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DOI:
10.1111/apt.17755

Received: 28 July 2023 | First decision: 2 August 2023 | Accepted: 26 September 2023

DOI: 10.1111/apt.17755

AP&T Alimentary Pharmacology & Therapeutics WILEY

Open-label, clinical trial extension: Two-year safety and efficacy results of seladelpar in patients with primary biliary cholangitis

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The Handling Editor for this article was Dr Rohit Loomba, and it was accepted for publication after full peer-review.

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Funding information
CymaBay Therapeutics

Summary

Background: Seladelpar is a potent and selective peroxisome proliferator-activated receptor-δ agonist that targets multiple cell types involved in primary biliary cholangitis (PBC), leading to anti-cholestatic, anti-inflammatory and anti-pruritic effects.

Aims: To evaluate the long-term safety and efficacy of seladelpar in patients with PBC.

Methods: In an open-label, international, long-term extension study, patients with PBC completing seladelpar lead-in studies continued treatment. Seladelpar was taken orally once daily at doses of 5 or 10 mg with dose adjustment permitted for safety or tolerability. The primary analysis was for safety and the secondary efficacy analysis examined biochemical markers of cholestasis and liver injury. The study was terminated early due to the unexpected histological findings in a concurrent study for non-alcoholic steatohepatitis, which were subsequently found to predate treatment. Safety and efficacy data were analysed through 2 years.

Results: There were no serious treatment-related adverse events observed among 106 patients treated with seladelpar for up to 2 years. There were four discontinuations for safety, one possibly related to seladelpar. Among 53 patients who completed 2 years of seladelpar, response rates increased from years 1 to 2 for the composite endpoint (alkaline phosphatase [ALP] <1.67 × ULN, ≥15% decrease in ALP, and total bilirubin ≤ULN) and ALP normalisation from 66% to 79% and from 26% to 42%, respectively. In those with elevated bilirubin at baseline, 43% achieved normalisation at year 2.

Conclusions: Seladelpar was safe, and markedly improved biochemical markers of cholestasis and liver injury in patients with PBC. These effects were maintained or improved throughout the second year. Clinicaltrials.gov: NCT03301506; Clinicaltrialsregister.eu: 2017-003910-16.

1 | INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic, rare cholestatic liver disease characterised by immune and inflammatory destruction of the small intrahepatic bile ducts[1,2] leading to cholestasis, inflammation and fibrosis. The quality of life for patients with PBC is commonly and significantly affected by pruritus, fatigue and deterioration of social, emotional and cognitive aspects of daily life.[3–5] Even with currently available treatments, PBC may progress to cirrhosis and its complications, liver failure requiring transplantation, and death.[3,4,6,7]

Ursodeoxycholic acid (UDCA) is the currently approved first-line treatment for PBC.[8] An insufficient biochemical response to treatment with UDCA, as determined by alkaline phosphatase (ALP) levels, occurs in approximately 30%–40% of patients.[4,9–11] Obeticholic acid (OCA) was conditionally approved in 2016[12,13] as second-line add-on therapy for patients with inadequate response to UDCA, or as monotherapy for those intolerant to UDCA. However, in clinical trials, as well as in real world data reports, OCA add-on treatment results in only about half of the patients achieving an adequate response, and it has been accompanied by dose-dependent worsening or new onset of pruritus in some patients.[6,14–17] Additionally, OCA is contraindicated in patients with compensated cirrhosis with evidence of portal hypertension and in those with decompensated cirrhosis.[18] Fibrates, which are not approved to treat PBC, are sometimes co-administered as therapy with UDCA[3,4,19] but not all patients achieve full biochemical response[17,19–21] and discontinuations from adverse events such as hepatotoxicity and myalgia have been noted.[17,19,22]

In clinical research, as well as in medical practice, serum markers of cholestasis consist of elevated levels of ALP, total bilirubin (TB) and gamma-glutamyltransferase (GGT). These markers are accepted as being characteristic of chronic cholestatic liver disease[3] and are associated with ductopenia and disease progression.[23–29] Levels of ALP and TB, alone or together, can predict liver transplantation or death in patients with PBC, with lower levels of these markers being associated with better transplant-free survival.[25,27,29] Additional treatment options for PBC are needed due to many patients lacking a complete response with or intolerance to current treatments and/or persistent clinical symptoms that impact quality of life.[3,4,9,18,30,31]

Seladelpar is a first-in-class, potent and selective peroxisome proliferator-activated receptor (PPAR)-δ agonist with many effects that impact PBC, including cholestasis, hepatocellular injury,

inflammation, fibrosis and lipid metabolism.[32–38] PPARδ is a nuclear receptor expressed in hepatocytes, cholangiocytes, macrophages and stellate cells. Activation of PPARδ regulates the transcription of genes with impact in pathways important in the pathobiology of PBC.[39,40] In clinical studies in patients with PBC,[32,35,36,41] seladelpar significantly reduced markers of cholestasis (ALP, GGT, 5′-nucleotidase, and TB) and bile acid synthesis (7α-hydroxy-4-cholesten-3-one [C4] and total serum bile acids), decreased markers of liver injury (ALT and aspartate aminotransferase [AST]), and improved patient-reported pruritus.

Here, we report on the safety and efficacy of seladelpar during an extension of two clinical trials in patients with PBC. In both previous trials, an open-label Phase 2 study (NCT02955602),[36] and the Phase 3 ENHANCE study (NCT03602560),[41] seladelpar demonstrated clinically meaningful improvements in biochemical markers of cholestasis and liver injury up to 52 weeks. Both studies also revealed improvements in patient-reported pruritus.[35,41]

The objectives of this current study were to evaluate the long-term safety, tolerability and efficacy of seladelpar at 5 and 10 mg once daily during the long-term extension of treatment. Efficacy endpoints evaluated response on the composite endpoint of ALP and TB, and the normalisation of ALP. Absolute and relative changes in liver biochemistries including ALP, ALT, AST, GGT, TB and low-density lipoprotein cholesterol (LDL-C) were also evaluated.

2 | MATERIALS AND METHODS

2.1 | Patients

Patients with PBC were eligible to enrol in this long-term extension study if they had successfully completed a prior study of seladelpar. The previous studies (open-label Phase 2 or ENHANCE Phase 3) enrolled adults 18–75 years of age diagnosed with PBC in accordance with international guidelines.[3,4] Prior to these studies, patients had received a stable and recommended dose of UDCA (13–15 mg/kg) for the prior 12 months or were intolerant to UDCA. All patients had levels of ALP ≥1.67 × upper limit of normal (ULN), TB ≤2 mg/dL (2 × ULN for ENHANCE) and ALT and AST <3 × ULN. Additional eligibility criteria for these studies have been previously described.[36,41]

Consented patients enrolling directly from one of the two aforementioned studies (drug interruption less than 4 weeks) were only excluded from entry for reasons of safety or tolerability based on parental study laboratory findings or investigator judgement. All but two patients completing the Phase 2 study enrolled in this extension trial, but neither of the two was excluded by the protocol for reasons of safety. Both patients completing ENHANCE enrolled in the study. Patients consenting to participate but having study drug interruption greater than 4 weeks could not be enrolled if they met any of the exclusion criteria. Key exclusion criteria included a treatment emergent adverse event (TEAE) leading to study drug discontinuation in the parental studies, a medical condition other than PBC, that would have precluded full participation in the study or confounded its results (e.g. cancer), evidence of advanced PBC as defined by the Rotterdam criteria (albumin <1 × lower limit of normal [LLN] and TB >1 × ULN), or had other chronic liver diseases. Additional exclusion criteria include AST or ALT >3 × ULN, TB >2 × ULN, creatinine kinase >2.5 × ULN, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (calculated by Modification of Diet in Renal Disease [MDRD] formula) or a model for end-stage liver disease (MELD) score ≥15. Patients were also excluded if they used colchicine, methotrexate, azathioprine or long-term use of systemic steroids (>2 weeks) within 2 months prior to screening or current use of fibrates or OCA.

