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

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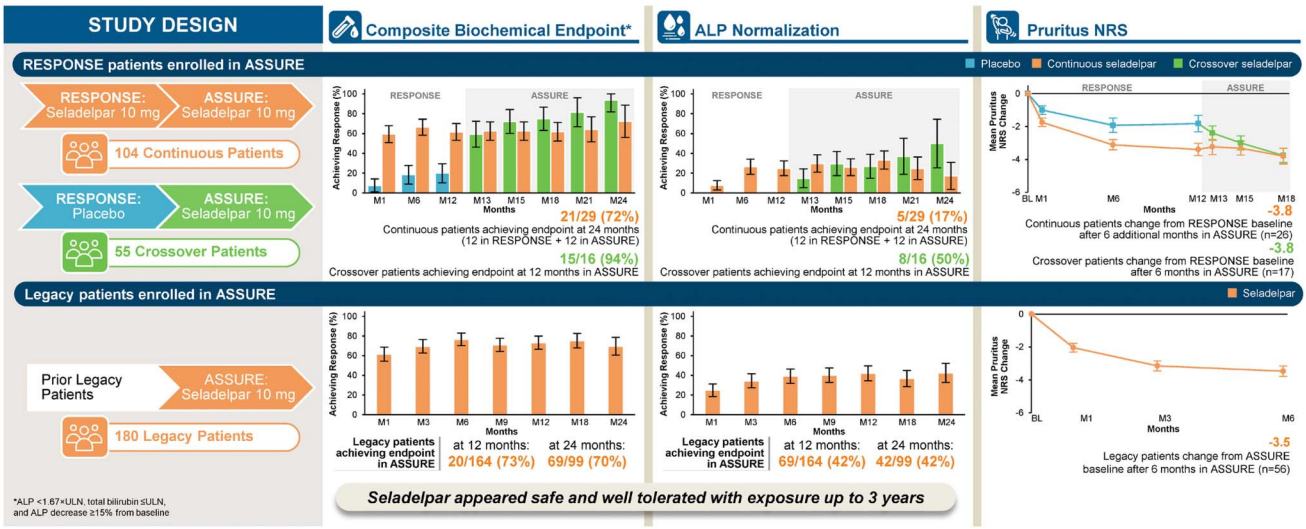
Long-term Efficacy and Safety of Seladelpar



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LIVER

INTRODUCTION: **The objective of these analyses was to evaluate interim data from the ongoing, open-label, long-term efficacy and safety ASSURE study of seladelpar, a selective peroxisome proliferator-activated receptor δ agonist, in primary biliary cholangitis.**

METHODS: **Patients rolling over from the phase 3, randomized, placebo-controlled, 12-month RESPONSE study or with previous participation in earlier legacy seladelpar studies were enrolled. Interim evaluations included composite biochemical response (alkaline phosphatase <1.67× upper limit of normal, total bilirubin ≤ upper limit of normal, and alkaline phosphatase decrease ≥15%), pruritus numerical rating scale (NRS) change among patients with a baseline score ≥4, and safety.**

RESULTS: **At interim cutoff, 337 patients were enrolled and received ≥1 seladelpar 10 mg dose: 54 placebo-treated and 104 seladelpar-treated from RESPONSE and 179 from legacy studies. The composite response rate at RESPONSE completion was 62% (79/128) with seladelpar and 20% (13/65) with placebo. After 12 months in ASSURE, among patients who rolled over from RESPONSE, response rates were 72% (21/29) in patients continuing seladelpar and 94% (15/16) in crossover seladelpar patients. In legacy trial patients, response rates were 73% (120/164) and 70% (69/99) after 12 and 24 months of treatment in ASSURE, respectively. The NRS decrease at RESPONSE completion in seladelpar-treated patients with baseline NRS ≥4 (−3.4) was maintained after 6 additional months of treatment (−3.8); changes were similar in crossover seladelpar (−3.8) and legacy patients (−3.5) after 6 months of treatment in ASSURE. No seladelpar-related serious adverse events were reported.**

DISCUSSION: **Seladelpar demonstrated durable improvements in cholestatic biomarkers and pruritus in patients with primary biliary cholangitis with up to 2 years of treatment and remained overall safe with long-term use. Clinicaltrials.gov: NCT03301506.**

KEYWORDS: cholestasis; liver; peroxisome proliferator-activated receptor delta; pruritus

ABBREVIATIONS: AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; CERC, Critical Event Review Committee; GGT, gamma-glutamyltransferase; MedDRA, Medical Dictionary for Regulatory Activities; NRS, numerical rating scale; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; SAE, serious adverse event; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D690

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INTRODUCTION

Primary biliary cholangitis (PBC) is a rare, autoimmune, chronic liver disease that can progress to cirrhosis and liver failure (1,2). Common symptoms include pruritus and fatigue, which can significantly affect quality of life. Elevated alkaline phosphatase (ALP) and total bilirubin values are validated predictors of risk for disease progression, including hepatic decompensation, need for liver transplantation, and death (3,4). Accordingly, decreases in these biomarkers are used to appraise the efficacy of new therapies (5,6).

Ursodeoxycholic acid (UDCA) is the established first-line therapy for PBC; however, up to 40% of patients do not achieve an adequate biochemical response with UDCA (7). The farnesoid X receptor agonist obeticholic acid was approved as second-line therapy in 2016 (8). UDCA does not improve pruritus, and obeticholic acid may actually worsen pruritus (5,7). There is an unmet need for second-line PBC treatments with acceptable safety and tolerability that improve biomarkers of disease and pruritus. Other agents used to treat PBC include the pan-peroxisome proliferator-activated receptor (PPAR) agonist bezafibrate (6), the PPARα agonist fenofibrate (9), and other fibrates used off-label in some geographies. More recently, elafibranor, which results in activation of PPAR α/δ/γ per *in vitro* studies, received accelerated approval in the United States (US) and conditional approval in the European Union (10–12). Seladelpar, which also recently received accelerated approval in the US and conditional approval in the European Union (13,14), offers an additional option that improves PBC biomarkers and has been confirmed to improve PBC-associated pruritus.

PPARs are transcription factors expressed in multiple organs, including the liver (15). Seladelpar is a potent, selective PPARδ agonist, or delpar. The PPARδ isotype is broadly expressed in hepatic cells that play an important role in PBC pathobiology (15–19). Among other actions expected to exert a therapeutic effect in patients with PBC, PPARδ activation releases fibroblast growth factor 21 from hepatocytes, resulting in inhibition of cholesterol 7a-hydroxylase, the rate-limiting enzyme in bile acid synthesis (20,21).

Since 2016, 6 studies have evaluated seladelpar at ≤10 mg daily in patients with PBC, including 540 who had received seladelpar as of January 2024. Initial studies included a phase 2, open-label, dose-ranging study (22); the phase 3, placebo-controlled ENHANCE study (23); and a long-term, open-label safety study (24). Subsequent studies include an open-label, phase 1b hepatic impairment study and the phase 3 program: the registrational RESPONSE study (25) and the ongoing, long-term, open-label ASSURE study.

