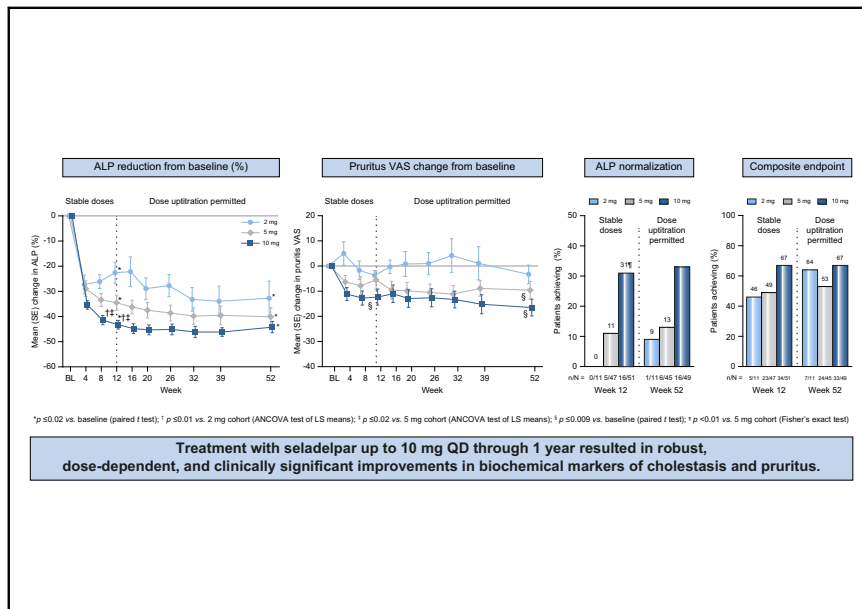


# A phase II, randomized, open-label, 52-week study of seladelpar in patients with primary biliary cholangitis

## Graphical abstract



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## Lay summary

Current treatment options for patients living with primary biliary cholangitis (PBC) are not optimal due to inadequate effectiveness or undesirable side effects. Patients with PBC who took seladelpar, a new treatment being developed for PBC, at increasing doses (2, 5, or 10 mg/day) for 1 year had clinically significant, dose-dependent improvements in key liver tests. Treatment appeared safe and was not associated with any worsening in patient self-reported itch scores.

## Highlights

- Seladelpar (2, 5, 10 mg) was assessed in patients with primary biliary cholangitis.
- ALP was dose-dependently reduced by 23% to 43% at Week 12.
- ALP was normalized in 33% of patients in the 10 mg cohort at Week 52.
- Up to 67% of patients met the composite ALP and bilirubin endpoint at Week 52.
- Seladelpar was safe, with no treatment-related serious adverse events or deaths.



## A phase II, randomized, open-label, 52-week study of seladelpar in patients with primary biliary cholangitis

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**Background & Aims:** We examined the efficacy and safety of seladelpar, a selective peroxisome proliferator-activated receptor-delta agonist, in adults with primary biliary cholangitis (PBC) at risk of disease progression (alkaline phosphatase [ALP]  $\geq 1.67$  upper limit of normal [ULN]) who were receiving or intolerant to ursodeoxycholic acid.

**Methods:** In this 52-week, phase II, dose-ranging, open-label study, patients were randomized (1:1) to seladelpar 5 mg/day (n = 53) or 10 mg/day (n = 55) or assigned to 2 mg/day (n = 11; United Kingdom sites after interim analysis) for 12 weeks. Doses could then be uptitrated to 10 mg/day. The primary efficacy endpoint was ALP change from baseline to Week 8.

**Results:** Mean baseline ALP was 300, 345, and 295 U/L in the 2 mg, 5 mg, and 10 mg cohorts, respectively. Twenty-one percent of patients had cirrhosis, 71% had pruritus. At Week 8, mean  $\pm$  standard error ALP reductions from baseline were

26  $\pm$  2.8%, 33  $\pm$  2.6%, and 41  $\pm$  1.8% in the 2 mg (n = 11), 5 mg (n = 49), and 10 mg (n = 52) cohorts (all  $p \leq 0.005$ ), respectively. Responses were maintained or improved at Week 52, after dose escalation in 91% and 80% of the 2 mg and 5 mg cohorts, respectively. At Week 52, composite response (ALP  $< 1.67$  xULN,  $\geq 15\%$  ALP decrease, and normal total bilirubin) rates were 64%, 53%, and 67%, and ALP normalization rates were 9%, 13%, and 33% in the 2 mg, 5 mg, and 10 mg cohorts, respectively. Pruritus visual analog scale score was decreased in the 5 mg and 10 mg cohorts. There were no treatment-related serious adverse events, and 4 patients discontinued due to adverse events.

**Conclusions:** Seladelpar demonstrated robust, dose-dependent, clinically significant, and durable improvements in biochemical markers of cholestasis and inflammation in patients with PBC at risk of disease progression. Seladelpar appeared safe and well tolerated and was not associated with any increase in pruritus.

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**Lay summary:** Current treatment options for patients living with primary biliary cholangitis (PBC) are not optimal due to inadequate effectiveness or undesirable side effects. Patients with PBC who took seladelpar, a new treatment being developed for PBC,

Keywords: Clinical study; Primary biliary cholangitis; Seladelpar.

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at increasing doses (2, 5, or 10 mg/day) for 1 year had clinically significant, dose-dependent improvements in key liver tests. Treatment appeared safe and was not associated with any worsening in patient self-reported itch scores.

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## Introduction

Primary biliary cholangitis (PBC) is a rare autoimmune liver disease predominantly afflicting middle-aged women, with approximately 1 in 1,000 women over 40 years old diagnosed globally.<sup>1,2</sup> This complex cholangiopathy is characterized by immune-mediated destruction of small intrahepatic bile ducts<sup>3–6</sup> leading to cholestasis, with accumulation of toxic bile acids that are believed to perpetuate chronic, progressive inflammation and fibrosis, which can progress to biliary cirrhosis and liver-related death.<sup>7</sup>

Elevated alkaline phosphatase (ALP) and total bilirubin are independent risk factors for decreased transplant-free survival in patients with PBC treated with first-line approved therapy, ursodeoxycholic acid (UDCA).<sup>8–10</sup> Normalization of ALP and bilirubin levels have been proposed as ideal treatment goals.<sup>11</sup> The only other approved PBC treatment is obeticholic acid (OCA), a bile acid analog and farnesoid X receptor (FXR) agonist used as a second-line add-on therapy for patients with inadequate response to UDCA or as monotherapy for those intolerant to UDCA.<sup>2,5,6,12</sup> However, less than half of patients treated with OCA, alone or in combination with UDCA, achieved the composite biochemical response used for its approval (ALP <1.67x upper limit of normal [ULN] and  $\geq 15\%$  decrease from baseline and normal total bilirubin levels).<sup>13</sup> Furthermore, OCA therapy can induce or worsen pruritus in a dose-dependent manner.<sup>13,14</sup>

Peroxisome proliferator-activated receptor (PPAR) agonists have gained attention as potential therapies for PBC and other cholestatic liver diseases.<sup>15</sup> PPAR $\delta$  is a broadly expressed, fatty acid-activated transcription factor involved in fatty acid metabolism and inflammation.<sup>16–18</sup> In the liver, PPAR $\delta$ -regulated genes are expressed in hepatocytes, Kupffer cells, and hepatic stellate cells.<sup>15,19</sup> Importantly, PPAR $\delta$  plays a critical role in bile acid homeostasis and has antifibrotic effects.<sup>1,16–18,20</sup>

Seladelpar is a novel, potent, selective, first-in-class PPAR $\delta$  agonist being developed for the treatment of PBC in patients who do not respond to or are intolerant to UDCA.<sup>21</sup> In a previous study, seladelpar at doses of 50 and 200 mg/day reduced ALP >60% in patients with PBC; however, 3 cases of rapid, reversible, asymptomatic elevations in hepatic aminotransferases were reported.<sup>21</sup> Herein, we report the results of a phase II, dose-ranging, open-label study to establish the safety and efficacy of seladelpar using 5- to 100-fold lower doses. The initial objective of this study was to assess the efficacy, safety, and tolerability of seladelpar doses up to 10 mg once daily (QD) in patients with PBC after 8 weeks of treatment. The study design was subsequently amended to examine the effects of seladelpar at 2, 5, and 10 mg QD through 12 weeks and 1 year of treatment. Efficacy endpoints focused on changes from baseline in ALP and bilirubin and other relevant liver biochemistries, including gamma-glutamyl transferase (GGT), 5'-nucleotidase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

## Patients and methods

### Patients

Eligible patients were 18 to 75 years of age, met established diagnostic criteria<sup>5,6</sup> for PBC, and were either UDCA intolerant or receiving stable recommended doses of UDCA for the prior 12 months. PBC diagnostic criteria<sup>5,6</sup> included  $\geq 2$  of the following: history of ALP >ULN for  $\geq 6$  months, positive antimitochondrial antibody titers (>1:40 on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay) or positive PBC-specific antinuclear antibodies, and liver biopsy histology consistent with PBC. Patients were also required to have ALP levels  $\geq 1.67$ xULN. Patients with compensated cirrhosis (diagnosed by liver histology, imaging tests, or liver elastography) were eligible.

