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A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis

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

ABSTRACT

BACKGROUND

Effective treatments for patients with primary biliary cholangitis are limited. Seladelpar, a peroxisome proliferator–activated receptor delta agonist, has potential benefits.

METHODS

In this phase 3, 12-month, double-blind, placebo-controlled trial, we randomly assigned (in a 2:1 ratio) patients who had had an inadequate response to or who had a history of unacceptable side effects with ursodeoxycholic acid to receive oral seladelpar at a dose of 10 mg daily or placebo. The primary end point was a biochemical response, which was defined as an alkaline phosphatase level less than 1.67 times the upper limit of the normal range, with a decrease of 15% or more from baseline, and a normal total bilirubin level at month 12. Key secondary end points were normalization of the alkaline phosphatase level at month 12 and a change in the score on the pruritus numerical rating scale (range, 0 [no itch] to 10 [worst itch imaginable]) from baseline to month 6 among patients with a baseline score of at least 4 (indicating moderate-to-severe pruritus).

RESULTS

Of the 193 patients who underwent randomization and treatment, 93.8% received ursodeoxycholic acid as standard-of-care background therapy. A greater percentage of the patients in the seladelpar group than in the placebo group had a biochemical response (61.7% vs. 20.0%; difference, 41.7 percentage points; 95% confidence interval [CI], 27.7 to 53.4, P<0.001). Normalization of the alkaline phosphatase level also occurred in a greater percentage of patients who received seladelpar than of those who received placebo (25.0% vs. 0%; difference, 25.0 percentage points; 95% CI, 18.3 to 33.2, P<0.001). Seladelpar resulted in a greater reduction in the score on the pruritus numerical rating scale than placebo (least-squares mean change from baseline, –3.2 vs. –1.7; least-squares mean difference, –1.5; 95% CI, –2.5 to –0.5, P=0.005). Adverse events were reported in 86.7% of the patients in the seladelpar group and in 84.6% in the placebo group, and serious adverse events in 7.0% and 6.2%, respectively.

CONCLUSIONS

In this trial involving patients with primary biliary cholangitis, the percentage of patients who had a biochemical response and alkaline phosphatase normalization was significantly greater with seladelpar than with placebo. Seladelpar also significantly reduced pruritus among patients who had moderate-to-severe pruritus at baseline. The incidence and severity of adverse events were similar in the two groups. (Funded by CymaBay Therapeutics; RESPONSE ClinicalTrials.gov number, NCT04620733; EudraCT number, 2020-004348-27.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Hirschfield can be contacted at gideon.hirschfield@uhn.ca or at Toronto General Hospital, Toronto Centre for Liver Disease, 9th Fl. Eaton Bldg., North Wing 219-B, 200 Elizabeth St., Toronto, ON M5G 2C4, Canada.

*The investigators in the RESPONSE Study Group are listed in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Primary biliary cholangitis is a rare liver disease, characterized by the destruction of the small intrahepatic bile ducts and accumulation of toxic bile acids, resulting in cholestasis, inflammation, and biliary fibrosis, which can progress to cirrhosis and liver failure.[1-4] Common symptoms are pruritus and fatigue.

Ursodeoxycholic acid is the only agent currently approved by the Food and Drug Administration (FDA) for first-line treatment of primary biliary cholangitis.[2,5,6] However, up to 40% of patients treated with ursodeoxycholic acid have a persistently elevated alkaline phosphatase level, bilirubin level, or both, which portends disease progression.[2,3,5] Although peroxisome proliferator–activated receptor (PPAR) agonists[7] and budesonide[8] are used off-label, obeticholic acid is the only FDA-approved second-line treatment for primary biliary cholangitis.[2,6,9-11] In a phase 3, placebo-controlled trial, 47% of patients who had had an inadequate response to or who had a history of unacceptable side effects with ursodeoxycholic acid and who were treated with obeticholic acid for primary biliary cholangitis had a response with respect to the levels of alkaline phosphatase and bilirubin; however, pruritus and serious adverse events were more common with obeticholic acid than with placebo.[10] Additional FDA-approved therapies for primary biliary cholangitis are needed.

Seladelpar is a drug candidate for the treatment of primary biliary cholangitis that selectively activates PPARδ.[12] PPARδ is unique among PPAR isotypes, with broad expression in cells that play a key role in the pathobiology of primary biliary cholangitis: hepatocytes, cholangiocytes, Kupffer cells, and stellate cells.[13-15] The activation of PPARδ by seladelpar releases fibroblast growth factor 21 (FGF21) from hepatocytes, which in turn reduces the accumulation of bile acids by inhibiting the expression of cholesterol 7α-hydroxylase, the rate-limiting enzyme for bile acid synthesis.[16,17] Seladelpar decreases proinflammatory macrophages,[18] an effect that is consistent with the known effect of PPARδ to promote the antiinflammatory M2 phenotype in Kupffer cells and macrophages.[15,19]

In a phase 2, open-label trial involving patients with primary biliary cholangitis, treatment with seladelpar for 1 year decreased alkaline phosphatase and bilirubin levels, patient-reported pruritus, sleep disturbance, and fatigue.[20,21] In a placebo-controlled trial, after 3 months of treatment, patients who received seladelpar had significantly lower levels of alkaline phosphatase, bilirubin, and aminotransferases and greater amelioration of pruritus than those who received placebo.[22] In both trials, no worrisome safety signals with seladelpar were reported. We report here the results of RESPONSE, a phase 3 trial to evaluate the efficacy and safety of oral, once-daily seladelpar over the course of 12 months in patients with primary biliary cholangitis.