2.2 | Study design

This was an open-label, partially randomised, uncontrolled, international, multicentre and long-term extension study in patients with PBC. A placebo group was not included and patient responses were compared to their baseline values in the parental studies. The study was conducted at 31 clinical sites in the United States, Canada, Germany and the United Kingdom. The first subject began treatment on 11 December, 2017 and the last subject completed the study on 11 February, 2020. The study was approved by independent ethics committees and conformed to all local requirements. All patients provided written informed consent. The study was conducted in strict accordance with the principles of the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. Clinical Trial Number: NCT03301506; EudraCT Number: 2017-003910-16.

Patients enrolled after completing one of the lead-in studies and continued to receive the same daily oral dose of seladelpar (2, 5 or 10 mg), most often without dose interruption. No patients taking placebo in ENHANCE completed the 12 months required to enter the long-term extension. During the extension treatment period, the dose could be adjusted for reasons related to safety or efficacy. Increasing the dose up to 10 mg due to an inadequate biochemical response could be made at any time based on investigator judgement for those patients who were taking 2 or 5 mg in their parental study. Seladelpar was administered as an add-on to standard of care UDCA therapy for patients who tolerated UDCA. For patients with UDCA intolerance, seladelpar was administered as a monotherapy. See Figure S1 for the study design.

Clinic visits in the extension period occurred on day 1, month 1 and then at quarterly intervals starting at month 3 until the study was terminated. For clarity in reporting results in this long-term study, treatment duration and clinic visits will reference to the baseline (day 1) visit in the parental study. For example, month 3 in the extension period will be referred to as the month 15 (3 months in this extension study plus 12 months in the lead-in study). Treatment was expected to continue for up to approximately 5 years. However, the study was terminated early as a precautionary measure (at the same time as early termination of the lead-in Phase 3 ENHANCE study) due to unexplained histology findings in a concurrent Phase 2 biopsy study of seladelpar in patients with non-alcoholic steatohepatitis

(NCT03551522). An independent review by a panel of pathologists found that the histological features were present before treatment with seladelpar. The study was placed on hold on 25 November 2019 and formally terminated on 20 December 2019. The long-term extension study was open for over 21 months prior to its termination, which allowed patients to be treated with seladelpar for up to 33 months. Due to early termination and a broad range of treatment durations, safety and efficacy endpoints were amended to month 24 (year 2).

2.3 | Study outcomes and assessments

The primary outcome evaluated in this study was safety and tolerability of seladelpar in patients during the extension period. The safety and tolerability endpoints were assessed by TEAEs as well as biochemistry and haematology laboratory results. The severity of adverse events was graded by investigators using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The secondary outcome of this study was to evaluate the long-term efficacy of seladelpar from baseline in the lead-in study through 12 months in the extension (total 24 months of treatment). Efficacy endpoints were serum biochemical markers to evaluate response on the composite endpoint of ALP and TB, proportion of patients with normalisation of ALP, and the absolute and relative changes in ALP, AST, ALT, GGT, bilirubin (total and direct), triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and LDL-C. The composite biochemical responder endpoint was defined as meeting all three criteria consisting of an ALP level <1.67×ULN, ≥15% decrease from baseline in ALP levels, and TB levels ≤ULN.

Assessments for safety were made for all patients receiving one or more doses throughout their entire participation in the long-term extension period. Efficacy was assessed for those patients entering the long-term extension study at all parental study and long-term extension study visits through 24 months.

2.4 | Statistical analysis

Some of the results reported here are derived from a post-hoc analysis of study data. These results were characterised by descriptive statistics. Descriptive statistics for continuous variables consist of mean, SD, median and range, and include count and proportion for categorical variables. There was no formal sample size justification for the study. Safety analyses were conducted using all patients who received at least one dose of seladelpar (safety set). Efficacy analyses were conducted using the efficacy population set, which includes all patients who received at least one dose of seladelpar at 5 or 10 mg and have at least one post-baseline evaluation on treatment in this long-term study (beginning of year 2) (efficacy set). Baseline values for laboratory parameters were defined as the corresponding baseline value collected for the patient in their parental study. Safety and efficacy were analysed by the initial dose assigned in the parental study for each patient.

The efficacy outcome analyses included the rate for the composite biochemical response for each patient having ALP <1.67×ULN with a ≥15% decrease in ALP and TB ≤ ULN. The rate of normalisation of ALP was defined as proportion of patients who achieved ALP ≤1.0×ULN. Summary statistics of the composite response rate and normalisation of ALP by each treatment group were performed with corresponding exact two-sided 95% confidence interval using the Clopper–Pearson method at each time point. Absolute and relative changes in ALP, ALT, AST, GGT, TB and LDL-C were summarised descriptively. The weighted average daily dose was defined as the sum of (dose in mg×number of days on seladelpar at that dose)/total treatment period in days excluding drug interruption or drug holiday.

3 | RESULTS

3.1 | Patient disposition

A total of 106 patients with PBC who completed either one of the two previous trials of seladelpar enrolled in this long-term extension study; 104 patients were from the open-label Phase 2 study (NCT02955602)[36] and two patients were from the ENHANCE study (NCT03602560).[41] Only two patients had completed the ENHANCE study when it was terminated early along with the long-term study. There were 99 patients enrolled in the long-term study when it was terminated based on the sponsor's decision (Figure 1). Due to the early termination, there was a wide range in the duration of participation during the parental plus long-term extension study with a mean (standard deviation [SD]) duration of 24 (6.5) months and a range of 12–36 months.

An analysis by dose cohorts entering this long-term extension study was selected to allow for continuity of comparisons to parental studies and are described by the dose allocated at the beginning of these studies. At parental study baseline, the number of subjects in each cohort were 2 mg ($n=10$), 5 mg ($n=46$) or 10 mg ($n=50$; Figure 1); there is no placebo cohort because none of the patients randomised to placebo in ENHANCE completed month 12 prior to its termination and so none entered the long-term extension. Dose titrations were allowed after week 12 in the Phase 2 study and at week 26 in ENHANCE. Dose titrations were also allowed during the long-term extension study (Figure S1). Patients ($N=106$) received 2 mg ($N=1$), 5 mg ($N=18$) or 10 mg ($N=87$) of seladelpar at entry to the long-term extension (month 12) and those that completed 2 years ($N=53$) were taking 2 mg ($N=0$), 5 mg ($N=10$) or 10 mg ($N=43$) at month 24 (Figure 1). Details regarding the mean weighted dose and dose adjustments by cohort and month for all patients and patients completing 2 years are summarised in Tables S1 and S2, and Figure S2. Most dose adjustments took place in the Phase 2 study (NCT02955602)[36] with only five patients up-titrating from 5 to 10 mg in the long-term extension (one of five patients was in the 2 mg cohort and had previously uptitrated to 5 mg).

A total of 106 patients received at least one dose of seladelpar in the long-term study and were included in the safety population.

