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A double-blind, randomized, placebo-controlled phase 2 proof of concept study of seladelpar (MBX-8025), a selective PPAR- δ agonist, in patients with Primary Biliary Cholangitis with an inadequate response to ursodeoxycholic acid

Running title: PPAR- δ agonism in PBC

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Abstract

Background: Many patients with primary biliary cholangitis (PBC) show an inadequate response to first line therapy with ursodeoxycholic acid (UDCA). Seladelpar is a potent, selective agonist for the peroxisome proliferator-activated receptor-delta which is implicated in bile acid homeostasis. This first in class study evaluated the anti-cholestatic effects and safety of seladelpar in patients with an inadequate UDCA response.

Methods: A 12-week, double-blind, placebo-controlled, phase 2 study in patients with alkaline phosphatase (AP) ≥ 1.67 x the upper limit of normal despite UDCA. The study (NCT02609048 and EudraCT2015-002698-39) planned to randomize 75 patients to placebo, 50 mg or 200 mg/day of seladelpar while UDCA was continued. Randomisation was performed centrally in a 1:1:1 ratio by a computerized system using an interactive voice/web response system (IXRS) with a block size of three. Randomisation was stratified by region (North America and Europe). The primary outcome was the AP percentage change. Secondary outcomes were response rates and changes in other markers of cholestasis. Other outcomes explored the mechanism of action of seladelpar.

Findings: During recruitment, three patients developed fully reversible, asymptomatic grade 3 alanine aminotransferase increases on seladelpar (one on 50 mg, two on 200 mg) and the study was terminated after 41 randomizations. Mean baseline AP were 233, 312, and 248 U/L in the placebo, 50 mg and 200 mg seladelpar groups, respectively. The mean percentage decrease in AP were -2, -53, and -63 in the placebo, 50 mg, and seladelpar 200 mg groups, respectively. Both seladelpar groups changes were significant ($p < 0.0001$ vs. placebo), with no significant difference between them. All patients (5/5) who received seladelpar for 12 weeks normalized their AP values. Seladelpar, at both doses, was also associated with decreases in γ -glutamyl transferase (GGT) and C4 levels.

There was no indication that seladelpar was associated with drug-induced pruritus.

Interpretation: Twelve-week treatment with seladelpar normalized AP without inducing pruritus. The effect appears mediated by a decrease in bile acid synthesis. Treatment was associated with transient increase in transaminases and more transaminase elevations occurred in the 200 mg group than in the 50 mg group. The benefits of seladelpar should be explored at lower doses.

The study was funded by CymaBay Therapeutics.

Key words: seladelpar; PPAR- δ agonist; primary biliary cholangitis, bile acids, cholestasis.

Research in context

Evidence before this study:

Primary biliary cholangitis (PBC) is a progressive cholangitic liver disease which, if untreated, progresses to cirrhosis and death or liver transplant. We performed a literature search in PubMed (US National Library of Medicine, National Institute of Health. No language limitations were used. The search terms were "Primary Biliary Cirrhosis", "Primary Biliary Cholangitis", "Liver Cirrhosis, Biliary", "Trial", "Drug", and "Therapy". We also performed a search for clinical trials in Primary Biliary Cirrhosis or Primary Biliary Cholangitis in Clintrials.Gov database. Both searches were censored on April 20, 2017. In PBC, the standard of care for over 20 years has been the hydrophilic bile acid ursodeoxycholic acid (UDCA). It has become increasingly clear in recent years that the response to UDCA is variable, with a significant proportion of patients (up to 40%) showing an inadequate response in terms of liver biochemistry improvement and significantly reduced survival. UDCA nonresponse is more frequent in younger patients increasing the level of unmet need in PBC. Appreciation of the need for better therapy in high risk PBC patients led to the development of the first

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second-line therapy, obeticholic Acid (OCA) which was approved for use in both the USA and Europe in 2016 in patients showing an inadequate response to UDCA. OCA which is a synthetic bile acid has its actions through agonism of the Farnesoid X Receptor (FXR) which regulates bile acid homeostasis. OCA has, however, two important limitations as second-line therapy. The first is that it is itself incompletely effective with 50% of high risk patients treated with it showing inadequate response in the Phase 3 trial. The second is that it can cause worsening of pruritus (a key symptom of PBC) and induce pruritus in previously symptom-free patients. Given the association between high risk disease (and thus need for OCA) and pruritus this represents an important potential limitation in its utility. With these limitations, the search for additional and alternative second-line therapies is ongoing.

