Lyvdelzi®

(Seladeplar)

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Clinical Study Results

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1. INTRODUCTION

As of 2020, Gilead discloses clinical study results of newly authorized products in Switzerland by Swissmedic according to the requirements laid out in Art. 71-73 TPO (Ordinance on Therapeutic Products).

Below you will find the information for clinical studies relevant for the marketing authorization for Lyvdelzi® (Seladelpar) in Switzerland.

2. OVERVIEW ON CLINICAL STUDIES

Study number	Study title:	Indication:	EudraCT-Number:
CB8025-32048	**RESPONSE:** A Placebo-controlled, Randomized, Phase 3 Study to Evaluate the Efficacy and Safety of Seladelpar in Patients with Primary Biliary Cholangitis (PBC) and an Inadequate Response to or an Intolerance to Ursodeoxycholic Acid (UDCA)	Primary Biliary Cholangitis (PBC)	2020-004348-27

3. STUDY SYNOPSIS CB8025-32048 (RESPONSE)

Name of Sponsor/Company: CymaBay Therapeutics, Inc. **Name of Finished Product:** Seladelpar **Name of Active Ingredient:** Seladelpar, 2-[4-[[(2R)-2-ethoxy-3-[4-(trifluoromethyl)phenoxy]propyl]thio]-2-methylphenoxy]acetic acid, lysine dihydrate	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study:
RESPONSE: A Placebo-controlled, Randomized, Phase 3 Study to Evaluate the Efficacy and Safety of Seladelpar in Patients with Primary Biliary Cholangitis (PBC) and an Inadequate Response to or an Intolerance to Ursodeoxycholic Acid (UDCA)

Investigators: A total of 178 Principal Investigators conducted this study for this clinical study report (CSR).

Study centers: A total of 164 unique sites in the Asia Pacific, Europe, Latin America, and North America were activated for this study; 90 of these activated sites enrolled subjects.

Publications (reference): None

Studied period:
21 April 2021 (first subject randomized) – 11 August 2023 (last subject last visit [LSLV])

Phase of development: Phase 3

Objectives:
The primary objectives were as follows:

- To evaluate the treatment effect of seladelpar on composite biochemical improvement in cholestasis markers based on alkaline phosphatase (ALP) and total bilirubin at 12 months of treatment compared with placebo
- To evaluate the safety of seladelpar over 12 months of treatment compared with placebo

The secondary objectives were as follows:

Key secondary objectives:

- To evaluate the effect of seladelpar on the normalization of ALP values at 12 months of treatment compared with placebo
- To evaluate the effect of seladelpar on pruritus at 6 months of treatment compared with placebo in subjects with baseline moderate to severe pruritus

Other secondary objectives:

- To evaluate the effect of seladelpar on other measures of cholestasis, metabolic markers, and PBC prognostic criteria
- To evaluate the effect of seladelpar on quality of life (QoL)
- To evaluate the effect of seladelpar on PBC-associated clinical outcomes

The exploratory objectives were as follows:

- To evaluate the effect of seladelpar on liver histology, additional measures of QoL, biomarkers of cholestasis and inflammation, lipids and auto-antibody profiles, bile acid synthesis, liver fibrosis and liver injury
- To evaluate the plasma concentrations of seladelpar and metabolites

Methodology:

This was a phase 3, international, multicenter study using a randomized, double-blind, placebo controlled, parallel-arm design where study drug (seladelpar or placebo) was administered daily for up to 12 months as an oral capsule in subjects with PBC who had an inadequate response to or an intolerance to UDCA. The primary endpoints were the proportion of subjects who were considered responders at 12 months based on the composite biochemical

endpoint of ALP < 1.67× upper limit of normal (ULN), ≥15% decrease in ALP and total bilirubin ≤1.0× ULN and the safety of seladelpar over 12 months of treatment relative to placebo. The key secondary endpoints comprised the proportion of subjects with normalization of ALP (ALP ≤ 1.0× ULN) at 12 months and change from baseline in weekly averaged Pruritus numerical rating scale (NRS) score in subjects with baseline NRS ≥ 4 at 6 months.

Approximately 180 eligible subjects were planned to be randomized in a 2:1 ratio (seladelpar: placebo) across approximately 180 sites worldwide to the following arms:

- Seladelpar arm: Oral seladelpar 10 mg capsule once daily (qd)
- Placebo arm: Oral seladelpar-matched placebo qd

To be enrolled in this study, subjects were required to have received UDCA for 12 months (> 3 months of stable dose prior to Screening) or have intolerance to UDCA (last dose of UDCA > 3 months prior to Screening). During the study, study drug was administered as an add-on to UDCA therapy for subjects who tolerated UDCA; for subjects with UDCA intolerance, study drug was administered as a monotherapy.

Enrolled subjects had to have confirmed PBC as defined by having any 2 of the following 3 diagnostic criteria: (1) history of ALP above 1.0× ULN for at least 6 months; (2) positive antimitochondrial antibody (AMA) titer (> 1:40 on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay [ELISA]) or positive PBC-specific antinuclear antibodies (ANAs) titer; and (3) documented liver biopsy results consistent with PBC.

On Day 1, subjects were randomized to the seladelpar or placebo arm in a 2:1 ratio. Subjects were also stratified at randomization according to ALP level (< 350 U/L vs ≥ 350 U/L) and the presence of clinically important Pruritus NRS (< 4 vs ≥ 4) to ensure even distribution across treatment arms.

The total duration of participation in the study for each subject was up to approximately 14 months and consisted of the following study periods:

- Screening Period (up to 3 weeks):
  Subject eligibility was confirmed during this period.
- Run-in Period (up to 2 weeks):
  This period started 2 weeks prior to the planned Day 1 Visit. At this visit, subjects started their pruritus evaluation (using an electronic diary [e-diary]) along with other study procedures as specified in Table 3.
- Treatment Period (maximum duration up to 12 months)
  On Day 1, subjects entered the Treatment Period. Subjects received double-blinded treatment for up to 12 months. After initiation of study drug, subjects had a visit at Month 1, Month 3 and then every 3 months through Month 12. Visits could occur in the clinic or remote with the assistance of a home health service or using virtual technologies. After completion of the Treatment Period, subjects were invited to enroll into an open-label, long-term study (CB8025-31731-RE) wherein each subject in the seladelpar arm continued treatment with seladelpar and subjects in the placebo arm initiated seladelpar treatment.
- Safety Follow-up Period (2 weeks [14 days +3] after the last dose of study drug)
  Subjects who did not participate in the long-term study (CB8025-31731-RE) had a Follow-up visit performed 2 weeks (14 days +3) after the last dose of study drug.

In order to establish the histological status of their liver before and after treatment, all subjects were encouraged to have a liver biopsy during the Screening Period (unless a historical biopsy meeting quality standards was available) and after 12 months of treatment, or at Early Termination (ET), if the subjects withdrew from the study early, provided that they had received at least 6 months of treatment. A follow-up liver biopsy was performed only in subjects with a baseline liver biopsy. A pathology review committee (PRC) was formed to evaluate the biopsies in accordance with a histopathology plan defined separately from the study protocol.

Transient liver elastography via FibroScan® was performed to assess liver stiffness at baseline and during the Treatment Period or at ET at selected sites.

