PROTOCOL TITLE:	**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)
PROTOCOL NUMBER:	CB8025-32048
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SHORT TITLE:	RESPONSE: Response to Seladelpar in Subjects with Primary Biliary Cholangitis (PBC) and an Inadequate Control to or an Intolerance to Ursodeoxycholic Acid (UDCA)
SPONSOR:	CymaBay Therapeutics, Inc. 7575 Gateway Blvd, Suite 110 Newark, CA 94560 United States of America
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Protocol Approval - Sponsor Signature

PROTOCOL TITLE: 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).

Protocol Number: CB8025-32048
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Protocol accepted and approved by:

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 09-Feb-2022 | 17:52 PST
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PPD
Chief Medical Officer
CymaBay Therapeutics, Inc.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AIH	Autoimmune hepatitis
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Antimitochondrial antibody(ies)
ANA	Antinuclear antibody(ies)
AST	Aspartate aminotransferase
C4	7α-hydroxy-4-cholesten-3-one
CERC	Critical event review committee
CI	Confidence interval
CK	Creatine kinase
CMH	Cochran-Mantel-Haenszel
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
DSMB	Data safety monitoring board
e-diary	Electronic diary
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELF	Enhanced liver fibrosis
ELISA	Enzyme linked immunosorbent assay
EMR	Electronic medical record
EOT	End of Treatment
FGF19	Fibroblast growth factor 19
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL-C	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HoFH	Homozygous familial hypercholesterolemia
hs-CRP	High sensitivity C-reactive protein

Abbreviation	Definition
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
INR	International normalized ratio
ITT	Intent-to-treat
IWRS	Interactive web response system
LDL-C	Low density lipoprotein cholesterol
LPLV	Last patient last visit
LS	Least squares
M1, M2, M3	Seladelpar (MBX-8025) metabolites
MBX-8025	Seladelpar
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
mITTb	Modified intent-to-treat biopsy
MMRM	Mixed models repeated measures
MSPN	Moderate to severe pruritus numerical rating scale
n	Number of subjects
NASH	Nonalcoholic steatohepatitis
NCI	National Cancer Institute
NRS	Numerical rating scale
OCA	Obeticholic acid
PBC	Primary biliary cholangitis
PBC-40 QoL	quality of life measure for use in primary biliary cholangitis
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PP	Per-protocol
PPAR	Peroxisome proliferator-activated receptor
PRC	Pathology review committee
PSC	Primary sclerosing cholangitis
PT	Prothrombin time
QoL	Quality of life
RNA	Ribonucleic acid
SAE	Serious adverse event

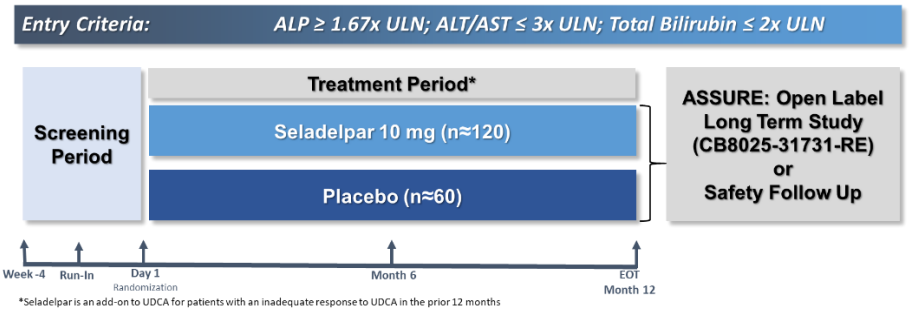
Abbreviation	Definition
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
UNS	Unscheduled visit
US	United States
VAS	Visual analogue scale
WBC	Leukocyte count

1. SYNOPSIS

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)
Protocol Number	CB8025-32048
Phase	3
Investigational Product	Seladelpar
Objectives	Primary Objective: • Efficacy: 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 to placebo • Safety: To evaluate the safety of seladelpar over 12 months of treatment compared to placebo Key Secondary Objectives: • To evaluate the effect of seladelpar on the normalization of ALP values at 12 months of treatment compared to placebo • To evaluate the effect of seladelpar on pruritus at 6 months of treatment compared to placebo in subjects with baseline moderate to severe pruritus CCI [redacted]