Patients were excluded if they had AST or ALT levels >3xULN; total bilirubin >2.0 mg/dl (34.2  $\mu$ mol/L); total bilirubin >ULN and albumin <lower limit of normal (Rotterdam advanced stage<sup>8</sup>), except for patients with Gilbert's syndrome (excluded if direct bilirubin >ULN; criteria in the US-specific protocol amendment); or other medical conditions that would preclude full participation or confound study results (details provided in the [supplementary methods](#)).

### Study design

This phase II, international, open-label, dose-ranging, randomized study of seladelpar was conducted at 32 centers in 4 countries (Canada, Germany, United Kingdom, and the US). Enrollment began in November 2016, and the last patient completed the study in July 2019. All patients provided written informed consent. The study was approved by independent ethics committees and conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines.

Patients received seladelpar (CymaBay Therapeutics, Newark, California) along with UDCA at their prestudy dose levels unless they were UDCA intolerant.

### Initial study design

The initial study design included an 8-week dose-ranging period followed by an 18-week extension period ([Fig. S1A](#)). After a 2-week screening period, patients were centrally randomized (1:1 using an interactive voice/web response system) to treatment with seladelpar 10 or 5 mg QD. A planned interim analysis was conducted after the enrollment of the 24th patient in the 10 mg and 5 mg cohorts, initially to determine whether a 25 mg cohort should be enrolled.

### Amended study design

At the initial 8-week interim analysis, patients who had completed the dose-ranging treatment period had significant declines in ALP without elevations in aminotransferases. The sponsor subsequently amended the protocol to adjust the study design to add a 2 mg QD cohort (up to 18 patients), increase the dose-ranging period from 8 to 12 weeks, increase the sample size to 116, and increase the total treatment period to 52 weeks ([Fig. S1B](#)). Since the decreases in ALP in the 10 mg cohort at that time were approaching those of the 50 mg cohort in the prior study,<sup>21</sup> it was also decided not to enroll the seladelpar 25 mg cohort.

Randomization to the 5 or 10 mg QD doses continued, and after the amendment, patients at sites in the United Kingdom

were registered in chronological order to treatment with seladelpar 2 mg QD for 12 weeks until the cohort was enrolled. Among patients in the 2 mg and 5 mg cohorts, beginning at Week 12 (Week 26 for patients with cirrhosis), the seladelpar dose could be titrated up to 10 mg QD based on investigator judgment for patients with an inadequate biochemical response. The seladelpar dose could be titrated down at any time during the study for safety reasons.

### Study endpoints and assessments

The primary efficacy endpoint was the mean percent change in ALP from baseline at Week 8. Secondary efficacy endpoints included mean absolute and percent changes from baseline at Weeks 12 and 52 in ALP, responder rates for a composite endpoint of ALP and total bilirubin (ALP  $<1.67 \times \text{ULN}$ ,  $\geq 15\%$  decrease in ALP from baseline, and normal total bilirubin), and ALP  $\leq \text{ULN}$ . Additional secondary endpoints included changes from baseline at Weeks 12 and 52 in total and direct (conjugated) bilirubin, AST, ALT, GGT, 5nucleotidase, lipids (as summarized in the supplementary methods), and pruritus intensity using a visual analog scale (VAS; 0 to 100; 0 = no itch, 100 = worst itch imaginable). Responder rates for published PBC response criteria<sup>8,12,22–24</sup> were also assessed. Exploratory efficacy endpoints included change in bile acid precursor 7 $\alpha$ -hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF19) levels from baseline.

Assessments for efficacy and safety were conducted at each study visit and at a follow-up visit 4 weeks after the end of treatment. Safety assessments included treatment-emergent adverse events (TEAEs), laboratory analyses, vital signs, physical examinations, and concomitant medications (details provided in the [supplementary methods](#)).

### Statistical analysis

The final planned sample size was 49 patients each in the 10 mg and 5 mg cohorts (increased from 12), and up to 18 in the 2 mg cohort, allowing for detection of at least a 10% mean difference in ALP percent change between the 5 mg and 10 mg cohorts with a 15% SD at 90% power using a 2-sided, 2-sample *t* test at  $\alpha = 0.05$  significance level. Efficacy analyses were conducted using data from the modified intent-to-treat (mITT) population (any patient diagnosed with PBC who received  $\geq 1$  dose of seladelpar with  $\geq 1$  post-baseline ALP measurement). A sensitivity analysis on the intent-to-treat (ITT) population (any patient who received  $\geq 1$  dose of seladelpar with  $\geq 1$  post-baseline ALP measurement) was also conducted. Safety analyses were conducted for all patients who received  $\geq 1$  dose of seladelpar (safety population). Efficacy and safety were analyzed by initial dose assignment. Select efficacy endpoints were also analyzed for patients who were randomized to seladelpar 5 mg QD and remained on this dose (5/5 mg cohort) or uptitrated to 10 mg QD (5/10 mg cohort).

Demographic and baseline characteristics were summarized using descriptive statistics for continuous variables and frequency distributions for discrete variables. Where specified, the last observation carried forward was used for missing laboratory data; other missing data were not imputed. Primary and secondary efficacy analyses were carried out using 2-sided tests at the  $\alpha = 0.05$  significance level. For biochemistry measures, within-group comparisons with baseline using a paired *t* test were performed at Weeks 12 and 52, and pairwise comparisons

of least squares (LS) means between treatment cohorts using an analysis of covariance model were performed at Weeks 8, 12, and 52. Since the seladelpar dose was uptitrated in the majority of patients in the 2 mg and 5 mg cohorts after Week 12, the differences among treatment cohorts were not reported after that time point. Responder rates were compared between treatment cohorts using Fisher's exact test.

## Results

### Patient disposition and baseline characteristics

Among 192 patients screened, 121 were randomized to daily oral seladelpar at doses of 2 mg ( $n = 11$ ), 5 mg ( $n = 53$ ), and 10 mg ( $n = 55$ ), with 11, 49, and 52 patients included in the mITT populations, respectively ([Fig. 1](#)). Details of dose titration and final dose are provided in the supplementary results. Among patients in the mITT population randomized to 5 mg (5 mg cohort) who completed the study ( $n = 43$ ), 35 (81%) uptitrated to 10 mg at or after Week 12 (53% at or before Week 26) ([Fig. S2](#)). Among patients assigned to 2 mg (2 mg cohort) who completed the study ( $n = 10$ ), 5 patients each (100%) uptitrated to 5 or 10 mg at or after Week 12 (90% at or before Week 26). A total of 105 patients (88.2%) completed Week 52, 104 of whom rolled over into a long-term extension study. Fourteen (11.8%) patients in the safety population discontinued the study: 6 due to withdrawal of consent, 4 due to adverse events (AEs), 1 due to loss of follow-up, and 3 due to protocol violations.