Added value of this study

This study is a first-in-class, randomised, placebo-controlled trial of a PPAR- δ agonist in PBC. The mode of action of the drug on bile acid synthesis and inflammation, and its non-bile-acid-based structure make it an intuitive agent to explore as second-line therapy in PBC. The trial demonstrates 2 important positive findings and one caution. The positive finding, albeit based on a limited number of patients, is a normalisation of liver biochemistry in patients reaching 12 weeks of therapy; a higher degree of effect than OCA which typically improves rather than normalises biochemistry. Improvement was also seen in other cholestatic markers suggesting a true anti-cholestatic effect and the mechanism of action appeared to be through reduced bile acid synthesis as predicted. The second positive finding was that there was no evidence of pruritus as a side effect. The caution was that 3 patients showed rapidly reversible ALT elevation that appeared to be dose dependent.

Implication of all the available evidence

Seladelpar has the potential to be an improved second-line therapy in high risk PBC with increased efficacy and reduced pruritus risk. A study at lower doses is underway to identify effective doses that do not cause ALT elevation (NCT 029556020 and EudraCT 2016-002996-91). If ALT elevation risk can be

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eliminated whilst retaining efficacy, the drug offers the potential for routine liver biochemistry normalisation in high risk PBC patients.

Introduction

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is a chronic, progressive, cholestatic liver disease.¹ The liver shows a lymphocytic infiltration with progressive lobular bile ducts damage which leads to impaired bile flow. Although the condition is presumed to have an autoimmune aetiology, chronic cholestasis drives the pathophysiological process, and can lead to cirrhosis. PBC occurs predominantly in females and is often first suspected by persistent elevations of serum alkaline phosphatase (AP) on routine blood tests. Patients progress at varying rates, although a diagnosis at younger age appears to negatively impact prognosis.² Inadequate medical treatment puts patients at risk of liver death and need for liver transplantation. At present, two drugs, ursodeoxycholic acid (UDCA) and obeticholic acid (OCA), have been approved to medically treat PBC.^{3,4}

UDCA, a non-cytotoxic bile acid (BA), has been the mainstay of therapy for more than twenty-years.^{1,5} However, up to 40 percent of patients have persistent elevation of AP and/or bilirubin despite UDCA administration and are considered inadequate responders.⁶ These patients have a worse hepatic transplant-free survival rate compared to UDCA responders.^{7,8} Consequently, AP levels, when combined with total bilirubin, are now considered surrogate markers of PBC severity that predict the progression of the disease.⁹

OCA, a synthetic analogue of chenodeoxycholic acid (CDCA), was recently conditionally approved based on its ability to significantly decrease AP levels when used as an add-on therapy in PBC patients who are inadequate responders to UDCA. It is also approved for patients who cannot tolerate UDCA (around 5% of patients). In contrast to UDCA, OCA activates the farnesoid X receptor (FXR)¹⁰ and exerts its effects through a distinct mechanism of action. When using a dichotomous biochemical response, however, approximately 50 percent of patients with PBC still lack an adequate response to a combination of UDCA

and OCA.⁴ Also, OCA has been associated with inducing or worsening pruritus, a characteristic symptom of PBC, which can require treatment interruption.⁴ Accordingly, there is still a significant medical need to develop new therapies for PBC¹¹.

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that direct the transcription of genes involved in bile acids/sterols, lipids, and glucose metabolism, as well as inflammation.^{12,13,14} Three PPAR subtypes, α , γ , and δ , are known¹³, each of which have their own distinct but overlapping cellular expression, target genes, pathway regulation, and biological functions. Fenofibrate, a PPAR- α agonist¹⁵, and bezafibrate, a pan-PPAR agonist¹⁶, have shown promising activity in decreasing markers of cholestasis in PBC subjects, although there are concerns about potential toxicity. Their primary effects result from decreasing hepatocellular bile acid concentrations by regulation of genes responsible for bile acid synthesis and transport.^{17,18} Seladelpar (MBX-8025) is an oral, once-daily administered, potent and selective PPAR- δ agonist.¹² Like PPAR- α , PPAR- δ is also expressed in hepatocytes¹⁹ where it controls genes involved in bile acid homeostasis. Seladelpar down regulates the expression of *cyp7a1* which encodes cholesterol 7 α -hydroxylase (**Appendix page 8**), the enzyme that hydroxylates cholesterol in the first step in the synthesis of bile acids. Unlike PPAR- α , for which liver expression is mainly restricted to hepatocytes²⁰, PPAR- δ is also expressed in cholangiocytes²¹, Kupffer cells and hepatic stellate cells¹⁹, and its activation in these cells has implications for modifying progression of PBC. Cholangiocytes utilize PPAR- δ ²¹ to regulate transporters involved in the absorption and secretion of bile components. Indeed, seladelpar regulates the cholesterol transporter ABCG5/ABCG8 in mouse liver (**Appendix page 9**) and another PPAR- δ agonist was shown to increase bile flow three-fold in mice.²² Activation of PPAR- δ also results in anti-inflammatory effects in macrophages²³, including Kupffer cells.²⁴ Seladelpar, in a mouse model, reduces markers of liver inflammation, including reductions in macrophages numbers, reductions of fibrosis and reduction in other markers of stellate cell activity.²⁵ Thus, the rationale for

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assessing PPAR- δ as a target for cholestatic diseases includes the impact on bile acid retention, cholangiocytes function and anti-inflammatory and anti-fibrotic effects on Kupffer and stellate cells.

