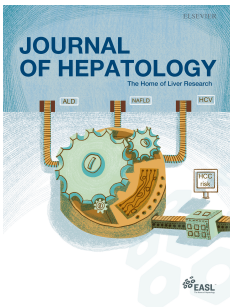
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Seladelpar for alkaline phosphatase normalization in primary biliary cholangitis: The IDEAL phase III randomized controlled trial

Cynthia Levy, Susheela Carroll, Kris V. Kowdley, Christopher L. Bowlus, Ira M. Jacobson, Marlyn J. Mayo, Sonal Kumar, Stuart C. Gordon, Hin Hin Ko, Mitchell L. Shiffman, Ziad Younes, Yan Zhou, Mark Sheng, Anna Zagorska, Daria B. Crittenden

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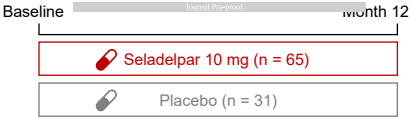
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IDEAL phase III randomized-controlled trial

Key inclusion criteria

- PBC with intolerance or inadequate response to UDCA
- ALP 1-1.67× ULN



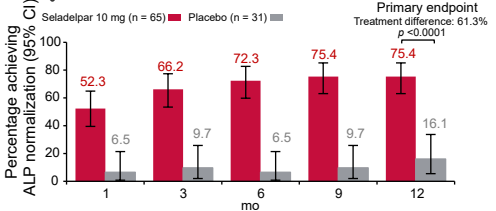
Primary endpoint

- ALP normalization defined as ALP ≤ULN with ≥15% decrease from baseline at month 12

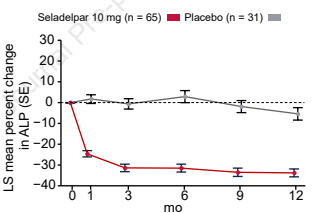
Secondary endpoints

- ALP normalization and change in ALP at each timepoint

Primary endpoint: ALP normalization



ALP reduction from baseline (%)



Safety

	Seladelpar 10 mg (n = 65)	Placebo (n = 31)
AEs	78.5%	83.9%
SAEs	3.1%	12.9%
AEs leading to discontinuation	1.5%	6.5%

In patients with PBC and ALP between 1-1.67× ULN, seladelpar treatment led to ALP normalization in a higher proportion *vs.* placebo, with no new safety concerns

Seladelpar for alkaline phosphatase normalization in primary biliary cholangitis: The IDEAL phase III randomized controlled trial

Short title: Seladelpar and ALP normalization in PBC

Clinical trial number: ClinicalTrials.gov, NCT06060665

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Keywords: primary biliary cholangitis, alkaline phosphatase, normalization, seladelpar, PPAR delta, disease progression, pruritus, fatigue, safety

Background & Aims: Alkaline phosphatase (ALP) <1.67× the upper limit of normal (ULN) has historically been a treatment goal in primary biliary cholangitis (PBC). However, elevation in ALP below this threshold has been shown to increase the risk of disease progression, especially in patients with additional risk factors. We evaluated the effect of seladelpar, a selective peroxisome proliferator-activated receptor delta agonist approved for PBC, on ALP normalization when levels are above normal but <1.67× ULN.

Methods: In this phase III, double-blind trial, patients receiving ursodeoxycholic acid (UDCA) or intolerant to UDCA with ALP between 1–1.67× ULN were randomized 2:1 to receive once-daily seladelpar 10 mg or placebo for 12 months. The primary endpoint was ALP normalization defined as a composite of ALP ≤ULN with at least a 15% decrease from baseline at Month 12. Secondary endpoints included ALP change over time.

Results: Overall, 96 patients underwent randomization. At Month 12, ALP normalization based on the composite endpoint occurred in a significantly higher proportion of patients receiving seladelpar (75.4%, 49/65) compared with placebo (16.1%, 5/31; stratum-adjusted treatment difference [95% CI]:

61.3% [44.9%, 77.7%], *p* <0.0001). ALP reduction with seladelpar was observed starting from Month 1 and throughout the treatment period (least squares [LS] mean percent change from baseline at Month 12 was −33.8% for the seladelpar group and −5.4% for the placebo group). Adverse event incidence was similar between seladelpar and placebo groups; serious adverse events occurred in 3.1% and 12.9% of patients, respectively.

Conclusions: Seladelpar normalized ALP in a substantial proportion of patients with PBC and ALP levels between 1–1.67× ULN despite UDCA use and was generally safe and well tolerated in this population.

Impact and implications

Most clinical trials in primary biliary cholangitis (PBC) have enrolled patients with alkaline phosphatase (ALP) ≥1.67× the upper limit of normal (ULN). However, evidence indicates that any ALP elevation reflects disease activity and may increase the risk of serious clinical events, including liver transplantation and death. Interest is growing in normalizing biochemical markers in PBC, particularly for patients with high liver stiffness, advanced disease, younger age at diagnosis, or other high-risk features. This is the first phase III study of second-line treatment in patients with PBC and ALP above normal but <1.67× ULN using seladelpar. Compared with placebo, seladelpar led to ALP normalization (ALP ≤ULN with at least a 15% decrease from baseline) in a significantly higher proportion of patients at Month 12, and was consistently observed across subgroups, including those with features associated with disease progression. No new safety concerns were identified. These findings show that ALP normalization with seladelpar is achievable in

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patients with PBC and baseline ALP levels between 1–1.67× ULN, which may help guide its clinical use.

<H1>Introduction

Primary biliary cholangitis (PBC) is a chronic, progressive, cholestatic liver disease that can lead to cirrhosis and hepatic decompensation without adequate treatment.[1,2] Symptoms, including pruritus and fatigue, impair quality of life. Treatment response is usually measured by reduction in alkaline phosphatase (ALP), a key marker of cholestasis, with total bilirubin as another key marker of disease severity. Historically, ALP <1.67× the upper limit of normal (ULN) was considered an adequate response to first-line therapy, ursodeoxycholic acid (UDCA), with second-line treatment recommended when levels were higher.[1,2] Accordingly, registrational trials for second-line therapies have consistently evaluated patients with ALP levels above this threshold.[3-5]

However, there is increasing evidence that any elevation in ALP >ULN, even when <1.67× ULN, reflects disease activity and may increase risk of progression to serious clinical events including liver transplant and death.[6-9] Longer duration of ALP elevation is associated with increasingly higher risk of these outcomes.[10] Lower total bilirubin is also relevant, with ALP normalization and total bilirubin ≤0.6× ULN associated with the lowest risk.[6,7,9] In addition to elevated ALP and total bilirubin levels, emerging risk factors for poor outcomes in PBC include liver stiffness ≥10 kPa, cirrhosis or portal hypertension, higher BMI, Hispanic ethnicity, male sex, and younger age at PBC diagnosis.[2,6,9,11-21]

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Seladelpar is a first-in-class delpar (selective peroxisome proliferator-activated receptor delta agonist) approved as second-line therapy that targets cells implicated in the pathobiology of PBC.[22-24] In the registrational RESPONSE trial (NCT04620733) evaluating patients with PBC and ALP ≥1.67× ULN, seladelpar significantly reduced ALP with a safety profile overall similar to placebo.[5] Seladelpar also significantly improved pruritus, a key secondary endpoint, along with reductions in the pruritogenic cytokine IL-31.[5,25,26] Efficacy and safety were consistent through two years of open-label treatment (NCT03301506),[27] and were overall similar in patients with cirrhosis.[28]

There are no data from randomized, controlled trials evaluating patients with PBC and ALP above the ULN but below the historical 1.67× ULN threshold for approved second-line treatments, like seladelpar. For the first time, we report the primary results from IDEAL (NCT06060665), a phase III trial evaluating the effect of seladelpar treatment on ALP normalization over one year in this population, including among subgroups with features reflecting high risk of progression.