Subjects were asked to use an e-diary to evaluate pruritus and QoL during the study participation. An e-diary was dispensed at the Run-in Visit and included the following questionnaires: Pruritus NRS, 5-D Itch, Patient Global Impression of Severity (PGI-S), Patient Global Impression of Change (PGI-C) and PBC-40 QoL. Subjects performed an evaluation of their pruritus on a daily basis, via Pruritus NRS, starting from the Run-in Visit through the first 6 months of treatment. After 6 months, pruritus was evaluated on a monthly basis until End of Treatment (EOT)/Month 12 using Pruritus NRS for 7 consecutive days each month. The 5-D Itch scale was evaluated biweekly from the Run-in Visit up through the first 6 months of treatment and monthly after that. The PGI-S and

PBC-40 QoL were assessed at the Run-in Visit, randomization, Month 1, Month 3 and then every 3 months through Month 12/ET. PGI-C was assessed at Month 1, Month 3, and every 3 months through Month 12/ET.

During the study, subjects were regularly evaluated for progression of their disease by collecting information about PBC clinical outcomes. A critical event review committee (CERC) was established to analyze and adjudicate PBC clinical outcome events that occurred during the study; the CERC also adjudicated events consistent with potential drug-induced liver injury (DILI). Subjects who met any predefined PBC clinical outcome criteria were terminated from the study and instructed to complete an ET Visit.

Subjects who discontinued study drug treatment for any reason other than a defined PBC clinical outcome were asked to stay in the study without study drug intake. Subjects who discontinued study drug treatment and did not stay in the study completed an ET Visit. For subjects who declined to stay in the study without study drug intake or who did not participate in the long-term study (CB8025-31731-RE), a phone call was performed to inform on PBC outcomes on an annual basis until the end of the study (ie, last subject last visit).

Safety monitoring in the study included adverse events (AEs), serious adverse events (SAEs), treatment-emergent AEs (TEAEs), laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), physical examination and abdominal ultrasound, with individual stopping criteria. Additional safety monitoring criteria were implemented to monitor subjects for liver, renal, muscle, and pancreatic safety, and to define interruption and stopping criteria. Actions taken included continuation of study drug, dose interruption, dose reduction, discontinuation of study drug in addition to standard of care or investigation of the case prior to action with study drug based on the protocol-specified monitoring criteria. Study drug could be down-titrated to a lower dose if deemed necessary by the Investigator for safety or tolerability reasons in a blinded fashion. Subjects receiving seladelpar at 10 mg could be down-titrated to 5 mg, and subjects receiving placebo could be down-titrated to placebo. A data safety monitoring board (DSMB) was convened to review study data on a regular basis during study conduct to ensure subjects' welfare and preserve study integrity. The DSMB also reviewed all SAEs, liver-related safety events, and elevations in ALT, AST, serum creatinine, CK, amylase and lipase that met safety monitoring criteria.

Subjects were invited to participate in a pharmacokinetic (PK) sample collection. Subjects who consented to participate in this PK sample collection provided 1 predose (-30 minutes prior to dosing) and 2 postdose samples at 1 hour ± 30 minutes and at 3 hours ± 30 minutes at Month 3 and at Month 12.

Number of Subjects (Planned and Analyzed): Approximately 180 subjects were planned for evaluation in this study. A total of 193 subjects were enrolled into the study.

Diagnosis and Main Eligibility Criteria

Inclusion Criteria:

Subjects were required to meet all of the following criteria to be eligible for study participation:

1. Must have given written informed consent (signed and dated) and any authorizations required by local law
2. Must be 18-75 years old (inclusive)
3. Male or female with a diagnosis of PBC based on any two of the following criteria:
   a. History of ALP > 1.0× ULN for at least 6 months
   b. Positive AMA titer (> 1:40 on immunofluorescence or M2 positive by ELISA) or positive PBC specific ANAs titer
   c. Documented liver biopsy results consistent with PBC
4. UDCA use for the past 12 months (stable dose for > 3 months prior to Screening) or intolerant to UDCA (last dose of UDCA > 3 months prior to Screening)
5. Laboratory parameters measured by the Central Laboratory at Screening:
   a. ALP ≥ 1.67× ULN
   b. Aspartate aminotransferase (AST) ≤ 3× ULN
   c. Alanine aminotransferase (ALT) ≤ 3× ULN
   d. Total bilirubin ≤ 2× ULN
   e. Estimated glomerular filtration rate (eGFR) > 45 mL/min/1.73m^2 (calculated by the Modification of Diet in Renal Disease study equation)

f. International normalized ratio (INR) < 1.1× ULN

For subjects on anticoagulation therapy, INR must have been maintained in the range required for prophylaxis for their specific disease

g. Platelet count ≥ $100\times10^3/\mu L$

NOTE: Prothrombin time (PT), INR, and platelets could have been performed locally at the Screening Visit, if deemed necessary by the Investigator after consultation with the Medical Monitor, in cases where centrally read samples were deemed invalid

6. Females of reproductive potential were required to use at least 1 barrier contraceptive and a second effective birth control method during the study and for at least 90 days after the last study drug dose. Male subjects who were sexually active with female partners of reproductive potential were required to use barrier contraception, and their female partners were required to use a second effective birth control method during the study and for at least 90 days after the last dose.

Exclusion Criteria:

Subjects were required to not have met any of the following criteria to be eligible for study participation:

1. Previous exposure to seladelpar (MBX-8025)
2. A medical condition other than PBC that, in the Investigator's opinion, would preclude full participation in the study (eg, cancer) or confound its results (eg, Paget's disease, any active infection)
3. Advanced PBC as defined by the Rotterdam criteria (albumin below the lower limit of normal AND total bilirubin above 1.0× ULN)
4. Presence of clinically important hepatic decompensation, including the following:
   a. History of liver transplantation, current placement on liver transplantation list, or current Model for End-Stage Liver Disease (MELD) score ≥ 12. For subjects on anticoagulation medication, evaluation of the baseline INR, in concert with their current dose adjustments of their anticoagulant medication, was taken into account when calculating the MELD score. This was done in consultation with the Medical Monitor.
   b. Complications of portal hypertension, including known esophageal varices, history of variceal bleeds or related interventions (eg, transjugular intrahepatic portosystemic shunt placement), ascites, and hepatic encephalopathy
   c. Cirrhosis with complications, including history or presence of spontaneous bacterial peritonitis, hepatocellular carcinoma or hepatorenal syndrome
5. Other chronic liver diseases:
   a. Current features of autoimmune hepatitis as determined by the Investigator based on immunoserology, liver biochemistry or historic confirmed liver histology
   b. Primary sclerosing cholangitis determined by the presence of diagnostic cholangiographic findings
   c. History or clinical evidence of alcoholic liver disease
   d. History or clinical evidence of alpha-1-antitrypsin deficiency
   e. History of biopsy-confirmed Nonalcoholic steatohepatitis (NASH)
   f. History or evidence of Gilbert's syndrome with elevated total bilirubin
   g. History or evidence of hemochromatosis
   h. Hepatitis B, defined as the presence of hepatitis B surface antigen at Screening
   i. Hepatitis C, defined as the presence of hepatitis C virus ribonucleic acid at Screening
   j. History, evidence or high suspicion of hepatobiliary malignancy based on imaging, screening laboratory values and/or clinical symptoms
6. Known history of human immunodeficiency virus (HIV) or positive antibody test at Screening