METHODS

PATIENTS

Patients 18 to 75 years of age who had received a diagnosis of primary biliary cholangitis were recruited at 90 sites in 24 countries. Inclusion criteria were treatment with ursodeoxycholic acid for at least 12 months or a history of unacceptable side effects with ursodeoxycholic acid (last dose, >3 months before screening), an alkaline phosphatase level of at least 1.67 times the upper limit of the normal range (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels up to 3 times the ULN, a total bilirubin level up to 2 times the ULN, an estimated glomerular filtration rate of more than 45 ml per minute per 1.73 m^2, an international normalized ratio of less than 1.1 times the ULN, and a platelet count of at least 100,000 per cubic millimeter. Key exclusion criteria were advanced primary biliary cholangitis (an albumin level below the lower limit of the normal range and a total bilirubin level above the ULN),[23] hepatic decompensation, and any other chronic liver disease. Full eligibility criteria can be found in the Supplementary Appendix, available with the full text of this article at NEJM.org. All patients provided written informed consent.

TRIAL OVERSIGHT AND DESIGN

The protocol (available at NEJM.org) was approved by the appropriate institutional review boards or ethics committees, and the trial was conducted according to the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Employees of the funder (CymaBay Therapeutics) designed the trial and performed site monitoring, data collection, and data analysis. The first seven and last four authors vouch for the accuracy and

completeness of the data and for the fidelity of the trial to the protocol. The initial manuscript draft was prepared by a medical writer funded by CymaBay. Subsequent revisions and the final decision to submit the manuscript for publication were made by all the authors.

In this phase 3, multicenter, double-blind, randomized, placebo-controlled trial, patients were randomly assigned, in a 2:1 ratio, to receive oral seladelpar at a dose of 10 mg daily or matching placebo for up to 12 months, along with ursodeoxycholic acid, or without ursodeoxycholic acid in patients who had a history of unacceptable side effects with that therapy. Randomization was performed centrally through an interactive online response system, with stratification according to the baseline alkaline phosphatase level (<350 or ≥350 U per liter) and the pruritus numerical rating scale (NRS) score[24] (<4 or ≥4, with scores on the NRS ranging from 0 [no itch] to 10 [worst itch imaginable]). Investigators performed assessments, including safety and laboratory evaluations, at baseline and months 1, 3, 6, 9, and 12. The pruritus NRS score and quality-of-life[25,26] data were collected with the use of an electronic diary. Pruritus NRS data were collected daily from the run-in visit through month 6 and then for 7 consecutive days during each month up to the end of the treatment period. Liver stiffness was assessed with use of transient elastography (FibroScan, Echosens)[27] at baseline and at months 6 and 12. Adverse events and results of laboratory tests for safety assessments were monitored at each visit. Patients who completed the trial could enroll in an open-label, long-term extension trial (ClinicalTrials.gov number, NCT03301506) at participating sites. Otherwise, patients had a follow-up visit 2 weeks after completion of the trial for safety assessment (see the Supplementary Appendix for additional details).

END POINTS

The primary end point was a biochemical response — an alkaline phosphatase level less than 1.67 times the ULN, with a decrease of 15% or more from baseline, and a total bilirubin level up to 1.0 times the ULN — at month 12. Key secondary end points were normalization of the alkaline phosphatase level (≤1.0 times the ULN) at month 12 and a change from baseline in the weekly mean pruritus NRS score at month 6 among patients with moderate-to-severe pruritus (NRS ≥4) at baseline.[24] Primary and key secondary end points were also assessed in prespecified patient subgroups.

Other secondary and exploratory end points that were assessed at trial visits through month 12 (i.e., at months 1, 3, 6, 9, and 12) were the biochemical response, alkaline phosphatase thresholds, ALT normalization, and risk criteria for primary biliary cholangitis[5,28-32]; changes in serum levels of alkaline phosphatase, ALT, AST, bilirubin, γ-glutamyltransferase, 5′-nucleotidase, FGF21,[17] pruritogenic cytokine interleukin-31,[33] and lipids, in markers of fibrosis (liver stiffness[27,34] and the enhanced-liver-fibrosis score), and in high-sensitivity C-reactive protein, IgM, the bile acid intermediate 7α-hydroxy-4-cholesten-3-one (C4), and total bile acids; changes in the pruritus NRS score, the total score and the itch-domain score on the primary biliary cholangitis-40 (PBC-40) quality-of life questionnaire, and the 5-D itch scale among patients with moderate-to-severe pruritus and in the overall population; and clinical outcomes related to primary biliary cholangitis. Scores on the PBC-40 quality-of-life questionnaire range from 1 (or 0 in some items related to itch, social function, and symptoms) to 5 for each of the 40 items, with higher scores indicating worse quality of life.[25] Scores on the 5-D (degree, duration, direction [improvement or worsening], disability [effect on daily activities], and distribution of itching) itch scale range from 5 to 25, with higher scores indicating worse itch-related quality of life.[26] All end points reported here were prespecified (Table S1 in the Supplementary Appendix). Safety end points included adverse events, serious adverse events, and laboratory evaluations.

STATISTICAL ANALYSIS

On the basis of estimates that 55% of patients who received seladelpar at a dose of 10 mg daily and 20% of patients who received placebo would have a biochemical response and that 25.5% and 2.5%, respectively, would have normalized alkaline phosphatase levels,[22] we calculated that a sample size of 180 patients would provide more than 90% power to detect a significant difference between treatment groups with a two-sided test of equality of binomial proportions using Fisher's exact test with a type I error rate of 0.05.