<H1>Patients and methods

<H2>Patients

Patients diagnosed with PBC aged 18 to 75 years were recruited at sites in the US and Canada. Eligible patients received UDCA for ≥12 months prior to screening (stable dose for >3 months prior) or had a history of UDCA intolerance and had at least one ALP value >ULN but <1.67× ULN during screening (assessed via a central laboratory with ULN defined as 116 U/L for women and men).

Key exclusion criteria were previous seladelpar exposure, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5× ULN, total bilirubin >2× ULN, clinically important hepatic decompensation, or other chronic liver diseases. Prior treatment with other second-line therapy was allowed if there was no use within 6 weeks of screening (full eligibility criteria in supplementary methods).

<H2>Trial oversight and design

The protocol 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.[29,30] All patients provided written informed consent.

In this phase III, multicenter, double-blind, randomized, placebo-controlled trial, patients were randomized 2:1 to receive seladelpar 10 mg or placebo for one year via a once-daily oral capsule. The trial drug was administered alongside a stable dose of UDCA unless the patient was intolerant. Randomization was performed centrally via an interactive response technology system. The stratified permuted blocks allocation method was used for randomization, with stratification by ALP level (<1.3× ULN *vs.* ≥1.3× ULN) for equal distribution of patients in the higher and lower ALP range across treatment groups, and pruritus numeric rating scale (NRS; <4 *vs.* ≥4). Investigators performed laboratory and safety assessments at baseline and Months 1, 3, 6, 9, and 12 (weeks 4, 12, 26, 39, and 52, respectively). A safety follow-up visit occurred two weeks after the end of treatment (Fig. S1).

<H2>Endpoints

The primary endpoint was ALP normalization defined as a composite of ALP ≤ULN with at least a 15% decrease from baseline at Month 12. Secondary endpoints assessed biochemical response at each timepoint including ALP level ≤ULN and ALP normalization as defined above. Change from baseline in ALP at each visit was evaluated. The safety and tolerability of seladelpar compared to placebo over 52 weeks was assessed as a primary endpoint based on adverse events (AEs), with laboratory findings also evaluated.

Exploratory endpoints over 12 months included change from baseline in total bilirubin, ALT, AST, and gamma-glutamyltransferase (GGT); the proportion of patients achieving total bilirubin ≤0.6× ULN; and those with a deep response defined as normal (≤ULN) ALP, total bilirubin, ALT, and AST. Changes in IL-31, IgM, high-sensitivity C-reactive protein (hsCRP), bile acid precursor 7α-hydroxy-4-cholesten-3-one (C4), total bile acids, fibroblast growth factor 21 (FGF21), liver stiffness by transient elastography (FibroScan or comparable device), and lipids were assessed. Change in pruritus NRS, PBC-40 quality-of-life questionnaire, and 5-D Itch scores were also evaluated. NRS scores ranged from 0 (no itch) to 10 (worst itch imaginable).[31]

The primary endpoint was examined using prespecified subgroups, which included patients with features known to increase risk of disease progression such as age <50 years at PBC diagnosis, male sex, and total bilirubin >0.6× ULN. Additional *post hoc* subgroups evaluated patients with liver stiffness ≥10 kPa and patients with ≥1 risk factor for disease progression (defined by elevated liver stiffness or ≥1 of the other risk factors based on age at PBC diagnosis, sex, or total bilirubin).

Additional details are included in the supplementary methods.

<H2>Statistical analysis

Seladelpar and placebo response rates for the primary endpoint at Month 12 were assumed to be 75% and 30%, respectively, based on changes in ALP from previous trials.[5,32] Allowing for a 10% dropout rate, a sample size of 90 patients was calculated to provide at least 90% power to detect a difference between treatment groups using a chi-square test at a significance level of 0.05. Efficacy and safety analyses included all randomized patients who received at least one dose of seladelpar or placebo.

Efficacy data were analyzed with an intention-to-treat principle according to group assignment. The Cochran-Mantel-Haenszel test was used to compare the primary endpoint between treatment groups, stratified by baseline ALP level (<1.3× ULN *vs.* ≥1.3× ULN). The stratified Cochran-Mantel-Haenszel chi-square *p* value is provided, with significance indicated as $p \leq 0.05$.

Secondary and exploratory endpoint results were not adjusted for multiple testing; descriptive point estimates and variability, along with 95% CIs for treatment differences, are reported. For dichotomized secondary efficacy endpoints, the same methodology as for the primary endpoint was used. Patients with missing measurements were considered non-responders for categorical endpoints. Continuous secondary and exploratory efficacy endpoints were analyzed using descriptive statistics, in addition to a mixed-effects model for repeated measures, when appropriate, with no imputation for missing data. Safety data were analyzed based on investigational product received (seladelpar *vs.* placebo).

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AEs were summarized according to preferred terms in the Medical Dictionary for Regulatory Activities (v28.1), with severity graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (v5.0). Additional information can be found in the supplementary methods.

<H1>Results

<H2>Patients

A total of 96 patients were randomized to receive seladelpar (65 patients) or placebo (31 patients). Patients were enrolled from 34 sites in the US and one site in Canada; the first patient was enrolled on September 5, 2023, and the last trial visit was on May 6, 2026. Overall, 89 patients completed the trial; three withdrew from the seladelpar group, and four withdrew from the placebo group (Fig. 1).

Baseline characteristics were generally similar between the groups (Tables 1 and S1). Mean ALP was 153 U/L (1.3× ULN) and mean total bilirubin was 0.62 mg/dl, with 30 (31.3%) patients having total bilirubin >0.6× ULN. Mean pruritus NRS was 2.1. Nineteen (19.8%) patients reported an NRS score of ≥4; among these, mean NRS was 6.0. Metabolic syndrome was present in 30.2% of patients (Table S1). Mean values were 198 mg/dl for total cholesterol, 104 mg/dl for LDL-C, and 71 mg/dl for HDL-C; approximately 40% of all patients were receiving a statin at baseline (Table S1). A total of 57 enrolled patients (59.4%) met ≥1 criterion for high risk of disease progression (Table 1). A high-risk GLOBE score of >0.3 was observed in 34.4% of enrolled patients (Table S1).