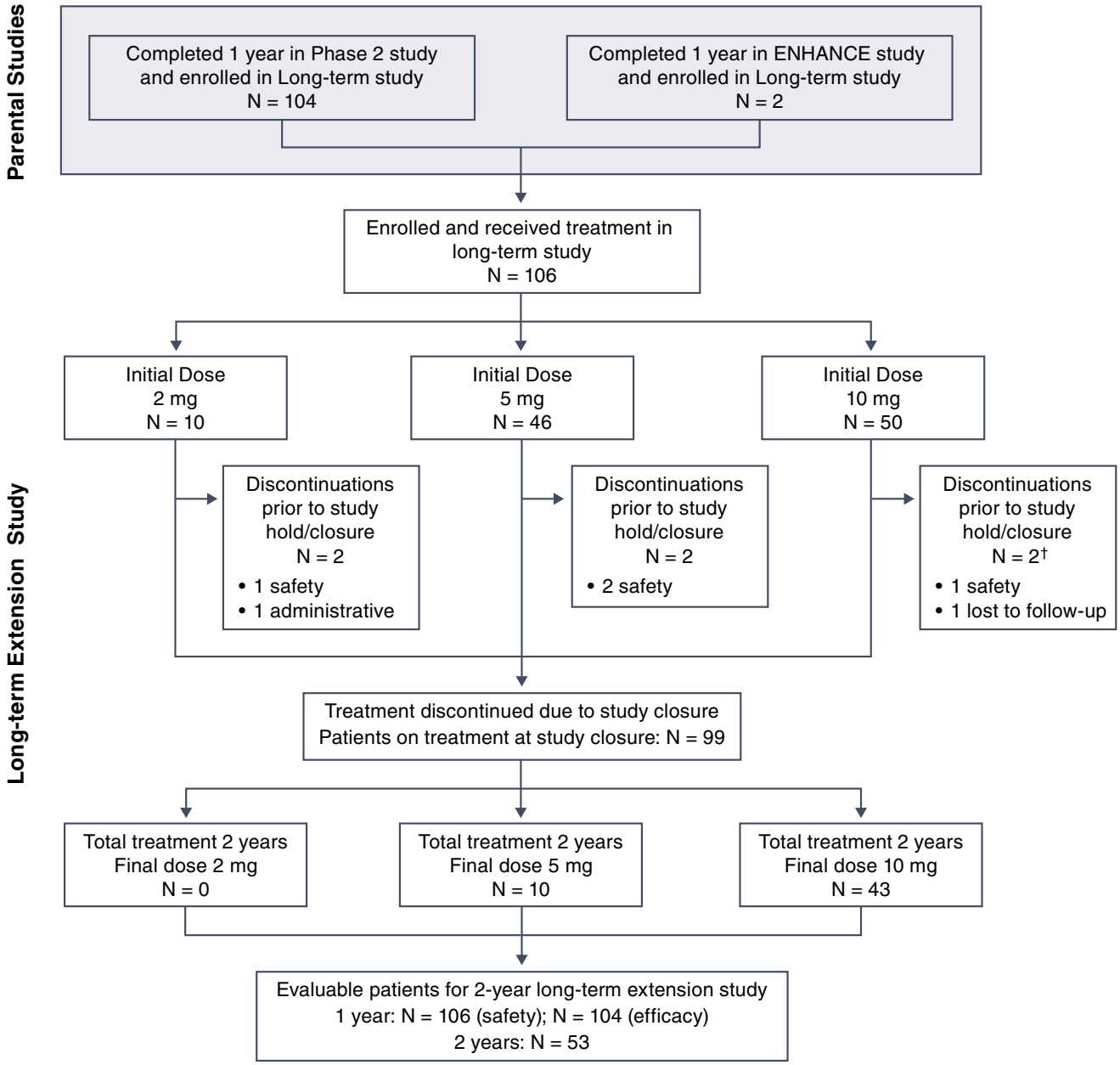


FIGURE 1 Patient disposition. Seladelpar dose was defined as the dose initially assigned during the parental study. Per investigator decision, in these studies (year 1) dose titration was allowed starting at week 12 in the Phase 2 study and week 26 in the ENHANCE study. Dose titrations were also allowed during the long-term extension study (year 2). †One additional discontinuation in the 10 mg cohort for safety occurred after 2 years, but prior to study closure. Additional information on patient discontinuations prior to study closure can be found in the Supporting Information.

Six of these 106 patients discontinued the long-term study prior to study closure. Four patients discontinued the study for safety-related reasons, while two patients discontinued for reasons unrelated to safety (lost to follow-up and investigator's administrative decision) (Figure 1). Discontinuations are summarised for both lead-in studies elsewhere.[36,41] Overall, the number of evaluable patients in the efficacy population was 104 at year 1 and 53 at year 2. The safety and efficacy populations only differ by two patients at baseline and month 12 with one less patient in each of the 5 and 10 mg seladelpar efficacy cohorts. The mean weighted seladelpar dose in the efficacy population was nearly identical to that in the safety population (Table S1).

3.2 | Demographics and baseline disease characteristics

Baseline demographics and disease characteristics for the safety population ($N = 106$) were generally similar among treatment cohorts (Table 1). In the study population, the majority of patients

TABLE 1 Baseline demographics and disease characteristics.

Demographics and characteristics, mean (SD)[a]	Seladelpar			
	2 mg (*N* = 10)	5 mg (*N* = 46)	10 mg (*N* = 50)	Total (*N* = 106)
Sex, female, *n* (%)	10 (100.0)	45 (97.8)	45 (90.0)	100 (94.3)
Race, White, *n* (%)	9 (90.0)	44 (95.7)	46 (92.0)	99 (93.4)
Age (years)	54 (9.6)	58 (8.3)	59 (9.7)	58 (9.1)
BMI (kg/m^2)	29.9 (7.48)	27.0 (5.73)	28.1 (5.40)	27.8 (5.76)
Age at PBC diagnosis (years)	46 (8.7)	47 (8.1)	49 (8.8)	48 (8.5)
Duration of PBC (years)	9 (6.7)	11 (7.2)	10 (6.7)	10 (6.9)
AMA positive, *n* (%)	9 (90.0)	42 (91.3)	43 (86.0)	94 (88.7)
Cirrhosis, *n* (%)	0 (0.0)	10 (21.7)	10 (20.0)	20 (18.9)
History of pruritus, *n* (%)	6 (60.0)	34 (73.9)	35 (70.0)	75 (70.8)
ALP (37–116 U/L)	308.1 (125.13)	353.0 (197.61)	289.9 (128.14)	319.0 (163.29)
ALT (6–41 U/L)	54.9 (25.77)	49.0 (26.45)	46.1 (22.75)	48.2 (24.60)
AST (9–34 U/L)	44.3 (20.16)	45.2 (20.98)	43.2 (17.25)	44.2 (19.06)
GGT (F: 7–38 U/L; M: 11–52 U/L)	254.7 (151.05)	243.8 (143.36)	235.8 (200.70)	241.1 (172.03)
INR (0.8–1.2)	1.1 (0.14)	1.0 (0.09)	1.0 (0.08)	1.0 (0.09)
Total bilirubin (0.1–1.1 mg/dL)	0.6 (0.13)	0.7 (0.36)	0.8 (0.34)	0.8 (0.34)
Direct bilirubin (0.0–0.2 mg/dL)	0.2 (0.05)	0.2 (0.19)	0.2 (0.18)	0.2 (0.18)
Albumin (3.5–5.5 g/dL)	4.1 (0.20)	4.0 (0.34)	4.1 (0.37)	4.1 (0.34)
Platelet count (140–400 × 10^3/μL)	250.2 (84.57)	223.0 (86.24)	246.7 (74.93)	236.9 (80.97)
Triglycerides (50–150 mg/dL)	93.1 (35.48)	114.9 (55.76)	120.6 (57.94)	115.5 (55.38)
Total cholesterol (100–200 mg/dL)	225.1 (29.36)	249.0 (50.47)	241.3 (52.85)	243.1 (50.17)
HDL-C (35–60 mg/dL)	79.8 (26.45)	81.7 (25.79)	74.6 (26.37)	78.2 (26.10)
LDL-C (50–130 mg/dL)	126.6 (23.35)	144.3 (44.05)	142.5 (44.78)	141.8 (42.89)
UDCA intolerant, *n* (%)	0 (0.0)	4 (8.7)	3 (6.0)	7 (6.6)
Concomitant UDCA, *n* (%)	10 (100.0)	43 (93.5)	47 (94.0)	100 (94.3)
UDCA dose (mg/kg/day)	13 (3.7)	15 (3.1)	15 (4.2)	15 (3.7)
History of OCA/Fibrates, *n* (%)	1 (10.0)	6 (13.0)	7 (14.0)	14 (13.2)
MELD score	7 (1.3)	7 (1.1)	7 (1.1)	7 (1.1)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibodies; AST, aspartate aminotransferase; BMI, body mass index; F, female; GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; INR, international normalised ratio; LDL-C, low-density lipoprotein cholesterol; M, male; MELD, model for end-stage liver disease; OCA, obeticholic acid; PBC, primary biliary cholangitis; SD, standard deviation; UDCA, ursodeoxycholic acid.