Whilst PBC is an autoimmune disease, the ensuing cycle of biliary epithelial injury, cholestasis and fibrosis is felt to be substantially more important as a determinant of outcome for patients, with multiple strands of evidence supporting the importance of biliary epithelial responses to injury in driving the clinical course. The effects on cholestasis, inflammation and fibrosis resultant from PPAR- δ agonism are therefore predicted to impact disease progression. Indeed, in healthy volunteers, seladelpar decreased the intestinal absorption of cholesterol, decreased the synthesis of cholesterol and modulated bile acid synthesis.²⁶ In subjects with mixed dyslipidemia¹² or homozygous familial hypercholesterolemia²⁷, seladelpar decreased low density lipoprotein cholesterol (LDL-C) and also induced sustained decreases in biochemical markers of cholestasis, such as AP, γ -glutamyl transpeptidase (GGT), and total bilirubin.²⁷ Lastly, seladelpar treatment decreased biochemical markers of inflammation¹², an activity that could be of benefit to treat auto-immune diseases such as PBC. So far, approximately 140 subjects have received seladelpar at doses ranging from 50 to 200 mg/day and for up to 12 weeks. Seladelpar appeared safe and well tolerated with no specific adverse reaction definitively associated with the drug.^{12,26,27} Notably, seladelpar was not associated with drug-induced pruritus.

The aim of the present, first in class, study was to explore the efficacy and safety of seladelpar in patients with PBC who are inadequate responders to UDCA treatment.

Methods

Subjects

The study was approved by country specific Health Authorities (USA, Canada, Germany, Poland, and UK) and Independent Ethics Committees. All patients provided written informed consent to participate. The study was conducted in accordance with the principles of The Declaration of Helsinki and Good Clinical Practice Guidelines.

The study enrolled subjects aged 18 to 75 with a diagnosis of PBC. The diagnosis required the presence of at least two of the following criteria: a history of AP above the upper limit of normal (ULN) for at least six months, a positive autoantibody test (antimitochondrial antibody > 1:40 on immunofluorescence or M2 positivity by enzyme linked immunosorbent assay or positive PBC-specific anti-nuclear antibodies), a documented liver biopsy consistent with PBC. Patients were required to be on a stable and recommended dose of UDCA for the past twelve months and to have an AP $\geq 1.67 \times$ ULN.

Patients were excluded if they had any other liver conditions, or any medical condition that would preclude full participation, confound the results or compromise their safety. Other exclusions were an alanine amino transferase (ALT) or an aspartate amino transferase (AST) > 3 x ULN, total bilirubin > 2 x ULN, creatine kinase (CK) or serum creatinine above the ULN. The use of colchicine, methotrexate, azathioprine or systemic steroids within two months prior to screening were not permitted. Patients taking fibrates or simvastatin were also excluded, as well as any subjects on experimental PBC treatment, including OCA. For females and males of reproductive age, appropriate methods of contraception were to be used.

Study design

This was an international, multicenter, double-blind, randomized, placebo-controlled, parallel, dose-ranging study of 18-week duration. All patients were to continue their UDCA treatment at the same dose during the study. After signing informed consent, patients underwent a four-week screening period to confirm eligibility.

Randomisation and masking

Eligible patients were randomized (1:1:1) to placebo, or seladelpar 50 or 200 mg orally daily using a centralized online response system (IXRS) and entered the double-blind 12-week treatment period. The randomisation was stratified by region (North America and Europe) and used a block size of three. A third-party vendor (Perceptive Informatics Waltham, Massachusetts, USA, now Parexel Informatics™) was responsible for generating the randomisation scheme and managing randomisation activities. Each subject was assigned a unique study identification number by the IXRS, and this triggered blinded, patient-specific, on demand shipment of study drug. To maintain blinding, all study medication capsules were identical in appearance. Subjects, investigators, clinical trial site staff, and sponsor staff directly involved with the study were masked to treatment assignment throughout the study. Medication blinding was completed by the blinding of AP values. GGT or ALT/AST, that could be necessary for safety monitoring, were not blinded.

Procedures

During treatment, site visits occurred at weeks two, four, eight and 12 and telephone contact were made at weeks six and 10. A follow-up assessment took place two weeks after the end of treatment.