<H2>Efficacy

<H3>Biochemical response

At Month 12, the primary endpoint of ALP ≤ULN with a decrease of ≥15% from baseline was met by 75.4% of patients receiving seladelpar and 16.1% of patients receiving placebo (stratum-adjusted treatment difference [95% CI]: 61.3% [44.9% to 77.7%]; *p* <0.0001; Fig. 2A). Normalization as assessed by the composite endpoint was consistently achieved by more patients receiving seladelpar *vs.* placebo at all timepoints, including the first on-treatment visit at Month 1 (52.3% *vs.* 6.5%, stratum-adjusted treatment difference [95% CI]: 47.9% [32.2% to 63.6%]). Across predefined patient subgroups, including among patients with risk factors for progression based on age at PBC diagnosis, sex, or baseline total bilirubin, results were generally similar to the overall patient population and in favor of seladelpar (Fig. 3). Results were also similar for *post hoc* analyses of patients with liver stiffness ≥10 kPa and with ≥1 risk factor for disease progression (Fig. 3). Across all timepoints, a higher proportion of patients receiving seladelpar achieved ALP ≤ULN compared with placebo. At Month 12, 76.9% of patients receiving seladelpar and 16.1% of patients receiving placebo achieved ALP ≤ULN (stratum-adjusted treatment difference [95% CI]: 63.1% [46.9% to 79.2%]; Fig. S2). Least squares (LS) mean levels of ALP decreased from baseline with a change of –33.8% in patients receiving seladelpar *vs.* –5.4% in patients receiving placebo at Month 12 (LS mean difference –28.4%; 95% CI –35.4% to –21.4%; Fig. 2B). LS mean ALP values were reduced from baseline at Month 12 with a change of –52 U/L for the seladelpar group compared with –8 U/L for the placebo group (LS mean difference –44 U/L; 95% CI –55 U/L to –33 U/L; Fig. S3).

Total bilirubin was reduced in the seladelpar group *vs.* the placebo group for the percent change from baseline at Months 1 and 6, although it

was similar between groups at Month 12 (Fig. 4A). Of patients with baseline total bilirubin >0.6× ULN, 57.9% (11/19) receiving seladelpar had total bilirubin ≤0.6× ULN at Month 12 *vs.* 27.3% (3/11) receiving placebo (Fig. S4). Greater decreases in ALT were observed in patients receiving seladelpar *vs.* patients receiving placebo at Month 12 (LS mean percent change from baseline –22.5% *vs.* –5.6%; LS mean difference –16.8%; 95% CI –29.3% to –4.4%; Fig. 4B), while AST levels remained stable from baseline in both groups (Fig. S5). GGT decreased for the seladelpar *vs.* placebo group at Month 12 (–29.9% *vs.* –4.4%; LS mean difference –25.4%; 95% CI –37.9% to –13.0%; Fig. 4C). In the seladelpar group, 66.2% (43/65) achieved deep response at Month 12 *vs.* 16.1% (5/31) in the placebo group (Fig. S6).

<H3>Biomarkers of pruritus, immune reactivity and inflammation, bile acids, liver stiffness measurement, and lipids

Decreases in levels of the pruritogenic cytokine IL-31 were observed with seladelpar treatment, whereas IL-31 levels increased in the placebo group at Month 12 (–39.0% *vs.* 11.2%; LS mean difference –50.2%; 95% CI –78.4% to –22.1%; Fig. 5A). Reductions in immune reactivity and inflammatory markers IgM and hsCRP were also observed with seladelpar treatment, along with a numerical reduction in total bile acids (Fig. 5B–D); in addition, seladelpar led to numerical decreases in bile acid synthesis intermediate C4 and increases in FGF21, a negative regulator of bile acid synthesis (Fig. S7). Liver stiffness remained stable through Month 12 in both groups (Table S2). The seladelpar-treated group had decreases in total cholesterol and LDL-C, and increases in HDL-C compared with the placebo group (Table S3).

<H3>Pruritus, sleep disturbance, and fatigue

A total of 14 patients (21.5%) in the seladelpar group and 5 (16.1%) in the placebo group had moderate-to-severe pruritus (NRS score ≥4) at baseline (Table 1). Among these patients, mean (SD) pruritus NRS score decreased from baseline by –3.1 (2.2) points and –1.8 (1.5) points in the seladelpar and placebo groups at Month 12, respectively, with similar numerical trends observed at earlier timepoints (Table 2; Fig. S8). The percentage of patients with moderate-to-severe pruritus at baseline achieving ≥3-point decline in NRS was 9/14 (64.3%) in the seladelpar group and 1/5 (20.0%) in the placebo group at Month 12 (Table 2). Among patients with moderate-to-severe pruritus, mean decreases from baseline in PBC-40 itch domain, PBC-40 sleep disturbance item, PBC-40 fatigue domain, and 5-D itch scale scores were numerically greater in the seladelpar group than in the placebo group over 12 months (Table 2; Fig. S8). Change in pruritus NRS and PBC-40 fatigue domain scores in the overall population at Month 12 are reported in Table S4; fatigue scores remained stable overall in both groups.

<H2>Safety

The safety of seladelpar was assessed as a primary endpoint. A total of 77 (80.2%) patients reported AEs, with a similar incidence in the two treatment groups (Table 3). Within the seladelpar group, all but three events were mild or moderate in severity. The most frequently reported events among patients who received seladelpar were arthralgia, pruritus, and fatigue, all of which were mild or moderate in severity. Serious AEs were reported in 3.1% of patients who received seladelpar and 12.9% who received placebo (Table S5); none were deemed related to the trial drug by the investigators. Three patients overall discontinued trial treatment due to AEs (breast cancer in the

seladelpar group; pruritus and lung cancer in the placebo group). There were no deaths.

There were no AEs reflecting liver toxicity among patients receiving seladelpar and no instances of ALT or AST >3× ULN in either group. No AEs associated with renal function changes were reported. Muscle-related AEs occurred at a similar frequency in both groups (seladelpar: 4.6%; placebo: 3.2%). One patient receiving seladelpar with a history of osteoporosis had a wrist fracture after a fall. Serum creatinine and creatine kinase remained stable in both treatment groups (Fig. S9). Additional information is available in the supplementary safety results.

<H1>Discussion

This is the first phase III randomized clinical trial to assess second-line treatment for PBC in patients with ALP that is elevated but <1.67× ULN, the historical threshold for treatment escalation. We show that seladelpar treatment led to ALP normalization in a significantly higher proportion of patients, with 75.4% achieving the normalization composite endpoint compared with 16.1% of placebo patients. These findings are clinically important and timely, since data suggest that any ALP elevation predicts increased likelihood of adverse outcomes, particularly when other risk factors are present.[6-9] Recent professional society consensus includes ALP normalization as part of the ideal treatment response in PBC, with an emphasis on patients with liver stiffness ≥10 kPa or those aged ≤60 years.[33,34] Consistent with prior seladelpar trials evaluating patients with ALP ≥1.67× ULN[5], seladelpar led to rapid and sustained reductions in ALP in this trial, a finding of particular clinical relevance given that prolonged exposure to

elevated ALP has been associated with an increased risk of adverse outcomes.[10] Improvements in other biochemical markers with seladelpar were also observed. Seladelpar reduced the liver injury markers ALT and GGT, and a higher proportion of patients receiving seladelpar achieved a deep response, defined as normalization of ALP, total bilirubin, ALT, and AST. Among patients with baseline total bilirubin >0.6× ULN, a threshold associated with increased risk of progression,[6,7,9] over half who received seladelpar had values below this threshold by Month 12, and ≥90% had normalized ALP. Improvements in markers of immune reactivity, inflammation, and bile acid levels support additional effects of seladelpar in this population. Lipids also improved with seladelpar, which is notable given that almost one-third of patients had metabolic syndrome.