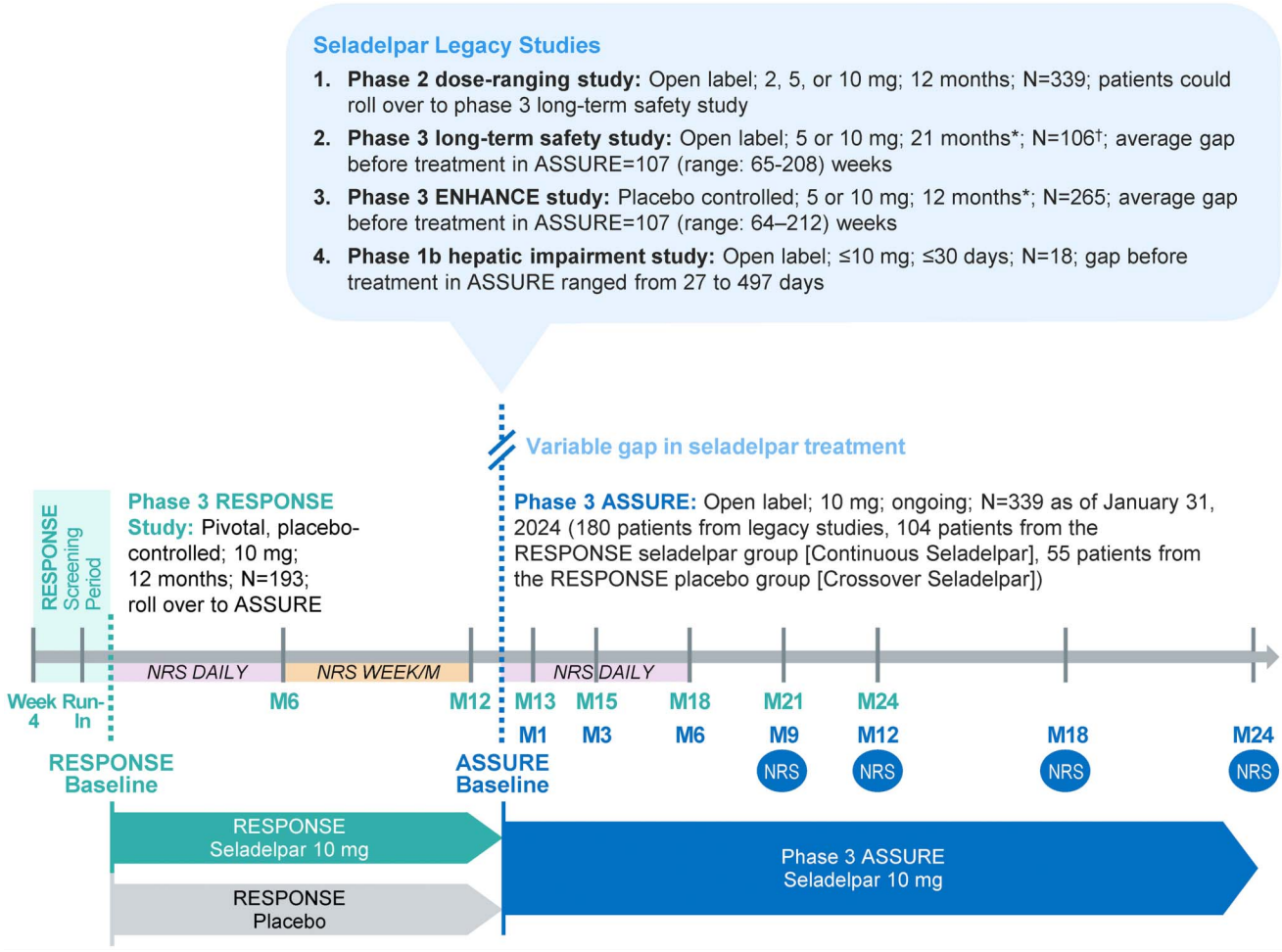

Figure 1. ASSURE study design through month 24. *Terminated early; the phase 3 long-term safety study (NCT03301506) was planned for 60 months but was terminated at 21 months (23); ENHANCE (NCT03602560) was planned for 12 months but was terminated early, the primary analysis time point was adjusted to 3 months (22). †Two patients enrolled after completion of ENHANCE and were treated for 1–4 days before study termination. The phase 2 dose-ranging study is registered at clinicaltrials.gov, NCT02955602 (21). The phase 1b hepatic impairment study is registered at clinicaltrials.gov, NCT04950764. The phase 3 RESPONSE study is registered at clinicaltrials.gov, NCT04620733 (24). The phase 3 ASSURE study is registered at clinicaltrials.gov, NCT03301506. Laboratory samples were collected at all study visits. In RESPONSE, pruritus NRS was collected daily via e-diary through month 6 then for 1 week each month through month 12. In ASSURE, pruritus NRS was again collected daily through e-diary from day 1 through month 6, then at each study visit. Change from baseline in pruritus NRS was evaluated only in patients with baseline NRS ≥4. M, month; NRS, numerical rating scale.

In RESPONSE, in patients with PBC with persistently elevated ALP (≥1.67×upper limit of normal [ULN]), 1 year of treatment with seladelpar 10 mg led to a significantly greater proportion of patients achieving the composite biochemical response (ALP <1.67×ULN, total bilirubin ≤ULN, and ALP decrease ≥15% from baseline) and ALP normalization compared with placebo (25). Seladelpar also significantly improved pruritus in patients with moderate-to-severe baseline pruritus. Overall, seladelpar was safe and well tolerated.

Patients completing RESPONSE could roll over into ASSURE. Participants in earlier seladelpar studies were also eligible to screen for ASSURE. In this study, we report interim ASSURE results, an important source for evaluating long-term effects of seladelpar treatment. We include data from patients who rolled over from the RESPONSE study and, separately, from patients who participated in the other seladelpar PBC studies described above, analyzed as 1 legacy group.

METHODS

Study design and participants

ASSURE (NCT03301506) is an ongoing, 5-year, open-label, uncontrolled study conducted at 88 international sites. Patients completing the pivotal, phase 3, 12-month RESPONSE study (NCT04620733) (25) at a participating site could roll over directly to ASSURE. Patients with PBC who participated in other seladelpar studies could enroll if they met ASSURE eligibility criteria. These legacy studies include the phase 2, dose-ranging study (NCT02955602) (22); the phase 3 long-term safety study (NCT03301506) (24); ENHANCE (NCT03602560) (23); and the PBC hepatic impairment study (NCT04950764) (Figure 1). Patients who participated in the phase 2 study, the long-term study, and ENHANCE had an average gap of approximately 2 years from their last visit in the prior study to treatment in ASSURE. Patients in the hepatic impairment study received seladelpar for <30 days and had a variable gap (range, 27–497 days) in treatment before treatment in ASSURE. All studies

except the hepatic impairment study enrolled only patients with PBC who had an inadequate response or intolerance to UDCA.

Patients from legacy studies were eligible for ASSURE unless they had discontinued study drug because of a treatment-related adverse event (AE) during the parent study, met laboratory exclusion criteria of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $>3\times$ULN or total bilirubin $>2\times$ULN during screening, or had received fibrates or obeticholic acid within 3 months of screening. Patients from the hepatic impairment study could have Child-Pugh-B cirrhosis but could not be decompensated (see Supplementary Methods, Supplementary Digital Content, http://links.lww.com/AJG/D690).

The study was conducted in accordance with ethical principles originating in the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable national and local laws and regulations. The protocol was approved by each site's institutional review board or independent ethics committee, and all patients provided written informed consent.

Procedures

Patients were enrolled through interactive web response system to receive an oral dose of seladelpar 10 mg once daily. A seladelpar 5 mg dose was available for patients in the event of safety or tolerability concerns based on investigator judgment.

ASSURE scheduled study visits were screening; day 1; months 1, 3, 6, 9, 12; and then every 6 months. At each visit, assessments were conducted for AEs and blood was collected for laboratory evaluations. Patients completed the pruritus numerical rating scale (NRS; ranging from 0 [no itch] to 10 [worst itch imaginable]) (26) through e-diary during screening and daily from day 1 until month 6. After month 6, patients completed the NRS at each scheduled study visit. RESPONSE procedures and outcomes have been previously described (25).