Outcomes

The primary efficacy assessment was change in AP levels. Secondary assessments included tolerability and safety and additional efficacy parameters. Secondary efficacy assessments included (i) a composite of an AP < 1.67 x ULN with normal total bilirubin and a decrease of at least 15 percent from baseline; (ii) an evaluation of published PBC response criteria (Paris I and II, Toronto I and II) and the UK-PBC risk

score, (iii) AST, ALT, GGT, 5' nucleotidase, bilirubin (total, conjugated, unconjugated), bone-specific AP, (iv) triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C), and (v) pruritus evaluated with a visual analog score (VAS), the 5D-itch questionnaire and the PBC-40 quality of life (QoL).

Exploratory efficacy measures included serum or plasma levels of the following: bile acid precursor 7 α -hydroxy-4-cholesten-3-one (C4); high-sensitivity C-reactive protein (hs-CRP); BAs [UDCA, cholic acid (CA), CDCA, deoxycholic acid (DCA) and lithocholic acid (LCA), their glyco- and tauro-conjugates]; IgM, AMA, and homocysteine; 7 α -hydroxy cholesterol; intermediates of cholesterol synthesis (squalene, lanosterol, desmosterol, lathosterol, and 7-dehydrocholesterol); markers of intestinal cholesterol absorption (β -sitosterol, campesterol, and stigmasterol); cholestanol and coprostanol. In selected centers, shear wave elastography of the liver was to be performed. Levels of fibroblast-growth factor 19 (FGF-19), an enterokine released after FXR activation, were measured post-hoc.

Trough plasma levels of seladelpar and its metabolites (M1, M2 and M3) were measured at week four and week 12.

Safety was assessed throughout the study by physical examination, ECG, the monitoring of adverse events (AEs), treatment emergent adverse events (TEAEs), the recording of concomitant medications, and laboratory assessments. The severity of AEs and laboratory abnormalities were graded as per the common terminology criteria for adverse events (CTCAE), version 4.03. An independent Data and Safety Monitoring Board periodically reviewed safety data. A central laboratory performed hematological and biochemical determinations (Medpace Reference Laboratories; Cincinnati, OH, USA and Leuven, Belgium). Seladelpar and its metabolites were analyzed by MicroConstants (San Diego, CA, USA).

Statistical analysis

The safety population included any randomized patient who received at least one dose of medication.

The modified intent to treat (mITT) population comprised any randomized patient who received at least one dose of medication and had at least one post baseline AP evaluation.

It was assumed that the mean percent AP decrease would not be more than five percent in the placebo group and at least 25 percent in the seladelpar groups with a standard deviation for the percent change from baseline to end of treatment of 20 percent. Based on these assumptions, using a two-sided comparison of means at the $\alpha = 0.05$ level of significance with a sample size of 23 patients per group, the study had a 90 percent power to detect a difference of 20 percentage points between the active and placebo groups. To account for up to two subjects per group who might be excluded from the mITT population, the planned sample size was 25 subjects per group.

The safety analysis was conducted on the safety population. The efficacy analyses were conducted on the mITT population.

Baseline was defined as the mean between screening and baseline (Day 1) values for the primary analysis and as baseline values for other analyses.

Descriptive statistics such as means, medians and measures of dispersion were to be presented and the last observation carried forward (LOCF) was used for missing laboratory data.

The primary efficacy analysis compared the mean percentage change from baseline to end of treatment in AP levels between the seladelpar 200 mg treatment group and the placebo group. If this analysis was significant, the next comparison was between the seladelpar 50 mg treatment group and the placebo group. For the primary analysis, an analysis of covariance using baseline and treatments as cofactor was used. A similar analysis was used for secondary analyses on normally distributed parameters. In the absence of normality, a non-parametric test was used (Wilcoxon). The study was registered in the US (NCT02609048) and Europe (EudraCT2015-002698-39).

CymaBay Therapeutics sponsored this clinical study and supported study design, data collection,

analysis, and study operation. All authors had access to the datasets and statistical analysis plan and had rights to audit data. Y-JC, AS, MV, HC, RM, CAM, and PFB supported study design, data collection, analysis, and study operation. DJ, CLB, MR, BB, YD, NG, GCS, JAD, DS, M-AW, VC, LC, HH, MEJ, AEK, GFM, PB, BLF, CL, JMV, DEB, MH, EJ, FR, HS, MLS, JHS, GMH were investigators in this study. All authors had access to the datasets and statistical analysis plan and had rights to audit data. DJ, PFB, MGS, CLB, and GMH finalized data presentation and had responsibility to submit the manuscript after obtaining the agreement of all the authors. DJ and PFB contributed equally to the manuscript. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Subjects disposition and baseline characteristics

Between November 4th 2015 and May 26th 2016, 70 patients were screened at 30 sites in North America and Europe, and 41 patients were randomized (**Figure 1**).

Patients' baseline characteristics are presented on **Table 1**. The mean age was 55 years old with the expected female predominance. There was an imbalance in mean (+/- standard deviation- SD) baseline AP with the highest value in the seladelpar 50 mg group (312 +/-95) compared to seladelpar 200 mg (248 +/- 89) and placebo (233 +/- 73) groups. Similarly, GGT were higher in the seladelpar 50 mg group. Other baseline characteristics were well balanced.