7. Clinically important alcohol consumption, defined as more than 2 drink units per Day (equivalent to 20 g) in women and 3 drink units per Day (equivalent to 30 g) in men, or inability to quantify alcohol intake reliably
8. History of malignancy diagnosed or treated actively or within 2 years, or ongoing evaluation for malignancy; localized treatment of squamous or noninvasive basal cell skin cancers and cervical carcinoma in situ was allowed if appropriately treated prior to Screening
9. Treatment with obeticholic acid (OCA) and fibrates (eg, bezafibrate, fenofibrate, elafibranor, lanifibranor, pemafibrate, and saroglitizar) 6 weeks prior to Screening
10. Treatment with colchicine, methotrexate, azathioprine, or long-term systemic corticosteroids (> 2 weeks) during 2 months prior to Screening. See Section 7 of the study protocol (Appendix 16.1.1) for additional medications that might be excluded
11. Treatment with antipruritic drugs (eg, cholestyramine, naltrexone, rifampicin, sertraline, or any experimental approach) must have been on a stable dose within 1 month prior to Screening
12. Treatment with any other investigational therapy or device within 30 days or within 5 half-lives, whichever was longer, prior to Screening
13. For females, pregnancy or breastfeeding
14. Any other condition(s) that would compromise the safety of the subject or compromise the quality of the clinical study, as judged by the Investigator
15. Immunosuppressant therapies (eg, cyclosporine, tacrolimus, anti-Tumor Necrosis Factor alpha, or other immunosuppressive biologics)
16. Other medications that affect liver or GI functions, such as absorption of medications or the Roux-en-Y gastric bypass procedure, could have been prohibited and had to be discussed with the Medical Monitor on a case-by-case basis
17. Active Coronavirus disease 2019 (COVID-19) infection during Screening

Test product, dose and mode of administration, and batch number:

Seladelpar 10 mg oral capsules were taken once daily. The study drug could be down-titrated in a blinded manner to a lower dose (5 mg) if deemed necessary by the Investigator for safety or tolerability reasons.

Lot numbers used on study are as follows:

Seladelpar 5 mg capsules: 20J001, 21B004, 21C001, 21G001, 21J001, 21L002

Seladelpar 10 mg capsules: 20J001, 21B004, 21C001, 21G001, 21J001, 21L002

Duration of treatment:

The study treatment duration was planned to be 12 months per protocol.

Reference therapy, dose and mode of administration, batch number:

Placebo 10 mg oral capsules were taken once daily. Subjects receiving placebo could be down-titrated in a blinded manner to a lower dose if deemed necessary by the Investigator for safety or tolerability reasons.
Lot numbers are as follows:
Placebo 5 mg capsules: 20J001, 21B004, 21C001, 21G001, 21J001, 21L002

Placebo 10 mg capsules: 20J001, 21B004, 21C001, 21G001, 21J001, 21L002

Endpoints for evaluation defined per protocol:

Primary Endpoints

1. Proportion of subjects who were considered responders at 12 months based on the following composite endpoint of ALP and total bilirubin at 12 months requiring
   a. ALP < 1.67× ULN
   b. ≥ 15% decrease in ALP
   c. Total bilirubin ≤ 1.0× ULN

2. Assessment of treatment-emergent AEs (TEAEs) (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0), biochemistry and hematology

Key Secondary Endpoints

1. Proportion of subjects with ALP ≤ 1.0× ULN at 12 months (eg, normalization)
2. Change from baseline in weekly averaged Pruritus NRS in subjects with baseline NRS ≥ 4 at 6 months

Other Secondary Endpoints

1. Proportion of responders based on the composite endpoint of ALP and total bilirubin at 6 months
2. Proportion of subjects with ALP ≤ 1.0× ULN at 6 months
3. Proportion of subjects with ALP < 1.67× ULN and ALP < 1.5× ULN at 6 and 12 months
4. Absolute and relative changes in ALP at 3, 6, and 12 months
5. Proportion of subjects with a decrease in NRS ≥ 2, NRS ≥ 3, or NRS ≥ 4 in subjects with baseline NRS ≥ 4 at each visit
6. Changes from baseline in Pruritus NRS in subjects with baseline NRS ≥ 4 at 3 and 12 months
7. Change from baseline in QoL measure for use in PBC-40 questionnaire (PBC-40 QoL) at each visit (total score and domain score)
8. Change from baseline in United Kingdom – Primary Biliary Cirrhosis and Global PBC Study Group risk scores at each visit
9. Absolute and relative changes in ALT, AST, gamma-glutamyl transferase (GGT), bilirubin (total, direct, and indirect), and 5'-nucleotidase at each visit
10. The first occurrence of PBC clinical outcomes as defined by the following:
    a. Overall death
    b. Liver transplantation
    c. MELD score ≥ 15 for at least 2 consecutive visits
    d. Ascites requiring treatment
    e. Hospitalization for new onset or recurrence of any of the following:
        - Variceal bleeding
        - Hepatic encephalopathy (as defined by a West Haven score ≥ 2)
        - Spontaneous bacterial peritonitis (confirmed by culture from diagnostic paracentesis)

Exploratory Endpoints

1. Liver histology changes based on pathology review of biopsy tissues
2. PBC response criteria results (Barcelona, Paris I and II, Toronto I and II, Rotterdam)
3. Changes from baseline in Pruritus NRS based on additional thresholds for improvement and baseline itch status
4. Changes from baseline in PBC-40 QoL itch domain and the 5-D Itch scale, PGI-C, and PGI-S
5. Absolute and relative changes in lipids, bile acids, sterols and biomarkers of bile acid synthesis: 7-alpha-Hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF19)
6. Plasma concentrations of seladelpar and its metabolites (M1, M2, and M3)
7. Absolute and relative changes in markers of inflammation/immune reactivity (eg, high sensitivity C-reactive protein [hs-CRP], fibrinogen, haptoglobin, tumor necrosis factor-alpha, and anti-antibodies)
8. Absolute and relative changes in markers of enhanced liver fibrosis (ELF) as measured by liver stiffness using FibroScan®
9. Absolute and relative changes in markers of liver injury: CK18 (M65) and miR-122

Safety:

Safety assessments comprised TEAEs and SAEs per CTCAE Version 5.0, and concomitant medications; biochemistry and hematology clinical laboratory assessments; vital signs; physical examination; 12-lead ECGs; abdominal ultrasound and liver histology. Specific safety monitoring algorithms for liver, renal, or pancreatic injury and muscle toxicity were incorporated into the study. Pregnancy testing was also performed.

Statistical Methods

Sample size determination and power for the primary and key secondary efficacy endpoints

For the purposes of sample size estimation, the placebo group response rate for the primary efficacy endpoint (the composite biochemical response endpoint of ALP and total bilirubin) evaluated at 12 months was estimated as 20%. The seladelpar 10 mg dose group response rate was estimated as 55%. With the use of a 2-sided test of equality of binomial proportions based on Fisher's exact test at the 0.05 level of significance, a sample size of 180 randomized subjects who received study drug provided > 90% power to detect a difference between the 10 mg seladelpar arm and the placebo arm, where any subject who did not provide a 12-month assessment was considered as a nonresponder.

The analysis of the key secondary efficacy endpoint of normalization of ALP levels was estimated to have a placebo response rate and a seladelpar response rate of 2.5% and 25.5%, respectively. A sample size of 180 randomized subjects who received study drug provided > 90% power to detect a difference between the seladelpar and placebo arms, based on a 2-sided Fisher's exact test at a 0.05 level of significance, where any subject who did not provide a 12-month assessment was considered as a nonresponder.