PBC clinical outcome events assessed throughout ASSURE included death, liver transplantation, Model for End-Stage Liver Disease score $\geq$15 for at least 2 consecutive visits, ascites requiring treatment, hospitalization for new onset or recurrence of any variceal bleeding, hepatic encephalopathy (as defined by a West Haven score $\geq$2), and spontaneous bacterial peritonitis (confirmed by culture from diagnostic paracentesis). An independent Critical Event Review Committee (CERC) adjudicated PBC clinical outcomes and liver safety monitoring events leading to drug discontinuation to identify potential drug-induced liver injury. Patients who had a PBC clinical outcome event discontinued treatment and the study. Patients who discontinued seladelpar for any reason other than a PBC clinical outcome event were asked to stay in the study without receiving seladelpar and complete annual follow-up visits.

Outcomes

Efficacy outcomes evaluated at each study visit were composite biochemical response (ALP $<1.67\times$ULN, total bilirubin $\leq$ULN, and ALP decrease $\geq$15% from baseline); ALP normalization ($\leq1\times$ULN); ALT normalization ($\leq$ULN) among patients with baseline levels $>$ULN (post hoc); relative and absolute changes in ALP; levels of total, direct, and indirect bilirubin, gamma-glutamyltransferase (GGT), ALT, and AST; and changes from baseline in lipid levels. Change from baseline in pruritus NRS was summarized for the period of daily NRS collection (i.e., through Month 6 in ASSURE) among patients with a baseline NRS $\geq$4 (25). NRS data that were collected at each study visit after Month 6 were also explored. PBC clinical outcome events were also reported. Safety was evaluated by assessing AEs occurring after initiation of seladelpar or within 30 days of the last dose and laboratory assessments.

Statistical analysis

All results for this interim analysis are descriptive. The timing of this analysis was chosen to meet regulatory requirements.

The primary safety and efficacy populations included all patients who received $\geq$1 dose of seladelpar 10 mg in ASSURE. Data were analyzed separately for the RESPONSE and legacy parent study groups. For RESPONSE rollover patients, those who had received seladelpar 10 mg in RESPONSE and continued to receive seladelpar 10 mg in ASSURE are designated as the continuous seladelpar group, and patients who had received placebo in RESPONSE and crossed over to seladelpar 10 mg in ASSURE are designated as the crossover seladelpar group; changes from baseline were based on RESPONSE baseline. Patients from legacy studies were analyzed as 1 group considered functionally naïve to seladelpar; changes from baseline were based on ASSURE baseline.

For RESPONSE results presented here, which include all patients in the placebo-controlled study, responder rate end points were calculated using the intention-to-treat principle; patients with missing data at any time point were considered as nonresponders at that time point (25). The mean change in pruritus NRS was calculated using the weekly average NRS, with missing data imputed as an average of the 2 adjacent weekly averages. Missing data were not imputed for continuous outcomes.

For ASSURE, data at each time point included patients evaluable at that time point. For responder analyses, a patient was evaluable at a visit if there was an assessment for that visit or the time from the first-dose date to the cutoff date was greater than the time point +28 days. Evaluable patients with missing data because of study discontinuation for treatment-related AEs or use of prohibited concomitant medications were considered nonresponders. The mean change in pruritus NRS was calculated using the weekly average NRS through month 6. After month 6, the mean change from baseline was based on the NRS reported at each study visit. Through month 6, missing NRS data were imputed as described above for RESPONSE. After month 6, NRS data were not imputed. Patients who discontinued treatment or the study for reasons other than treatment-related AEs or the use of prohibited concomitant medications were excluded from the analyses after discontinuation.

Safety and efficacy data were reported as descriptive summaries. Safety outcomes were also separately analyzed among patients with cirrhosis at baseline.

Exposure-adjusted safety analyses were conducted to assess safety over time. Data were reported as incidence per 100 patient-years, including exposure in RESPONSE (placebo or seladelpar 10 mg) and ASSURE (seladelpar 10 mg) for years 1, 2, and 3 of seladelpar exposure. Adverse events were mapped to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms version 24.0, and AE severity was graded using National Cancer Institute Common Terminology for Adverse Events version 5.0. Adverse events of interest (potentially indicating liver, muscle, or renal toxicity) were identified using predefined standardized MedDRA and US Food and Drug Administration query search strategies (see Supplementary Methods, Supplementary Digital

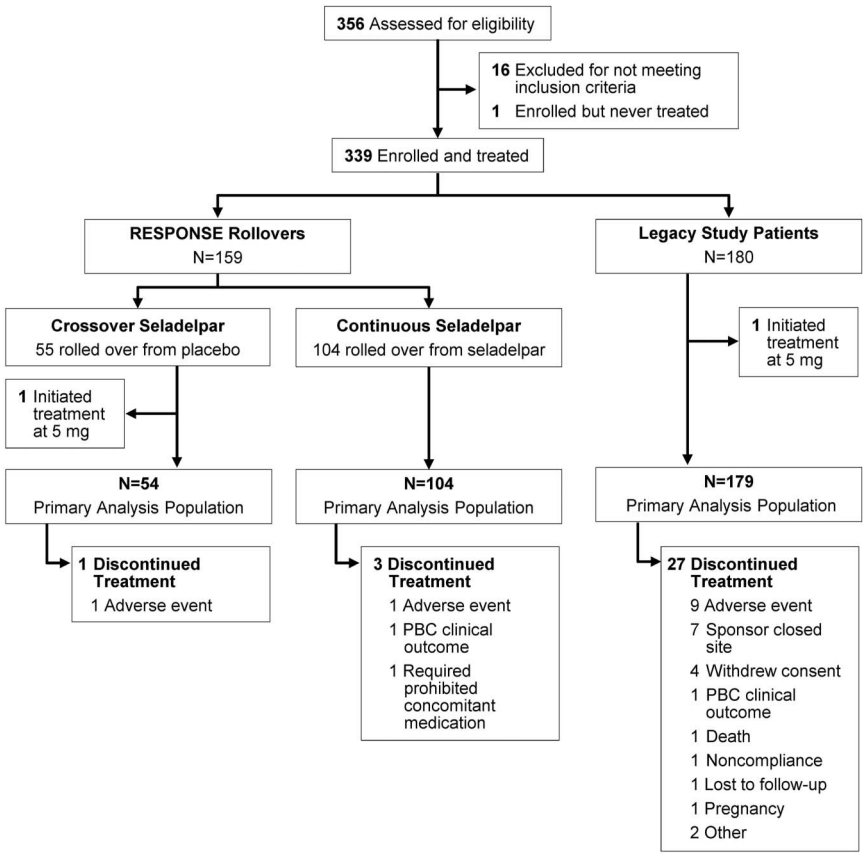

Figure 2. Patient disposition. Seladelpar was downtitrated to 5 mg daily in 2 legacy group patients; the dose was subsequently uptitrated back to 10 mg daily in 1 patient. PBC, primary biliary cholangitis.

Content, http://links.lww.com/AJG/D690). Pruritus-related AEs were defined as any AE with a MedDRA-preferred term containing "prur."

RESULTS

Patient disposition and baseline characteristics

The first patient enrolled in ASSURE on February 12, 2021, and as of the January 31, 2024, data cutoff, 339 patients were enrolled. Overall, 159 of 166 eligible patients (96%) rolled over from RESPONSE (55 from the placebo group and 104 from the seladelpar group) and 180 patients had participated in legacy studies (Figure 2). Two patients (1 each in the crossover seladelpar and legacy groups) initiated seladelpar at 5 mg per investigator preference and were excluded from the analyses. As of the cutoff, 97% (154/158) of patients from RESPONSE had received at least 6 months of seladelpar treatment in ASSURE and 91% (163/179) from legacy studies had received at least 1 year of seladelpar treatment in ASSURE. Overall, 31 patients (9%) discontinued treatment and 24 of these patients also discontinued the study. The most common reasons for treatment discontinuation were AEs (3%), Russian study site terminations due to ongoing geopolitical conflict (2%), and withdrawal of consent (1%). Patient demographics at ASSURE baseline were similar across groups; the median age was approximately 60 years, and most patients were female and White (Table 1).