While recruitment was still ongoing, three patients on blinded treatment developed grade 3 transaminase elevations (>5 x ULN to 20 x ULN). All three cases were deemed to be drug related.

Consequently, on May 27th, 2016, the sponsor terminated the study and informed study sites, the DSMB and health authorities of its decision. The study was stopped to protect patients and because large decreases in GGT and 5' nucleotidase indicated that the proof of concept for activity was likely to have

been achieved. In addition, new results from a rat disposition study revealed that seladelpar and its metabolites were almost exclusively eliminated through bile, which potentially suggested that higher than expected hepatic concentration of seladelpar may have occurred in subjects with PBC. Patients were requested to discontinue their treatment, return to study sites to complete an end of treatment visit, and then proceed to a follow-up (off-treatment) end of study visit two weeks later.

Two patients did not receive treatment because the study was discontinued after randomization but prior to dosing, and one patient developed a variceal bleed after randomization but prior to dosing. The 38 patients who received either placebo or seladelpar constituted the safety population. Fifteen subjects completed 8-week of treatment (6 on placebo, 5 on seladelpar 50 mg, and 4 on seladelpar 200 mg) and nine subjects completed 12 weeks of treatment (4 on placebo, 3 on seladelpar 50 mg, and 2 on seladelpar 200 mg) (**Table 2**).

Primary outcome of efficacy

AP changes from baseline over 12 weeks are presented in **Figure 2**. The mean percentage change in AP in both seladelpar groups was significant compared to placebo, with a decrease from baseline of 53% in the 50 mg group and a decrease from baseline of 63% in the 200 mg group (both $p < 0.0001$). There were no clinically relevant or statistically significant differences between the seladelpar groups. Over 12 weeks, patients on both doses of seladelpar had a rapid and decrease in AP while patients on placebo had stable AP levels (**Figure 3**). Decreases in AP were seen after two weeks of treatment, the first assessment in the study, with a slower decline up to week 12. All (100%) patients on seladelpar who reached 12 weeks on treatment normalized their AP values (5/5) (**Table 2**). No (0%) patient on placebo had a normalization of AP after 12 weeks (0/4). As early as eight weeks, eight (89%) of nine patients on seladelpar had their AP values normalized. For the composite outcome of AP and total bilirubin, at 12 weeks, 100% (5/5) patients on seladelpar and 0% (0/4) on placebo were responders.

Secondary outcomes of efficacy

Changes in other markers of cholestasis: AP decreases were associated with decreases in the levels of other cholestasis associated enzymes, GGT and 5'-nucleotidase (**Appendix page 1**). There were no significant differences in the GGT or 5'-nucleotidase changes between the seladelpar groups. The mean percentage changes in total bilirubin, indirect bilirubin and direct bilirubin are shown in **Appendix page 1**.

Changes in hs-CRP and lipid parameters: Significant decreases in hs-CRP and in LDL-C were seen in both seladelpar groups compared to placebo (**Appendix page 1**). The mean percentage changes in HDL-C and TG are also presented in **Appendix page 1**.

Changes in cholesterol and BAs metabolism: Over 12 weeks, there were significant decreases in C4, a marker of de novo bile acid synthesis, in both seladelpar groups (**figure 4**), with no significant difference between seladelpar groups. The decrease in C4 were accompanied by decreases in 7- α -hydroxy-cholesterol, the precursor of C4 (**Appendix page 2**). The median percentage change in BAs are presented in **Appendix page 2 and 3**. The median percentage changes in lathosterol, and β -sitosterol campesterol and stigmasterol are presented in **Appendix page 4**. FGF-19 median % changes were -13.9, -49.0, and -78.1 in the placebo, 50 mg and 200 mg groups, respectively. These changes were statistically significant versus placebo (p-values 0.047 for 50 mg and 0.006 for 200 mg) (**Appendix page 10**).

Safety

There were no deaths during the study and no serious adverse event during the treatment period. Apart from ALT events previously described, there were no AE considered severe. The most frequently

reported AEs were pruritus (15.8%), nausea (13.2%), diarrhea (10.4 %) and abdominal discomfort, muscle spasms, myalgia, and dizziness (each 7.9%). There were no apparent differences in the distribution of AEs between groups apart from the grouping of muscle-related AEs (myalgia/muscle spasms/musculo-skeletal pain). The distribution of muscle-related AEs was one in the placebo group, one in the seladelpar 50 mg group, and five in the seladelpar 200 mg group (including the subject who discontinued for a muscle AE).