Patient demographics and baseline disease characteristics in the safety population ( $n = 119$ ) were similar among the treatment cohorts at baseline, although the small number of patients in the 2 mg cohort makes comparisons difficult ([Table 1](#)). The majority of patients were female (94.1%) and White (91.6%), and mean age was 57.2 years. Mean PBC duration was 9.7 years, 70.6% of patients had a history of pruritus, 21.0% of patients had cirrhosis, and 6.7% were intolerant to UDCA. Notably, baseline ALP was greater in the 5 mg cohort (345.4 U/L) vs. the 2 mg (300.4 U/L) and 10 mg (295.3 U/L) cohorts. Overall, mean total bilirubin levels were 0.8 mg/dl (13.2  $\mu\text{mol/L}$ ). Concomitant UDCA was received by 93.2% of patients at a mean daily dose of 15.0 mg/kg. Baseline characteristics in the mITT population were similar to those in the safety population (data not shown).

### Efficacy

#### ALP

At Week 8, mean reductions in ALP from baseline (primary endpoint) were dose dependent: 2 mg (26%), 5 mg (33%), and 10 mg (41%) ([Fig. 2A–B](#)). At the end of the dose-ranging period (Week 12), mean ALP levels were significantly (all  $p \leq 0.005$ ) reduced from baseline by 68 U/L (23%) in the 2 mg cohort, 136 U/L (35%) in the 5 mg cohort, and 128 U/L (43%) in the 10 mg cohort. Reductions were maintained or continued to decline through Week 52 in the 2 mg (101 U/L [33%]), 5 mg (158 U/L [40%]), and 10 mg (134 U/L [44%]) cohorts (all  $p \leq 0.01$  vs. baseline). ALP reduction was significantly greater in the 10 mg (42%) vs. the 2 mg (27%) and 5 mg (33%) cohorts at Week 8 (both  $p = 0.002$ ) and Week 12 (44% vs. 23% and 34%, respectively; both  $p \leq 0.005$ ) ([Table S1](#)). Overall, ALP decreased from baseline in the majority of patients at Week 52 ([Fig. 2C](#)). ALP normalization was observed in 31% of patients in the 10 mg cohort as early as Week 12 and was maintained at 33% through Week 52 ([Fig. 2D](#)). In contrast, in the 2 mg and 5 mg cohorts, normalization occurred

in 0% and 11% of patients, respectively, at Week 12 and in 9% and 13%, respectively, at Week 52. Similar results were observed for the ITT population (data not shown).

*Composite and published criteria response rates*

At Weeks 12 and 52, the composite biochemical response endpoint was achieved by 46% and 64% of patients, respectively, in the 2 mg cohort; 49% and 53%, respectively, in the 5 mg cohort; and 67% in the 10 mg cohort at both time points (Fig. 2E). Responder rates for published PBC response criteria, including the Barcelona, Paris, and Toronto criteria (59 to 79% for 10 mg), were consistent with rates for the composite endpoint (Table S2). Additionally, Global PBC Study Group (GLOBE) and United Kingdom–Primary Biliary Cirrhosis (UK-PBC) 5-, 10-, and 15-year risk scores decreased from baseline in a dose-dependent manner at Weeks 12 and 52 (Table S3). The main efficacy outcomes for the initial treatment cohorts are summarized in Table S4.

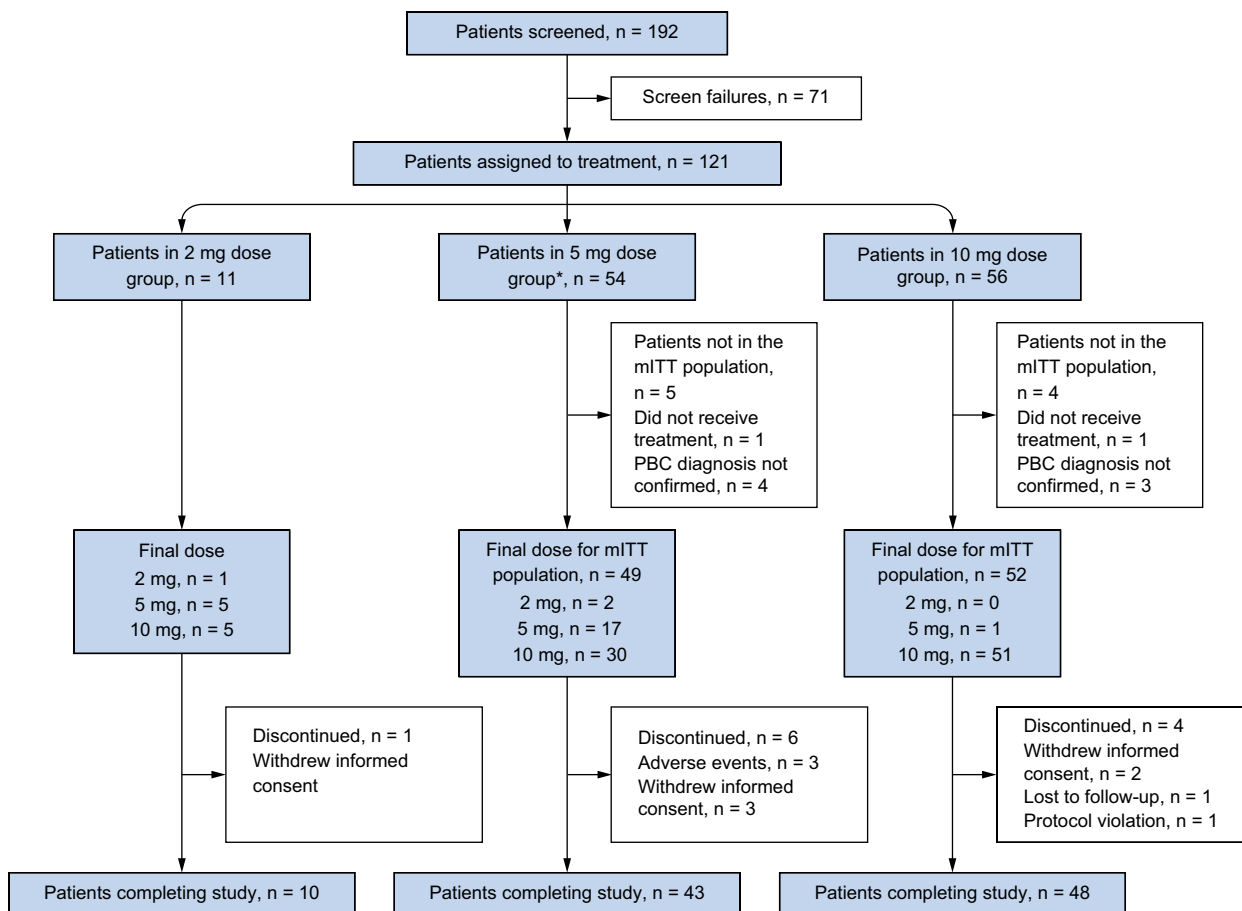
The effects of seladelpar among patients randomized to 5 mg QD who remained at this dose (5/5 mg cohort) and those who uptitrated to 10 mg QD after Week 12 (5/10 mg cohort) are summarized in Table S5. Mean absolute and relative reductions from baseline in ALP were observed in both cohorts at Weeks 12 and 52 and were significant in both cohorts at both time points (all  $p \leq 0.04$ ), except for the 5/5 mg cohort at Week 12. The

proportions of patients achieving ALP normalization or the composite endpoint were greater in the 5/5 mg cohort (i.e., in patients with an early sustained response not requiring uptitration). In contrast, patients in the 5/10 mg cohort had higher baseline ALP and smaller absolute and relative changes in ALP, which resulted in lower normalization and composite response rates.

*Bilirubin, ALT, GGT, AST, and 5'-nucleotidase*

Mean changes from baseline in biochemical parameters are summarized in Table S1. Mean total and direct bilirubin levels remained stable through Week 52 in all cohorts (Fig. 3A–D). Mean reductions in ALT from baseline differed according to dose at Week 12 (6 U/L [11%], 11 U/L [17%], and 11 U/L [22%], respectively) but coalesced to similar values at Week 52 (14 to 17 U/L [25% to 31%]) (Fig. 4A–B). Similarly, at Week 12, decreases from baseline in GGT were 44 U/L (20%), 75 U/L (29%), and 81 U/L (34%) in the 2 mg, 5 mg, and 10 mg cohorts, respectively. Decreases ranged from 79 to 91 U/L (32% to 34%) at Week 52 (Fig. 4C–D).