Methodology/ Study Design	This is an international, multicenter evaluation of seladelpar in a randomized, double-blind, placebo-controlled, parallel-group study in patients with PBC. Approximately 180 subjects will be randomized in 2:1 ratio (seladelpar: placebo) across approximately 180 sites worldwide. Enrolled subjects will have confirmed PBC as defined by having any 2 of the following 3 diagnostic criteria: (1) history of ALP above 1.0× the upper limit of normal (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); and (3) documented liver biopsy results consistent with PBC. Enrolled subjects must have received UDCA for at least 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, the study drug will be administered as an add-on to UDCA therapy for subjects who tolerate UDCA; for subjects with UDCA intolerance, the study drug will be administered as a monotherapy. Subjects with the presence or history of cirrhosis with complications, Gilbert's syndrome with elevated total bilirubin, primary sclerosing cholangitis (PSC), current features of autoimmune hepatitis (AIH), biopsy-confirmed nonalcoholic steatohepatitis (NASH), alcoholic liver disease, or chronic hepatitis B or C will be excluded. In order to establish the histological status of their liver before and after treatment, all subjects will be encouraged to have a liver biopsy during the Screening Period (unless a historical biopsy meeting quality standards can be supplied) and after 1 year of treatment, or at Early Termination if the subjects withdraw from the study, provided that they have received at least 6 months of treatment. A follow-up liver biopsy will be performed only in subjects with baseline liver biopsy. Transient elastography via FibroScan® will be performed to assess liver stiffness at baseline and during the Treatment Period or at Early Termination at select sites. On Day 1, subjects will be randomized into one of two treatment arms (seladelpar 10 mg or placebo) in a 2:1 ratio. Subjects will be stratified at randomization according to ALP <350 U/L versus ≥350 U/L and pruritus numerical rating scale (NRS) (<4 versus ≥4) to ensure even distribution across the treatment groups. The total duration of participation in the study for each subject will be up to ~14 months and consists of Screening Period (up to 3 weeks), a Run-in Period (up to 2 weeks), a Treatment Period with a maximum duration of up to 12 months, and a Safety Follow-up Period (2 weeks [14 days +3] after the last dose of study drug, only for subjects who are not enrolled in the long-term study). The Screening Period will be up to 3 weeks, during which time subject eligibility will be confirmed. The Run-in Period will start 2 weeks prior to the planned Day 1 Visit; at this visit, subjects start their pruritus evaluation using an e-diary. Liver biopsy will be performed at any time between Screening and Day 1 for subjects willing to undergo the procedure and after their eligibility is confirmed (unless a historical biopsy meeting quality standards can be supplied). At Day 1, subjects will enter the Treatment Period. Subjects will receive double-blinded treatment for 12 months. After the completion of the Treatment Period, subjects will be invited to enroll into an open-label, long-term study (Study CB8025-31731-RE) in which each subject will be administered seladelpar and subjects on placebo will initiate seladelpar treatment. Subjects who do not participate in the long-term study will have a follow-up visit performed 2 weeks (14 days +3) after the last dose of study drug.

Methodology/ Study Design (*continued*)	During the 12-month Treatment Period, subjects will have a visit at Month 1 and then every 3 months beginning from Month 3 through Month 12. Visits may occur in clinic, with the assistance of a home health service, or using virtual technologies. Subjects will be asked to use an electronic diary (e-diary) to evaluate pruritus and QoL during the study participation. E-diary will be dispensed at the Run-in Visit and will include 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. Subjects will perform 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 will be evaluated on a monthly basis until Month 12 using pruritus NRS for 7 consecutive days each month. 5-D Itch scale will be evaluated biweekly from the Run-in Visit up for the first 6 months of treatment and monthly after that. PBC-40, PGI-S, and PGI-C will be evaluated after 1 month and every 3 months from the treatment initiation and over the whole study duration. During the study, subjects will be regularly evaluated for the progression of their disease by collecting information about PBC clinical outcomes. Subjects who discontinued study drug treatment for any reason other than a defined PBC clinical outcome will be asked to stay in the study without study drug intake. Subjects who discontinue study drug treatment anytime, and do not stay in the study, will complete an Early Termination Visit. For subjects who decline to stay in the study without study drug intake, or who do not participate in the long-term study, a phone call will be performed for PBC outcomes on an annual basis. Safety monitoring in the study implements individual and study stopping criteria, criteria to be considered for stopping the study, and safety criteria to monitor subjects with potential drug-induced liver injury (DILI), renal injury, muscle toxicity, or pancreatic injury with actions to either stop the study drug or to investigate the case prior to actions with the study drug based on protocol-specified monitoring criteria. The study design also defines PBC clinical outcome criteria to evaluate the subjects for the progression of PBC, for example, events related to hepatic decompensation. The study drug might be down-titrated to a lower dose if deemed necessary by the investigator for safety or tolerability reasons. Subjects receiving 10 mg will be down-titrated to 5 mg, and subjects receiving placebo will be down-titrated to placebo. Down-titration will be performed in a blinded manner. Subjects who meet one of the defined PBC clinical outcome criteria will be terminated from the study and will complete an Early Termination Visit. **PK Sample Collection** Subjects will be invited to participate in a pharmacokinetic (PK) sample collection to evaluate the plasma concentrations of seladelpar and its metabolites. Subjects who consent to participate in this PK sample collection will provide 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. The primary efficacy outcome will be a responder analysis (composite biochemical response) after 12 months of treatment with study drug. A data safety monitoring board (DSMB) will be convened to review the study data on a regular basis during study conduct to ensure subjects' welfare and preserve study integrity. A Critical Event Review Committee (CERC) will be established to analyze and adjudicate clinical events that occur during the study. A Pathology Review Committee (PRC) will be established to evaluate the biopsies in accordance with a defined histopathology plan.