Five patients discontinued treatment before the study termination. One subject on seladelpar 50 mg discontinued because of a grade 3 ALT elevation. Four subjects on seladelpar 200 mg discontinued treatment, two because of grade 3 ALT elevations, one because of an increase in CK associated with muscle pain, and one was lost to follow-up.

Three patients developed grade 3 ALT elevations that were judged probably drug related. ALT elevations were similar: rapid onset (identified during the first on treatment visit at week 2), asymptomatic, and fully reversible two to four weeks after treatment discontinuation. There were no eosinophilia or concurrent elevation in total bilirubin. Interestingly, all ALT elevations were associated with decreases in GGT, as well as decreases in AP (**Appendix page 11**). Two additional subjects developed grade 2 ALT elevations that did not lead to treatment interruption. Both subjects were on seladelpar 200 mg (**Appendix page 7**).

Pruritus was reported as an AE by one patient on placebo, four on seladelpar 50 mg and one on seladelpar 200 mg. Three pruritus AEs were considered treatment related, one on placebo, two on seladelpar 50 mg and none on seladelpar 200 mg. Thirteen patients (34 %) were considered to have pruritus at baseline (as judged with a pruritus VAS ≥ 30), four on placebo, four on seladelpar 50 mg, and five on seladelpar 200 mg (**Table 1**). At baseline, mean pruritus VASs were 18, 21, and 33 in the placebo, seladelpar 50 mg, and seladelpar 200 mg groups, respectively. The mean VASs at end of treatment were 27, 21, and 31 in the placebo, seladelpar 50 mg, and seladelpar 200 mg groups, respectively. The 5D-itch

mean total scores at baseline were 11, 11, and 11 in the placebo, seladelpar 50 mg, and seladelpar 200 mg groups, respectively. At the end of treatment, the 5D-itch mean total scores were 11, 12, and 11 in the placebo, seladelpar 50 mg, and seladelpar 200 mg groups, respectively.

There were no relevant changes in hematology parameters. The mean percentage changes in hemoglobin, serum creatinine and serum homocysteine are presented in **Appendix page 1**.

Seladelpar plasma exposure data indicated that, at trough (pre-dose samples), levels did not appear higher than expected, notably for subjects with grade 3 transaminase elevation (**Appendix page 12**).

Discussion

The objectives of this study were to evaluate the safety and efficacy of seladelpar to decrease AP levels in PBC patients showing an inadequate response to UDCA. Seladelpar is the first potent and selective PPAR- δ agonist to be evaluated in PBC and the key role played by PPAR- δ in the regulation of bile acid synthesis, inflammation and fibrosis justified this objective. Seladelpar, originally developed to lower lipids in subjects with mixed dyslipidemia, was also previously associated with consistent decreases in markers of cholestasis, including AP and GGT.¹²

The study used a dose ranging, placebo-controlled, double-blind design that has been previously used in this setting, and applied similar eligibility criteria to facilitate comparison with OCA.²⁸ Specifically, inadequate responders to UDCA treatment, according to accepted criteria, were enrolled and seladelpar was used as an add-on therapy. The study intended to exclude patients with decompensated cirrhosis but one randomized patient developed a variceal bleeding complication before receiving any treatment. It is known that some PBC patients can develop gastro-esophageal varices before being cirrhotic.²

The study was discontinued when approximately half of the number of subjects were enrolled.

Seladelpar treatment, both at the 50 and 200 mg doses, elicited large percentage AP decreases and normalized AP in all PBC patients who completed 12 weeks of therapy.

The three cases of grade 3 ALT elevation which led to stopping the study were judged related to seladelpar and were clinically similar. There was a rapid onset of elevation on treatment initiation, a rapid return to baseline levels after drug interruption, and the increases were not associated with total bilirubin elevation or signs of idiosyncrasy, such as allergic reaction or eosinophilia. In each case, the transaminases elevations were associated with a parallel decrease in markers of cholestasis, such as AP, but also GGT. Based on available data, there were no clinical or biological characteristics that could differentiate patients with transaminase elevation from the other patients. Examining all cases of ALT elevation during treatment, whether grade 2 and grade 3, there was a suggestion that ALT elevations were dose-related, with more cases on seladelpar 200 mg.

The transaminase elevations were unexpected, as this was not seen in previous studies where subjects were treated with seladelpar for up to 12 weeks and with daily dose of up to 200 mg.^{12,26,27} This phenomenon could thus be specific to PBC and its underlying cholestasis. Recent data in rats indicate that seladelpar, and its metabolites, are almost exclusively excreted into the bile (CymaBay Therapeutics, data not shown). Therefore, increased drug retention in PBC could have led to higher liver concentration in this study compared to studies in non-cholestatic patients. Although, seladelpar trough plasma levels did not suggest a higher exposure, either in patients with transaminase elevations relative to subjects with no elevation, or in the PBC patients overall compared to other studies. However, only a full PK profile would provide evidence to the hypothesis that seladelpar exposure was unexpectedly increased in PBC subjects. We also would have to assume that plasma levels of seladelpar and its metabolites truly reflect their intra-hepatic levels. Alternatively, seladelpar, or its metabolites, may evoke an immune reaction in PBC patients which would not occur in non-PBC patients. Concerning the