Small decreases from baseline in mean AST levels (3 U/L [9%] at Week 12 and 6 U/L [14%] at Week 52) were observed in the 10 mg cohort (Fig. S3A–B). Mean AST levels were slightly decreased from baseline in the 2 mg and 5 mg cohorts at Week



**Fig. 1. Patient disposition.** \*Per investigator decision, at some point after Week 12, 36 patients randomized to 5 mg uptitrated to 10 mg (5/10 mg cohort) and 17 patients remained at 5 mg (5/5 mg cohort).

**Table 1. Baseline demographics and characteristics (safety population).**

	Seladelpar			
	2 mg (n = 11)	5 mg (n = 53)	10 mg (n = 55)	Total (n = 119)
Sex, female, n (%)	11 (100.0)	51 (96.2)	50 (90.9)	112 (94.1)
Race, White, n (%)	10 (90.9)	50 (94.3)	49 (89.1)	109 (91.6)
Age (years)	55.2 (9.6)	57.5 (8.1)	57.4 (9.7)	57.2 (9.0)
BMI (kg/m <sup>2</sup> )	29.4 (7.3)	26.6 (5.7)	27.7 (5.3)	27.4 (5.7)
Duration of PBC (years)	9.3 (6.9)	10.0 (7.0)	9.4 (6.2)	9.7 (6.6)
Cirrhosis, n (%)	0	14 (26.4)	11 (20.0)	25 (21.0)
History of pruritus, n (%)	7 (63.6)	38 (71.7)	39 (70.9)	84 (70.6)
ALP (U/L)	300.4 (121.4)	345.4 (188.0)	295.3 (136.0)	318.1 (160.9)
ALT (U/L)	54.1 (24.6)	46.2 (26.1)	45.8 (22.7)	46.7 (24.3)
AST (U/L)	45.0 (19.3)	43.2 (20.3)	43.6 (18.7)	43.5 (19.3)
GGT (U/L)	254.5 (143.3)	234.9 (149.4)	234.3 (192.9)	236.4 (169.2)
INR	1.1 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)
Total bilirubin (mg/dl) <sup>a</sup>	0.6 (0.1)	0.8 (0.4)	0.8 (0.3)	0.8 (0.3)
Albumin (g/L)	0.4 (0.02)	0.4 (0.04)	0.4 (0.04)	0.4 (0.03)
Platelets (×10 <sup>3</sup> /μl)	242.4 (84.2)	214.9 (88.5)	243.5 (74.1)	230.7 (82.3)
UDCA intolerant, n (%)	0	5 (9.4)	3 (5.5)	8 (6.7)
Concomitant UDCA, n (%)	11 (100)	48 (90.6)	52 (94.5)	111 (93.2)
UDCA dose (mg/kg/day), n	11	48	51	110
Mean (SD)	13.6 (4.0)	15.1 (3.2)	15.1 (4.9)	15.0 (4.1)
Previous treatment with OCA, n (%)	0	8 (15.1)	7 (12.7)	15 (12.6)
Pruritus VAS score, n	11	52	55	118
Mean (SD)	15 (18)	24 (23)	31 (29)	26 (26)
MELD score <sup>b</sup> , n	11	49	52	NC
Mean (SD)	7.3 (1.3)	6.9 (1.2)	6.9 (1.1)	NC
Rotterdam <sup>c</sup>				
Early	11 (100.0)	43 (81.1)	42 (76.4)	96 (80.7)
Moderately advanced	0	10 (18.9)	11 (20.0)	21 (17.6)
Advanced	0	0	2 (3.6)	2 (1.7)

Values are mean (SD) unless otherwise noted.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; INR, international normalized ratio; MELD, model for end-stage liver disease; mITT, modified intent-to-treat; NC, not calculated; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; VAS, visual analog scale.

<sup>a</sup>Multiply by 17.1 to convert to SI units (μmol/L).

<sup>b</sup>MELD score was calculated using the mITT population.

<sup>c</sup>Rotterdam score categories were early (normal total bilirubin and normal albumin), moderately advanced (abnormal albumin OR abnormal total bilirubin), and advanced (abnormal albumin AND abnormal total bilirubin).

12 (3 U/L [4%] and 1 U/L [3%], respectively), with greater decreases from baseline observed at Week 52 in both cohorts (7 U/L [16%] and 6 U/L [13%], respectively). In all cohorts, 5'-nucleotidase levels decreased 23% to 30% from baseline at Weeks 12 and 52 (Fig. S3C–D).

### Lipids

Mean changes from baseline in lipids are summarized in Table S2. High-density lipoprotein cholesterol levels were maintained or increased through Week 52, while overall other lipids were modestly decreased from baseline in all cohorts (Fig. S4A–H). Mean triglyceride levels were decreased by 11 to 23 mg/dl (0.12 to 0.26 mmol/L; 13% to 14%) in all cohorts at Week 12 and by 18 to 25 mg/dl (0.20 to 0.28 mmol/L; 14% to 19%) at Week 52 (Fig. S4A–B). Mean low-density lipoprotein cholesterol levels were also decreased from baseline in the 2 mg, 5 mg, and 10 mg cohorts at Week 12 (3 mg/dl [0.08 mmol/L; 1%], 15 mg/dl [0.39 mmol/L; 9%], and 13 mg/dl [0.34 mmol/L; 8%], respectively) and Week 52 (10 mg/dl [0.26 mmol/L; 6%], 16 mg/dl [0.41 mmol/L; 10%] and 27 mg/dl [0.70 mmol/L; 17%], respectively) (Fig. S4C–D).

### C4 and FGF19

At Week 12, median levels of the bile acid precursor, C4, were decreased from baseline by 4.5 ng/ml in the 5 mg cohort, and 7.2 ng/ml in the 10 mg cohorts, and increased by 2.5 ng/ml in the

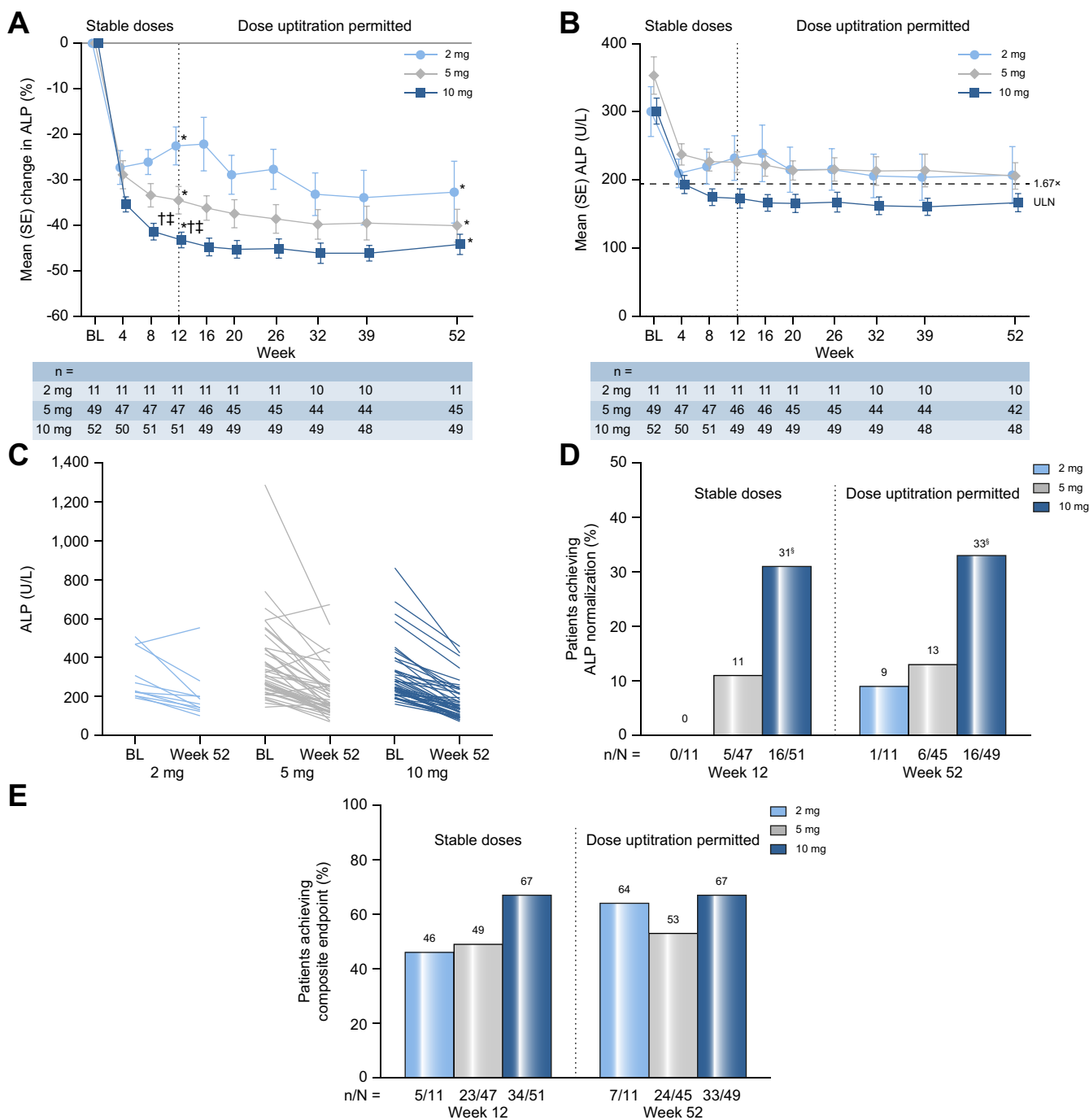
2 mg cohort (Fig. 5A). At Week 52, median levels of FGF19 were decreased from baseline by 17%, 6%, and 15% in the 2 mg, 5 mg, and 10 mg cohorts, respectively (Fig. 5B).