We estimated that a total of 48 patients with a baseline pruritus NRS score of at least 4 would provide more than 80% power to detect a clinically important difference of 2 or more points[35] between treatment groups using a two-sample two-sided t-test with a type I error rate of 0.05.

Safety and efficacy analyses included data from the intention-to-treat population (all patients who underwent randomization and received ≥1 dose of seladelpar or placebo). Pruritus NRS end points were analyzed among patients with a baseline NRS score of at least 4 and in the intention-to-treat population. Efficacy data were analyzed according to group assignment. Safety data were analyzed according to the trial product (seladelpar or placebo) the patients received. Statistical testing was two-sided and performed at the 0.05 alpha level. For the primary and key secondary efficacy end points, we maintained the 0.05 type I error using a hierarchical fixed-sequence method in the following order: the primary end point; normalization of alkaline phosphatase levels at month 12; and the change in pruritus NRS score from baseline to month 6. Other end points are reported as point estimates and measures of variability that were not adjusted for multiple testing and should not be used to infer definitive benefits of treatment. We analyzed the primary end point and the normalization of alkaline phosphatase levels using a Cochran–Mantel–Haenszel test adjusted for randomization stratification variables. For all categorical end points, patients with missing data at any time point were considered not to have had a response at that time point.

A mixed-effect model for repeated measures was used to evaluate the change from baseline in the pruritus NRS score and other continuous end points. The least-squares mean changes (with 95% confidence intervals) according to randomization group and the least-squares mean difference between the groups and associated two-sided 95% confidence intervals and two-sided P values were derived from the model. For pruritus NRS end points, data for a missing assessment at a specific time point were imputed as the mean of the adjacent 2 weeks (i.e., the week before and the week after the missing time point). Daily inputs were averaged to create weekly means. If assessment data were still missing, no further imputation was performed. A mixed-effect model for repeated measures was used to analyze the change in weekly mean pruritus NRS scores under a missing-at-random assumption. Missing data were not imputed for other continuous end points.

Adverse events were summarized according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 24.0. Severity was graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (see the Supplementary Appendix for details).

RESULTS

PATIENTS

A total of 193 patients underwent randomization and received either seladelpar (128 patients) or placebo (65 patients) (Fig. S1). The first patient was enrolled on April 21, 2021, and the last visit of the last patient to enroll was on August 11, 2023. Overall, 174 patients (90.2%) completed the trial; 11 (8.6%) who received seladelpar and 8 (12.3%) who received placebo withdrew from the trial. Of 166 patients who completed the trial at sites offering enrollment in the long-term extension, 160 (96.4%) enrolled.

At baseline, the mean alkaline phosphatase level was 314.3 U per liter (2.7 times the ULN), the mean total bilirubin level was 0.76 mg per deciliter (0.69 times the ULN), and the mean ALT level was 47.7 U per liter (1.2 times the ULN) (Table 1). Alkaline phosphatase levels were at least 350 U per liter (3 times the ULN) in 27.5% of the patients (53 of 193) and total bilirubin levels were higher than the ULN in 13.0% (25 of 193). The mean baseline pruritus NRS score was at least 4 in 37.3% of the patients (72 of 193; mean score, 6.3). At baseline, 83.4% of the patients (161 of 193) were positive for antimitochondrial antibodies, 14.0% (27 of 193) had cirrhosis, and 93.8% (181 of 193) were taking ursodeoxycholic acid (mean total daily dose, 15.0 mg per kilogram of body weight); 17.1% of the patients (33 of 193) had previously received obeticholic acid or fibrates (Table S2). The representativeness of the trial population is summarized in Table S3.

EFFICACY

Biochemical Response

The primary end-point criteria (alkaline phosphatase level <1.67 times the ULN, with a decrease of ≥15% from baseline, and a total bilirubin level ≤1.0 times the ULN) were met in 61.7% of the patients (79 of 128) treated with seladelpar and

in 20.0% (13 of 65) receiving placebo (difference, 41.7 percentage points; 95% confidence interval [CI], 27.7 to 53.4; P<0.001) (Fig. 1). Figure S2A shows the primary end-point results at additional trial visits. Results appeared to be generally consistent among patients with and those without cirrhosis and among patients who received seladelpar alone and those who received seladelpar with ursodeoxycholic acid (Fig. S2B). Results of analyses performed according to various risk criteria for primary biliary cholangitis are summarized in Tables S4 and S5.

Normalization of the alkaline phosphatase level at month 12 was observed in 25.0% of the patients (32 of 128) treated with seladelpar and in none of the patients receiving placebo (difference, 25.0 percentage points; 95% CI, 18.3 to 33.2; P<0.001) (Fig. 1). The least-squares mean alkaline phosphatase level decreased by 42.4% (133.9 U per liter) in patients who received seladelpar as compared with 4.3% (16.9 U per liter) in patients who received placebo at month 12 (least-squares mean difference, −38.2 percentage points; 95% CI, −46.3 to −30.1) (Fig. 2A). Additional data can be found in Figures S3 and S4.

The total bilirubin level appeared to remain stable through month 12 in both groups (Fig. 2B). The ALT level was reduced by 23.5% from baseline to month 12 in patients who were treated with seladelpar and by 6.5% in patients who received placebo (least-squares mean difference, −17.0 percentage points; 95% CI, −28.1 to −5.9). The percentage of patients with a normal ALT level at month 12 also appeared to be greater with seladelpar than with placebo (56.3% vs. 25.0%; least-squares mean difference, 31.3 percentage points; 95% CI, 11.6 to 47.8) (Fig. S5). Levels of AST and direct and indirect bilirubin appeared to remain stable in both groups through month 12. Reductions in levels of γ-glutamyltransferase and 5′-nucleotidase appeared to be greater with seladelpar than with placebo (Fig. S4).