Pruritus was evaluated as an exploratory endpoint. Decreases in pruritus NRS, 5-D itch, PBC-40 itch, and PBC-40 fatigue scores were observed in the 19 patients who had moderate-to-severe pruritus at baseline, consistent with the previously established effect of seladelpar on pruritus and as mechanistically supported by decreased levels of IL-31.[5,25]

Seladelpar has consistently demonstrated a safety profile generally similar to placebo across earlier studies and during continued treatment in the open-label setting,[5,27,32] and no new safety concerns were identified in this trial. Reported rates of pruritus and fatigue as AEs were consistent with those expected in this patient population. There were no liver, muscle, or renal safety concerns.

This trial expands the evidence for seladelpar beyond the earlier registrational RESPONSE trial, which evaluated patients with baseline ALP

≥1.67× ULN and demonstrated ALP normalization in 25% of patients who received seladelpar *vs.* no patients who received placebo.[5] The high rate of ALP normalization with seladelpar in this trial shows that improvements are possible for patients with ALP between 1–1.67× ULN. These data may help simplify future treatment algorithms for PBC by providing evidence on second-line treatment across the spectrum of ALP elevation and demonstrating that biochemical normalization is a feasible goal.

Here, we show that a greater proportion of seladelpar-treated patients achieved ALP normalization than patients receiving placebo across all subgroups examined, including those with elevated liver stiffness and other high-risk features. However, additional studies are needed to understand which patients will benefit the most from ALP normalization. Although more advanced liver fibrosis and younger age have been identified as factors associated with greater benefit from ALP normalization, additional, as-yet-unidentified patient characteristics, either individually or in combination, may contribute to an increased risk of disease progression and strengthen the rationale for achieving ALP normalization. The optimal timing for initiating second-line therapy may also warrant further evaluation. Although guidelines recommend escalation to second-line treatment if the response to UDCA alone is inadequate after 12 months, initiation of first-line combination therapy in treatment naïve patients has been shown to lead to greater ALP reductions *vs*. UDCA alone and may be a consideration for select patients.[1,2,35] Ultimately, as evidence on treatment paradigms grows, patient care should be individualized based on risk profile, patient preferences, and emerging data.

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A limitation of this trial is the lack of racial diversity and geographical restriction since enrollment occurred nearly entirely in the US; results may not be generalizable to a broader population. The low enrollment of patients with cirrhosis and elevated liver stiffness, and the high average BMI, may also limit generalizability. Another constraint was the low number of patients with moderate-to-severe pruritus, which limited our ability to measure effects on pruritus. This trial was designed to evaluate the effects of seladelpar on biochemical markers of PBC not clinical outcomes, which will be addressed in the ongoing AFFIRM trial (NCT06051617). The study was also not designed to determine which patients would benefit the most from ALP normalization; real-world evidence will be important to address this question.

This trial evaluated patients with PBC and ALP that was elevated but <1.67× ULN despite UDCA – a previously understudied population at risk for progression to adverse outcomes. Seladelpar led to a significantly higher proportion of patients achieving ALP normalization compared to placebo with no new safety concerns.

<H1>Abbreviations

AEs, adverse events; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; hsCRP, high-sensitivity C-reactive protein; NRS, numeric rating scale; LS, least squares; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

<H1>Financial support

This trial was sponsored by Gilead Sciences, Inc., who designed and sponsored the study, collected and interpreted the data, and conducted the

analyses. Gilead Sciences, Inc. also participated in the writing, reviewing, and approval of the manuscript.

<H1>Conflicts of interest

Cynthia Levy: Reports receiving research grants paid to her institution from Calliditas Therapeutics, CymaBay Therapeutics, Escient Pharmaceuticals, Gilead Sciences, Inc., GSK, Intercept Pharmaceuticals, Ipsen, Kowa, Mirum Pharma, Pliant Therapeutics, Target RWE, and Zydus Pharmaceuticals; Susheela Carroll: Employee of Gilead Sciences, Inc., and may own stock in Gilead Sciences, Inc.; Kris V. Kowdley: Reports receiving consulting fees from 89Bio, CymaBay Therapeutics, Genfit, Gilead Sciences, Inc., GSK, HighTide Biopharma, Inipharm, Intercept Pharmaceuticals, Ipsen, Madrigal Pharmaceuticals, Mirum Pharma, NGM Bio, and Zydus Pharmaceuticals; grants or contracts from 89Bio, Boston Pharmaceuticals, Corcept Therapeutics, CymaBay Therapeutics, Genfit, Gilead Sciences, Inc., GSK, Hanmi Pharmaceuticals, Intercept Pharmaceuticals, Ipsen, Janssen, Madrigal Pharmaceuticals, Mirum Pharma, Novo Nordisk, NGM Bio, Pfizer, Pliant Therapeutics, Terns Pharmaceuticals, Viking Therapeutics, and Zydus Pharmaceuticals; stock or stock options with Inipharm; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Gilead Sciences, Inc., Intercept Pharmaceuticals, Ipsen, Madrigal, and Novo Nordisk; royalties or licenses from UpToDate; and participation on a data safety monitoring board or advisory board with CTI and Medpace; Christopher L. Bowlus: Reports receiving consulting fees from Alnylam Pharmaceuticals, Astra Zeneca, Chemomab Therapeutics, CymaBay Therapeutics, Eli Lilly and Company, Esperion, Gilead Sciences, Inc., GSK,

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

<H1>Authors' contributions

Substantial contributions to trial conception or design: CL, SC, KVK, CLB, MJM, YZ, MS, DBC; substantial contributions to acquisition, analysis, or interpretation of the data: CL, SC, KVK, CLB, IMJ, MJM, SK, SCG, HHK, MLS, ZY, YZ, MS, AZ, DBC; drafting the article or reviewing it critically for important intellectual content: CL, SC, KVK, CLB, IMJ, MJM, SK, SCG, HHK, MLS, ZY, YZ, MS, AZ, DBC; final approval of the version of the article to be published: CL, SC, KVK, CLB, IMJ, MJM, SK, SCG, HHK, MLS, ZY, YZ, MS, AZ, DBC. The authors vouch for the accuracy and completeness of these data and the fidelity of the trial to the protocol.

<H1>Data availability

Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Sciences' discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datasharing@gilead.com. The full trial protocol and statistical analysis plan can be accessed at https://www.journal-of-hepatology.eu.

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Table 1. Baseline characteristics.