specific mechanism of the observed transaminase elevations there is currently no further information available to invoke one. While an acute transaminase elevation is usually interpreted as a sign of hepatocyte cytolysis²⁹, it is also known that PPAR agonists can upregulate transaminase genes expression.^{30,31} Post-hoc analyses of stored samples evaluating more specific makers of liver injury³² is necessary to further explore this issue. Animal studies could be useful to determine the relationship between hepatic and plasma levels of seladelpar. In this study, the levels of CDCA or LCA, which have been associated with hepatotoxicity³³, were not increased compared to baseline, which makes this mechanism of action unlikely.

Seladelpar did not appear to be associated with drug induced/worsened pruritus. This feature may, if replicated, differentiate seladelpar from OCA, as the tolerability of OCA is limited by this side-effect.⁴ The size of the current study, however, precludes any conclusion on whether seladelpar may have a beneficial effect on pruritus of PBC, as has been suggested for bezafibrate.³⁴

With regard to other safety parameters, at the 200 mg dose of seladelpar one patient discontinued treatment with muscle pain and increased CPK level that were considered treatment related. In contrast to other PPARs, the δ receptor is expressed in muscle. While such adverse events were not observed with seladelpar when prescribed in patients with homozygous familial hypercholesterolemia on maximally tolerated statin therapy²⁷, caution should be exercised. Seladelpar was also associated with dose-dependent elevations of serum homocysteine and serum creatinine levels which are commonly observed with other PPARs.^{35,36,37} The increase in serum creatinine could be problematic as it is used clinically as a marker of decreased renal glomerular filtration and the glomerular filtration rate is estimated with a formula that is based on serum creatinine levels.³⁸ Indeed, one patient had an increase in serum creatinine that was considered clinically significant by the investigator. Previous studies have demonstrated that increased serum creatinine associated with some PPAR agonists, such as PPAR α ,

pan-PPAR, or mixed PPAR α/δ , were neither linked to relevant decrease in measured glomerular filtration rate, nor changes in measured creatinine clearance, as serum creatinine and creatinine urinary excretion increased in similar proportions.³⁹ Long-term prospective studies of fenofibrate, a PPAR α agonist, in diabetic patients with compromised renal function, did not demonstrate a negative effect on renal function, despite small increases in serum creatinine.⁴⁰ Finally, increases in serum creatinine associated with PPARs, as was seen in the current study, are reversible⁴¹, which rules out a permanent kidney damage. The PPAR-mediated increase in serum creatinine has been postulated to result from an increased release of creatine from muscle. Creatine is stored in muscles to supply energy and is rapidly converted to creatinine in the serum.⁴²

All patients who received seladelpar for 12 weeks normalized their AP levels. This activity in patients who are inadequate responders to UDCA appears greater than that seen with OCA in a similarly designed phase 2 study.²⁸ In contrast to the transaminase elevations, seladelpar's activity was not dose related, and the effect seemed already maximal at 50 mg, which calls for the use of lower doses to optimize the risk benefit ratio of the drug. The decrease in AP was also associated with decreases in other markers of cholestasis, including GGT and 5'Nucleotidase and the 50 mg dose of seladelpar was also associated with decreases in total bilirubin levels. Lastly, similar to UDCA and OCA^{2,28}, the changes in markers of cholestatic injury returned to baseline levels when seladelpar treatment was stopped.

The study has important limitations however. Because the study was discontinued before its completion and its small sample size, these data are preliminary and should be confirmed in larger studies. Notably, the conclusion regarding AP normalisation is only based on five patients who have reached 12 weeks of treatment, and the transaminase elevation was concerning enough to terminate the study.

Nevertheless, the normalization of AP with seladelpar, if confirmed at lower doses in the absence of a safety signal, offers promise for a new treatment approach in PBC patients who do not respond fully to UDCA therapy.