Pruritus and Quality of Life

A total of 49 patients (38.3%) in the seladelpar group and 23 (35.4%) in the placebo group had moderate-to-severe pruritus at baseline. Among these patients, the reduction from baseline in the pruritus NRS score at month 6 was significantly greater in patients who were treated with seladelpar than in patients who received placebo (change from baseline, −3.2 points vs. −1.7 points; least-squares mean difference, −1.5 points; 95% CI, −2.5 to −0.5; P=0.005) (Fig. 3A). In the overall population, the change in the pruritus NRS score from baseline to month 6 was −1.3 points in the seladelpar group and −0.4 points in the placebo group (least-squares mean difference, −0.9 points; 95% CI, −1.4 to −0.5) (Fig. 3B). Among patients with moderate-to-severe pruritus at baseline as well as in the overall population, reduction in itch from baseline to month 12, as measured by the 5-D itch total score and in all individual domains except direction, appeared to be greater in patients who were treated with seladelpar than in patients who received placebo (Figs. S6 and S7). Similar findings were observed with respect to PBC-40 quality-of-life questionnaire scores (Figs. S8 and S9). The results with respect to the primary and key secondary end points appeared to be generally consistent in the prespecified subgroups (Fig. S10).

Markers of Disease Progression, Inflammation, Immune Reactivity, and Bile Acid Synthesis

No meaningful changes in liver stiffness or enhanced-liver-fibrosis scores were observed at month 12 (Table S6). Changes in levels of high-sensitivity C-reactive protein, IgM, total bile acids, C4, and lipids through month 12 are shown in Tables S7 and S8 and Figure S11. Increases in FGF21 levels appeared to be greater with seladelpar than with placebo at months 3 and 6 but were similar in the two groups at month 12. Decreases in interleukin-31 levels appeared to be greater with seladelpar than with placebo at months 3, 6, and 12 (Fig. S12).

SAFETY

A total of 166 patients had adverse events, with a similar incidence in the two groups (Table 2). The most common adverse events overall (occurring in ≥10% in either group) were coronavirus disease 2019 (Covid-19) and pruritus. The percentage of patients who reported pruritus adverse events was greater among patients who received placebo than among those who received seladelpar, a finding consistent with the positive effect of seladelpar on the pruritus NRS score. Adverse events that were reported more often in the seladelpar group than in the placebo group (i.e., with a between-group difference of >1 percentage points) included Covid-19 (18.0% vs. 15.4%), headache (7.8% vs. 3.1%), abdominal pain (7.0% vs.

1.5%), nausea (6.2% vs. 4.6%), and abdominal distention (6.2% vs. 3.1%); these were mild or moderate in severity and did not result in discontinuation of seladelpar or placebo. Serious adverse events were reported in 7.0% of the patients who received seladelpar and in 6.2% of those who received placebo. No serious adverse event occurred in more than one patient and none were deemed by the investigators to be related to seladelpar (Table S9). Adverse events that resulted in discontinuation of the regimen were uncommon in both groups (4.6% of the patients in the placebo group and 3.1% in the seladelpar group). One patient with cirrhosis at baseline who was treated with seladelpar had variceal bleeding after completion of the treatment period; this was the only event that was adjudicated as a clinical outcome related to primary biliary cholangitis. Additional safety details are summarized in the Supplementary Appendix.

Muscle-related adverse events occurred in 7.7% of the patients who received placebo and in

Table 1. Baseline Demographic and Clinical Characteristics.*

Characteristic	Placebo (N=65)	Seladelpar (N=128)
Age — yr	57.0±9.2	56.6±10.0
Age at diagnosis — yr	49.3±10.9	49.2±9.9
Female sex — no. (%)	60 (92.3)	123 (96.1)
Race or ethnic group — no. (%)†		
White	56 (86.2)	114 (89.1)
Asian	4 (6.2)	7 (5.5)
Black	2 (3.1)	2 (1.6)
American Indian or Alaska Native	3 (4.6)	3 (2.3)
Hispanic or Latino	27 (41.5)	29 (22.7)
Duration of disease — yr	8.6±6.5	8.2±6.7
Positive for antimitochondrial antibodies — no. (%)‡	55 (84.6)	106 (82.8)
Ursodeoxycholic acid		
History of unacceptable side effects — no. (%)	4 (6.2)	8 (6.2)
Daily dose — mg/kg§	14.9±3.3	15.0±3.1
Alkaline phosphatase level — U/liter¶	313.8±117.7	314.6±123.0
≥350 U/liter 3×ULN — no. (%)	18 (27.7)	35 (27.3)
Total bilirubin level — mg/dl‖	0.74±0.3	0.77±0.3
>ULN — no. (%)	5 (7.7)	20 (15.6)
ALT level — U/liter**	48.2±22.8	47.4±23.5
AST level — U/liter††	41.7±16.0	39.6±16.1
γ-glutamyltransferase — U/liter‡‡	287.5±249.6	269.0±240.0
Albumin level — g/dl	4.1±0.2	4.2±0.3
Platelet count — $\times 10^3/mm^3$§§	241.9±84.5	241.7±78.9
History of pruritus — no. (%)	48 (73.8)	91 (71.1)
Pruritus NRS score¶¶	3.0±3.0	3.0±2.8
≥4 — no. (%)	23 (35.4)	49 (38.3)
≥4 — mean score	6.6±1.4	6.1±1.4
Liver stiffness — kPa‖‖	8.7±4.2	9.8±6.2
Cirrhosis — no. (%)***	9 (13.8)	18 (14.1)
Portal hypertension	3 (4.6)	0

Table 1. (Continued.)