As expected, at ASSURE study entry, the mean ALP level was lower among patients in the continuous seladelpar group (183.1 U/L, 8% with levels ≥350 U/L), who had been receiving seladelpar for 12 months in RESPONSE, compared with the crossover seladelpar group (288.7 U/L, 30% with levels ≥350 U/L) (Table 1). Cirrhosis diagnosis criteria were met by 13% (13/104) and 11% (6/54, including 1 with portal hypertension) of continuous and crossover group patients, respectively. In the subgroups of 23 placebo-treated and 49 seladelpar-treated RESPONSE rollover patients with moderate-to-severe pruritus (NRS ≥4) at RESPONSE baseline, the mean baseline NRS was 6.6 and 6.1, respectively.

In the legacy group, at the first ASSURE visit, the mean ALP level was similar to that in the RESPONSE crossover group (274.2 U/L, 24% with levels ≥350 U/L) (Table 1). Sixty-three (35%) of 179 patients had moderate-to-severe pruritus, with a mean NRS of 6.4. Cirrhosis diagnosis criteria were met by 20% (35/179) of patients, including 8 with portal hypertension.

The mean total bilirubin levels were similar across all groups at ASSURE enrollment: 0.74 mg/dL (10% with levels >ULN) in the continuous seladelpar group, 0.69 mg/dL in the crossover seladelpar group (11% with levels >ULN), and 0.77 mg/dL (15% with levels >ULN) in the legacy group (Table 1). At ASSURE enrollment, 96% of patients were receiving UDCA treatment and 18% had previously received obeticholic acid or fibrates.

Efficacy

Biochemical. The composite biochemical response was achieved by 62% (79/128; 95% confidence interval [CI] 53–70) of

Table 1. Patient demographics and characteristics at ASSURE study entry

Category	RESPONSE rollover patients		Legacy patients (N = 179)
	Continuous seladelpar (N = 104)	Crossover seladelpar (N = 54)	
Age, median (IQR), yr	59 (52–65)	59 (51–64)	60 (52–66)
Sex, n (%)			
Female	99 (95%)	50 (93%)	169 (94%)
Male	5 (5%)	4 (7%)	10 (6%)
Race, n (%)			
White	93 (89%)	45 (83%)	153 (86%)
Asian	6 (6%)	4 (7%)	14 (8%)
American Indian or Alaska Native	2 (2%)	3 (6%)	6 (3%)
Black or African American	2 (2%)	2 (4%)	3 (2%)
Missing	1 (1%)	0	3 (2%)
Duration of diagnosed PBC, median (IQR), yr	6.9 (3.8–13.3)	8.2 (4.3–12.0)	10.3 (6.5–15.2)
Cirrhosis at baseline, n (%)[a]	13 (13%)	6 (11%)	35 (20%)
Portal hypertension, n (%)	0	1 (17%)	8 (23%)
Child-Pugh class, n (%)			
A	12 (92%)	6 (100%)	31 (89%)
B	1 (8%)	0	4 (11%)
MELD score, mean (SD)	8.2 (1.9)	6.8 (0.8)	7.5 (1.7)
<12, n (%)	12 (92%)	6 (100%)	34 (97%)
ALP, n	103	54	179
Mean (SD), U/L	183.1 (112.1)	288.7 (125.5)	274.2 (133.1)
≥350 U/L, n (%)[b]	8 (8%)	16 (30%)	43 (24%)
Total bilirubin, n	103	54	174
Mean (SD), mg/dL	0.74 (0.48)	0.69 (0.28)	0.77 (0.37)
>ULN (1.1 mg/dL), n (%)[b]	10 (10%)	6 (11%)	27 (15%)
ALT, mean (SD), U/L	35.2 (24.1)	41.4 (21.3)	41.1 (23.5)
AST, mean (SD), U/L	36.5 (19.8)	37.0 (14.3)	37.5 (17.2)
GGT, mean (SD), U/L	174.6 (165.2)	232.8 (209.3)	208.8 (177.5)
Albumin, mean (SD), g/dL	4.2 (0.3)	4.1 (0.3)	4.1 (0.3)
Platelet count, mean (SD), $10^3/\mu L$	249.6 (90.9)	239.3 (85.3)	236.3 (75.7)
Liver stiffness, mean (SD), kPa	9.7 (8.3)	9.9 (10.1)	10.6 (8.5)
Category, n (%)[c]			
<8 kPa	48 (46%)	29 (54%)	92 (51%)
8–15 kPa	33 (32%)	22 (41%)	49 (27%)
>15 kPa	11 (11%)	2 (4%)	32 (18%)
Previous OCA/fibrate use, n (%)	17 (16%)	11 (20%)	34 (19%)
Concomitant UDCA, n (%)	96 (92%)	53 (98%)	173 (97%)
Dose, mean (SD), mg/kg	14.9 (3.0)	14.9 (3.5)	14.8 (3.2)
Concomitant lipid-modifying agent, n (%)	35 (34%)	28 (52%)	61 (34%)

Note that the presence of antimitochondrial antibodies and Sp100 antibodies was assessed as part of the parent studies but not at entry into ASSURE.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; IQR, interquartile range; MELD, model for end-stage liver disease; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
[a]Diagnosis criteria included liver biopsy, clinical history, laboratory findings, imaging findings, and/or clinical determination by the investigator (see Supplementary Methods, Supplementary Digital Content, http://links.lww.com/AJG/D690). For RESPONSE rollover patients, cirrhosis is defined at RESPONSE baseline.
[b]Data were missing from 1 patient in the continuous seladelpar group.
[c]Liver stiffness measurements are not available for all patients; therefore, reported percentages do not add up to 100.