[a]Data are expressed as mean (SD) unless otherwise noted. Normal ranges for laboratory values are expressed as (normal range).

were female (94.3%), White (93.4%) and with a mean age of 58 years. A diagnosis of PBC was made at a mean age of 48 years with 88.7% of the patients being AMA positive. The mean duration of PBC was 10 years. A history of pruritus was reported in 70.8% of patients while 18.9% had cirrhosis. Mean baseline laboratory results showed an overall markedly elevated ALP and GGT, slightly elevated ALT and AST and TB and albumin within the normal range. Notably, ALP was greater in the 5 mg cohort (353.0 U/L) when compared to the 2 mg (308.1 U/L) and 10 mg (289.9 U/L) cohorts. Lipid biochemistries showed mean LDL-C results were lower and just within normal limits in the 2 mg cohort (126.6 mg/dL) when compared to the 5 mg (144.3 mg/dL) and 10 mg cohorts (142.5 mg/dL), both of which were elevated. Mean triglyceride levels were within normal limits but lower in the 2 mg cohort (93.1 mg/dL) compared to the 5 mg (114.9 mg/dL) and 10 mg cohorts (120.6 mg/dL). Overall, mean total cholesterol levels were slightly elevated in all cohorts, but lower in the 2 mg cohort (225.1 mg/dL) compared to the 5 mg (249.0 mg/dL) and 10 mg cohort (241.3 mg/dL). Mean HDL-C levels were elevated and generally similar among treatment cohorts. At baseline, 100 (94.3%) of patients received UDCA at dose of 15 mg/kg/day and 13.2% of patients had a history of OCA/fibrate use. Baseline demographics and characteristics were similar in the efficacy population (data not shown).

TABLE 2 Summary of treatment emergent adverse events over 2 years on seladelpar.

	Seladelpar			
	2 mg (*N* = 10)	5 mg (*N* = 46)	10 mg (*N* = 50)	Total (*N* = 106)
Any TEAE	10 (100)	42 (91)	49 (98)	101 (95)
Any treatment-related TEAE	6 (60)	17 (37)	16 (32)	39 (37)
Any Grade ≥3 treatment-related TEAE	0	0	1(2)	1 (1)
Any safety-related discontinuations	1 (10)	2 (4)	1 (2)	4 (4)
Any serious TEAE	1 (10)	9 (20)	11 (22)	21 (20)
Any Grade ≥3 serious treatment-related TEAE	0	0	0	0
Deaths	0	1 (2)	0	1 (1)
TEAEs occurring in ≥10% of patients in total treatment cohort	10(100.0)	42 (91.3)	49 (98.0)	101 (95.3)
Pruritus	5 (50.0)	11 (23.9)	10 (20.0)	26 (24.5)
Nausea	5 (50.0)	9 (19.6)	9 (18.0)	23 (21.7)
Fatigue	3 (30.0)	12 (26.1)	5 (10.0)	20 (18.9)
Arthralgia	1 (10.0)	8 (17.4)	10 (20.0)	19 (17.9)
Diarrhoea	3 (30.0)	6 (13.0)	10 (20.0)	19 (17.9)
Urinary tract infection	2 (20.0)	8 (17.4)	9 (18.0)	19 (17.9)
Nasopharyngitis	4 (40.0)	4 (8.7)	7 (14.0)	15 (14.2)
Vomiting	4 (40.0)	6 (13.0)	4 (8.0)	14 (13.2)
Abdominal pain upper	2 (20.0)	7 (15.2)	4 (8.0)	13 (12.3)
Headache	3 (30.0)	6 (13.0)	4 (8.0)	13 (12.3)
Abdominal pain	3 (30.0)	4 (8.7)	5 (10.0)	12 (11.3)
Back pain	3 (30.0)	4 (8.7)	5 (10.0)	12 (11.3)
Dizziness	1 (10.0)	7 (15.2)	4 (8.0)	12 (11.3)
Gastro-oesophageal reflux disease	1 (10.0)	6 (13.0)	5 (10.0)	12 (11.3)
Upper respiratory tract infection	1 (10.0)	7 (15.2)	4 (8.0)	12 (11.3)

Note: Data are expressed as *N* (%). Adverse events were coded using MedDRA® version 22.0. Patients were counted one time even if they had multiple occurrences. Data presented are for all patients in the safety population during year 1 (parental study) and year 2 (extension study).

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment emergent adverse event.

3.3 | Safety

Overall, 101 patients (95%) had at least 1 TEAE during the 2-year study with similar instances occurring among drug cohorts (Table 2). The most common (≥10%) TEAEs over the 2-year treatment period were pruritus (24.5%), nausea (21.7%), fatigue (18.9%), arthralgia (17.9%), diarrhoea (17.9%), urinary tract infection (17.9%), nasopharyngitis (14.2%), vomiting (13.2%), abdominal pain upper (12.3%), headache (12.3%), abdominal pain (11.3%), back pain (11.3%), dizziness (11.3%), gastro-oesophageal reflux disease (11.3%) and upper respiratory tract infection (11.3%). During the second year, the frequency of TEAE occurrences tended to decrease, with notable decreases in pruritus (22.6%–2.8%), nausea (15.1%–7.5%) and fatigue (12.3%–9.4%) from years 1 to 2, respectively. In the 10 mg cohort, treatment-related TEAEs were reported in 16 patients (32%), of which one subject had a Grade 3 or higher TEAE that was treatment-related during the second year of the study. Treatment-related TEAEs also occurred in the 5 mg (17 [37%]) and 2 mg (6 [60%]) cohorts, but none were Grade 3 or higher (Table S3). Almost half (42%) of the treatment-related TEAEs occurred during the first 2 months receiving seladelpar in the parental studies, with only 12% occurring during the entire 12 months of the long-term extension portion of the study (Figure S3).

During the 2-year study, serious TEAEs were reported in 11 patients (22%) in the seladelpar 10 mg group, in 9 (20%) patients in the seladelpar 5 mg group, and 1 (10%) patient in the 2 mg group, but none were treatment-related (Table 2). There were no serious TEAEs that were liver related. During the second year of the study, four patients discontinued the study prior to study closure due to safety-related reasons. The events leading to discontinuation that were unrelated to seladelpar were an elevated TB level that met the study liver safety monitoring criteria (grade 2, increase

>1.5×baseline value), which was attributed to progression of PBC (severe ductopenia noted on a post-treatment biopsy), a serious adverse event (SAE) related to systemic scleroderma, which was a pre-existing condition, and a malignant neoplasm in which the patient subsequently died 7 months after discontinuation from the study. In a fourth patient, a non-SAE of periodic increases in liver function tests (Grade 2 TB, Grade 2 AST) with a temporal relationship with rheumatoid arthritis flares and increased use of non-steroidal anti-inflammatory drugs, which resolved upon discontinuation of seladelpar, was considered possibly related to seladelpar. Additional information about study discontinuations can be found in the Supporting Information. Safety data for parental studies are summarised elsewhere.[36,41]

3.4 | Efficacy

3.4.1 | Composite endpoint and ALP response

At year 1 (the beginning of this long-term seladelpar study), approximately 2/3 of patients (63% to 66%) met the composite endpoint criteria. After a second year of treatment, 79% of patients met the composite endpoint criteria at year 2 (Figure 2A). Likewise, achievement of ALP normalisation also showed an increased rate of patients responding to seladelpar at year 2 versus year 1. In approximately 1/4 of patients (23%–26%), ALP was normalised at year 1. After an additional year of treatment with seladelpar, 42% of patients normalised ALP at year 2 (Figure 2B). Additionally, seladelpar's treatment effect on composite endpoint response and ALP normalisation analysed by dose cohorts showed an increase in the percentage of patients achieving the composite endpoint and ALP normalisation in each of the 2, 5 and 10 mg dose cohort from baseline over 2 years (Table S4). Dose cohorts were also analysed based on the initial/uptitrated dose received in the study with the 5/5 and 5/10 mg cohorts also showing an increase in the percentage of patients achieving the composite endpoint and ALP normalisation over the 2 years in study (Table S5).

Patients showed improvements in mean percent and mean absolute changes in ALP values from baseline to year 2. An initial rapid drop in mean ALP of 32.0% was observed in patients at 4 weeks on seladelpar, then the mean percent change from baseline ALP values continued to decline through year 2. Overall at year 2, patients showed a 49.8% mean decrease in ALP values from baseline (Figure 3A). At baseline, the mean ALP value was 320.8 U/L for all patients in the study. The mean value of ALP approached 1.67×ULN (194 U/L) at week 4 (210.3 U/L), fell below 1.67×ULN at week 16 (192.4 U/L), and continued to decrease to a mean value of 142.7 U/L or 1.22×ULN, at year 2. The mean change in absolute value for ALP from baseline was −155.6 U/L for those who completed year 2 (Figure 3B).