Characteristic	Seladelpar 10 mg (n = 65)	Placebo (n = 31)	Overall (N = 96)
Age, years, mean (SD)	61 (8.1)	60 (9.3)	61 (8.5)
Age <50 years at diagnosis, n (%)	25 (38.5)	12 (38.7)	37 (38.5)
Sex, n (%)			
Female	61 (93.8)	29 (93.5)	90 (93.8)
Male	4 (6.2)	2 (6.5)	6 (6.3)
Race or ethnic group, n (%)*			
White	58 (89.2)	25 (80.6)	83 (86.5)
Black or African American	3 (4.6)	3 (9.7)	6 (6.3)
Asian	3 (4.6)	0	3 (3.1)
Other	0	1 (3.2)	1 (1.0)
Hispanic/Latino	9 (13.8)	6 (19.4)	15 (15.6)
BMI, kg/m^2, mean (SD)	30 (6.6)	30 (8.0)	30 (7.1)
Duration of disease, years, mean (SD)	8.8 (7.3)	7.0 (5.6)	8.2 (6.8)
On ursodeoxycholic acid, n (%)	62 (95.4)	30 (96.8)	92 (95.8)
Daily dose, mg/kg, mean (SD) [Q1, Q3]	13.8 (3.6) [12.7, 16.2]	13.8 (2.4) [12.9, 15.6]	13.8 (3.2) [12.7, 15.7]
Prior use of obeticholic acid and/or fibrate, n (%)†	5 (7.7)	4 (12.9)	9 (9.4)
ALP, U/L, mean (SD)‡	154 (22.7)	150 (22.9)	153 (22.7)
≥1.3× ULN, n (%)	34 (52.3)	13 (41.9)	47 (49.0)
Total bilirubin, mg/dl, mean (SD)§	0.61 (0.19)	0.62 (0.22)	0.62 (0.20)
>0.6× ULN, n (%)	19 (29.2)	11 (35.5)	30 (31.3)
AST, U/L, mean (SD)¶	26 (7.6)	27 (10.9)	26 (8.7)
ALT, U/L, mean (SD)‖	28 (14.8)	27 (13.8)	27 (14.4)
GGT, U/L, mean (SD)**	76 (75.5)	75 (50.0)	76 (68.0)
Albumin, g/dL, mean (SD)	4.3 (0.2)	4.2 (0.3)	4.3 (0.2)
Platelet count, 10^3/µl, mean (SD)	261 (55.5)	250 (71.0)	257 (60.8)
Cirrhosis, n (%)††	1 (1.5)	1 (3.2)	2 (2.1)
Liver stiffness, kPa, mean (SD)	6.3 (2.3)	7.8 (3.5)	6.8 (2.8)
≥10 kPa, n (%)	5 (7.7)	5 (16.1)	10 (10.4)
Pruritus NRS score, mean (SD)‡‡	2.2 (2.3)	1.8 (2.4)	2.1 (2.4)
Pruritus NRS ≥4, n (%)	14 (21.5)	5 (16.1)	19 (19.8)
Pruritus NRS ≥4, mean (SD)	5.9 (1.2)	6.5 (1.8)	6.0 (1.3)
≥1 risk factor for disease progression, n (%)§§	38 (58.5)	19 (61.3)	57 (59.4)

*Patients could report multiple race or ethnicity categories; therefore, percentages do not sum to 100%. Race was not reported in 1 (1.5%) and 2 (6.5%) patients in the seladelpar and placebo groups, respectively; ethnicity was not reported in 3 (4.6%) and 1 (3.2%) patients in the seladelpar and placebo groups, respectively. †All patients who received fibrates received fenofibrate. ‡ALP ULN:116 U/L in men and women. §Total bilirubin ULN: 1.10 mg/dl in men and women. ¶AST ULN: 34 U/L in men and women. ‖ALT ULN: 41 U/L in men and women. **GGT ULN: 52 U/L in men and 38 U/L in women. ††Cirrhosis is defined in the supplementary methods. ‡‡Scores on the pruritus NRS range from 0 to 10, with 0 indicating no itch and 10 indicating the worst itch imaginable.[31] §§≥1 risk factor for disease progression was identified post-hoc and is defined as meeting at least one of the following categories at baseline: age <50 years at diagnosis, total bilirubin >0.6× ULN, liver stiffness ≥10 kPa, and/or male sex. Criteria were not mutually exclusive; therefore,

proportions of patients meeting each criterion were calculated independently and the number and percentage of patients meeting each criterion are shown in their respective rows above in Table 1. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; NRS, numeric rating scale; ULN, upper limit of normal.

Table 2. Pruritus NRS, PBC-40 itch domain, and 5-D itch scores at Month 12 among patients with baseline pruritus NRS ≥4.

	Seladelpar 10 mg	Placebo
Pruritus NRS		
Baseline, n	14	5
Mean (SD)	5.9 (1.2)	6.5 (1.8)
Month 12, n	14	5
Mean (SD) change from baseline	–3.1 (2.2)	–1.8 (1.5)
≥3-point decrease in pruritus NRS from baseline		
Baseline, n	14	5
Month 12, n (%) [95% CI]	9 (64.3%) [35.1% to 87.2%]	1 (20.0%) [0.5% to 71.6%]
PBC-40 itch domain		
Baseline, n	14	5
Mean (SD)	7.8 (2.4)	8.8 (2.2)
Month 12, n	12	4
Mean (SD) change from baseline	–1.9 (2.7)	0.8 (2.2)
5-D itch total score		
Baseline, n	14	5
Mean (SD)	15.7 (2.5)	16.3 (3.3)
Month 12, n	14	5
Mean (SD) change from baseline	–3.5 (3.4)	–0.5 (3.1)

NRS scores range from 0 (no itch) to 10 (worst itch imaginable).[31] Change from baseline and ≥3-point decrease in pruritus NRS from baseline were calculated based on weekly average of NRS values. Higher scores within the ranges of PBC-40 Itch domain (0–15) indicate worse quality of life.[36] Total 5-D Itch scores range from 5–25, with higher scores indicating worse itch-related quality of life.[37] NRS, numeric rating scale; PBC, primary biliary cholangitis.

Table 3. Safety summary.

	Seladelpar 10 mg (n = 65)	Placebo (n = 31)
Any adverse event, n (%)	51 (78.5)	26 (83.9)
Any serious adverse event, n (%)	2 (3.1)	4 (12.9)
Grade ≥3 adverse event, n (%)	3 (4.6)	4 (12.9)
Any adverse event leading to treatment discontinuation, n (%)	1 (1.5)	2 (6.5)
Adverse events in ≥5% of patients overall, n (%)*		
Influenza	1 (1.5)	5 (16.1)
Arthralgia	9 (13.8)	2 (6.5)
Constipation	5 (7.7)	4 (12.9)
Pruritus	8 (12.3)	3 (9.7)
Fatigue	7 (10.8)	1 (3.2)
Rash	3 (4.6)	3 (9.7)
COVID-19	6 (9.2)	2 (6.5)
Dry eye	4 (6.2)	2 (6.5)
Sinusitis	4 (6.2)	2 (6.5)

Dry mouth	3 (4.6)	2 (6.5)

Details regarding discontinuations of trial intervention due to adverse events and serious adverse events are provided in the supplementary safety results section. Common adverse events occurring in ≥5% of total patients are listed by MedDRA preferred term. Multiple adverse events were counted only once per patient for each preferred term. *Urinary tract infections occurred in 4 (6.2%) patients receiving seladelpar; none occurred in patients receiving placebo. COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities.

Fig. 1. Patient disposition in IDEAL. *In the placebo group, one patient who completed trial drug was lost to follow-up prior to the post-treatment safety follow-up visit and did not complete the trial. Of the four patients who discontinued the trial drug, one remained on trial and completed the trial visits without receiving the trial drug and is counted among the 27 patients who completed the trial.

Fig. 2. Primary endpoint of ALP normalization and ALP percent change from baseline over time. (A) Percentages of patients who achieved ALP normalization, defined as a composite of ALP ≤ULN [116 U/L] with ≥15% decrease from baseline, through Month 12. Treatment differences are stratum-adjusted. n/N is defined as number of responders/patients in the full analysis set. Two-sided *p* value for pair-wise comparison was based on the Cochran-Mantel-Haenszel test stratified by the baseline ALP level (<1.3× ULN *vs.* ≥1.3× ULN). (B) LS mean percent change from baseline in ALP through Month 12. Reference ranges for ALP are 37–116 U/L. Post-baseline percent changes were assessed using the MMRM. *p <0.0001 *vs.* placebo. ALP,

alkaline phosphatase; MMRM, mixed-effects model for repeated measures; ULN, upper limit of normal.