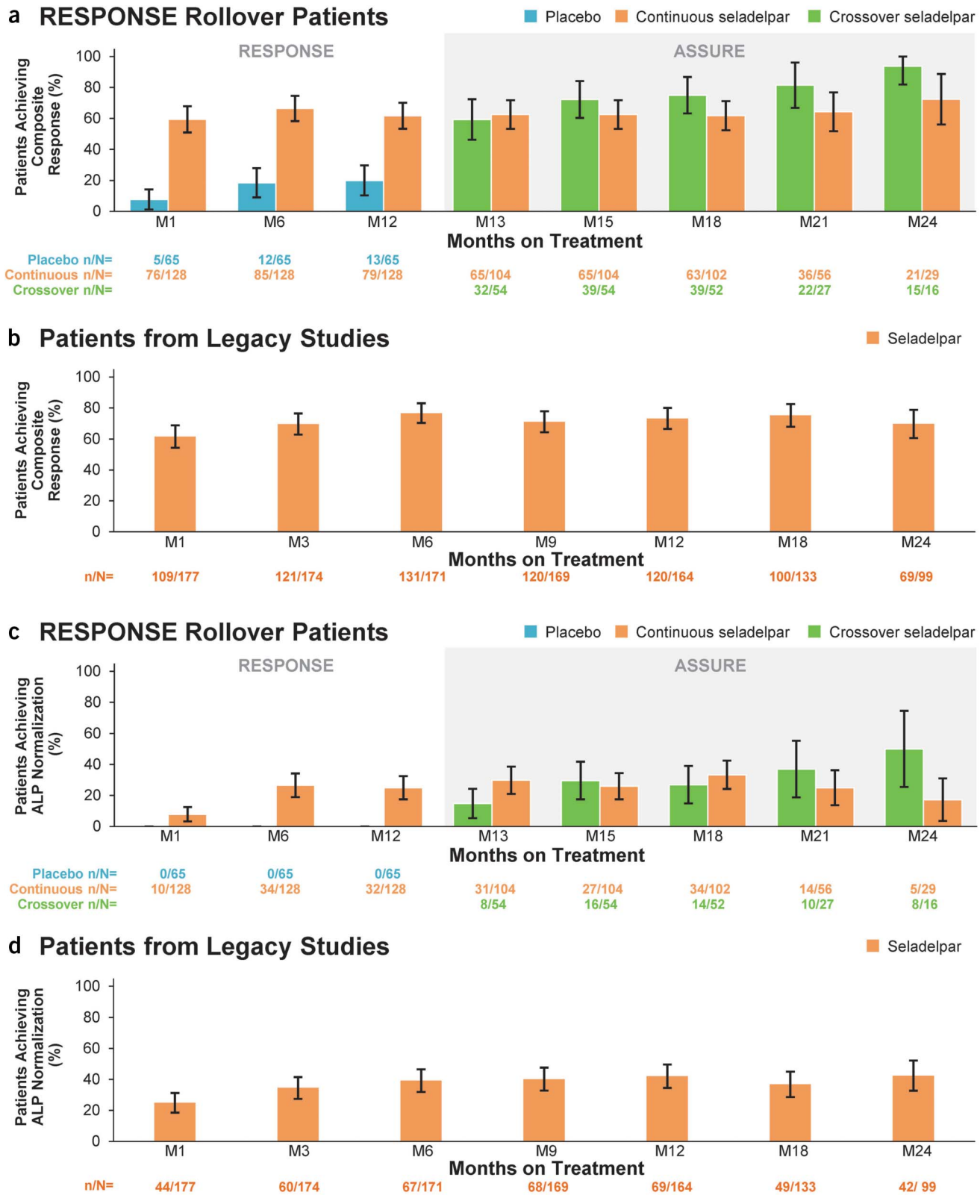

Figure 3. Achievement of composite biochemical response and ALP normalization over time in RESPONSE rollover patients and patients from legacy studies. Composite biochemical response was ALP <1.67×ULN, total bilirubin ≤ULN, and ALP decrease ≥15% from baseline. In RESPONSE rollover graphs, months 13, 15, 18, 21, and 24 indicate ASSURE months 1, 3, 6, 9, and 12. Baseline refers to RESPONSE study entry for RESPONSE rollover patients and ASSURE study entry for legacy patients. Bars indicate 95% confidence interval. ALP, alkaline phosphatase; M, month; ULN, upper limit of normal.

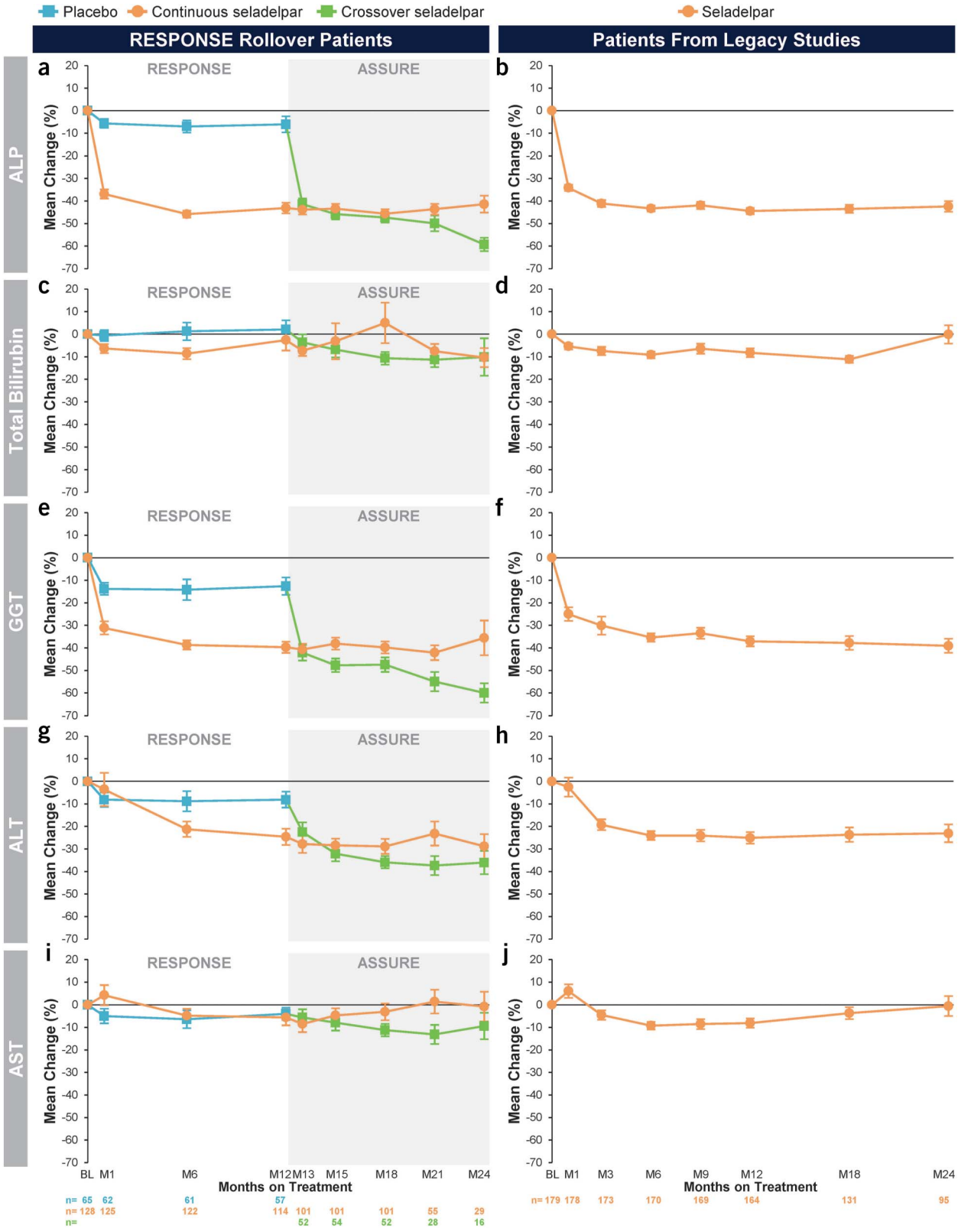

Figure 4. Mean change from baseline over time in levels of ALP, total bilirubin, ALT, GGT, and AST in RESPONSE rollover patients and patients from legacy studies. In RESPONSE rollover graphs, months 13, 15, 18, 21, and 24 indicate ASSURE months 1, 3, 6, 9, and 12. Bars indicate standard error. Baseline refers to RESPONSE study entry for RESPONSE rollover patients and ASSURE study entry for legacy patients. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; GGT, gamma-glutamyltransferase; M, month.

seladelpar-treated and 20% (13/65; 95% CI 10–30) of placebo-treated patients after 12 months in RESPONSE (Figure 3a) (25). This response rate was maintained among continuous seladelpar group patients who completed 12 additional months of treatment in ASSURE (72% [21/29]; 95% CI 56–89). In the crossover seladelpar group, composite biochemical response was achieved by 94% (15/16; 95% CI 82–100) of patients completing 12 months of seladelpar treatment in ASSURE. In the legacy group, composite biochemical response was achieved by 73% (120/164; 95% CI 66–80) and 70% (69/99; 95% CI 61–79) of patients completing 12 and 24 months, respectively, of seladelpar treatment in ASSURE (Figure 3b). When data were pooled for all patients who received seladelpar in RESPONSE, continuously treated patients in ASSURE, and legacy patients completing 12, 18, and 24 months of seladelpar treatment, the composite biochemical response rate was 70% (214/308), 70% (165/237), and 70% (90/128), respectively.