3.4.2 | Bilirubin

Mean TB levels were within the normal range and showed a slight decrease from baseline through year 2. Mean TB levels ranged from 0.77 mg/dL at baseline to 0.66 mg/dL through year 2 with 0.7 mg/dL reflecting the 0.6×ULN value (Figure 4A). Over the 2-year period, the mean percent change of TB showed a decrease from baseline ranging from −1.7% to −9.8% (Figure 4B). The mean percent change from baseline to year 2 decreased 4.8% (absolute values ranged from 0.3 to 1.5 mg/dL). Mean absolute and mean percent change in direct bilirubin levels are shown in Figure S4.

In patients with baseline TB >1×ULN, 54% and 43% achieved TB ≤1×ULN in 1 and 2 years, respectively (Figure 4C). Likewise, in patients with baseline TB>0.6×ULN, 34% and 37% achieved TB ≤0.6×ULN in 1 and 2 years, respectively (Figure 4D). When further examining TB based on patient response, 84% of patients with baseline TB ≤0.6×ULN maintained TB at this level at year 1 and 96% of patients maintained this level after 2 years receiving seladelpar (Table S6).

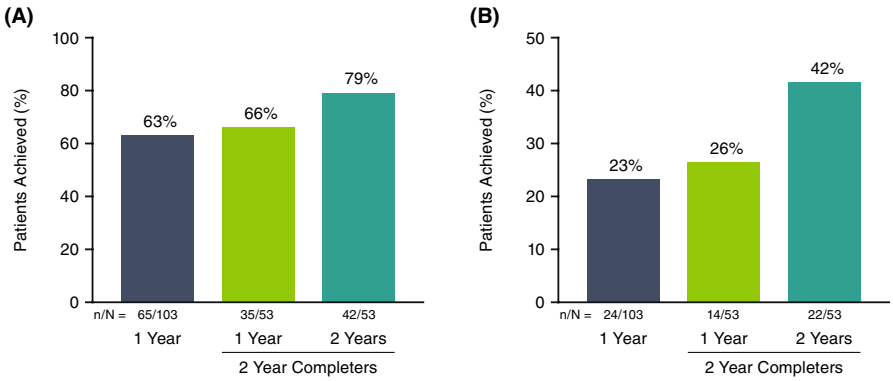
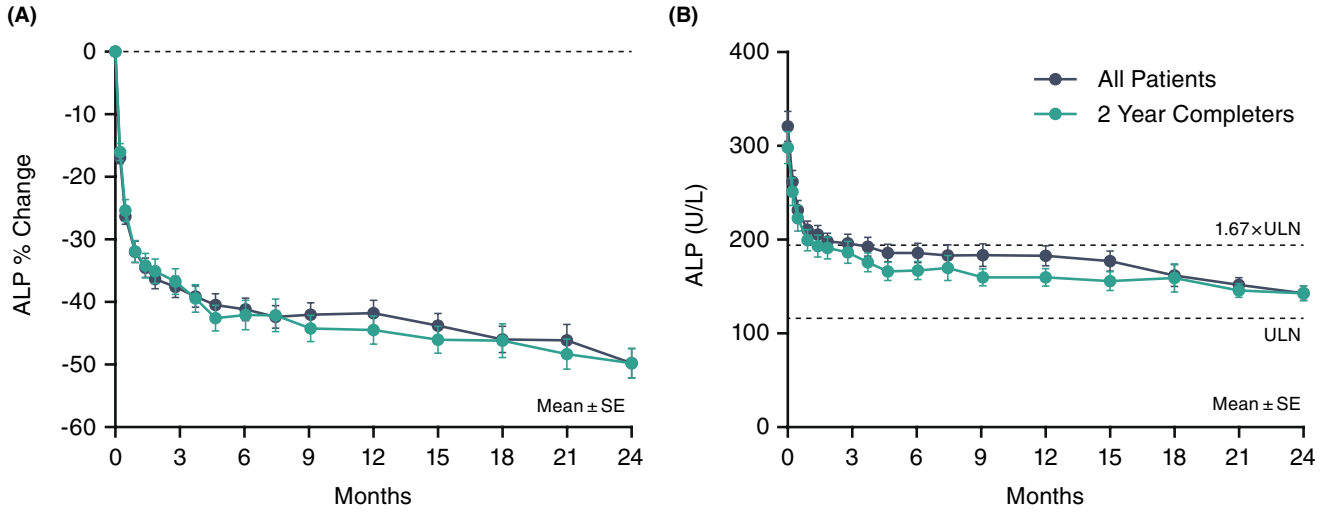


FIGURE 2 Effect of seladelpar on composite endpoint response and normalisation of ALP at year 1 and year 2. (A) Percentage of patients who achieved the composite endpoint at years 1 and 2. The composite endpoint was defined as ALP <1.67×ULN, ≥15% decrease in ALP, and total bilirubin ≤ ULN. (B) Percentage of patients who achieved ALP normalisation at years 1 and 2. ALP normalisation was defined as ALP ≤116 U/L. Data for year 1 were grouped by both all patients and only patients who completed 2 years on seladelpar. One patient who completed 2 years did not have a year 1 visit. ALP, alkaline phosphatase; ULN, upper limit of normal.



N	M0	M3	M6	M9	M12	M15	M18	M21	M24
All Patients	104	104	103	103	103	100	80	65	53
2 Year Completers	53	53	52	52	52	53	53	53	53

FIGURE 3 Effect of seladelpar on mean percent change and mean absolute change in ALP from baseline through month 24. (A) Mean percent change in ALP from baseline to month 24. (B) Mean absolute change in ALP from baseline to month 24. Data shown for all patients in the study (dark blue line) and only those patients who completed 2 years on seladelpar (green line). Data expressed as mean ± SE. ALP, alkaline phosphatase; LLN, lower limit of normal; SE, standard error; ULN, upper limit of normal.

3.4.3 | ALT, AST, GGT and LDL-C

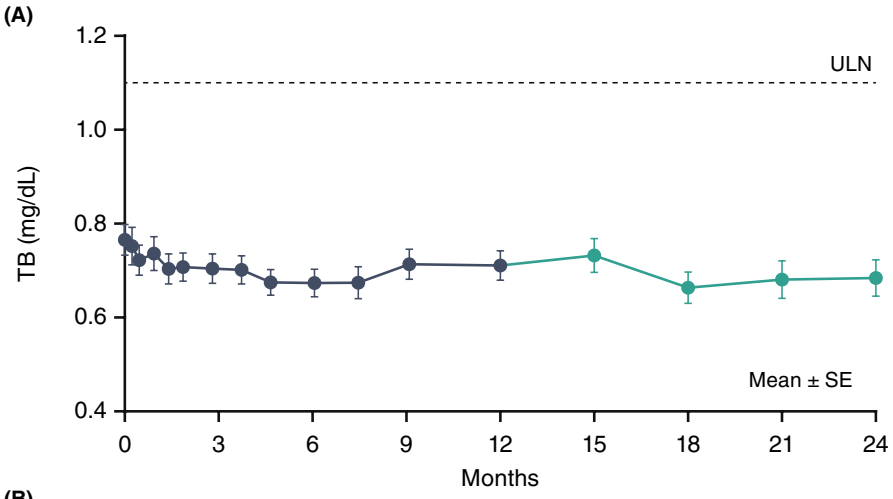
In the parental studies, a rapid decline in the mean percent change of ALT (−18.2%) from baseline to week 2 returned mean levels (39.3 U/L) to within the normal range. ALT levels continued to decrease in all patient cohorts and patients observed a 30.9% decrease in mean baseline ALT values at year 1. During the long-term extension study, a reduction in the mean percent change from baseline continued to nearly a 40% decrease (39.3%) in mean ALT values from baseline to year 2 (27.1 U/L; Figure 5A). In year 1 of the study, 57% of patients decreased ALT from ≥ULN to <ULN. During year 2, an increased number of these patients (75%) saw ALT decrease from ≥ULN to <ULN (Table S7). Of the 53 patients completing 2 years, 92.5% (49/53) saw decreases in ALT (Figure S5), three had increases of ≤2 U/L and one increased from baseline by 15.5 U/L (baseline 34.5–50 U/L, 1.4 × ULN). AST also generally decreased during the parental studies and continued to decrease in the long-term extension study with a mean percent decrease from baseline of 19.2% (44.6–32.8 U/L) at year 2 (Figure 5B).