The analysis of the key secondary efficacy endpoint of change from baseline in weekly averaged Pruritus NRS at Month 6 sample size calculation was based on a 2-sample 2-sided t-test with a significance level of 0.05. The common standard deviation was estimated as 2. Under these assumptions, a total of 48 randomized subjects who received study drug having a baseline NRS $\geq$ 4 and NRS at Month 6 provided > 80% power to detect a treatment difference of $\geq$ 2 between the 10 mg seladelpar and placebo arms.

The assumptions for these power calculations were based on results from study CB8025-31735. Additionally, for responder analyses, a dropout rate of approximately 10% was assumed.

Analysis Sets

- All Subjects Screened Analysis Set: All subjects who were screened for enrollment in the study regardless of whether they were enrolled in the study; this analysis set was used for summarizing reasons for screen failures.
- Intent-To-Treat (ITT) Analysis Set: Any subject who was randomized into the study and received at least 1 dose of study drug. The ITT Analysis Set was the primary analysis set used for efficacy analyses with the exception of secondary endpoints evaluated for subjects with moderate to severe pruritus. Subjects were analyzed according to randomized treatment assignment.
- Moderate to Severe Pruritus NRS (MSPN) Analysis Set: Subjects in the ITT Analysis Set who had a baseline NRS value $\geq$ 4. The MSPN Analysis Set was the primary analysis set for secondary endpoints based on NRS evaluations. Subjects were analyzed according to randomized treatment assignment.
- Per-protocol (PP) Analysis Set: Any subject who was in the ITT Analysis Set and had at least 1 postbaseline ALP and total bilirubin evaluation without any protocol violation that was deemed to impact the efficacy analysis.
- Biopsy Analysis Set: Any subject who had a baseline or Month 12/ET biopsy; this analysis set was used to examine the histopathology changes over time or the lack thereof. Subjects were analyzed in the group based on treatment received if this differed from the treatment assignment.
- Safety Analysis Set: Any subject who received at least 1 dose of study drug. Subjects were included in the group based on treatment received if this differed from the treatment assignment. All safety analyses were completed using the Safety Analysis Set.
- The PK analysis set included any subject who participated in the PK sample collection. All PK analyses were completed using the PK analysis set. Future pooling of the concentration data from this study with data from other studies to facilitate development and/or updating of a population PK model will be reported separately. The sample collection dates / time and concentration results were listed.

Demographic and baseline characteristics (medical histories, physical examinations and concomitant medications

and procedures) were summarized.

The primary efficacy endpoint of the proportion of subjects achieving the composite biochemical response evaluated at Month 12 was analyzed using Cochran-Mantel-Haenszel (CMH) test adjusted for both randomization stratification variables (ALP level: < 350 U/L and ≥ 350 U/L; Pruritus NRS: < 4 and ≥ 4) in the ITT Analysis Set.

The key secondary efficacy endpoint of the proportion of subjects who achieved normalization of ALP levels at Month 12 was analyzed in the ITT Analysis Set using the same approach as described for the primary efficacy endpoint analysis.

Change from baseline in weekly averaged Pruritus NRS at 6 months, the other key secondary endpoint, was analyzed using a mixed-effect model for repeated measures (MMRM) for subjects in the MSPN Analysis Set. The model included terms for baseline NRS, randomization stratum (ALP level < 350 U/L vs ≥ 350 U/L), treatment group, week, and treatment-by-week interaction.

Control of study-wide Type I error was maintained at 5% using a hierarchical fixed-sequence methodology for the primary and key secondary efficacy analyses as defined in the SAP.

Selected analyses of efficacy were planned to be conducted using the PP Analysis Set as defined by the Statistical analysis plan (SAP). If the PP Analysis Set differed from the ITT Analysis Set by less than 5 subjects, then PP analyses were not to be performed. Sensitivity and subgroup analyses were performed per the SAP.

Additional analyses for other efficacy endpoints were performed per the SAP.

Treatment-emergent AEs, treatment-emergent SAEs, ≥ Grade 3 TEAEs, TEAEs leading to discontinuation of study drug, TEAEs leading to study discontinuation and TEAEs leading to deaths were summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), preferred term (PT), severity and causal relationship to study drug, as appropriate. Listings that included the verbatim term, PT, and SOC as well as full details of all AEs for all subjects in the Safety Analysis Set were presented. Separate listings for subjects in the Safety Analysis Set were prepared for ≥ Grade 3 TEAEs, treatment-emergent SAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to study discontinuation.

To assess AEs of interest, predefined MedDRA search strategies were implemented to identify TEAEs potentially reflecting liver, muscle, renal, and pancreatic safety, corresponding to the categories for which safety monitoring criteria were utilized during the study. A listing of safety monitoring criteria met by subjects in the Safety Analysis Set was also provided. Summary tables were presented for clinical laboratory tests with numeric values by treatment arm for subjects in the Safety Analysis Set. A listing of abdominal ultrasound results, vital sign data and physical examination results by subject was also provided. Changes from baseline for ECG QTcF and shift tables for biochemistry parameters of interest were provided. All safety laboratory parameter data were provided in subject data listings. Additional safety analyses including subgroup analyses were performed as described in the SAP.

Summary of Results:

Efficacy results:

This pivotal, international, double-blind, placebo-controlled study included 193 subjects randomized in a 2:1 ratio to receive seladelpar or placebo across 90 sites in 24 countries. A total of 128 subjects were randomized to the seladelpar arm and 65 to the placebo arm. The majority of subjects enrolled (90.7%) completed study treatment.

Demographic and baseline characteristics were overall balanced between the two treatment arms. Most subjects were female (94.8%), White (88.1%), and non-Hispanic or Latino (69.9%), and the mean age was 56.7 years. In addition to subjects with mild disease severity, the study population included subjects with moderate disease severity (eg, 25 [13.0%] subjects with total bilirubin levels above ULN at baseline, 27 [14.0%] subjects with moderate Rotterdam stage, and 27 [14.0%] subjects with cirrhosis at baseline). Mean ALP, total bilirubin levels, and Pruritus NRS were well balanced at baseline. Most subjects (93.8%) received seladelpar or placebo in addition to UDCA, while 6.2% of subjects were intolerant to UDCA and received study drug as monotherapy. Mean treatment compliance was over 98% through Month 12.

The ITT Analysis Set was used for efficacy analyses with the exception of secondary endpoints evaluated in subjects with moderate to severe pruritus, defined as baseline Pruritus NRS ≥ 4.

The study met the primary efficacy endpoint of the composite biochemical response of ALP $< 1.67\times$ ULN, $\geq 15\%$ reduction in ALP, and total bilirubin ≤ 1.0 ULN at Month 12. A significantly higher percentage of subjects receiving seladelpar (61.7%; 79/128) achieved the primary efficacy endpoint compared with placebo (20.0%; 13/65) ($p < 0.0001$). At Month 12, 65.6% of subjects in the seladelpar arm compared with 26.2% in the placebo arm achieved the ALP $< 1.67\times$ ULN component of the composite biochemical response endpoint. In addition, a higher percentage of subjects receiving seladelpar (83.6%) experienced a decrease from baseline of $\geq 15\%$ in ALP levels, compared with subjects who received placebo (32.3%). The percentage of subjects with total bilirubin $\leq 1.0\times$ ULN was 81.3% and 76.9% in the seladelpar and placebo arms, respectively. Higher percentages of responders in the seladelpar arm compared with placebo were observed as early as Month 1, and these differences were maintained with ongoing treatment throughout the course of the study.