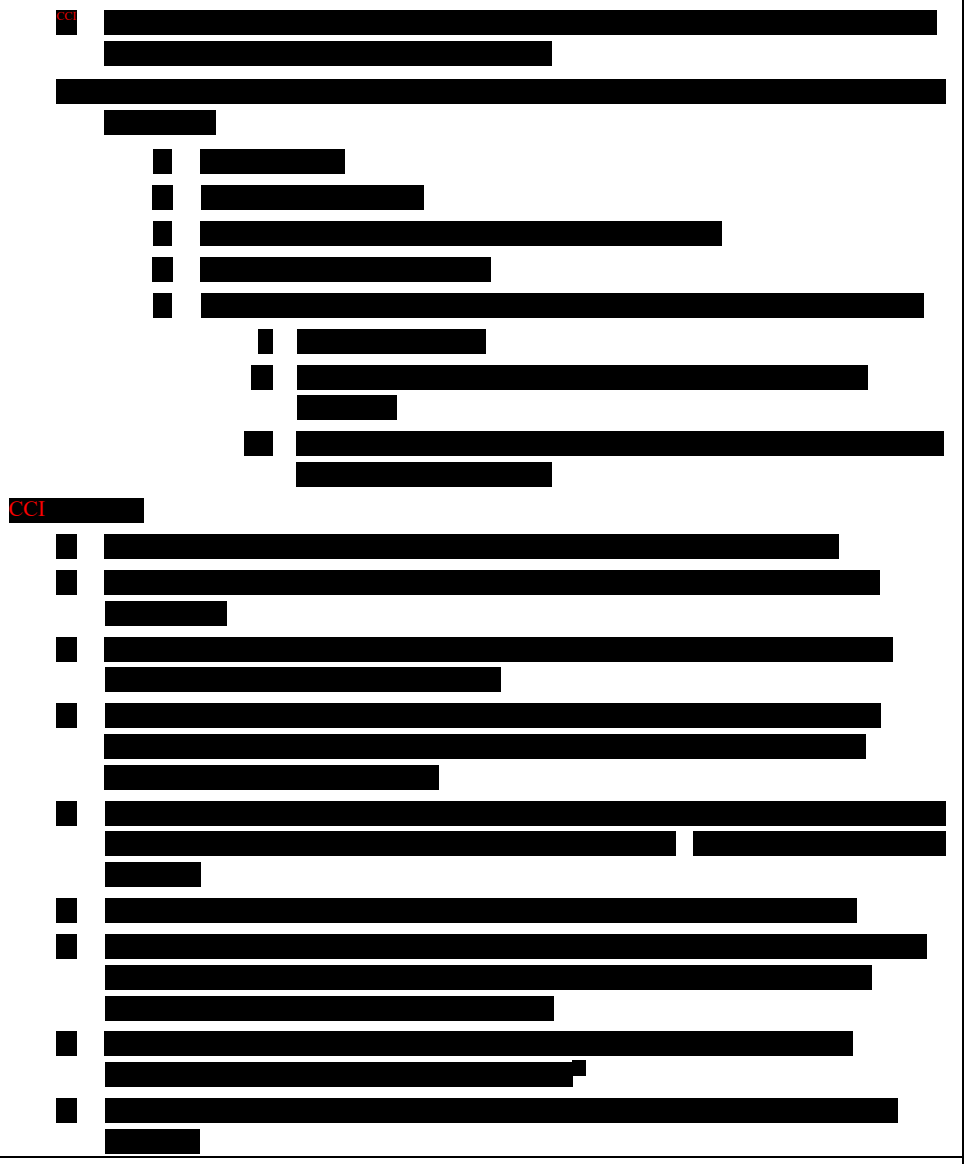
Study Design Schema	 ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; EOT=End of Treatment; UDCA=ursodeoxycholic acid; ULN=upper limit of normal. [a] Seladelpar is an add-on to UDCA for patients with an inadequate response to UDCA in the prior 12 months.
Subjects	Approximately 180 subjects randomized
Randomization	2:1 (seladelpar 10 mg: placebo) Randomization will be stratified by the following factors: • ALP level <350 U/L versus ALP level ≥350 U/L • Pruritus NRS <4 versus NRS ≥4
Study Sites	Approximately 180 sites worldwide
Test Product(s)	Seladelpar or placebo will be supplied as a single capsule intended to deliver 5 mg (for down-titration, if needed), 10 mg, or placebo administered orally, once daily.
Duration of Treatment	Total duration: up to 14 months • Screening Period: Up to 3 weeks • Run-in Period: 2 weeks • Treatment Period: Maximum of 12 months with an option to enter an open-label long-term study (Study CB8025-31731-RE) • Safety Follow-up Period: Up to 17 days (only for subjects who are not enrolled in the long-term study)
Population	Subjects with PBC and an inadequate response to UDCA or intolerance to UDCA.