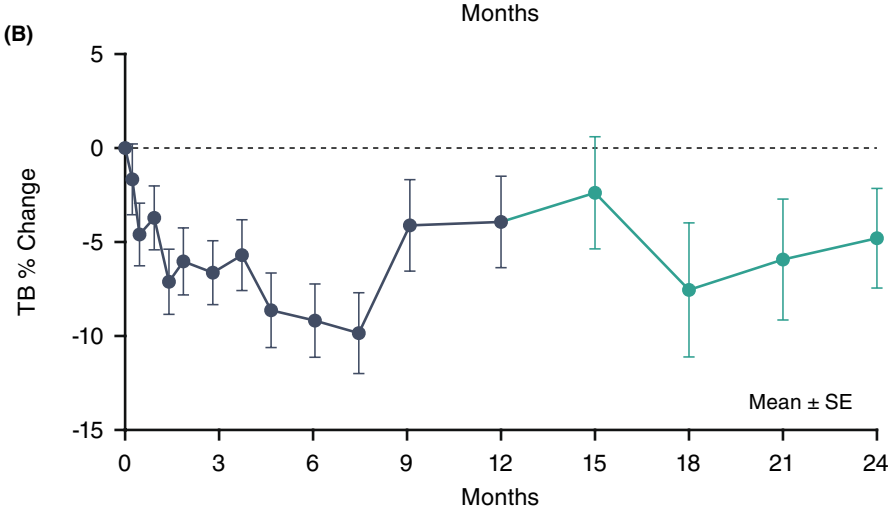
Similar to ALT and AST, GGT observed an initial rapid decrease in the mean baseline absolute value from 245.1 to 173.4 U/L in 4 weeks. GGT levels continued to decrease with a mean percent decrease of 34.2% from baseline to year 1 (157.1 U/L) and a decrease of 45.6% from baseline to year 2 (117.0 U/L; Figure 5C). An additional post-hoc analysis of GGT showed that out of 104 patients who completed 1 year in the long-term extension study, 78 (75%) had a baseline GGT ≥3.2 × ULN, which has been shown to be indicative of increased risk for liver transplant or liver-related death.[28] Of these, 40% ($N = 31$) showed a response with a GGT level <3.2 × ULN at year 1. Of the 53 patients on seladelpar completing year 2, 74% ($N = 39$) entered the parental study above the 3.2 × ULN GGT threshold and 56% of these (22/39) completed year 2 with a response based on the GGT level <3.2 × ULN. The overall shift from baseline as measured by GGT were similar between both the 5 and 10 mg groups at both year 1 (31% and 31%) and year 2 (46% and 41%), respectively, for those who entered the study with GGT above 3.2 × ULN and responded GGT below this response level (Table S8).

Likewise, the mean absolute value of LDL-C observed a rapid decrease in the baseline value from 142.9 to 129.0 mg/dL in 2 weeks. LDL-C levels showed a downward trend over time and observed a decrease in the mean percent value of 16.7% (113.3 mg/dL) at year 2 from baseline, bringing the mean value into the normal range (Figure 5D).

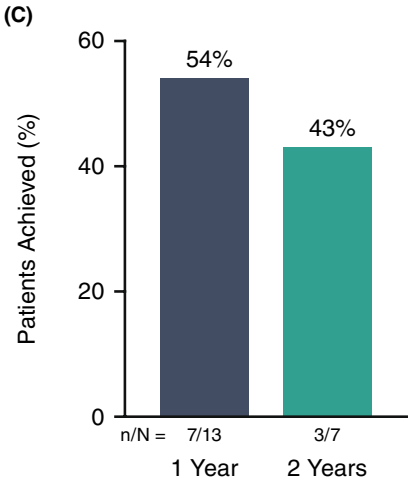
4 | DISCUSSION

Seladelpar had shown significant improvement in liver biomarkers in the two parental studies. In the first lead-in study, a 52-week, dose-ranging, open-label Phase 2 study (NCT02955602), seladelpar treatment resulted in composite biochemical responses of 64%, 53% and 67% in the 2, 5 and 10 mg cohorts, respectively.[36] The second lead-in study was the Phase 3 ENHANCE study (NCT03602560).[41] This was intended to be a 52-week, randomised, controlled study but it was terminated early out of precaution due to unexpected histological findings in a concurrent study for non-alcoholic steatohepatitis. While still





All Patients	M0	M3	M6	M9	M12	M15	M18	M21	M24
N	104	104	103	103	103	100	80	65	53



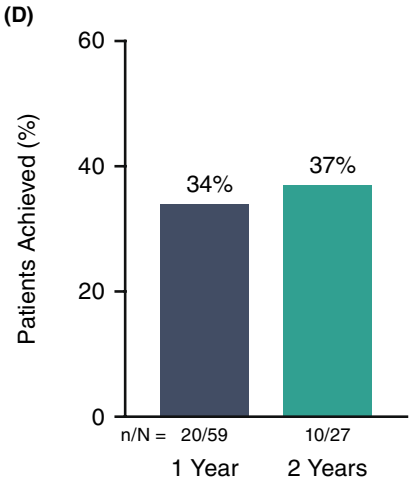
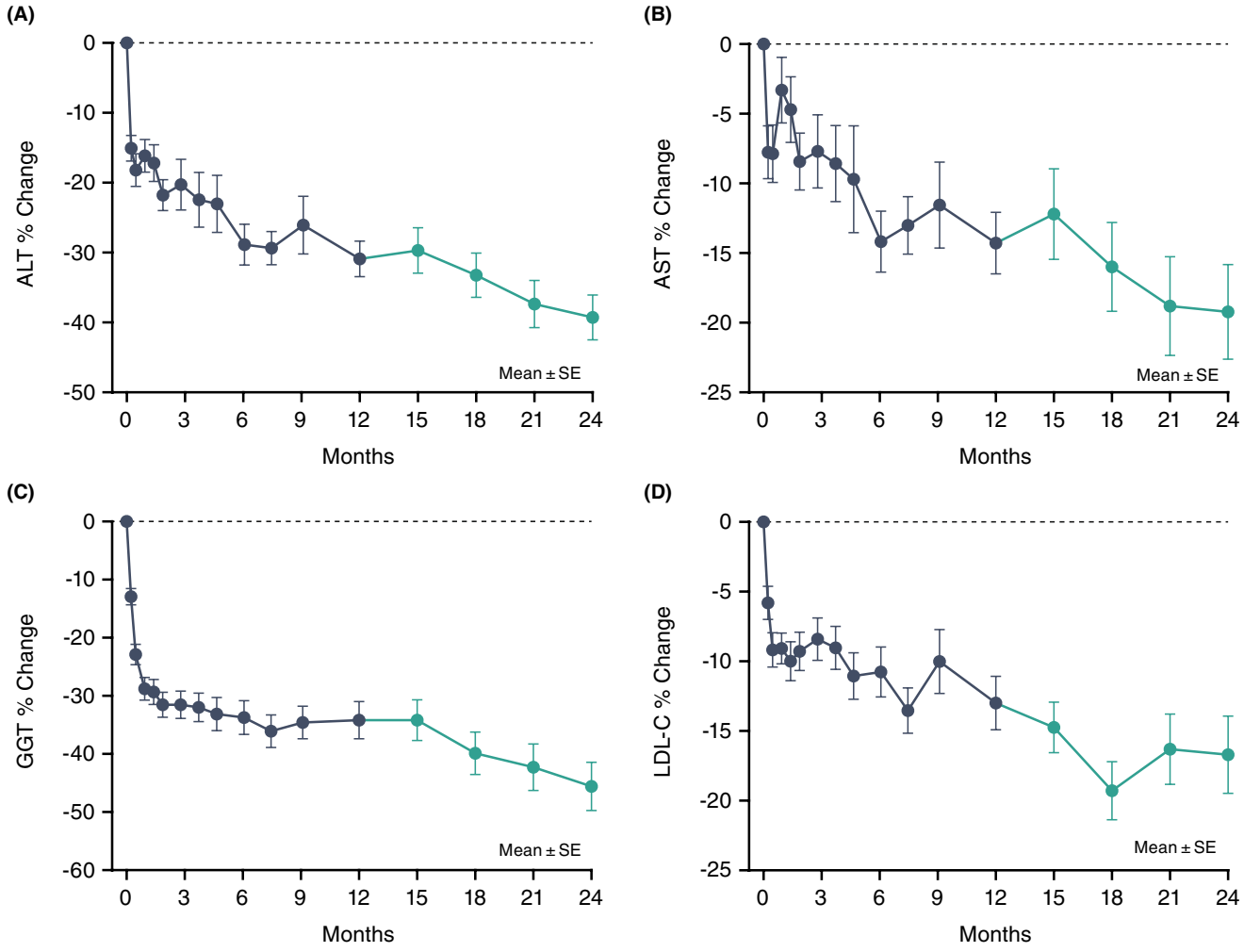