The study also met the key secondary efficacy endpoint of ALP normalization (ALP $\leq 1.0\times$ ULN) at Month 12. A significantly higher percentage of subjects in the seladelpar arm (25%) achieved ALP normalization compared with the placebo arm (0%) ($p < 0.0001$). Higher percentages of responders in the seladelpar arm compared with placebo were observed at Month 1 and these effects were maintained with ongoing treatment throughout the course of the study.

The other key secondary endpoint of change in Pruritus NRS at Month 6 in subjects with moderate to severe pruritus at baseline (Pruritus NRS ≥ 4) was also met. Seladelpar treatment led to a statistically significant improvement in Pruritus NRS compared with placebo with an LS mean change of -3.2 vs -1.7, respectively ($p=0.0047$). Greater decreases in Pruritus NRS in the seladelpar arm relative to placebo were observed as early as Month 1 and this effect was also seen from Month 6 through Month 12. In addition, the percentage of subjects with a decrease in Pruritus NRS ≥ 2, NRS ≥ 3, and NRS ≥ 4 in the seladelpar arm was higher compared with the placebo arm across all study timepoints. In the ITT Analysis Set, in which all subjects were evaluated regardless of baseline Pruritus NRS, subjects in the seladelpar arm also experienced greater decreases in Pruritus NRS compared with those receiving placebo, with reductions in the seladelpar arm vs placebo observed at all study timepoints. The LS mean change from baseline at Month 6 in the ITT Analysis Set was -1.3 for the seladelpar arm, relative to -0.4 in placebo ($p=0.0001$).

Results from multiple prespecified sensitivity analyses, including complete case and treatment policy strategy analyses, and control-based multiple imputation analysis of the primary and the two key secondary efficacy endpoints validated the robustness of the primary analyses of the corresponding efficacy endpoints. Results from the Tipping Point analyses also showed that even in the unlikely case wherein all subjects in the placebo arm with missing data at Month 12 were categorized as responders for the primary efficacy endpoint and the key secondary efficacy endpoint of ALP normalization, the seladelpar arm would still perform significantly better compared with the placebo arm.

Results from the analysis of prespecified subgroups are as follows:

- Consistent with the analyses in the ITT Analysis Set, analyses of prespecified subgroups revealed higher percentages of responders for subjects in the seladelpar arm compared with placebo for the composite biochemical response endpoint at Month 12 across evaluable subgroups.

  - Analyses of the primary efficacy biochemical response endpoint for subgroups including female vs male, age at Screening ≥ 65 years vs < 65 years, age at PBC diagnosis < 50 years vs ≥ 50 years, North America subjects vs Europe vs Rest of the world, prior use of OCA/fibrates vs no prior use, total bilirubin < 0.6× ULN vs ≥ 0.6× ULN, Pruritus NRS < 4 vs ≥ 4, cirrhosis vs no cirrhosis, and total bilirubin ≤ 1× ULN vs > 1× ULN at baseline demonstrated a generally similar treatment effect with seladelpar across subgroups.
  - A higher percentage of subjects with ALP ≥ 350 U/L at baseline in the seladelpar arm reached the primary efficacy endpoint (22.9%), compared with the placebo group (11.1%); however, the proportion of responders in the seladelpar arm was lower compared with that in the overall ITT Analysis Set and with subjects with ALP < 350 U/L at baseline, consistent with higher baseline ALP requiring greater reductions to achieve the ALP < 1.67× ULN component of the composite biochemical response endpoint.
  - Despite small group sizes, a higher percentage of subjects who received seladelpar as monotherapy achieved the primary efficacy endpoint compared with those who received placebo.
- A similar pattern favoring the seladelpar arm over placebo was observed for the key secondary efficacy endpoint of ALP normalization at Month 12 across evaluable subgroups.
  - There was an overlap in risk difference CIs between the overall ITT analysis set and individual subgroups and between subgroup pairs across evaluable subgroups, including subjects with cirrhosis and subjects with total bilirubin > 1× ULN at baseline. One exception to this was the subgroup with ALP ≥ 350 U/L at baseline in which no subjects achieved normalization of ALP levels in either treatment arm.
  - Despite small group sizes, a higher percentage of subjects who received seladelpar as monotherapy achieved normalization of ALP levels compared with those who received placebo.
- A similar pattern favoring the seladelpar arm over placebo was observed for the key secondary efficacy endpoint of changes in Pruritus NRS at Month 6 across evaluable subgroups, although some subgroups had small samples sizes.

Results from other secondary and exploratory endpoints are as follows:

- A higher percentage of subjects achieved ALP < 1.67× ULN and ALP < 1.5× ULN in the seladelpar arm compared with placebo over the course of the study. At Month 12, higher percentages of subjects with ALP < 1.67× ULN and ALP < 1.5× ULN were observed in the seladelpar arm (65.6% and 58.6%, respectively), compared with the placebo arm (26.2% and 12.3%, respectively). Similar findings were obtained at other study timepoints.
- Reductions in ALP levels were observed in the seladelpar arm compared with the placebo arm at each timepoint evaluated in the study. LS mean percent changes from baseline in ALP levels were -36.2% and -42.4% at Month 1 and Month 12, respectively, in the seladelpar arm compared with -4.8% and -4.3% in the placebo arm, respectively.
- Seladelpar treatment induced reductions in the cholestatic marker GGT compared with placebo starting at Month 1 and continuing through Month 12. LS mean percent changes from baseline in GGT levels at Month 12 were -39.1% in the seladelpar arm compared with -11.4% in the placebo arm, respectively. Postbaseline total bilirubin, direct bilirubin and indirect bilirubin levels were similar between treatment arms. A higher percentage of subjects with baseline total bilirubin > 1× ULN achieved total bilirubin normalization at Month 12 in the seladelpar arm (70.0%, CI: 49.9, 90.1) compared with that in the placebo arm (40%; CI: 0.0, 82.9), although the CIs were wide.
- Seladelpar treatment induced reductions in the liver biochemical marker ALT and in 5'-nucleotidase compared with placebo throughout the course of the study. Postbaseline reductions in ALT levels were greater in the seladelpar arm compared with the placebo arm starting at Month 3 and continuing through Month 12. LS mean percent changes from baseline in ALT levels at Month 12 were -23.5% in the seladelpar arm compared with -6.5% in the placebo arm. More than double the percentage of subjects with baseline ALT > 1× ULN achieved ALT normalization at Month 12 in the seladelpar arm (56.3%, CI: 44.8, 67.9) compared with that in the placebo arm (25.0%, CI: 10.9, 39.1). Postbaseline AST levels were similar between treatment arms.