Fig. 3. ALP normalization among subgroups.

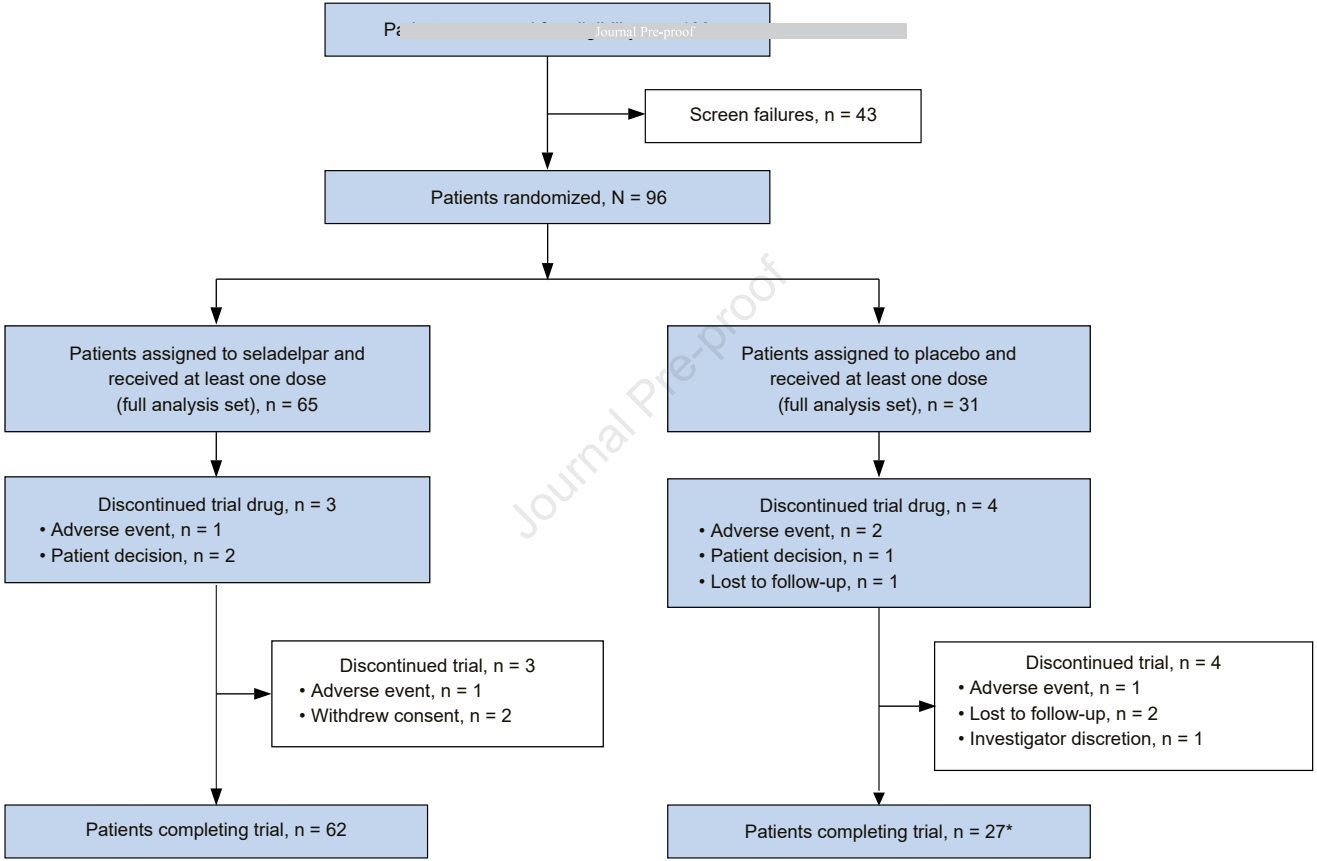
The primary endpoint of ALP normalization, defined as a composite of ALP ≤ULN [116 U/L] with ≥15% decrease from baseline, among patient subgroups at Month 12. The non-stratified treatment difference and 95% CI used the Miettinen-Nurminen method. n/N is defined as number of responders/patients in the full analysis set per subgroup. *One patient in the seladelpar group with race not reported achieved the primary endpoint. In the placebo group, two patients did not report their race, and one reported their race as Other. Treatment differences for the Asian race subgroup were not estimable. †Three patients in the seladelpar group and one in the placebo group did not report their ethnicity. ‡Analyses of patients by liver stiffness (≥10 kPa, <10 kPa) and ≥1 risk factor for disease progression (yes [defined as age <50 years at PBC diagnosis, total bilirubin >0.6× ULN, liver stiffness ≥10 kPa, and/or male sex], no) were performed *post hoc*. ALP, alkaline phosphatase; NE, not estimable; PBC, primary biliary cholangitis; ULN, upper limit of normal.

Fig. 4. Additional liver markers over time. LS mean percent change from baseline through Month 12 for (A) total bilirubin, (B) ALT, and (C) GGT. Reference range for total bilirubin is 0.1–1.1 mg/dl; for ALT is 6–41 U/L; and for GGT is 7–38 U/L in women and 11–52 U/L in men. Post-baseline percent changes were assessed using the MMRM. ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; LS, least squares; MMRM, mixed-effects model for repeated measures; TB, total bilirubin.

Fig. 5. IL-31, IgM, hsCRP, and total bile acids over time. LS mean percent change from baseline through Month 12 for (A) IL-31, (B) IgM, (C) hsCRP, and (D) total bile acids. The reference ranges for IgM and hsCRP are 40–230 mg/dl and ≤3.0 mg/L, respectively. Post-baseline percent changes were assessed using the MMRM, applied to either raw (IgM) or log-transformed (IL-31, hsCRP, and total bile acids) values based on normality assumptions. hsCRP, high-sensitivity C-reactive protein; LS, least-squares; MMRM, mixed-effects model for repeated measures.

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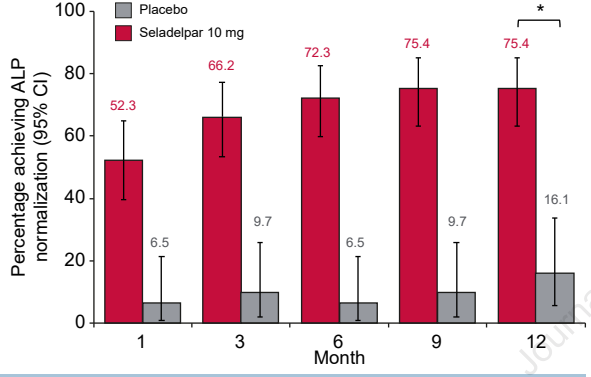
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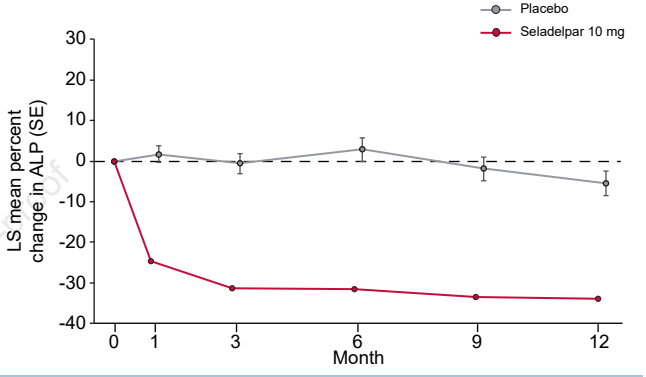
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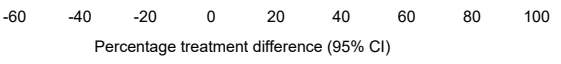