FIGURE 4 Effect of seladelpar on total bilirubin change over 2 years. (A) Mean absolute change in TB from baseline to month 24. (B) Mean percent change in TB from baseline to month 24. Data shown for year 1 (dark blue line) and year 2 (green line). (C) Proportion of patients with baseline TB > ULN who achieved TB ≤ULN at years 1 and 2. (D) Proportion of patients with baseline TB > 0.6 × ULN who achieved TB ≤0.6 × ULN at years 1 and 2. Data expressed as mean ± SE. LLN, lower limit of normal; SE, standard error; TB, total bilirubin; ULN, upper limit of normal.

blinded, the endpoints were amended to 3 months. The composite biochemical response at 3 months was highly significant versus placebo for patients receiving seladelpar 5 mg (57.1%) and 10 mg (78.2%) versus placebo (12.5%). ALP normalisation (≤1.0× ULN) was also highly significant with nearly one in three patients taking 10 mg (27.3%) achieving normal levels of ALP in as early as 3 months versus none in placebo, although the normalisation rate (5.4%) was not significant in those patients taking 5 mg.

This current study was an international, multicentre, open-label, Phase 3 long-term extension study in patients with PBC who had



All Patients	M0	M3	M6	M9	M12	M15	M18	M21	M24
N	104	102	103	103	103	100	80†	65	53

FIGURE 5 Effect of seladelpar on mean percent change in ALT, AST, GGT and LDL-C from baseline to month 24. (A) Mean percent change in ALT from baseline to month 24. (B) Mean percent change in AST from baseline to month 24. (C) Mean percent change in GGT from baseline to month 24. (D) Mean percent change in LDL-C from baseline to month 24. Data shown for year 1 (dark blue line) and year 2 (green line). Data expressed as mean ± SE. †For LDL-C timepoint at month 18, $N = 79$. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LDL-C, low-density lipoprotein cholesterol; LLN, lower limit of normal; SE, standard error; ULN, upper limit of normal.

completed one of the above mentioned parental studies with seladelpar. Patients entered the long-term extension study as they finished their participation in a prior PBC study, thereby allowing their treatment to continue without interruption. This long-term study demonstrated that seladelpar continued to show durable and progressive effects in serum biomarkers of cholestasis and liver injury effects in patients with PBC, who were UDCA intolerant or had an incomplete response to UDCA, through at least 2 years of treatment. Seladelpar was safe and well tolerated for over 2 years of treatment at 5 and 10 mg once daily.

Relevant safety findings indicate that serious safety events were minimal and generally did not appear to be due to seladelpar. Of the 106 patients in the safety population, four patients discontinued seladelpar due to safety-related reasons. In one of these patients, death occurred 7 months after discontinuation of seladelpar. Three of these events (including the one resulting in death) were determined to be unlikely/not related to seladelpar, and one (Grade 2 elevation in liver tests) was determined to be possibly related to seladelpar. In addition, there were no serious liver-related TEAEs or serious treatment-related TEAEs grade ≥3 during this study. Seladelpar appeared to be a safe and well-tolerated treatment in this study of patients with PBC, including in the nearly 20% with compensated cirrhosis.

The composite endpoint was achieved in nearly 80% of patients with 2 years of seladelpar treatment. In addition, over 40% of patients normalised ALP after 2 years of seladelpar treatment. The

continued decrease in mean ALP levels during year 2 cannot be explained by the small number of patients with seladelpar dose increases occurring during this year as only four patients titrated from 5 to 10 mg seladelpar during year 2. In addition, efficacy was retained at the patient level through 2 years for all except one patient with disease progression. This patient had an increase in ALP (not meeting safety monitoring criteria) at year 2 with a value higher than year 1 or the baseline value. Although the absolute change in TB was small and should be interpreted with caution in this small dataset, just over one-third of patients with baseline TB >0.6×ULN reduced TB levels to ≤0.6×ULN over 2 years of treatment. Improvements in these serum biomarkers, all of which have been shown to be associated with reduction in the risk for PBC disease progression, support clinically meaningful goals for the treatment of patients with PBC.

Reductions in biomarkers of cholestasis and hepatocellular injury, including ALT, AST and GGT continued to improve throughout the second year of treatment. Lipids, including LDL-C, also generally improved. All four of these markers showed a markedly rapid decline in absolute mean values during the first few weeks on seladelpar followed by a sustained, continual decrease in values through year 2. In addition, although only modestly increased at baseline, mean ALT and LDL-C levels were returned to within normal range in just 2 weeks of seladelpar treatment and continued to decrease.

Although elevated GGT is an early biochemical marker of cholestasis, inflammation and oxidative stress, it is not yet included in prognostic risk scores.[28] However, it has been suggested that GGT may be useful in assessing response to UDCA therapy in PBC.[3] Elevated GGT is an emerging new risk factor for PBC progression and this study has shown that seladelpar decreased GGT levels in 56% of patients with a baseline GGT ≥3.2×ULN to below this level in 2 years. Absolute mean values were decreased from 245.1 U/L at baseline to 117.0 U/L at year 2.

When comparing response rates between dose cohorts, the 5 mg cohort exhibited a better response rate than the 10 mg cohort (Table S5). It is important to recognise the cohorts were defined by the initial dose in the parental study, not the final dose on treatment; thus, the higher percentage of responders in the 5 mg cohort is likely due to many of them being uptitrated to 10 mg in the parental study with 30 of the 46 patients who started on 5 mg uptitrating to 10 mg by year 1. In addition, as a whole, baseline ALP levels were lower in the patients who remained in the 5 mg cohort compared to the 10 mg cohort implying that achieving a response could be easier as they had less of a decrease to achieve having started with lower laboratory values.

This study was intended to accumulate 5 years of safety and efficacy data on patients with PBC receiving either 5 or 10 mg of seladelpar once daily. Although this study was terminated early, there was evaluable safety data on 106 patients and efficacy data on 53 patients for a full 2 years. The data in this study continued to show reductions in biomarkers of cholestasis and hepatocellular injury in patients with PBC who were intolerant or showed an incomplete response with UDCA and continues to support that seladelpar could be a good candidate for second-line treatment of PBC. It should be noted that this study is limited by the lack of a placebo control in the long-term extension period and that selection and attrition bias can affect the validity of the results.

In conclusion, in patients with PBC not responding to or intolerant of UDCA at high risk for disease progression, seladelpar treatment reduced serum levels of biomarkers for cholestasis and liver injury with continued improvement throughout the second year of treatment. Seladelpar potentially offers another treatment option for UDCA-experienced patients, or for those whom are intolerant to UDCA.

AUTHOR CONTRIBUTIONS

Marlyn J. Mayo: Conceptualization (lead); investigation (equal); methodology (supporting); visualization (lead); writing – original draft (lead); writing – review and editing (lead). **John M. Vierling:** Conceptualization (lead); investigation (equal); methodology (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Christopher L. Bowlus:** Conceptualization (lead); investigation (equal); methodology (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Cynthia Levy:** Conceptualization (lead); investigation (equal); methodology (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Gideon M. Hirschfield:** Conceptualization (lead); investigation (equal); methodology (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Guy W. Neff:** Conceptualization (supporting); investigation (equal); methodology (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Michael R. Galambos:** Conceptualization (supporting); investigation (equal); methodology (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Stuart C. Gordon:** Conceptualization (supporting); investigation (equal); methodology (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Brian B. Borg:** Conceptualization (supporting); investigation (equal); methodology (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Stephen A. Harrison:** Conceptualization (supporting); investigation (equal); methodology (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Paul J. Thuluvath:** Conceptualization (supporting); investigation (equal); methodology (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Aparna Goel:** Conceptualization (supporting); investigation (equal); methodology (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Mitchell L. Shiffman:** Conceptualization (supporting); investigation (equal); methodology (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Mark G. Swain:** Conceptualization (supporting); investigation (equal); methodology (supporting); visualization (supporting); writing –

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ACKNOWLEDGEMENTS

We acknowledge the additional investigators who also contributed to this study. A list of their names and affiliations can be found in the Supporting Information.