### Pruritus VAS score

Mean pruritus VAS scores were decreased from baseline in all cohorts at Week 12: by 4 mm in the 2 mg cohort, 6 mm in the 5 mg cohort, and 12 mm in the 10 mg cohort (Fig. 6). At Week 52, mean VAS scores decreased further from baseline by 10 mm in the 5 mg cohort and 17 mm in the 10 mg cohort, but the initial decrease (3 mm) in the 2 mg cohort remained stable.

### Safety

Overall, 105 (88.2%) of the 119 patients treated with seladelpar had TEAEs, with similar incidences across cohorts (Table 2). The overall incidences of treatment-related TEAEs, Grade ≥3 TEAEs, and serious TEAEs (SAEs) were 35.3%, 11.8%, and 11.8%, respectively. These incidences were also similar across cohorts. The most common (≥10%) TEAEs were pruritus (24.4%), diarrhea (16.8%), nausea (16.0%), fatigue (15.1%), urinary tract infection (14.3%), abdominal pain upper (13.4%), nasopharyngitis (12.6%), arthralgia (11.8%), and vomiting (10.1%). Among the 29 patients who experienced pruritus, 18 had a history of pruritus. No patient experienced treatment-related SAEs, and no deaths or clinically meaningful changes in vital signs were reported during the study.

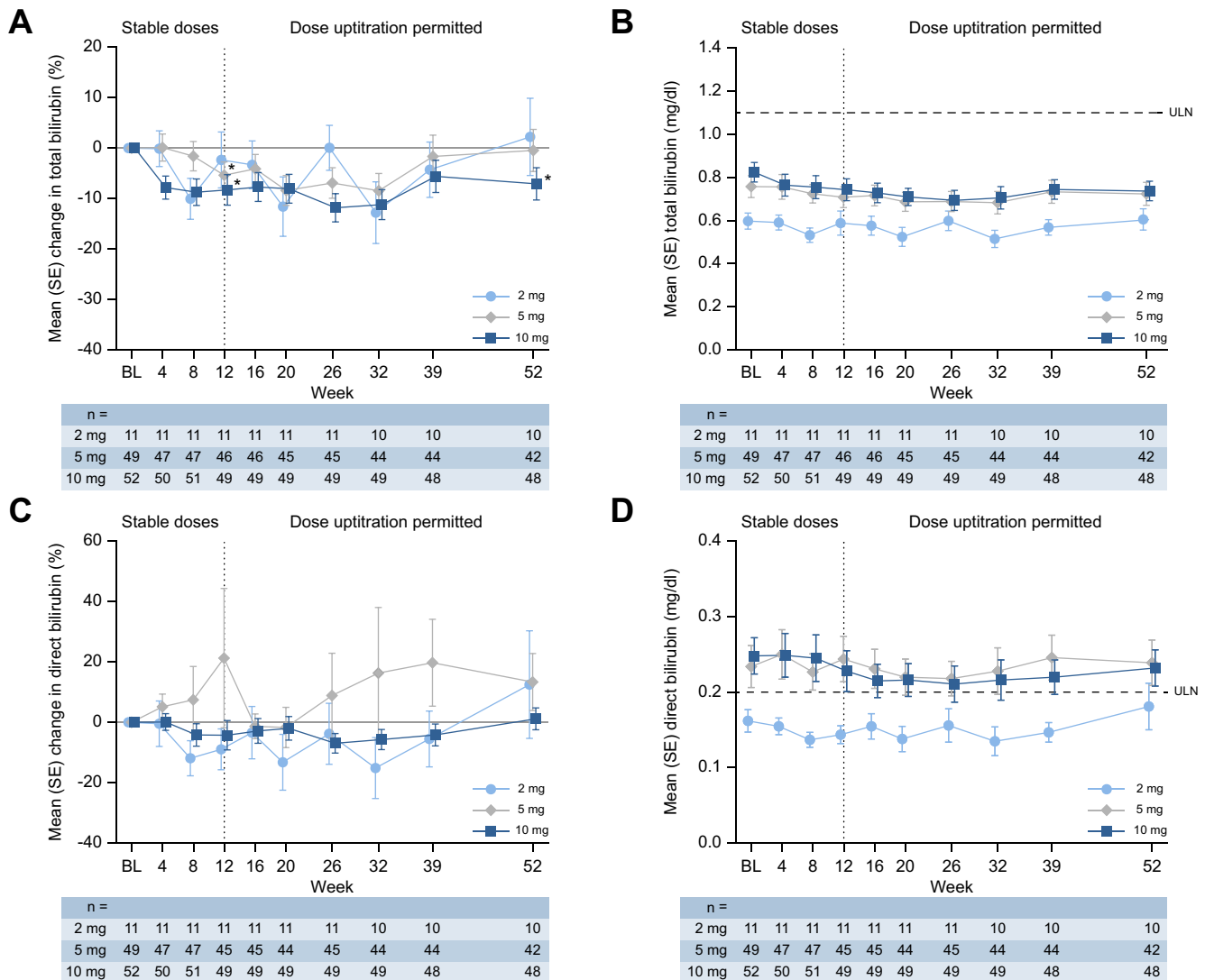


**Fig. 2. Effect of seladelpar on ALP and the composite endpoint through Week 52.** (A) Mean percent change in ALP from BL (imputed using LOCF). (B) Mean absolute ALP values (observed). (C) Change in ALP from BL in individual patients (observed). (D) Proportion of patients achieving ALP normalization (imputed using LOCF). (E) Proportion of patients achieving the composite endpoint (imputed using LOCF). \* $p \leq 0.02$  vs. BL (paired  $t$  test); <sup>†</sup> $p \leq 0.01$  vs. 2 mg cohort (ANCOVA test of LS means); <sup>‡</sup> $p \leq 0.02$  vs. 5 mg cohort (ANCOVA test of LS means); <sup>§</sup> $p \leq 0.03$  vs. 5 mg cohort (Fisher's exact test). ALP, alkaline phosphatase; ANCOVA, analysis of covariance; BL, baseline; LOCF, last observation carried forward; LS, least squares; ULN, upper limit of normal.

Four patients (3 in the 5 mg cohort and 1 in the 10 mg cohort) discontinued seladelpar due to TEAEs. The TEAEs leading to study drug discontinuation were gastroesophageal reflux (Grade 1, adjudicated as possibly related to seladelpar), pruritus (Grade 1, adjudicated as related to underlying PBC and unrelated to seladelpar), pneumonia (Grade 3, adjudicated as unrelated to seladelpar), and increases in ALT and AST levels (Grades 2 and 3,

respectively, concomitant with rifampicin use and adjudicated as possibly related to either seladelpar or rifampicin).