ALP normalization at Month 12 in RESPONSE was achieved by 25% (32/128; 95% CI 18–33) of seladelpar-treated and no placebo-treated patients (25). After an additional 12 months in ASSURE, ALP normalization was achieved by 17% (5/29; 95% CI 4–31) of continuous seladelpar group patients (Figure 3c). In the crossover seladelpar group, ALP normalization was achieved by 50% (8/16; 95% CI 26–75) of patients completing 12 months of seladelpar treatment. ALP normalization was achieved by 42% (69/164; 95% CI 35–50) of legacy group patients completing 12 months of seladelpar treatment, and this rate was maintained among patients completing 24 months of treatment (42% [42/99]; 95% CI 33–52) (Figure 3d).

The magnitude of ALP reduction from baseline was consistent across the RESPONSE rollover and legacy groups. After 12 months of treatment in RESPONSE, the mean change from baseline in ALP level was −43% (SE 2) in seladelpar-treated patients (mean baseline level 314.6 U/L) and −6% (SE 4) in placebo-treated patients (mean baseline level 313.8 U/L) (Figure 4a, Supplementary Table 1 [see Supplementary Digital Content, http://links.lww.com/AJG/D690]) (25). In the rollover groups, ALP reduction was maintained among the 29 continuous seladelpar group patients completing 12 months of additional seladelpar treatment in ASSURE (mean change, −41%; SE 4), and the mean change was −59% (SE 3) among the 16 crossover seladelpar group patients completing 12 months of seladelpar treatment. Comparable results were observed in the legacy group among the 164 and 95 patients completing 12 and 24 months of seladelpar treatment (mean changes, −44% [SE 1] and −42% [SE 2], respectively) (Figure 4b, Supplementary Table 2 [see Supplementary Digital Content, http://links.lww.com/AJG/D690]). Seladelpar resulted in reductions in ALP even among patients who did not achieve the composite biochemical response; the mean percent change from baseline in ALP in seladelpar nonresponders was −25% (SD, 35) at Month 12 in RESPONSE (27) and was maintained on continuation of seladelpar in ASSURE (data not shown).

As in RESPONSE, the mean total, direct, and indirect bilirubin levels were generally stable across all groups in ASSURE (Figure 4c,d, Supplementary Figure 1, Supplementary Tables 3–8 [see Supplementary Digital Content, http://links.lww.com/AJG/D690]). Improvement in other biomarkers of cholestasis and liver injury was observed in all groups. Reductions in GGT levels were similar to those observed with ALP (Figure 4e,f; see Supplementary Tables 9 and 10, Supplementary Digital Content, http://links.lww.com/AJG/D690). After 12 months of treatment in RESPONSE, the mean change from baseline in ALT level was −25% (SE 4) in seladelpar-treated patients (mean baseline level 47.4 U/L) compared with −8% (SE 4) in placebo-treated patients (mean baseline level 48.2 U/L) (Figure 4g, Supplementary Table 11 [see Supplementary Digital Content, http://links.lww.com/AJG/D690]) (25). ALT reduction was maintained among the 29 continuous seladelpar group patients completing 12 months of additional seladelpar treatment in ASSURE (mean change, −29% [SE 5]), and a similar mean reduction was observed in the crossover seladelpar group among the 16 patients completing 12 months of seladelpar treatment (mean change, −36% [SE 5]). Comparable reductions in mean ALT levels were observed among the 164 and 95 legacy group patients completing 12 and 24 months of seladelpar treatment (mean change, −25% [SE 3] and −23% [SE 4], respectively) (Figure 4h, Supplementary Table 12 [see Supplementary Digital Content, http://links.lww.com/AJG/D690]). In addition, ALT normalization was observed among patients with elevated baseline ALT levels in all groups throughout seladelpar treatment (see Supplementary Figure 2, Supplementary Digital Content, http://links.lww.com/AJG/D690). AST levels were generally stable throughout seladelpar treatment in all groups (Figure 4i,j; see Supplementary Tables 13-14, Supplementary Digital Content, http://links.lww.com/AJG/D690). Total cholesterol, low density lipoprotein cholesterol, and triglyceride levels were decreased with seladelpar, whereas high-density lipoprotein cholesterol levels remained unchanged (see Supplementary Figure 3, Supplementary Digital Content, http://links.lww.com/AJG/D690).

Pruritus. After 12 months of treatment in RESPONSE, the mean change from baseline in the weekly average NRS among patients with moderate-to-severe baseline pruritus was −3.4 (SE 0.4) in seladelpar-treated patients and −1.8 (SE 0.5) in placebo-treated patients, and a persistent decrease of −3.8 (SE 0.5) was observed among the 26 continuous seladelpar group patients completing an additional 6 months of seladelpar treatment in ASSURE (Figure 5a) (25). Mean change from baseline in weekly average NRS was −3.8 (SE 0.4) in the crossover seladelpar group (n = 17) and −3.5 (SE 0.3) in the legacy group (n = 56) after 6 months of seladelpar treatment in ASSURE (Figure 5a,b). Changes from baseline in pruritus NRS collected at each ASSURE study visit after Month 6 are shown in Supplementary Tables 15 and 16 (see Supplementary Digital Content, http://links.lww.com/AJG/D690).

During ASSURE, 4 patients had events that the CERC adjudicated as PBC clinical outcome events; 1 in a RESPONSE rollover patient in the continuous seladelpar group and 3 in the legacy group (see Supplementary Table 17, Supplementary Digital Content, http://links.lww.com/AJG/D690).

Safety

The ASSURE safety analysis population included 337 patients. The mean durations of seladelpar exposure for all RESPONSE rollover patients in ASSURE was 43.5 weeks (total seladelpar exposure duration, including patients who received seladelpar in RESPONSE and ASSURE was 85.6 weeks) compared with 99.4 weeks for legacy patients (including seladelpar treatment in ASSURE only) (see Supplementary Table 18, Supplementary Digital Content, http://links.lww.com/AJG/D690). Among rollover patients, 154 received ≥6 months of seladelpar treatment in ASSURE, 81 received ≥9 months, and 42 received ≥12 months. Among legacy patients, 171 received ≥6 months of seladelpar treatment in ASSURE, 169 received ≥9 months, 163 received ≥1 year, and 96 received ≥2 years.