- Subjects in the seladelpar arm experienced reductions in total cholesterol, LDL-C, and triglycerides levels compared with those receiving placebo throughout the course of the study. At Month 12, the LS mean percent changes for total cholesterol, LDL-C, and triglycerides were -8.6%, -12.7%, and -16.1%, respectively, for the seladelpar arm, and -4.2%, -3.7%, and -1.1%, respectively, for placebo. HDL-C levels were similar between treatment arms throughout the study with no notable changes from baseline.
- Seladelpar induced a pattern of greater postbaseline increases in serum FGF21 levels (defined as an exploratory endpoint in the SAP) compared with placebo in the FGF21 Analysis Set. At Month 12, LS mean percent changes were 76.2% and 33.5% in the seladelpar and placebo arms, respectively. Consistent with the established biological effects of FGF21 as a negative regulator of bile acid synthesis (Kouno 2022), the seladelpar arm also had greater reductions from baseline in total bile acid levels and other biomarkers of bile acid synthesis (C4) compared with placebo. At Month 12 the median percent change from baseline in C4 was -41.9% for the seladelpar arm compared with 6.4% for placebo.
- Inflammatory/immune reactivity markers (hs-CRP, fibrinogen, haptoglobin, IgM) were decreased following treatment with seladelpar compared with placebo. At Month 12, mean percent changes from baseline in hs-CRP levels were -1.43% in the seladelpar arm vs 13.43% in placebo, while mean percent changes from baseline in IgM levels were -11.9% in the seladelpar arm vs -4.8% in placebo.
- Serum levels of the pruritogenic cytokine IL-31 (defined as an exploratory endpoint in the SAP) were decreased from baseline in the seladelpar group, while in contrast they were increased in the placebo group throughout the course of the study. LS mean percent changes at Months 6 and 12 were -46.1% and -38.5%, respectively, in the seladelpar arm, compared with 5.5% and 31.4%, respectively, in the placebo arm.
- Results from the 5-D Itch scale total score, PBC-40 QoL Itch Domain, PGI-S, and PGI-C both in the MSPN and in the ITT Analysis Sets were consistent with those of the effect of seladelpar on Pruritus NRS at Month 6, highlighting an overall improvement of pruritus in subjects treated with seladelpar compared with those treated with placebo across a wide range of assessments.
- Correlation analyses comparing changes from baseline in PGI-C and PGI-S ratings with changes from baseline in Pruritus NRS in the ITT Analysis Set further supported the consistent findings obtained using multiple PROs. Moreover, correlation analyses between different measurements of pruritus, including Pruritus NRS, PBC-40 QoL Itch Domain, and 5-D Itch in the MSPN and the ITT Analyses Sets highlighted notable correlations between these assessments.
- Subjects on the seladelpar arm experienced greater decreases in several domains of the 5-D Itch scale, including distribution, degree, disability, and the sleep item, both in the MSPN and the ITT Analysis Sets compared with subjects receiving placebo, and similar improvements were observed in the sleep disturbance item of the PBC-40 QoL questionnaire.
- Seladelpar was associated with a greater decrease in the risk of clinical outcomes compared with placebo as assessed via risk scores. Analysis of the GLOBE risk scores showed a greater decrease in the risk of clinical outcomes in the seladelpar arm compared with placebo across all study timepoints. Seladelpar treatment was also associated with trend in decreased risk of clinical outcomes as evaluated by the 5-year, 10-year, and 15-year UK-PBC risk scores when compared with placebo.
- One subject in the seladelpar arm and no subjects in the placebo arm were positively adjudicated as having experienced a PBC clinical outcome event.
- Responder rates based on the Barcelona, Paris I, Paris II and Toronto I and Toronto II criteria were higher in the seladelpar arm versus the placebo arm, consistent with the improvement in response rates observed for the primary efficacy biochemical response endpoint.
- PK samples were analyzed from 71 subjects in the seladelpar arm (comprising 55.5% of the total seladelpar population in the ITT Analysis set).

Safety results:

In study CB8025-32048, seladelpar was generally safe and well tolerated. Data supporting this conclusion include the following:

- Exposure to study drug was similar between the 2 arms. The mean duration of exposure was 50.5 weeks in the seladelpar arm and 48.3 weeks in the placebo arm, and the mean average daily dose of study drug was 9.8 mg in the seladelpar arm and 9.9 mg in the placebo arm.

- The incidence of TEAEs was generally similar between the seladelpar and placebo arms (86.7% vs 84.6%). The most frequently reported TEAEs by PT occurring in ≥ 5% of subjects in the seladelpar arm were COVID-19, Headache, Abdominal pain, Arthralgia, Fatigue, Nausea, Abdominal distension, and Nasopharyngitis. The most frequently reported TEAEs by PT occurring in ≥ 5% of subjects in the placebo arm were COVID-19, Pruritus, Upper respiratory tract infection, Nasopharyngitis, Pharyngitis, Arthralgia, Asthenia, Fatigue, Hypertension, UTI, and Vertigo positional.
- Grade 3 or higher TEAEs were reported for 10.9% of subjects in the seladelpar arm and 7.7% in the placebo arm. There were no treatment-related Grade 3 or higher TEAEs that occurred during the study, and there were no Grade 5 TEAEs reported in the study. There was no pattern in the types of Grade 3 or higher TEAEs in either arm. All Grade 3 or higher events resolved, with the exception of 3 events (Hypertension and Invasive ductal breast carcinoma in the seladelpar arm and Pruritus in the placebo arm). Of the Grade 3 or higher AEs, 2 events in the seladelpar arm and 2 events in the placebo arm led to treatment discontinuation.
- The incidence of treatment-related TEAEs as assessed by the Investigator was 17.2% in the seladelpar arm and 12.3% in the placebo arm. The most common treatment-related TEAEs reported for ≥ 2 subjects by PT in the seladelpar arm were Headache, Diarrhea, Abdominal distension, Dizziness, Nausea, and Vomiting. The only treatment-related TEAE reported for ≥ 2 subjects by PT in the placebo arm was Dry mouth.
- The incidence of treatment-emergent SAEs was similar between the seladelpar and placebo arms (7.0% vs 6.2%, respectively). All SAEs were individually reported with the exception of COVID-19, which occurred in 1 subject in each arm. There were no treatment-related SAEs in either treatment arm.
- The incidence of TEAEs leading to study drug interruption was similar between the seladelpar and placebo arms (5.5% vs 6.2%, respectively). All TEAEs leading to study drug interruption were reported in 1 subject each. One subject in the seladelpar arm had a dose reduction following a study drug interruption associated with a TEAE attributed to use of a concomitant medication per the Investigator assessment. This was followed by an up-titration to 10 mg.
- The incidence of TEAEs leading to treatment discontinuation was similar between the seladelpar and placebo arms (3.1% vs 4.6%, respectively). All TEAEs leading to treatment discontinuation occurred in 1 subject each. Two subjects (1.6%) in the seladelpar arm had treatment-related TEAEs leading to treatment discontinuation, with PTs of Disease progression and Liver function test increased. TEAEs leading to study discontinuation were similar to TEAEs leading to treatment discontinuation.
- TEAEs of interest were those potentially reflecting liver-, muscle-, renal-, or pancreatic-related toxicity, identified by predefined search strategy.
    - TEAEs potentially reflecting liver-related toxicity were reported for 6.3% of subjects in the seladelpar arm and 9.2% of subjects in the placebo arm. The PTs included in this TEAE category were individually reported in each arm with the exception of Hepatic cirrhosis, which was reported for 3 subjects (2.3%) in the seladelpar arm and 1 subject (1.5%) in the placebo arm. All TEAEs in this category were Grade 1 or 2, with the exception of one Grade 3 event of Oesophageal varices haemorrhage occurring in 1 subject of the seladelpar arm in the setting of known cirrhosis at baseline.
    - TEAEs potentially reflecting muscle-related toxicity occurred in a similar percentage of subjects in the seladelpar and placebo arms (6.3% vs 7.7%, respectively). The incidence of reported PTs was generally similar across treatment arms. There were no events associated with notable CK increases related to seladelpar.
    - There were no TEAEs potentially reflecting renal-related toxicity reported during the study.
    - TEAEs potentially reflecting pancreatic-related toxicity occurred in a similar percentage of subjects in the seladelpar and placebo arms (1.6% vs 1.5%, respectively). All events were reported as Lipase increased and were Grade 1 or 2 in severity.
- TEAEs associated with safety monitoring criteria for liver, muscle, renal, and pancreatic safety were evaluated.
    - A total of 4 subjects had TEAEs associated with liver safety monitoring criteria (seladelpar 2.3% [n=3]; placebo 1.5% [n=1]). All events were Grade 1 or 2. One of these events resulted in a drug

interruption, and the other 3 events led to withdrawal of study drug. None of these events were attributed to DILI related to seladelpar.