Transient increases in bilirubin unrelated to seladelpar were noted in 2 patients, 1 patient had increased ALT concomitant with worsening of rheumatoid arthritis and use of ibuprofen, and 2 patients experienced ALT and AST elevations concomitant with rifampicin administration for pruritus. Of these latter patients



**Fig. 3. Effect of seladelpar on total and direct bilirubin through Week 52.** (A) Mean percent change in total bilirubin from BL (observed). (B) Mean absolute total bilirubin values (observed). (C) Mean percent change in direct bilirubin from BL (observed). (D) Mean absolute direct bilirubin values (observed). \*Nominal  $p < 0.02$  vs. BL (paired  $t$  test). BL, baseline; ULN, upper limit of normal.

with ALT/AST elevations, both were cirrhotic at baseline, one discontinued the study due to Grade 1 ALT and Grade 2 AST elevations after 23 weeks of treatment, and the other completed the study after aminotransferase elevations (Grade 2) resolved. There were 4 patients who experienced creatinine kinase  $>2.5 \times \text{ULN}$ , but all had a clinical explanation (see supplementary safety) and/or return to within normal limits while on study drug. Four patients had transient increases in amylase or lipase that were not considered clinically significant. No patients had concerning changes in serum creatinine or other renal markers.

### Efficacy and safety in patients with cirrhosis

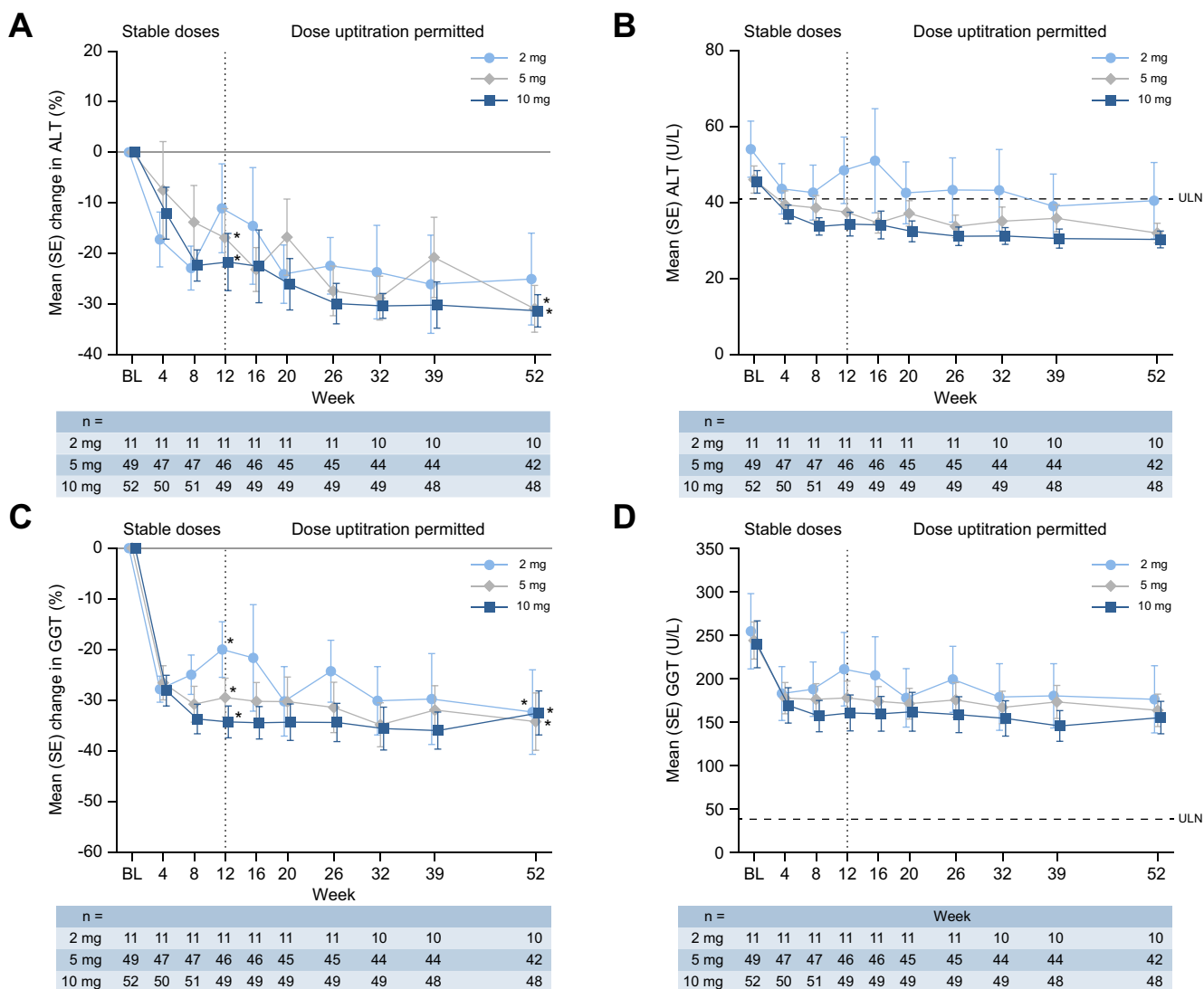
In a prespecified subgroup analysis of patients with and without clinically documented cirrhosis at baseline, reductions in ALP, total bilirubin, and ALT were generally similar between groups at Weeks 12 and 52 (Table S6). In the 10 mg cohort, at Week 52, ALP was reduced by 48.5% in patients with ( $n = 9$ ) and 43.2% in patients without cirrhosis ( $n = 40$ ). The reduction in ALP was

smaller in patients with cirrhosis in the 5 mg cohort ( $n = 13$ ) at both time points, although mean baseline ALP was also lower in this subgroup. Safety results were similar in patients with and without cirrhosis (Table S7).

### Discussion

This study demonstrates the significant anticholestatic effects of seladelpar in patients with PBC who had suboptimally responded to UDCA or were UDCA intolerant. Evidence of seladelpar's dose-dependent efficacy, safety, and improvement in patient-reported pruritus was substantial and durable. Biochemical improvement and safety were generally similar in patients with and without cirrhosis. Significant reductions in mean ALP levels were observed in all cohorts as early as 3 months, with a 43% reduction from baseline and normalization of ALP in 31% of patients in the 10 mg cohort. ALP reductions, an evidence-based surrogate for long-term transplant-free outcomes,<sup>9-11</sup> were maintained through 1 year in patients in the 10 mg cohort. In the 2 mg and





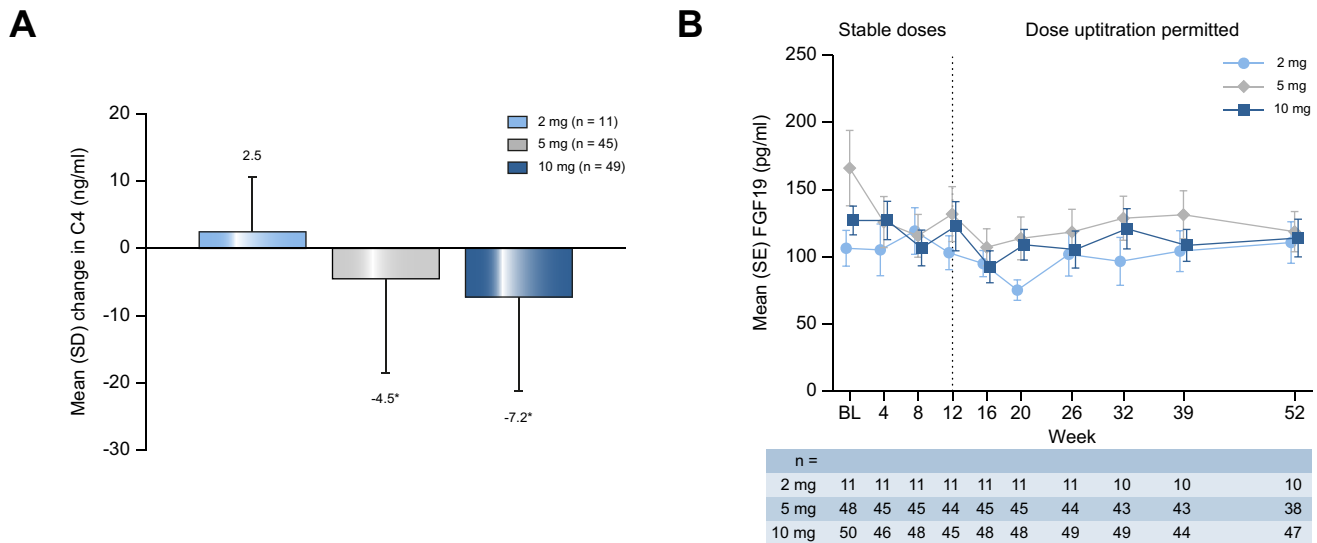
**Fig. 4. Effect of seladelpar on ALT and GGT through Week 52.** (A) Mean percent change in ALT from BL (observed). (B) Mean absolute ALT values (observed). (C) Mean percent change in GGT from BL (observed). (D) Mean absolute GGT values (observed). \*Nominal  $p < 0.05$  vs. BL (paired  $t$  test). ALT, alanine aminotransferase; BL, baseline; GGT, gamma-glutamyl transferase; ULN, upper limit of normal.