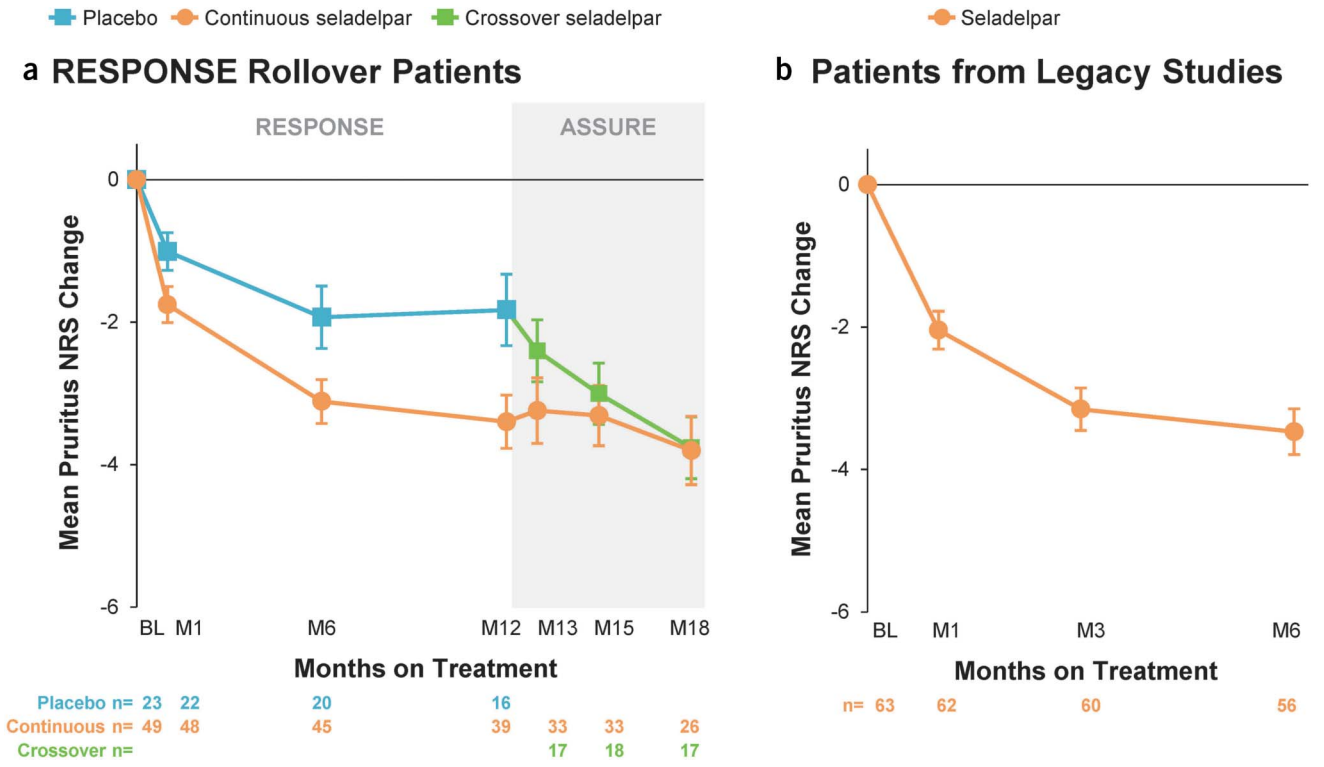

Figure 5. Mean change from baseline in weekly averaged pruritus NRS among patients with moderate-to-severe baseline pruritus in RESPONSE rollover patients and patients from legacy studies. In RESPONSE rollover graph, months 13, 15, and 18 indicate ASSURE months 1, 3, and 6. For all time points, mean change from baseline was based on the weekly average pruritus NRS score. Baseline was defined as the mean of all daily recorded scores during the run-in period and day 1 of RESPONSE for RESPONSE rollover patients and the mean of all daily recorded scores from 14 days prior to first dose up to day 1 first dose administered in ASSURE for legacy studies. Bars indicate standard error. BL, baseline; M, months; NRS, numerical rating scale.

Among RESPONSE rollover patients, 70% (73/104) in the continuous seladelpar group and 78% (42/54) in the crossover seladelpar group had ≥1 AE compared with 83% (149/179) of legacy group patients, consistent with the longer treatment duration in this group (Table 2). The most common AEs (≥5% of patients overall) were COVID-19, pruritus, urinary tract infection, nausea, diarrhea, fatigue, nasopharyngitis, upper abdominal pain, and arthralgia.

Serious AE (SAE) incidence was overall similar among groups (6% [6/104] in the continuous seladelpar group, 13% [7/54] in the crossover seladelpar group, and 13% [24/179] in the legacy group) (Table 2). No SAEs were considered related to treatment, and there was no consistent SAE type reported (see Supplementary Table 19, Supplementary Digital Content, http://links.lww.com/AJG/D690). The incidence of AEs leading to treatment discontinuation was numerically lower in the rollover groups (2% [2/104] and 2% [1/54] in the continuous and crossover groups, respectively) than in the legacy group (6% [11/179]). One death, determined to be unrelated to seladelpar, occurred in the legacy group.

Liver-related AEs, identified using prespecified search criteria, occurred in 7% (7/104) of continuous seladelpar group patients, none in the crossover group, and 10% (18/179) in the legacy group (Table 2). Most liver-related AEs were grade 1 or 2. Five liver-related AEs led to treatment discontinuation, 3 of which were SAEs (hyperbilirubinaemia, hepatorenal syndrome, and esophageal variceal hemorrhage) (see Supplementary Table 20, Supplementary Digital Content, http://links.lww.com/AJG/D690). No events were adjudicated positively by the CERC for drug-induced liver injury. Muscle-related AEs occurred in 3% (3/104) of continuous seladelpar group patients, none in the crossover group, and 10% (18/179) in the legacy group; all events were grade 1 or 2; none were associated with creatine kinase increases >3×ULN or led to treatment discontinuation. AEs indicating renal toxicity were rare. There was 1 renal AE of proteinuria that was considered mild (grade 1). Creatine kinase and serum creatinine levels remained stable in all groups (see Supplementary Tables 21–24, Supplementary Digital Content, http://links.lww.com/AJG/D690).

For the exposure-adjusted safety analyses, time in RESPONSE was used as seladelpar exposure Year 1 and 128 seladelpar-treated patients were included in this group. For continuously treated rollovers from RESPONSE, there were 104 patients contributing to exposure in year 2 of seladelpar and 28 contributing to exposure in year 3. Among crossover seladelpar patients, 54 contributed exposure time to crossover year 1 and 13 contributed time to crossover year 2. Among legacy group patients, 179 contributed time to exposure year 1, and 163 and 96 contributed to years 2 and 3, respectively. The placebo group in the RESPONSE study (N = 65) contributed to the placebo exposure time. Results of exposure-adjusted safety analyses were consistent with the overall safety incidences, with generally similar incidence and severity of AEs in years 1, 2, and 3 of seladelpar exposure compared with placebo (see Supplementary Table 25, Supplementary Digital Content, http://links.lww.com/AJG/D690). The incidence of pruritus was numerically higher among placebo patients compared with seladelpar patients.

Table 2. Summary of safety outcomes in ASSURE

Category	RESPONSE rollover patients		Legacy patients (N = 179)
	Continuous seladelpar (N = 104)	Crossover seladelpar (N = 54)	
Any AE	73 (70%)	42 (78%)	149 (83%)
SAE	6 (6%)	7 (13%)	24 (13%)
AE leading to treatment discontinuation	2 (2%)	1 (2%)	11 (6%)
Death[a]	0	0	1 (1%)
Pruritus AE	10 (10%)	0	24 (13%)
AEs of interest			
Muscle-related AE	3 (3%)	0	18 (10%)
Liver-related AE	7 (7%)	0	18 (10%)
Renal-related AE	0	1 (2%)	0
Common AEs (≥5% of patients in any group)			
COVID-19	5 (5%)	5 (9%)	38 (21%)
Pruritus	10 (10%)	0	24 (13%)
Urinary tract infection	7 (7%)	2 (4%)	17 (10%)
Nausea	5 (5%)	2 (4%)	16 (9%)
Diarrhea	2 (2%)	5 (9%)	15 (8%)
Fatigue	5 (5%)	1 (2%)	14 (8%)
Nasopharyngitis	5 (5%)	0	15 (8%)
Upper abdominal pain	5 (5%)	1 (2%)	12 (7%)
Arthralgia	3 (3%)	4 (7%)	11 (6%)
Headache	3 (3%)	5 (9%)	8 (5%)
Abdominal pain	3 (3%)	2 (4%)	9 (5%)
Upper respiratory tract infection	2 (2%)	1 (2%)	12 (7%)
Cough	3 (3%)	5 (9%)	5 (3%)
Hypertension	2 (2%)	3 (6%)	7 (4%)
Anemia	4 (4%)	4 (7%)	2 (1%)
Pyrexia	3 (3%)	3 (6%)	3 (2%)
Respiratory tract infection	1 (1%)	3 (6%)	2 (1%)
Productive cough	2 (2%)	3 (6%)	0

Data are n (%).
AE, adverse event; COVID-19, coronavirus disease 2019; SAE, serious adverse event.
[a]Autoimmune hemolytic anemia, assessed as unrelated to treatment.