* Plus–minus values are means ±SD. Shown are demographic and clinical characteristics at baseline in patients in the intention-to-treat population. Seladelpar and placebo were administered with standard-of-care ursodeoxycholic acid unless patients had a history of unacceptable side effects. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN the upper limit of the normal range.
† Race and ethnic group were reported by the patients; data on race and ethnic group were not collected in France. Data were missing for two patients in the seladelpar group.
‡ Equivocal results were observed in one patient in the placebo group and two patients in the seladelpar group.
§ Patients continued their pretrial ursodeoxycholic acid regimen as closely as possible.
¶ The ULN is 116 U per liter in men and women.
‖ To convert the values for total bilirubin to micromoles per liter, multiply by 17.1.
** The ULN is 41 U per liter in men and women.
†† The ULN is 34 U per liter in men and women.
‡‡ The ULN is 52 U per liter in men and 38 U per liter in women.
§§ Data were missing for three patients in the seladelpar group.
¶¶ Scores on the pruritus numerical rating scale (NRS) range from 0 to 10, with 0 indicating no itch and 10 indicating the worst itch imaginable.
‖‖ Liver stiffness was assessed by means of transient elastography (FibroScan, Echosens).[26] Scores range from 1.5 to 75 (measured in kilopascals [kPa]); higher scores indicate greater liver stiffness.
*** Cirrhosis was documented if one or more of the following criteria were met: a history of liver biopsy showing cirrhosis (e.g., Ludwig stage 4 or Ishak stage 5); current or a history of decompensated liver disease, including ascites, hepatic encephalopathy, esophageal varices, or other clinical conditions consistent with liver cirrhosis, portal hypertension, or both; liver stiffness (>16.9 kPa by FibroScan) at screening; the combination of a platelet count below 140×10^3 per cubic millimeter with a serum albumin level below 3.5 g per deciliter, an international normalized ratio higher than 1.3 (not due to antithrombotic agent use), or a total bilirubin level higher than 1.0 times the ULN; the presence of radiologic evidence of cirrhosis (a nodular liver) with concurrent splenomegaly; or clinical determination by the investigator. A diagnosis of portal hypertension was ascertained on a dedicated case-report form at screening; features supporting the diagnosis were entered as medical history and included esophageal varices, ascites, splenomegaly, nonesophageal varices, and thrombocytopenia.

6.2% of the patients who received seladelpar. All muscle-related adverse events in patients who were treated with seladelpar were grade 1 or 2. One event of grade 3 myalgia occurred in a patient who received placebo.

Postbaseline ALT or AST levels that were 3 or more times the ULN were observed in seven patients (10.8%) who received placebo and in nine (7.0%) who received seladelpar. One patient who received seladelpar had liver enzyme levels that were 5 or more times the ULN in the context of amoxicillin use; seladelpar administration was interrupted, but the patient subsequently completed treatment. Creatine kinase and serum creatinine levels were similar in the two groups (Table S10). Three patients (one receiving placebo and two receiving seladelpar) had postbaseline creatine kinase levels that were more than 3 times the ULN. One patient treated with seladelpar had a transient increase in creatinine levels to 1.5 or more times the baseline levels, but the levels were still within the normal range. There were no adverse events associated with a change in renal function. The safety profile was similar in patients who had cirrhosis at baseline and in those who did not have cirrhosis at baseline (Table S11).

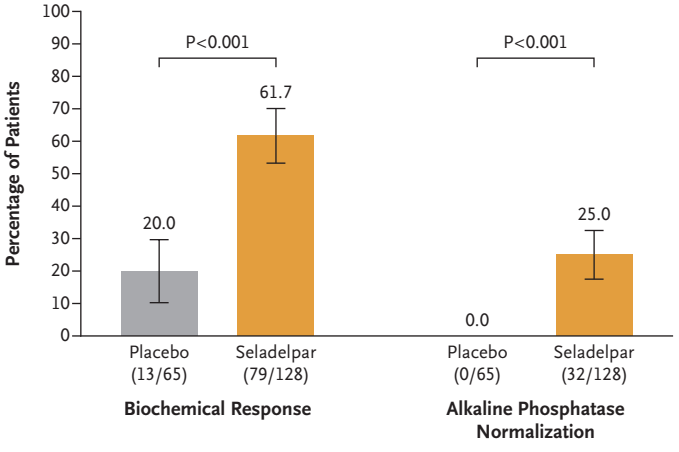
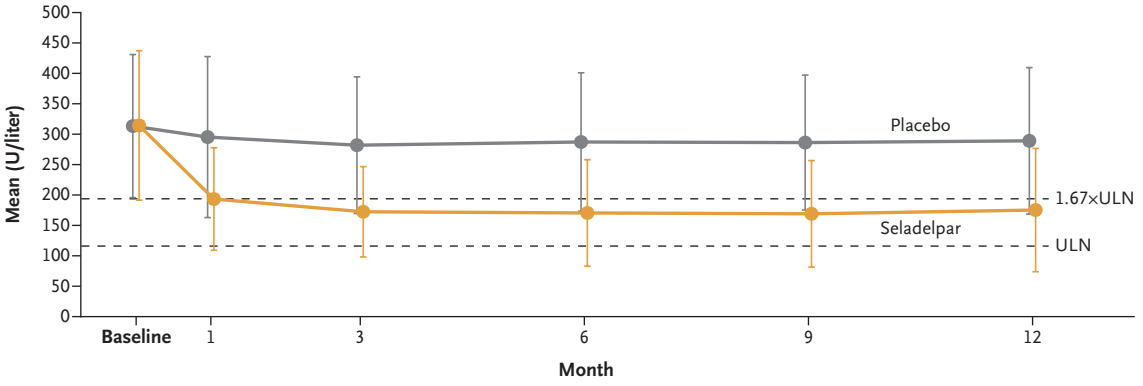


Figure 1. Biochemical Response and Normalization of Alkaline Phosphatase Levels.