This study provides evidence regarding the mechanism of action of seladelpar. First, there was a striking effect on hepatocyte bile acids synthesis as demonstrated by a decrease in serum C4 levels, a reliable marker of the activity of 7 α -hydroxylase which hydroxylates cholesterol in position 7 and constitutes the rate-limiting step in bile acids synthesis by the classical pathway.⁴³ The decrease in C4 levels was not meaningfully different between the two seladelpar doses. The C4 data were corroborated by a decrease in 7 α -hydroxy-cholesterol and by decreases in CA levels, the product of the classic pathway, and further by decreases in DCA, a metabolite of CA.⁴⁴ Additional reductions in hepatic BA may have resulted from decreases in cholesterol absorption and decreases in cholesterol synthesis intermediates. Overall, these data suggest that seladelpar can reduce BA levels by decreasing their synthesis as well as decreasing the availability of cholesterol as a substrate for their synthesis. UDCA treatment increases BAs transport into the canalicular space, which is believed to be hepatoprotective due to the lowering of BA levels within hepatocytes.⁴⁵ Seladelpar's inhibition of BA metabolism may therefore potentiate this beneficial effect by further lowering hepatocyte concentration of BAs. In addition, seladelpar-induced decreases in hs-CRP are consistent with an anti-inflammatory activity of the drug, an action first demonstrated in obese patients with mixed dyslipidemia.¹² Finally, the decreases in FGF-19 levels seen with seladelpar indicate that its action is not mediated through FXR agonism as is the case for OCA.⁴ It has also been suggested that FGF-19 may play a role in the development of hepatocellular carcinoma and its expression is induced in the liver under cholestatic and cirrhotic conditions.⁴⁶ As in the case with other chronic liver diseases, PBC patients are at an increased risk of hepatocellular carcinoma^{1,2}, and the decrease levels of FGF-19 induced by seladelpar could be of interest.

In conclusion, this study demonstrated that seladelpar, at both the 50 mg and 200 mg daily doses, has the potential to normalize biochemical markers of cholestasis in PBC patients who have inadequately

responded to UDCA. However, treatment with seladelpar was associated with transaminases elevations and, consequently, the study was interrupted before completion. As the elevation of transaminases was more frequent at 200 mg compared to 50 mg, while the anti-cholestatic activity was independent of doses, lower doses of seladelpar should be explored to optimize the risk benefit ratio in PBC patients. A low dose study of seladelpar in PBC patients has been initiated (NCT 02955602 and EudraCT 2016-002996-91).

Authors contribution:

CymaBay Therapeutics sponsored this clinical study and supported study design, data collection, analysis, and study operation. All authors had access to the datasets and statistical analysis plan and had rights to audit data. Y-JC, AS, MV, HC, RM, CAM, and PFB supported study design, data collection, analysis, and study operation. DJ, CLB, MR, BB, YD, NG, GCS, JAD, DS, M-AW, VC, LC, HH, MEJ, AEK, GFM, PB, BLF, CL, JMV, DEB, MH, EJ, FR, HS, MLS, JHS, GMH were investigators in this study. All authors had access to the datasets and statistical analysis plan and had rights to audit data. DJ, PFB, MGS, CLB, and GMH finalized data presentation and had responsibility to submit the manuscript after obtaining the agreement of all the authors. DJ and PFB contributed equally to the manuscript.

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Figure 1 Subjects disposition and study populations

Figure 2 Mean % Change in AP over 12 weeks (Last observation carried forward)

Figure 3 Mean (SEM) changes in ALP over 12 weeks per treatment

ULN upper limit of normal LLN lower limit of normal

Figure 4 Median % change over 12 weeks in 7- α -hydroxy-4-cholesten-3-one (C4) per treatment group with statistical analysis (Last observation carried forward)

Table 1. Subjects demographics and baseline characteristics

	Placebo	Seladelpar 50 mg	Seladelpar 200 mg
N	13	13	12
Age, years	54.5 (10)	54 (7)	55 (12)
Female, n (%)	12 (92)	12 (92)	12(100)
Age at diagnosis (years)	49 (10)	46 (7)	46 (10)
Duration of PBC (years)	6 (4)	9 (6)	11 (10)
BMI, kg/m ²	28 (6)	24 (5)	27 (4)
Pruritus (VAS $\geq$ 30), n (%)	4 (33)	4 (31)	5 (50)
ALP, U/L *	233 (73)	312 (95)	248 (89)
ALT, U/L	40 (24)	47 (31)	32 (15)
AST, U/L	36 (12)	37 (18)	32 (11)
GGT, U/L *	183 (123)	220 (152)	104 (41)
Total Bilirubin, mg/dL	0.68 (0.35)	0.73 (0.27)	0.75 (0.38)
Albumin, g/dL	4.3 (0.4)	4.3 (0.4)	4.1 (0.3)
Platelets, 10 ³ / μ L	235 (83)	271 (86)	227 (79)
Total UDCA dose, mg/kg/day	16 (2)	15 (3)	14 (2)

Data are Mean (SD) unless otherwise indicated * data calculated on the efficacy population

Table 2 Number of subjects with normalization of AP according to week(s) of treatment.

Number of Subjects with Normal AP*/Total N					
Treatment (Weeks)	0	2	4	8	12
Placebo	0/12	1/12	1/10	1/6	0/4
Seladelpar 50 mg	0/13	2/13	4/8	4/5	3/3
Seladelpar 200 mg	0/10	5/10	5/6	4/4	2/2

* Central laboratory upper limit of normal 116 U/L