5 mg cohorts, greater reductions in ALP levels from baseline and greater rates of ALP normalization were observed at Week 52 after uptitration of dose. The clinically significant and durable effects of the seladelpar 10 mg dose on ALP levels, the composite biochemical response endpoint, and ALP normalization strongly suggest that this dose is optimal for the majority of patients with PBC who have not adequately responded to UDCA or are UDCA intolerant.

The high response rate (53% to 67% at Week 52) observed in this study, based on the composite biochemical endpoint and confirmed by similarity with response rates of published PBC response criteria, and decreased GLOBE and UK-PBC scores suggest that seladelpar lowers the risk for PBC disease progression. The early sustained reductions of other independent biomarkers of cholestasis, including GGT and 5'-nucleotidase, further corroborate the anticholestatic activity of seladelpar.

The reductions in liver biochemical tests, including ALT, AST, and GGT levels suggest that seladelpar effectively improves markers of liver injury. Furthermore, although mean baseline cholesterol levels were modestly elevated in this patient population and about one-third of patients were receiving lipid-lowering medications, seladelpar favorably improved triglyceride and cholesterol levels.

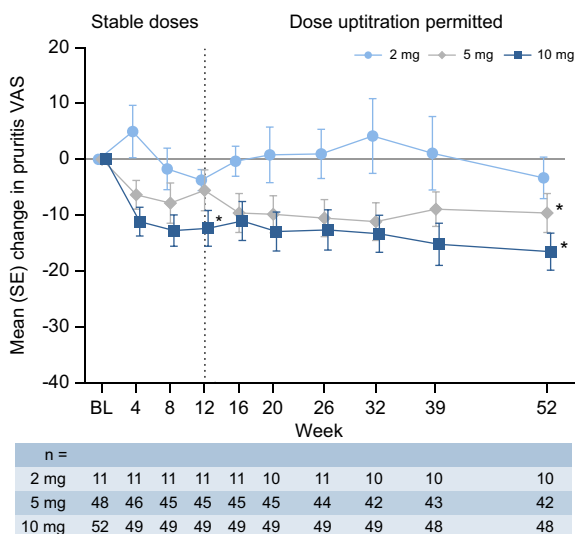
Synthesis of the bile acid precursor, C4, was dose-dependently reduced from baseline, indicating that seladelpar may protect against cholestatic liver injury by reducing production of bile acids through downregulation of bile acid synthesis.<sup>21</sup> In addition, median reductions from baseline in FGF19 levels of approximately 10% were observed in all cohorts through Week 52. Since FGF19 transcription is activated in response to bile acid binding to FXR, these results indicate that seladelpar's effect on bile acid synthesis is distinct from those of FXR agonists like OCA.<sup>13</sup>



**Fig. 5. Effect of seladelpar on observed serum levels of C4 and FGF19.** (A) Mean percent change in C4 at Week 12. (B) Mean FGF19 values through Week 52. \*Nominal  $p < 0.04$  vs. BL (paired  $t$  test). BL baseline; C4, 7 $\alpha$ -hydroxy-4-cholesten-3-one; FGF19, fibroblast growth factor 19.

Seladelpar was safe and well tolerated at doses up to 10 mg QD, and the safety profile was similar among treatment cohorts. There were no deaths during the study, and no other serious safety signal was identified for seladelpar at doses up to 10 mg QD. Reversible elevations in aminotransferases were observed in 2 patients, although both patients were cirrhotic at baseline and one was able to continue the study without further issue. Pruritus is among the most common symptoms of PBC and significantly reduces quality of life.<sup>25</sup> As expected, pruritus was the most commonly reported TEAE in this open-label study (24.4% of patients). However, investigators concluded that pruritus was possibly related or related to seladelpar in only 8.4% of patients. Importantly, 18 of the 29 patients who reported pruritus had a

history of pruritus, and seladelpar improved pruritus VAS score at Week 52. In analyses reported elsewhere, 58% and 93% of patients in the 5 mg and 10 mg cohorts, respectively, with moderate-to-severe pruritus (VAS  $\geq 40$ ) at baseline had a  $\geq 20$ -point decrease in pruritus VAS at 1 year.<sup>26</sup> Similar improvements in pruritus, sleep disturbance, and quality of life assessed using 5-D itch and PBC-40 questionnaires were observed in patients treated with seladelpar for 1 year.<sup>26</sup> Overall, these results indicate that seladelpar does not induce pruritus. In contrast, OCA, a currently approved second-line PBC treatment, induces itching in a dose-related manner.<sup>13,27</sup> Thus, the improvement in pruritus with seladelpar observed in this study appears to be advantageous for patients with PBC.



**Fig. 6. Effect of seladelpar on pruritus VAS through Week 52.** 0 = no itch, 100 = worst itch imaginable. \*Nominal  $p \leq 0.009$  vs. BL (paired  $t$  test). BL, baseline; VAS, visual analog score.

This study has several limitations that should be kept in mind when interpreting results. First, there was an imbalance in baseline ALP levels among cohorts; however, ALP reductions were compared with baseline, and several biochemical endpoints were evaluated. Second, the criteria for dose uptitration were not standardized, except that uptitration could only be done at or after Week 12. As no patients uptitrated their dose before Week 12, this does not affect comparisons among treatment cohorts at this time point; however, after Week 12, comparisons among treatment cohorts cannot be made. Third, this was not a placebo-controlled study. However, prior placebo-controlled studies in similar patient populations have reported small (<10%) ALP decreases in placebo-treated patients.<sup>13,28</sup> Finally, multiplicity adjustments were not made for efficacy endpoints. Nominal  $p$  values were provided for descriptive purposes.

In conclusion, among patients with PBC with suboptimal responses to UDCA or UDCA intolerance who have a heightened risk of disease progression, seladelpar demonstrated clinically significant dose-dependent biochemical efficacy, absence of concerning safety signals, and evidence that it might also improve pruritus. A pivotal phase III randomized, placebo-controlled clinical trial is ongoing (NCT04620733).