Shown are the percentages of patients who met the primary end-point criteria (biochemical response, defined as an alkaline phosphatase level <1.67 times the upper limit of the normal range [ULN], with a decrease of ≥15% from baseline, and a normal total bilirubin level at month 12) and the key secondary end-point criterion of normalization of alkaline phosphatase levels at month 12. P values were calculated with the use of a Cochran–Mantel–Haenszel test adjusted for stratification variables at randomization. A total of 8 patients in the placebo group and 14 in the seladelpar group were missing data for both end points. I bars indicate 95% confidence intervals. Seladelpar and placebo were administered with standard-of-care ursodeoxycholic acid unless patients had a history of unacceptable side effects.

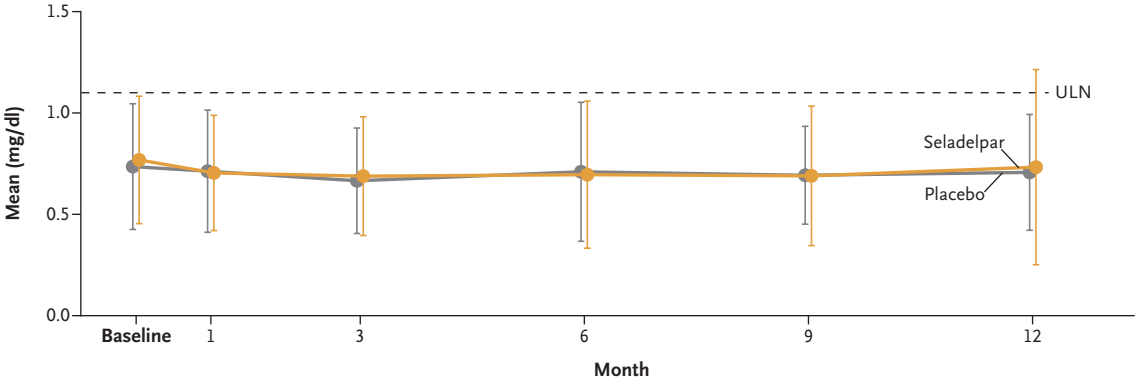
A Alkaline Phosphatase Serum Level



No. at Risk	Baseline	1	3	6	9	12
Placebo	65	62	62	61	58	57
Seladelpar	128	125	125	122	117	114

LSM Percent Change (95% CI)	1	3	6	9	12
Placebo	−4.8 (−10.2 to 0.5)	−8.0 (−12.2 to −3.9)	−5.9 (−10.9 to −1.0)	−4.5 (−11.0 to 2.0)	−4.3 (−11.1 to 2.6)
Seladelpar	−36.2 (−40.2 to −32.2)	−43.4 (−46.6 to −40.2)	−44.8 (−48.6 to −41.1)	−42.8 (−47.5 to −38.1)	−42.4 (−47.4 to −37.4)

B Total Bilirubin Serum Level



No. at Risk	Baseline	1	3	6	9	12
Placebo	65	62	62	61	58	57
Seladelpar	128	125	125	122	117	114

LSM Percent Change (95% CI)	1	3	6	9	12
Placebo	−0.7 (−6.2 to 4.7)	−5.8 (−10.5 to −1.0)	1.2 (−6.0 to 8.4)	2.5 (−5.3 to 10.4)	3.6 (−8.3 to 15.4)
Seladelpar	−6.1 (−10.0 to −2.2)	−8.8 (−12.3 to −5.4)	−8.2 (−13.4 to −3.1)	−6.7 (−12.3 to −1.2)	−0.4 (−8.7 to 8.0)

Figure 2. Alkaline Phosphatase and Total Bilirubin Levels through Month 12.

Panel A shows the mean observed alkaline phosphatase levels and the least-squares mean (LSM) percent change from baseline at each trial visit through month 12. Panel B shows the mean observed total bilirubin levels and the LSM percent change from baseline at each trial visit through month 12. I bars in both panels indicate standard deviations. The LSM difference at month 12 was −38.2 percentage points (95% CI, −46.3 to −30.1) for the alkaline phosphatase level and −3.9 percentage points (95% CI, −18.4 to 10.5) for the total bilirubin level. Seladelpar and placebo were administered with standard-of-care ursodeoxycholic acid unless patients had a history of unacceptable side effects.