n/N	34/65	2/31	43/65	3/31	47/65	2/31	49/65	3/31	49/65	5/31
ALP ≤ULN, n (%)	35 (53.8)	4 (12.9)	46 (70.8)	4 (12.9)	48 (73.8)	4 (12.9)	50 (76.9)	6 (19.4)	50 (76.9)	5 (16.1)
≥15% decrease in ALP, n (%)	52 (80.0)	2 (6.5)	58 (89.2)	4 (12.9)	56 (86.2)	2 (6.5)	56 (86.2)	5 (16.1)	57 (87.7)	10 (32.3)
Treatment difference, % (95% CI)	47.9 (32.2 to 63.6)		58.5 (42.7 to 74.4)		67.4 (52.6 to 82.1)		67.0 (51.6 to 82.3)		61.3 (44.9 to 77.7)	

Number of patients						
Seladelpar 10 mg	65	62	63	63	61	62
Placebo	31	30	30	28	27	26
LS mean percent change (SE)						
Seladelpar 10 mg		-24.6 (1.5)	-31.4 (1.8)	-31.5 (1.9)	-33.5 (1.9)	-33.8 (1.9)
Placebo		1.7 (2.1)	-0.6 (2.5)	2.9 (2.9)	-1.9 (2.9)	-5.4 (3.0)
LS mean of difference (95% CI)		-26.3 (-31.4 to-21.3)	-30.8 (-37.0 to-24.7)	-34.4 (-41.3 to-27.6)	-31.6 (-38.5 to-24.6)	-28.4 (-35.4 to-21.4)

Journal Pre-proof

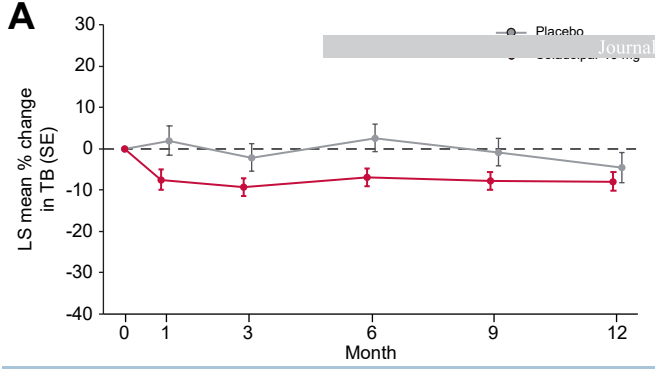
Patient group	←Favors placebo · Favors seladelpar 10 mg→	Seladelpar 10 mg n/N (%)	Placebo n/N (%)	Percentage treatment difference (95% CI)
Overall		49/65 (75.4)	5/31 (16.1)	61.3 (44.9 to 77.7)
Age at screening				
<65 yr		29/40 (72.5)	2/18 (11.1)	61.4 (35.6 to 77.0)
≥65 yr		20/25 (80.0)	3/13 (23.1)	56.9 (24.0 to 77.9)
Age at PBC diagnosis				
<50 yr		21/25 (84.0)	1/12 (8.3)	75.7 (44.1 to 89.6)
≥50 yr		28/40 (70.0)	4/19 (21.1)	48.9 (22.1 to 67.9)
Sex				
Female		46/61 (75.4)	4/29 (13.8)	61.6 (41.6 to 75.1)
Male		3/4 (75.0)	1/2 (50.0)	25.0 (–48.5 to 80.7)
Race*				
White		44/58 (75.9)	5/25 (20.0)	55.9 (33.5 to 71.5)
Black or African American		2/3 (66.7)	0/3	66.7 (–16.8 to 94.6)
Asian		2/3 (66.7)	0	NE
Ethnicity†				
Hispanic or Latinx		5/9 (55.6)	0/6	55.6 (6.3 to 81.7)
Not Hispanic or Latinx		41/53 (77.4)	5/24 (20.8)	56.5 (33.5 to 72.6)
Baseline alkaline phosphatase				
<1.3× ULN		26/31 (83.9)	5/18 (27.8)	56.1 (28.2 to 75.6)
≥1.3× ULN		23/34 (67.6)	0/13	67.6 (41.9 to 81.0)
Baseline total bilirubin				
≤0.6× ULN		31/46 (67.4)	1/20 (5.0)	62.4 (40.2 to 76.0)
>0.6× ULN		18/19 (94.7)	4/11 (36.4)	58.4 (25.7 to 81.5)
Liver stiffness measurement‡				
≥10 kPa		5/5 (100.0)	2/5 (40.0)	60.0 (0.1 to 89.0)
<10 kPa		44/60 (73.3)	3/26 (11.5)	61.8 (41.1 to 75.2)
≥1 risk factor for disease progression‡				
Yes		33/38 (86.8)	4/19 (21.1)	65.8 (40.2 to 81.9)
No		16/27 (59.3)	1/12 (8.3)	50.9 (18.6 to 70.5)



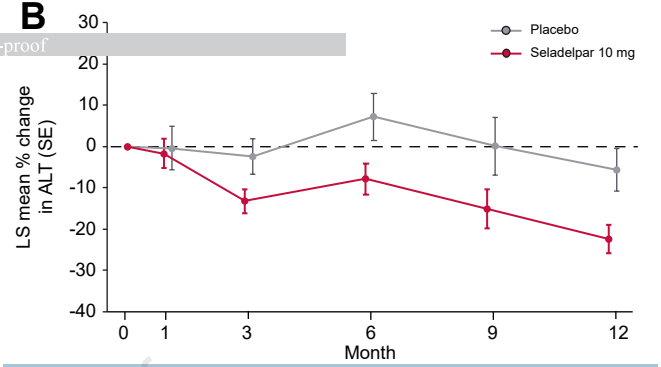
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A



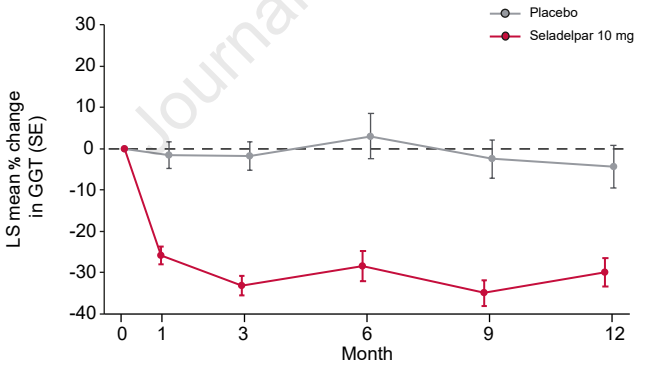
B



Number of patients						
Seladelpar 10 mg	65	62	63	63	61	62
Placebo	31	30	30	28	27	26
LS mean % change (SE)						
Seladelpar 10 mg		-7.5 (2.5)	-9.3 (2.2)	-6.9 (2.2)	-7.8 (2.2)	-7.9 (2.3)
Placebo		2.0 (3.6)	-2.1 (3.3)	2.6 (3.3)	-0.8 (3.3)	-4.5 (3.6)
LS mean of difference (95% CI)		-9.5 (-18.3 to-0.7)	-7.1 (-15.0 to 0.7)	-9.5 (-17.4 to-1.6)	-7.0 (-14.8 to 0.8)	-3.4 (-11.9 to 5.1)