**Table 2. Summary of treatment-emergent adverse events.**

	Seladelpar			
	2 mg (n = 11)	5 mg (n = 53)	10 mg (n = 55)	Total (n = 119)
Any TEAE	11 (100.0)	47 (88.7)	47 (85.5)	105 (88.2)
Any treatment-related TEAE	6 (54.5)	21 (39.6)	15 (27.3)	42 (35.3)
Any Grade $\geq 3$ TEAE	1 (9.1)	8 (15.1)	5 (9.1)	14 (11.8)
Any serious TEAE	1 (9)	8 (15.1)	5 (9.1)	14 (11.8)
Deaths	0	0	0	0
TEAEs occurring in $\geq 10\%$ of patients in any treatment cohort				
Pruritus	6 (54.5)	11 (20.8)	12 (21.8)	29 (24.4)
Diarrhea	4 (36.4)	7 (13.2)	9 (16.4)	20 (16.8)
Nausea	4 (36.4)	9 (17.0)	6 (10.9)	19 (16.0)
Fatigue	3 (27.3)	9 (17.0)	6 (10.9)	18 (15.1)
Urinary tract infection	1 (9.1)	8 (15.1)	8 (14.5)	17 (14.3)
Abdominal pain upper	3 (27.3)	8 (15.1)	5 (9.1)	16 (13.4)
Nasopharyngitis	4 (36.4)	5 (9.4)	6 (10.9)	15 (12.6)
Arthralgia	1 (9.1)	6 (11.3)	7 (12.7)	14 (11.8)
Vomiting	3 (27.3)	4 (7.5)	5 (9.1)	12 (10.1)
Back pain	3 (27.3)	5 (9.4)	3 (5.5)	11 (9.2)
Headache	2 (18.2)	6 (11.3)	3 (5.5)	11 (9.2)
Abdominal distension	2 (18.2)	4 (7.5)	4 (7.3)	10 (8.4)
Dizziness	2 (18.2)	5 (9.4)	3 (5.5)	10 (8.4)
Abdominal pain	3 (27.3)	3 (5.7)	3 (5.5)	9 (7.6)
Cough	2 (18.2)	4 (7.5)	3 (5.5)	9 (7.6)
Dry mouth	2 (18.2)	2 (3.8)	4 (7.3)	8 (6.7)
Oropharyngeal pain	2 (18.2)	1 (1.9)	4 (7.3)	7 (5.9)
Dry eye	2 (18.2)	1 (1.9)	4 (7.3)	7 (5.9)
Dyspepsia	3 (27.3)	2 (3.8)	1 (1.8)	6 (5.0)

All values are n (%).

Adverse events were coded using MedDRA® version 22.0. Patients were included only once, even if they experienced multiple occurrences.

TEAE, treatment-emergent adverse event.

### Abbreviations

ALP, alkaline phosphatase; ALT, alanine aminotransferase, AST, aspartate aminotransferase; C4, 7 $\alpha$ -hydroxy-4-cholesten-3-one; FGF19, fibroblast growth factor 19; FXR, farnesoid X receptor; GGT, gamma-glutamyl transferase; GLOBE, Global PBC Study Group; ITT, intent-to-treat; LS, least squares; mITT, modified intent-to-treat; OCA, obeticholic acid; LOCF, last observation carried forward; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; QD, once daily; SAE, serious treatment-emergent adverse event; TEAE, treatment-emergent adverse events; UDCA, ursodeoxycholic acid; UK-PBC, United Kingdom–Primary Biliary Cirrhosis; ULN, upper limit of normal; VAS, visual analog scale.

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### Conflict of interest

Christopher Bowlus has received grants from Arena Pharmaceuticals, Cara Therapeutics, Genfit, Genkyotex, and Novartis and grants and personal fees from CymaBay Therapeutics, Eli Lilly, Gilead, GlaxoSmithKline, and Intercept. Michael Galambos has received consulting and investigator fees from CymaBay Therapeutics. Richard Aspinall owns stock in CymaBay Therapeutics. Gideon M. Hirschfeld has received personal fees from CymaBay Therapeutics, Genfit, GlaxoSmithKline, HighTide, Intercept Pharma, Mirum, and Pliant. David E. Jones has received personal fees from Abbott and Falk and personal fees and a grant from Intercept. Stuart C. Gordon

has received personal fees and advisory board compensation from CymaBay Therapeutics and research support was paid to his institution by AbbVie, Brigham and Women's Hospital, CymaBay Therapeutics, DURECT, Eiger, Genfit, Gilead, GlaxoSmithKline, Intercept, Merck, Pliant, Shire, and Viking. Stephen A. Harrison has received personal fees from AgonAB, Altimmune, Boston Pharmaceuticals, B Riley FBR, Canfite Biopharma, Echosens North America, Fibronostics, Foresite Labs, Fortress Biotech, GNS Healthcare, Histoindex Pte, Inipharm, Ionis, Kowa Research Institute, Medpace, Microba Pty, Nutrasource, Piper Sandler & Co, Prometic Pharma Smt, Ridgeline Therapeutics, Sonic Incytes Medical Corporation, and Terns; grants from Cirius Therapeutics, Galmed Research & Development, Hepion Pharmaceuticals, and Pathai; personal fees and grants from Akeru Therapeutics, Axcella Health, Civi Biopharma, CymaBay Therapeutics, Enyo Pharma S.A., Galectin Therapeutics, Genfit, Gilead Sciences, High Tide, Intercept, Madrigal Pharmaceuticals, Metacrine, NGM Biopharmaceuticals, Northsea Therapeutics B.V., Novartis, Novo Nordisk, Poxel, Sagimet Biosciences, and Viking Therapeutics; advisory board compensation from 89Bio, Akeru Therapeutics, Altimmune, Arrowhead Pharmaceuticals, Axcella Health, Civi Biopharma, CymaBay Therapeutics, Echosens North America, Foresite Labs, Galectin Therapeutics, Galmed Research & Development, Genfit, Gilead, Hepion Pharmaceuticals, High Tide, Histoindex Pte, Indalo Therapeutics, Intercept, Madrigal Pharmaceuticals, Medpace, Metacrine, NGM Biopharmaceuticals, Northsea Therapeutics, Novartis, Novo Nordisk, Poxel, Prometic Pharma Smt, Ridgeline Therapeutics, Sagimet Biosciences, Terns, and Theratechnologies; and owns stock in Akeru Therapeutics, Cirius Therapeutics, Galectin Therapeutics, Genfit, Hepion Pharmaceuticals, Histoindex Pte, Metacrine, NGM Biopharmaceuticals, Northsea Therapeutics B.V., and Pathai. Andreas E. Kremer has received personal fees from AbbVie, Bayer,

CymaBay Therapeutics, Eisai, Eli Lilly, Escent, Falk, FMC, Gilead, GlaxoSmithKline, Mirum, MSD, Myr, Newbridge, Novartis, and Zambon and personal fees and a grant from Intercept. Marlyn J. Mayo has received consulting and investigator fees from CymaBay Therapeutics. Paul J. Thuluvath has received a grant from CymaBay Therapeutics. Cynthia Levy has received grants from Genkyotex, Gilead, High Tide, Intercept, Novartis, and Zydus and grants and personal fees from Cara Therapeutics, CymaBay Therapeutics, Genfit, and GlaxoSmithKline. Mark Swain has received grants from CymaBay Therapeutics and Genfit and a grant and personal fees from Intercept. Yvonne Dörffel, Guy Neff, David Sheridan, Carmen Stanca, Christoph Berg, and Aparna Goel have nothing to disclose. Mitchell L. Shiffman has received grants from CymaBay Therapeutics, High Tide, and Genfit and grants and personal fees from Intercept. John M. Vierling has received grants from Gilead, GlaxoSmithKline, and Intercept; personal fees from Intercept and Novartis; and personal fees and grants from CymaBay Therapeutics. Pol Boudes is a former employee of CymaBay Therapeutics who owns stock in CymaBay Therapeutics and holds a patent broadly relevant to this work. Alexandra Steinberg is a former employee of CymaBay Therapeutics who owns stock in CymaBay Therapeutics. Yun-Jung Choi is an employee of and owns stock in CymaBay Therapeutics. Charles McWherter is an employee of and owns stock in CymaBay Therapeutics and holds patents broadly relevant to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

### Authors' contributions

Study concept and design: PB, AS, Y-JC, CM. Acquisition, analysis, or interpretation of data: CB, MG, RA, GMH, DEJ, YD, SCG, SAH, AEK, MJM, PJT, CL, MS, GN, DS, CS, CB, AG, MLS, JMV, PB, AS, Y-JC, CM. Drafting of the manuscript: AS, Y-JC, CM, CB, GH, CL. Critical revision of the manuscript for important intellectual content: CB, MG, RA, GMH, DEJ, YD, SCG, SAH, AEK, MJM, PJT, CL, MS, GN, DS, CS, CB, AG, MLS, JMV, PB, AS, Y-JC, CM. AS, Y-JC, CM, CB, GH, CL had access to all of the data and can vouch for the integrity of the data analyses.

### Data availability statement

Data is available from the Study Sponsor CymaBay Therapeutics. The full trial protocol can be accessed at <https://www.journal-of-hepatology.eu>.

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### Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2022.02.033>.

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Author names in bold designate shared co-first authorship

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