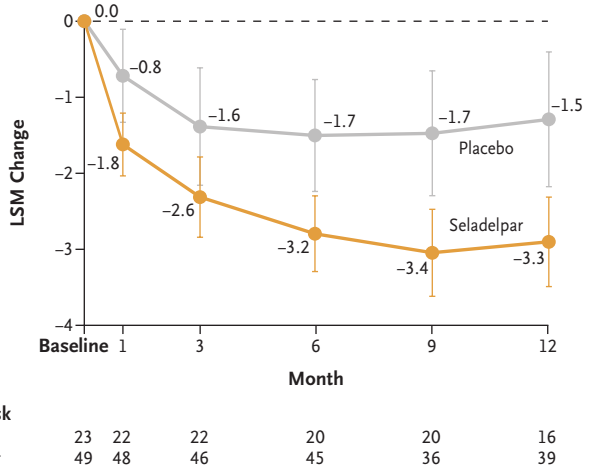
DISCUSSION

In this phase 3, 12-month, randomized, placebo-controlled trial, the selective PPARδ agonist seladelpar elicited biochemical responses while also reducing pruritus in patients with primary biliary cholangitis who had had an inadequate response to or who had a history of unacceptable side effects with ursodeoxycholic acid. A significantly greater percentage of patients treated with seladelpar (61.7%) than patients receiving placebo (20.0%) met the primary end-point criteria of an alkaline phosphatase level of less than 1.67 times the ULN, with a decrease of 15% or more from baseline, and a normal total bilirubin level at month 12. In addition, 25.0% of the patients treated with seladelpar had normalization of the alkaline phosphatase level at month 12 as compared with none of the patients receiving placebo. Reductions in alkaline phosphatase levels and other biochemical markers of the disease activity of primary biliary cholangitis, including reductions in ALT and γ-glutamyltransferase levels, appeared to occur early and to be sustained through month 12 in the seladelpar group.

In contrast to the finding of worsened pruritus observed with obeticholic acid,[10] the only FDA-approved second-line therapy for primary biliary cholangitis, pruritus decreased with seladelpar in patients with moderate-to-severe pruritus at baseline. Seladelpar also reduced other measures of itch and decreased levels of the pruritogenic cytokine interleukin-31.

The biochemical response observed in this trial is consistent with the results of the preliminary placebo-controlled trial of seladelpar at 3 months.[22] The reductions in alkaline phosphatase levels reported here are generally consistent with results previously reported for PPAR agonists that activate multiple PPAR subtypes.[7,36-43] The reductions in markers of cholestasis, liver injury, and inflammation with seladelpar reported here and published previously[20,22] are consistent with the antiinflammatory effects of PPARδ agonists.[14,15] Seladelpar appeared to reduce pruritus across multiple measures. Taken together, these findings provide evidence that seladelpar lessens the risk of disease progression and reduces symptoms in patients with primary biliary cholangitis.

Adverse events that resulted in discontinuation of seladelpar or placebo were rare, and the incidence of serious adverse events was similar in



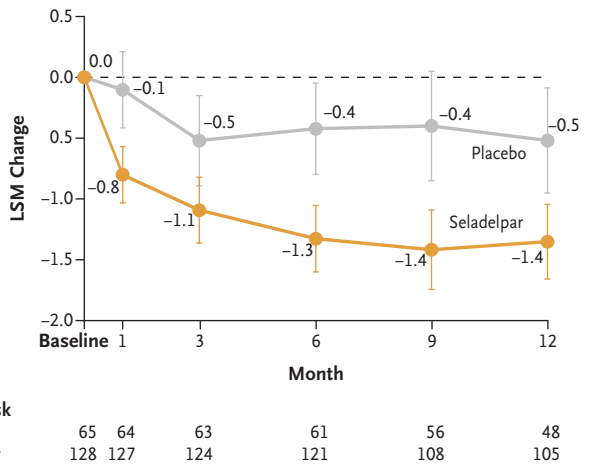


Figure 3. Change in Pruritus Numerical Rating Scale (NRS) Scores According to Time and Trial Group.

Shown are the LSM changes from baseline in pruritus NRS scores at all trial visits through month 12 among patients with a baseline NRS score of at least 4 (Panel A) and in the overall patient population (Panel B). For the key secondary end point of the change from baseline in pruritus NRS scores at month 6 among patients with a baseline pruritus NRS score of at least 4, the LSM difference was −1.5 points (95% CI, −2.5 to −0.5; P=0.005). For the change from baseline in pruritus NRS scores at month 6 in the overall population, the LSM difference was −0.9 points (95% CI, −1.4 to −0.5). I bars in both panels indicate 95% confidence intervals. A mixed-effect model for repeated measures was used to analyze the change in the weekly mean pruritus NRS scores under a missing-at-random assumption. A missing assessment at a specific time point was imputed as the mean of the adjacent 2 weeks (i.e., the week before and the week after the missing time point). If the assessment was still missing, no further imputation was performed. For Panel A, two patients in the seladelpar group were missing data at month 6. For Panel B, two patients in the placebo group and seven in the seladelpar group were missing data at month 6. Seladelpar and placebo were administered with standard-of-care ursodeoxycholic acid unless patients had a history of unacceptable side effects.