Declaration of personal interests: Marlyn J. Mayo has served as a consultant, and/or advisory board member and/or speaker for CymaBay Therapeutics, Inc., Glaxo-Smith Kline, Mirum Pharmaceuticals, Mallinckrodt Pharmaceuticals, Ipsen Biopharmaceuticals, Intra-Sana Laboratories, and has received research funding from CymaBay Therapeutics, Inc., Glaxo-Smith Kline, Target RWE, Mirum Pharmaceuticals, Mallinckrodt Pharmaceuticals and Intercept Pharmaceuticals. John M. Vierling has served on scientific advisory boards for Arena, Blade, CymaBay Therapeutics, Inc., Enanta, Gilead, Horizon, Lilly, Intercept, Ipsen, Kezar, Moderna, Novartis, Perspectum, Roche-Genentech, Taiwan J, IQDILI and DI-AIH, a board member for Athenex, Inc., received research grants from Allergan, Enanta, CymaBay Therapeutics, Inc., Escient, Genfit, Genkyotex, Gilead, Intercept, Lilly, NGM Biopharmaceuticals, Novartis, Roche-Genentech, Taiwan J and Zydus, and owns stock in Athenex, Inc. Christopher L. Bowlus has served as an advisor for CymaBay Therapeutics, Inc., GSK Pharmaceuticals, Invea Therapeutics and Ipsen Bioscience and has received research funding from Boston Scientific, Calliditas Therapeutics, ChemoMab, COUR Pharmaceuticals, CymaBay Therapeutics, Inc., Gilead Sciences, GSK Pharmaceuticals, Hanmi Pharmaceuticals, Intercept Pharmaceuticals, Ipsen Bioscience, Mirum Pharmaceuticals, Novo Nordisk, Pliant Therapeutics and Viking Therapeutics. Cynthia Levy has served as a consultant for Calliditas, CymaBay Therapeutics, Inc., Gilead, GSK, Gilead, Intercept, Ipsen and Pliant, received research grants (paid to institution) from Calliditas, Cara, CymaBay Therapeutics, Inc., Escient, Genfit, GSK, Gilead, Intercept, Ipsen, HighTide, Mirum, Novartis, Pliant, Zydus and Target RWE, serves as an associate editor for Hepatology and as a member for the ABIM Transplant Hepatology Approval Committee, and receives royalties from Up-to-Date. Gideon Hirschfield has served as a consult for CymaBay Therapeutics, Inc., Intercept, Ipsen, GSK, Escient and Mirum. Guy W. Neff has served as a speaker, a consultant and an advisory board member for Boehringer Ingelheim and Intercept Pharmaceuticals and has received research funding from Boehringer Ingelheim and Intercept Pharmaceuticals. Michael R. Galambos has participated in clinical research trials for CymaBay Therapeutics, Inc., with the study medication seladelpar and is an employee of Digestive Healthcare of Georgia. Stuart C. Gordon has served as a consultant and an advisory board member for Gilead, CymaBay Therapeutics, Inc., and Ipsen and has received research funding from AbbVie Pharmaceuticals, CymaBay Therapeutics, Inc., DURECT, Gilead Sciences, GlaxoSmithKline Intercept, Mirum, Pliant and Merck. Brian B. Borg has nothing to disclose. Stephen A. Harrison served as a consultant or scientific advisor for Akero, Alentis, Altimmune, Arrowhead, Axcella, Canfite, Cirius, CiVi Biopharma, CymaBay Therapeutics, Inc., Echosens, Fibronostics, Forest Labs, Galectin, Genfit, Gilead, Hepion, HistoIndex, Intercept, Madrigal, Medpace, Metacrine, NGM Bio, Northsea, Novartis, Novo Nordisk, PathAI, Poxel, Liminal, Ridgeline, Sagimet, Terns, Viking and 89 Bio; has received research funding from Akero, Axcella, BMS, Cirius, CiVi Biopharma, Conatus, CymaBay Therapeutics, Inc., Enyo, Galectin, Genentech, Genfit, Gilead, Hepion, Hightide, Intercept, Madrigal, Metacrine, NGM Bio, Novartis, Novo Nordisk, Northsea, Pfizer, Sagimet and Viking; and owns stock in Akero, Cirius, Galectin, Genfit, Hepion, HistoIndex, PathAI, Metacrine, NGM Bio and Northsea. Paul J. Thuluvath (Mercy Medical Center, Baltimore) received research funding from CymaBay Therapeutics, Inc. Aparna Goel has served as an advisory board member for Parvus Therapeutics and Ipsen. Mitchell L. Shiffman has served as a speaker for Intercept, a consultant and an advisory board member for Intercept and CymaBay Therapeutics, Inc., and has received research funding from Intercept, CymaBay Therapeutics, Inc., Genfit, Mirum and High Tide. Mark G. Swain has served as an advisory board member for Gilead, Ipsen, Pfizer, Roche and Novo Nordisk, as a speaker for Gilead and Abbott, and had received clinical trial or research support from Gilead, BMS, CymaBay Therapeutics, Inc., Intercept, Genfit, Pfizer, Novartis, Astra Zeneca, GSK, Celgene, Novo Nordisk, Axcella Health, Inc., Merck, Galectin Therapeutics, Calliditas Therapeutics and AbbVie. David E. J. Jones consults for, is on the speakers' bureau for and received funding from Intercept, consults for CymaBay Therapeutics, Inc, Kowa, and Umecrine, and is on the speakers bureau for

Falk, GlaxoSmithKline and Ipsen. Palak Trivedi has served as a lecturer for Dr Falk Pharma, Intercept/Advanz Pharma and Albireo, as an advisory and consult for Intercept/Advanz Pharma, Dr Falk Pharma, CymaBay Therapeutics, Inc., Pliant pharma, GSK, ChemoMab and Mirum, institutional support from Birmingham NIHR BRC, institutional funding from NIHR (UK), and grant funding from Core (Guts UK), PSC Support, Wellcome Trust, Medical Research Foundation, LifeArc Foundation, NIHR EME, EASL, Intercept/Advanz Pharma, Bristol Myers Squibb, Gilead sciences, GSK and BMS. Andreas E. Kremer has served as a speaker, a consultant and an advisory board member for Abbvie, Advanz, Alentis, AlphaSigma, AstraZenca, Avior, Bayer, BMS, CMS, CymaBay Therapeutics, Inc., Eisai, Escient, Falk, FMC, Gilead, GSK, Guidepoint, Intercept, Mirum, Medscape, MSD, Myr, Newbridge, Roche, Viofor and Zambon and has received research funding from Intercept. Richard J. Aspinall owns stock in CymaBay Therapeutics, Inc. David A. Sheridan has nothing to disclose. Yvonne Dörffel has nothing to disclose. Ke Yang is an employee of CymaBay Therapeutics, Inc., and owns stock in CymaBay Therapeutics, Inc. Yun-Jung Choi is an employee of CymaBay Therapeutics, Inc. Charles A. McWherter is an employee of CymaBay Therapeutics, Inc., owns stock in CymaBay Therapeutics, Inc., and owns patents on treatment of intrahepatic cholestatic diseases.

FUNDING INFORMATION

Funding for this study and manuscript preparation was provided by CymaBay Therapeutics, Inc, which had a role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. Writing assistance was provided by Leann M. Mikesh, PhD, of Synchrogenix, a Certara Company and funded by CymaBay Therapeutics, Inc.

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PATIENT CONSENT STATEMENT

All patients provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Mayo MJ, Vierling JM, Bowlus CL, Levy C, Hirschfield GM, Neff GW, et al. Open-label, clinical trial extension: Two-year safety and efficacy results of seladelpar in patients with primary biliary cholangitis. Aliment Pharmacol Ther. 2023;00:1–15. https://doi.org/10.1111/apt.17755