Number of patients						
Seladelpar 10 mg	65	62	63	63	61	62
Placebo	31	30	30	28	27	26
LS mean % change (SE)						
Seladelpar 10 mg		-1.7 (3.6)	-13.3 (3.0)	-7.9 (3.8)	-15.2 (4.7)	-22.5 (3.4)
Placebo		-0.4 (5.2)	-2.4 (4.3)	7.2 (5.7)	0.1 (7.0)	-5.6 (5.2)
LS mean of difference (95% CI)		-1.3 (-13.9 to 11.2)	-10.9 (-21.3 to-0.5)	-15.0 (-28.6 to-1.5)	-15.3 (-32.1 to 1.5)	-16.8 (-29.3 to-4.4)

C

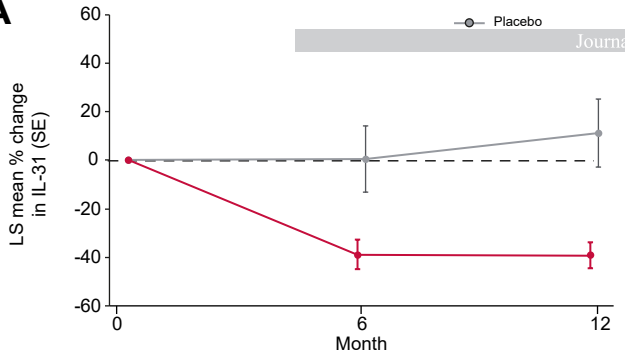


Number of patients						
Seladelpar 10 mg	65	62	63	63	61	62
Placebo	31	30	30	28	27	26
LS mean % change (SE)						
Seladelpar 10 mg		-25.8 (2.2)	-33.1 (2.4)	-28.4 (3.7)	-35.0 (3.1)	-29.9 (3.4)
Placebo		-1.5 (3.2)	-1.8 (3.5)	3.0 (5.5)	-2.5 (4.6)	-4.4 (5.2)
LS mean of difference (95% CI)		-24.4 (-32.1 to-16.6)	-31.4 (-39.7 to-23.0)	-31.4 (-44.7 to-18.1)	-32.5 (-43.6 to-21.5)	-25.4 (-37.9 to-13.0)

Journal Pre-proof

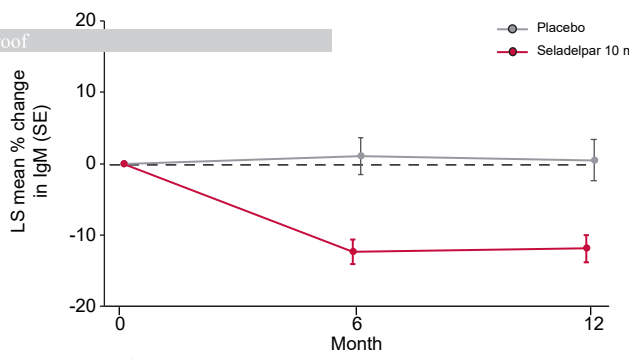
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A



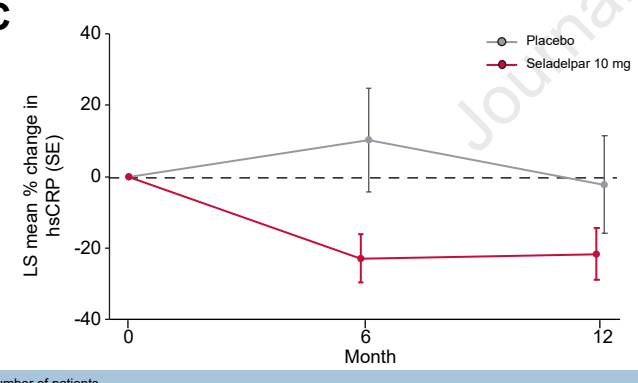
Number of patients			
Seladelpar 10 mg	60	60	58
Placebo	29	29	27
LS mean % change (SE)			
Seladelpar 10 mg		-38.8 (5.9)	-39.0 (5.4)
Placebo		0.5 (13.8)	11.2 (13.9)
Difference in LS means (95% CI)		-39.3 (-67.7 to-10.9)	-50.2 (-78.4 to-22.1)

B



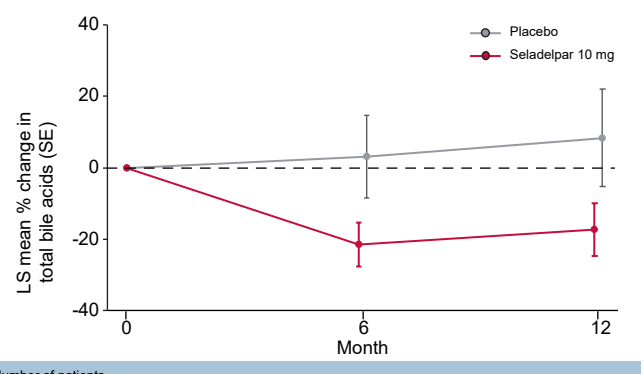
Number of patients			
Seladelpar 10 mg	62	62	61
Placebo	28	28	26
LS mean % change (SE)			
Seladelpar 10 mg		-12.3 (1.7)	-11.9 (1.9)
Placebo		1.1 (2.6)	0.5 (2.9)
LS mean of difference (95% CI)		-13.4 (-19.5 to-7.2)	-12.4 (-19.3 to-5.5)

C



Number of patients			
Seladelpar 10 mg	62	62	61
Placebo	28	28	26
LS mean % change (SE)			
Seladelpar 10 mg		-22.8 (6.7)	-21.6 (7.2)
Placebo		10.2 (14.5)	-2.2 (13.7)
Difference in LS means (95% CI)		-33.1 (-64.8 to-1.3)	-19.3 (-50.2 to 11.5)

D



Number of patients			
Seladelpar 10 mg	48	47	43
Placebo	24	24	22
LS mean % change (SE)			
Seladelpar 10 mg		-21.4 (6.2)	-17.3 (7.4)
Placebo		3.1 (11.5)	8.4 (13.7)
Difference in LS means (95% CI)		-24.5 (-50.9 to 2.0)	-25.7 (-57.0 to 5.7)

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HIGHLIGHTS

- In PBC, any ALP elevation above the ULN may increase risk for disease progression
- Seladelpar was assessed in patients with PBC and ALP between 1–1.67× ULN despite UDCA use
- The primary endpoint was ALP normalization (composite of ALP ≤ULN + ≥15% decrease from baseline) at Month 12
- ALP normalization was achieved in 75.4% of seladelpar vs. 16.1% of placebo patients
- The safety profile of seladelpar was overall consistent with prior studies

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