Table 2. Adverse Events and Serious Adverse Events.*

Event	Placebo (N=65)	Seladelpar (N=128)
	number (percent)	
Any adverse event	55 (84.6)	111 (86.7)
Any serious adverse event	4 (6.2)	9 (7.0)
Adverse events in ≥5% of patients		
Coronavirus disease 2019	10 (15.4)	23 (18.0)
Pruritus	10 (15.4)	6 (4.7)
Upper respiratory tract infection	6 (9.2)	1 (0.8)
Headache	2 (3.1)	10 (7.8)
Nasopharyngitis	5 (7.7)	7 (5.5)
Pharyngitis	5 (7.7)	4 (3.1)
Abdominal pain	1 (1.5)	9 (7.0)
Arthralgia	4 (6.2)	8 (6.2)
Fatigue	4 (6.2)	8 (6.2)
Nausea	3 (4.6)	8 (6.2)
Abdominal distention	2 (3.1)	8 (6.2)
Asthenia	4 (6.2)	5 (3.9)
Urinary tract infection	4 (6.2)	4 (3.1)
Hypertension	4 (6.2)	4 (3.1)
Positional vertigo	4 (6.2)	1 (0.8)

* Shown is the number of patients with at least one reported event. Details regarding discontinuations of treatment or placebo due to adverse events and all serious adverse events are provided in the Safety Results section and Table S9, respectively, in the Supplementary Appendix. Seladelpar and placebo were administered with standard-of-care ursodeoxycholic acid unless patients had a history of unacceptable side effects.

the two groups. No worrisome adverse events affecting the muscles were observed, including among patients receiving statins. Certain gastrointestinal events — abdominal pain, abdominal distention, and nausea — were reported more frequently in the seladelpar group than in the placebo group. A substantial percentage of eligible patients (96.4%) who participated in the RESPONSE trial chose to enroll in the extension trial to evaluate long-term safety and the side-effect profile of seladelpar. No clinically meaningful differences in efficacy or safety were apparent among the 14.0% of patients with cirrhosis or the 6.2% of patients who received the trial product without ursodeoxycholic acid as background therapy. There were no patients with advanced primary biliary cholangitis, including hepatic decompensation, in this trial, and seladelpar remains to be studied in these patients.

In this trial involving patients with primary biliary cholangitis who had had an inadequate response to or who had a history of unacceptable side effects with ursodeoxycholic acid, the percentage of patients who met the primary end-point criteria and had normalization of alkaline phosphatase levels was significantly greater with seladelpar than with placebo. Furthermore, seladelpar significantly reduced pruritus in patients who had had moderate-to-severe pruritus at baseline. Adverse events were not more common with seladelpar than with placebo.

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APPENDIX

The authors' full names and academic degrees are as follows: Gideon M. Hirschfield, Ph.D., Christopher L. Bowlus, M.D., Marlyn J. Mayo, M.D., Andreas E. Kremer, M.D., Ph.D., John M. Vierling, M.D., Kris V. Kowdley, M.D., Cynthia Levy, M.D., Alejandra Villamil, M.D., Alma L. Ladrón de Guevara Cetina, M.D., Ewa Janczewska, M.D., Ph.D., D.Sc., Ehud Zigmond, Ph.D., Sook-Hyang Jeong, M.D., Ph.D., Yusuf Yilmaz, M.D., Yiannis Kallis, Ph.D., Christophe Corpechot, M.D., Peter Buggisch, M.D., Pietro Invernizzi, M.D., Ph.D., Maria Carlota Londoño Hurtado, M.D., Sandrin Bergheanu, M.D., Ph.D., Ke Yang, Ph.D., Yun-Jung Choi, Ph.D., Daria B. Crittenden, M.D., and Charles A. McWherter, Ph.D.

The authors' affiliations are as follows: the Toronto Centre for Liver Disease, Division of Gastroenterology and Hepatology, University Health Network, Toronto General Hospital, Toronto (G.M.H.); the Division of Gastroenterology and Hepatology, University of California Davis School of Medicine, Sacramento (C.L.B.), and CymaBay Therapeutics, Newark (K.Y., Y.-J.C., D.B.C., C.A.M.) — both in California; the University of Texas Southwestern Medical School, Dallas (M.J.M.), and the Departments of Medicine and Surgery, Baylor College of Medicine, Houston (J.M.V.) — both in Texas; the Department of Gastroenterology and Hepatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland (A.E.K.); Liver Institute Northwest, Seattle (K.V.K.); the Division of Digestive Health and Liver Diseases, University of Miami, Miami (C.L.); the Liver Autoimmunity Unit, Hospital Italiano de Buenos Aires, Buenos Aires (A.V.); Centro de Investigación y Gastroenterología, Mexico City (A.L.L.G.C.); the Department of Basic Medical Sciences, Faculty of Public Health in Bytom, Medical University of Silesia, Bytom, Poland (E.J.); the Gastroenterology Institute, Tel Aviv Sourasky Medical Center, Israel and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (E.Z.); the Department of Internal Medicine, Seoul

National University Bundang Hospital, Seoul National University, College of Medicine, Seongnam, South Korea (S.-H.J.); the Department of Gastroenterology, School of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey (Y.Y.); Barts Liver Centre, Blizard Institute, Queen Mary University of London, London (Y.K.); the Reference Center for Inflammatory Biliary Diseases and Autoimmune Hepatitis, French Network for Rare Liver Disease in Children and Adults FILFOIE, European Reference Network RARE-LIVER, Saint-Antoine Hospital and Research Center, Assistance Publique–Hôpitaux de Paris, Sorbonne University, Paris (C.C.); Liver Centre Hamburg at Ifi-Institute, Hamburg, Germany (P.B.); the Division of Gastroenterology, Center for Autoimmune Liver Diseases, Department of Medicine and Surgery, University of Milan-Bicocca, and the European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Fondazione IRCCS San Gerardo dei Tintori — both in Monza, Italy (P.I.); the Liver Unit, Hospital Clínic Barcelona, Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer, CIBEREHD, European Reference Network on Hepatological Diseases (ERN-LIVER), University of Barcelona, Barcelona (M.C.L.H.); and Saberg Clinical Research, the Hague, the Netherlands (S.B.). Dr. Hirschfield is the Lily and Terry Horner Chair in Autoimmune Liver Disease Research at Toronto General Hospital.

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