  - There were no subjects who met muscle, renal, or pancreatic safety monitoring criteria.

- Pruritus TEAEs occurred more frequently in the placebo arm relative to the seladelpar arm (15.4% vs 5.5%, respectively).
- Cardiovascular TEAEs were identified by a predefined search strategy and reported for 10.2% of subjects in the seladelpar arm and 7.7% of subjects in the placebo arm. The majority of cardiovascular TEAEs were Grade 1 or 2 with one Grade 3 TEAE of Coronary artery disease reported in the seladelpar arm, which was assessed as unrelated to study drug by the Investigator. One event in this category was assessed as treatment-related by the Investigator, which was a Grade 1 TEAE of CK increased reported in the placebo arm.
- Mean values and percent changes in hematology parameters from baseline were generally similar between the seladelpar and placebo arms. Shifts of ≥ 2 grades from baseline in hematology parameters were reported for 14.1% of subjects in the seladelpar arm and 12.3% of subjects in the placebo arm. The most frequently reported abnormal hematology parameter in this category was decreased neutrophil count in both arms (seladelpar 8.6%; placebo 10.8%).
- In general, greater postbaseline reductions in liver biochemistry parameters were observed for ALP, GGT, ALT, and 5'-nucleotidase in the seladelpar arm compared with the placebo arm. Shifts of ≥ 2 grades from baseline in liver biochemistry parameters were observed in a similar percentage of subjects in the seladelpar and placebo arms (7.0% vs 6.2%, respectively). The most frequently observed abnormal biochemistry laboratory parameter in this category was increased blood bilirubin, which occurred at a similar frequency among subjects in both arms (seladelpar 4.7% vs placebo 4.6%).
- There were no meaningful differences in other biochemistry parameters between treatment arms. Specifically, mean CK values, creatinine, eGFR, cystatin C, lipase, and amylase remained within the normal range, and there were no significant changes in mean values in either treatment arm.
- A total of 8.6% of subjects (n = 11) in the seladelpar arm and 12.3% of subjects (n = 8) in the placebo arm had postbaseline laboratory values falling into the left upper, right upper, and right lower quadrants of the eDISH plots. Three subjects were identified as meeting potential Hy's Law criteria (defined as total bilirubin value ≥ 2.0× ULN occurring on or within 30 days after a postbaseline elevation of ALT or AST to ≥ 3× ULN, regardless of ALP value): 2 in the placebo arm and 1 in the seladelpar arm. None of these cases were consistent with DILI related to study drug.
- Laboratory safety parameters of interest were evaluated.
  - A total of 21 subjects met the liver biochemistry laboratory abnormality criteria, with 8.6% of subjects (n=11) in the seladelpar arm and 15.4% of subjects (n=10) in the placebo arm meeting criteria in at least one category. None of these laboratory abnormalities were associated with DILI related to study drug. Among subjects with ALT and AST above the upper limit of normal at baseline, increases to > 2× baseline values of AST or ALT were observed in 4 (6.2%) of placebo subjects and 3 (2.3%) of seladelpar subjects.
  - A higher percentage of subjects in the seladelpar arm experienced a decrease in eGFR of ≥ 25% than in the placebo arm (12 subjects [9.4%] vs 1 subject [1.5%]). In the seladelpar arm, most of these subjects (9/12 [75%]) had resolution at the next study visit without change in study drug dose. There was no observed pattern for timing of onset. Overall, changes were mild; no subject had a shift > 1 CTCAE grade. There were no TEAEs reported in association with these changes. Confounding comorbidities or medications were common. Because the eGFR calculation used a creatinine-based equation, a post-hoc analysis was conducted in which a cystatin C-based equation was used to calculate eGFR. Using this alternate calculation method, 9/12 subjects treated with seladelpar did not appear to have a decline in renal function. The 3 subjects with decline in eGFR using the cystatin C-based equation were assessed by the Sponsor as having a probable underlying renal etiology for the eGFR decrease in the setting of confounding factors (comorbid conditions, medications including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and/or non-steroidal anti-inflammatory drugs, or other

clinical events during the study). In two of these subjects, eGFR returned to baseline with ongoing treatment.

- A total of 3 subjects (seladelpar 2 [1.6%]; placebo 1 [1.5%]) met at least one criterion for muscle laboratory safety parameters of interest. CK elevations led to dose interruptions in 1 seladelpar subject and the CK elevations were assessed by the Investigator as not related to study drug.
- A total of 16 subjects (12.5%) in the seladelpar arm and 11 subjects (16.9%) in the placebo arm met at least one criterion for pancreatic laboratory abnormality parameters of interest. Three TEAEs of Lipase increased were reported (2 in the seladelpar arm and 1 in the placebo arm) in subjects who had elevations in lipase at baseline, and all resolved on study. There were no TEAEs associated with amylase increases.

- The incidence of TEAEs in the seladelpar arm was generally similar compared with placebo in subjects with cirrhosis at baseline, in subjects intolerant to UDCA, and in subjects with prior OCA and/or fibrate use. The safety profile of seladelpar in these subgroups was also generally consistent with that of the overall study population. A higher percentage of subjects with elevated total bilirubin at baseline had a TEAE, SAE, or ≥ Grade 3 TEAE compared with subjects with normal baseline total bilirubin in both the seladelpar and placebo arms, but subject incidence of these events was balanced between treatment arms, and the PTs of these events were generally reflective of more advanced disease in this population.
- There were no clinically meaningful changes in vital signs parameters in either treatment arm. There were more subjects with postbaseline systolic blood pressures >160 mmHg in the seladelpar arm than in the placebo arm (7.0% vs 1.5%). All these subjects but 2 (one in each treatment arm) had elevated systolic blood pressures prior to dosing.
- There were no concerning observations of increased QTcF postbaseline in either treatment arm.