Among the 54 patients with cirrhosis treated with seladelpar for ≥2 years, overall rates of AEs, SAEs, and AEs of interest were similar to those among patients treated with placebo in the exposure-adjusted analysis (data not shown).

DISCUSSION

These interim results of the open-label ASSURE study offer an important assessment of continued efficacy and safety of seladelpar beyond the 1-year, placebo-controlled, registrational RESPONSE study (25). PBC is a chronic disease requiring ongoing therapy, thus there is a compelling rationale to evaluate the long-term safety and efficacy profile of new treatments. This is particularly relevant as the landscape of available PBC treatments evolves, with emergence of new therapies including seladelpar, a novel delpar (selective PPARδ agonist).

The robust biochemical effect on cholestatic markers, including the composite biochemical response, ALP normalization, and ALP change from baseline seen with 1 year of seladelpar treatment in RESPONSE was sustained in the continuous seladelpar group after a second year of treatment in ASSURE. Crossover seladelpar group patients achieved a biochemical response in ASSURE similar in magnitude to that observed in seladelpar-treated patients in RESPONSE. Improvements in GGT and ALT seen in RESPONSE were also sustained or recapitulated with seladelpar treatment in ASSURE. Although improvements in biochemical outcomes in ASSURE were generally numerically greater in the crossover seladelpar group than in the continuous seladelpar group, the 95% CIs for the composite response and ALP normalization outcomes were overlapping and variability in biochemical measures is most likely due to the smaller number of patients in this group.

ASSURE also serves as a long-term study of seladelpar in legacy patients with a gap (>1 year in most instances) from participation in a prior seladelpar study, offering another population in which to assess efficacy and safety of seladelpar initiation. Most legacy patients had previously been treated with seladelpar but were considered functionally naïve upon ASSURE enrollment and had to meet ASSURE eligibility criteria. Mean baseline ALP levels in legacy patients at ASSURE enrollment was similar to that in crossover seladelpar patients, supporting this approach. Because legacy patients began enrolling in ASSURE before RESPONSE patients, they also have longer follow-up times. Despite the heterogeneity in this population, results were consistent with the RESPONSE population, i.e., the biochemical response was rapid and durable, with 70% and 42% of patients achieving the composite endpoint and ALP normalization, respectively, at 2 years.

As in RESPONSE, bilirubin was generally stable throughout treatment in ASSURE across all groups, perhaps in part a reflection of largely normal baseline mean total bilirubin. Reductions in ALT, including normalization in patients with elevated baseline levels, were observed out to 2 years of treatment, which may reflect improvements in inflammation and associated liver injury over time.

Among patients with moderate-to-severe pruritus at baseline (NRS ≥4), ASSURE confirmed a sustained effect of pruritus NRS reduction for 6 additional months in the continuous seladelpar group, and onset of reduction in patients starting seladelpar in ASSURE, reflecting a robust and reproducible effect in this important PBC symptom. Examination of data beyond 6 months in ASSURE, when pruritus was assessed only at study visits, appears to reflect an ongoing effect although should be interpreted with caution given sparse data collection (every 6 months) for a scale with a 24-hour recall period.

Although the exact mechanism by which seladelpar improves pruritus is not known, pruritus improvement with seladelpar treatment has been shown to be correlated with reduction in bile acids and the pruritogenic cytokine interleukin-31 (28). Baseline bile acids and interleukin-31 levels were elevated in patients with pruritus associated with PBC and were reduced in seladelpar-treated patients who experienced pruritus improvement (28).

In this interim analysis including patients with exposure beyond 2 years of treatment, seladelpar appeared safe and well tolerated, and no new safety signals were observed. There were no treatment-related SAEs and discontinuation of treatment due to AEs was low (3% overall). Liver-related AEs were typical of those observed in patients with PBC, with no consistent pattern. Exposure-adjusted analyses demonstrated that the incidence of these events did not appear to increase with long-term seladelpar use. Muscle-related AEs generally reflected common musculoskeletal complaints and were similar in incidence to placebo over time in the exposure-adjusted analysis. Despite concomitant use of lipid-modifying agents among 34%–52% of patients, there were no AEs associated with significant elevations in creatine kinase and no AEs of kidney injury, which have been observed with PPARα and pan-PPAR agonists (9–12). The safety evaluation included 54 patients with cirrhosis (including 8 with known portal hypertension), in whom no safety concerns were identified.

Due to the ongoing nature of ASSURE, not all patients have reached later time points, and follow-up time for RESPONSE rollover patients was more limited than for legacy patients. Longer term data from this ongoing study will continue to be informative, although this analysis does provide important insight into safety with extended treatment based on available follow-up time. Other study limitations include an open-label design, lack of control group, lack of racial diversity, and lack of FibroScan data in this interim analysis. Additionally, the different populations within ASSURE, including RESPONSE rollover patients and patients with variable prior seladelpar exposure followed by a treatment gap when other PBC treatment may have been received, limits interpretation of pooled analysis results. However, separate analyses of the groups within ASSURE affords an opportunity to assess consistency of effect among patients with different treatment experiences. These interim results are also consistent with the efficacy results of the previous phase 3 ENHANCE study and a previous long-term study in patients with PBC (23,24).

The sustained improvements in biochemical markers of cholestasis and liver injury with seladelpar in this interim analysis of ASSURE are comparable to those reported in smaller, open-label studies of obeticholic acid (29), fenofibrate (30), and bezafibrate (31). The pruritus improvement observed with seladelpar in this open-label study is consistent with that observed in the placebo-controlled RESPONSE study (25). This sets seladelpar apart as the only approved therapy confirmed to reduce pruritus in 2 placebo-controlled studies (23,25) based on the key secondary endpoint of pruritus NRS reduction, with an ongoing, persistent effect in the open-label setting. Elafibranor demonstrated a trend toward improvement in pruritus based on PBC-40 itch domain and 5-dimension (5-D) itch scale assessments in the placebo-controlled ELATIVE study, but did not meet the key secondary endpoint of pruritus NRS reduction (10). Shorter term data (21 days) with bezafibrate demonstrated a benefit over placebo (32). Data for bezafibrate over 2 years showed a trend in pruritus reduction versus placebo that was not statistically significant (6). It should also be noted that the study did not stratify for pruritus intensity and most patients had mild pruritus. Limited data available for fenofibrate suggest a potential effect on cholestatic itch, although to a lesser degree than bezafibrate (33).

In conclusion, these interim results demonstrated a durable effect on biochemical markers of PBC with seladelpar treatment up to 2 years, consistent with the significant improvements in disease markers observed in the phase 3, placebo-controlled RESPONSE study. The significant effect on pruritus seen in RESPONSE was sustained during the additional 6-month evaluation period in ASSURE. No new safety signals were identified among patients treated with seladelpar beyond 2 years. These interim data support seladelpar as an effective and safe long-term PBC treatment in patients who have had an inadequate response or intolerance to UDCA.

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Data availability: Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Science's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

Study Highlights

WHAT IS KNOWN

- ✓ In previous clinical studies, seladelpar at 10 mg daily was safe and effective in inducing a significant and clinically relevant biochemical response and improving pruritus in patients with primary biliary cholangitis (PBC) with an inadequate response or intolerance to ursodeoxycholic acid, the current first-line therapy.

WHAT IS NEW HERE

- ✓ Interim data from the 5-year, open-label ASSURE study evaluating seladelpar 10 mg once daily in patients with PBC demonstrate strong and durable improvements in cholestatic biomarkers sustained for up to 2 years with seladelpar treatment.
- ✓ Pruritus reduction among patients with pruritus at baseline was sustained for up to 18 months with seladelpar treatment.
- ✓ Seladelpar appeared safe and well tolerated among patients with exposure beyond 2 years, and no new safety signals were observed.

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