6	7.4	6.0	13.4	0	15.0	10.0	0
Treatment-related SAEs	0	0	0	1.3[b]	0	0	0	0
Grade ≥3 AEs (per CTCAE)	8.3	11.5	10.0	14.8	0	13.1	10.0	0
AEs leading to treatment discontinuation	5.0	3.3	5.0	2.7	0	1.9	2.5	0
AEs leading to death	0	0	0	0	0	0	0	0

Data are presented as (n/E) × 100. N = total number of patients. n = number of patients in the category. E = event rate per patient year (n/total exposure in years).
[a]These data have previously been reported.[5] [b]One patient initially reported with Grade 3 colitis, likely related to seladelpar, which was reassessed after the data cutoff as Grade 2, unrelated to seladelpar.
All AEs listed were treatment emergent unless otherwise stated.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event; SEL, seladelpar; Y, year.

- The exposure-adjusted patient incidence of AEs was generally stable over time in both continuous and crossover seladelpar patients acknowledging smaller samples sizes in year 3 of exposure in this ongoing study (Table 4)
- Rates of AEs leading to treatment discontinuation were consistently low across all years of seladelpar exposure