Conclusions:

Seladelpar was effective for the treatment of PBC as demonstrated by a significantly higher percentage of subjects achieving the composite biochemical response endpoint with seladelpar vs placebo, reflecting improvement in cholestatic markers associated with clinical outcomes. Seladelpar also led to a statistically significant improvement on the rate of ALP normalization, an increasingly recognized treatment goal for PBC, compared with placebo. In addition, a greater decrease in pruritus at Month 6, measured with the Pruritus NRS, was observed following treatment with seladelpar vs placebo in subjects with moderate to severe pruritus at baseline; this effect was observed as early as Month 1 and was also evident from Month 6 through Month 12. Consistency of seladelpar effect on key biochemical and pruritus endpoints was observed across a range of prespecified subgroups. Improvement in pruritus with seladelpar was observed in the overall ITT Analysis Set, regardless of baseline Pruritus NRS. Results from the 5-D Itch scale total score, PBC-40 QoL Itch Domain, PGI-S, and PGI-C corroborated the findings obtained from the Pruritus NRS, illustrating an overall clinically meaningful improvement of pruritus in subjects treated with seladelpar across a wide range of assessments. Seladelpar also improved ALT, a marker of liver injury, and led to greater reductions in cholesterol, bile acids, and inflammatory markers relative to placebo. Mechanistic biomarker changes related to cholestasis (FGF21 for bile acids levels) and pruritus (IL-31) were observed at most study timepoints and paralleled the pattern of improvements noted for the corresponding prespecified study endpoints.

Seladelpar was overall safe and well tolerated as demonstrated by the safety data from this study, including a comprehensive evaluation of TEAEs and laboratory parameters. In subgroups of subjects with cirrhosis, subjects with elevated total bilirubin at baseline, and subjects receiving seladelpar as monotherapy, the safety profile of seladelpar appeared similar to placebo, although subgroup sample sizes were small.

Overall, many patients with PBC do not respond adequately or tolerate currently available therapies, and often experience continued ALP elevation and disease progression despite treatment with UDCA. Pruritus remains a major debilitating symptom for many PBC patients, and current treatments do not improve, or may even worsen, this symptom. Seladelpar has the potential to offer a safe and effective therapy for the management of cholestasis and symptoms of patients with PBC.

Date of the report: 30 November 2023

3.1. Publication

Hirschfield GM, Bowlus CL, Mayo MJ, Kremer AE, Vierling JM, Kowdley KV, et al. A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis. N Engl J Med 2024a;390 (9):783-94.

3.2. Protocol Amendments and Description

3.2.1. Amendment 1.0 (Version 2.0)

Amendment 1, dated 01 December 2020, had the following key changes:

- Removed the statement that UDCA was not considered a study drug for the AE reporting purposes from Section 9.1. The change was made based on a recommendation from the US FDA to avoid potential misunderstandings regarding reporting of safety events.
- Clarified which women must use contraception per Clinical Studies Facilitation Arm Recommendations related to contraception and pregnancy testing in clinical studies (Version 1.1, 21 September 2020).
- •Added the following additional individual subject stopping criteria in Section 10.1.5:
    - Grade 3 events and above not already described by the safety monitoring criteria and related to study drug: any subject who experienced a CTCAE ≥ Grade 3 event that was considered possibly or probably related to study drug, was to be discontinued from study drug.
    - Grade 4 events not already described by the safety monitoring criteria and not related to study drug: Any subject was to be considered for discontinuation from study drug. The Investigator, in consultation with the Sponsor's Medical Monitor, could consider the specific medical nature of the event, the causality assessment, and the possible outcome of the event. Study drug could be continued after an imminent resolution or improvement in the event, if the subject was considered suitable for the clinical study, and if considered both safe and in their best interest to continue or restart study drug.
- Added additional overall study stopping criteria in Section 12; these were to be assessed by the DSMB (Section 14):
    - Three subjects develop the same Grade 3 CTCAE attributed to study drug
    - Two subjects develop any Grade 4 CTCAE attributed to study drug
    - One subject develops a Grade 5 CTCAE
- Clarified the threshold of abnormal eosinophilia (absolute count > 1× ULN) in Table 2 (DILI Criteria for Participants with Normal Baseline ALT and AST) and Table 3 (DILI Criteria for Participants with Abnormal Baseline ALT and AST).
- Added an appendix of normal ranges for safety laboratory parameters (Appendix J)

3.2.2. Amendment 2 (Version 3.0)

Amendment 2, dated 30 June 2021, had the following key changes:

- Removed the requirement of having at least 24 subjects to participate in PK sample collection for the evaluation of seladelpar and its metabolites plasma concentration

based on recommendations from the FDA. The intention was to allow all subjects to be invited to participate in PK sample collection to support the planned exposure-response analysis. The PK sample collection schedule was revised from Months 1 and 3 to Months 3 and 12, and the number of PK blood samples to be collected was revised from 2 to 3.

- Added the following 2 exclusion criteria, and updated the list of prohibited medications.
    - Immunosuppressant therapies (eg, cyclosporine, tacrolimus, anti-TNF, or other immunosuppressive biologics).
    - Other medications affecting liver or GI functions, such as absorption of medication or the Roux-en-Y gastric bypass procedure could be prohibited and should be discussed with the Medical Monitor on a case-by-case basis.
- Added text in Section 8.2.8 to allow use of liver biopsy tissues collected within 6 months prior to Screening to ease the burden from subjects.
- Outcomes related to AEs and definitions for action taken with study medication were revised to align with the Clinical Data Interchange Standards Consortium definitions.

3.2.3. Amendment 3 (Version 4.0)

Amendment 3, dated 09 February 2022, had the following key changes:

- The eGFR Inclusion Criterion 5e was revised to > 45 mL/min/1.73m2 from > 60 mL/min/1.73m^2 after review by the FDA of results from the seladelpar renal impairment study.
- Added a note in Inclusion Criterion 5 that prothrombin time, INR, and platelets could be performed locally at the Screening Visit, if deemed necessary by the Investigator after consultation with the Medical Monitor in cases in which centrally read samples were deemed invalid.
- Changed the washout period for use of prior OCA and fibrate from 3 months to 6 weeks in Exclusion Criterion 9 to more accurately reflect the washout period that spanned 5 half-lives per each drug's half-life.
- Added Exclusion Criterion 17: Active COVID-19 infection during screening.
- The Safety Follow-up Window for subjects who were not enrolled in the long-term study (CB8025-31731-RE) was reduced from 1 month (±7 days) to 14 (+3) days after last study drug dose based on the long-term safety of seladelpar in subjects with PBC and the half-life of seladelpar.
- The Screening and Run-in Period windows were revised to align with sites' average time to schedule screening assessments and to provide clarity.
- Clarified the text regarding which procedures subjects should follow after discontinuation of study treatment on study and added a new section of annual follow-up for PBC outcomes assessment.
- Added that ascites and encephalopathy information should be collected during the physical examination at specified timepoints to allow for CP score calculation.
- Updated the guideline for management of pancreatitis in Table 6 (Pancreatic Safety Criteria for Study Drug Interruption or Stopping Rules) based on recommendations from the US FDA.

3.2.4. Country-Specific Amendments

There was no country-specific protocol amendment to the original protocol. Amendments 1.0-3.0 each had a country-specific protocol amendment for Germany as follows:

- Amendment 1.1 (Version 2.1), dated 24 June 2021
- Amendment 2.1 (Version 3.1), dated 03 August 2021
- Amendment 3.1 (Version 4.1), dated 14 February 2022

All the country-specific amendments for Germany (provided in Appendix 16.1.1) conformed to their corresponding global amendments with the following added change:

  - Subjects who except for study participation would otherwise be eligible to receive OCA were excluded based on recommendations from the Ethics Committee for the Friedrich Alexander University of Erlangen-Nuremberg.

3.3. List of Principal Investigators

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