Criteria for Eligibility	Inclusion Criteria: Subjects must meet 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. 18 to 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 above 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 ANA. c. Documented liver biopsy results consistent with PBC. 4. UDCA 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 >45 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease study equation). f. International normalized ratio (INR) below 1.1× ULN For subjects on anticoagulation therapy, INR must be maintained in the range required for prophylaxis for their specific disease. g. Platelet count ≥100×10^3/μL. NOTE: PT, INR, and platelets can be performed locally at the Screening Visit, if deemed necessary by the investigator after consultation with the medical monitor, in cases where centrally read samples are deemed invalid. 6. Females of reproductive potential (Section 8.1.1) must 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 dose. Male subjects who are sexually active with female partners of reproductive potential must use barrier contraception, and their female partners must use a second effective birth control method during the study and for at least 90 days after the last dose. Exclusion Criteria: Subjects must not meet 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 (e.g., cancer) or confound its results (e.g., 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).

Criteria for Eligibility (*continued*)	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, will be taken into account when calculating the MELD score. This will be done in consultation with the medical monitor. b. Complications of portal hypertension, including known esophageal varices, history of variceal bleeds or related interventions (e.g., 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 AIH as determined by the investigator based on immunoserology, liver biochemistry, or historic confirmed liver histology. b. PSC 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 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. i. Hepatitis C, defined as the presence of hepatitis C virus ribonucleic acid. 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, active or within 2 years, or ongoing evaluation for malignancy; localized treatment of squamous or noninvasive basal cell skin cancers and cervical carcinoma in situ is allowed if appropriately treated prior to screening. 9. Treatment with obeticholic acid (OCA), and fibrates (e.g., bezafibrate, fenofibrate, elafibranor, lanifibranor, pemafibrate, 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 for additional medications that may be excluded. 11. Treatment with anti-pruritic drugs (e.g., cholestyramine, naltrexone, rifampicin, sertraline, or any experimental approach) must be 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 is 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 (e.g., cyclosporine, tacrolimus, anti-TNF or other immunosuppressive biologics). 16. Other medications that effect liver or GI functions, such as absorption of medications or the roux-en-y gastric bypass procedure, may be prohibited and should be discussed with the medical monitor on a case-by-case basis. 17. Active COVID-19 infection during Screening.
Concomitant Medications	All subjects will be instructed to remain on their current diet and lifestyle, including drinking habits, specifically alcoholic beverages, throughout the study. Subjects will continue UDCA intake in accordance with their prescribed dose. Dose adjustments or interruption in UDCA during the study will be documented. PBC symptomatic treatment (e.g., antipruritic drugs) should be discussed with medical monitor. Guidelines about PBC symptom management will be provided in a study manual. Subjects will be allowed to receive required medications to treat new or existing medical conditions.
Prohibited Treatment	• Obeticholic acid (OCA) • Fibrates (e.g., bezafibrate, fenofibrate, elafibranor, lanifibranor, pemafibrate, saroglitizar) • Colchicine, methotrexate, or azathioprine • Long-term systemic steroids (e.g., prednisone, prednisolone, budesonide) for >2 weeks • Experimental or unapproved treatment for PBC or related autoimmune diseases • Immunosuppressant therapies (e.g., cyclosporine, tacrolimus, anti-TNF or other immunosuppressive biologics) • Other medications that effect liver or GI functions such as absorption of medications may be prohibited and should be discussed with the medical monitor on a case-by-case basis
Criteria for Evaluation – Safety	Safety and tolerability will be assessed by monitoring adverse events (AEs) and concomitant medications. Additional assessments will include conducting physical examinations, collecting 12-lead electrocardiograms, measuring vital signs, collecting liver histology, and collecting clinical laboratory assessments. Specific safety monitoring algorithms for liver, renal, or pancreatic injury and muscle toxicity have been incorporated into the study.

Criteria for Evaluation – Efficacy and Pharmacodynamics	Primary Measures: 1. Proportion of subjects who are 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 Common Terminology Criteria for Adverse Events Version 5.0), biochemistry, and hematology Key Secondary: 1. Proportion of subjects with ALP ≤1.0× ULN at 12 months (e.g., normalization) 2. Change from baseline in weekly averaged pruritus NRS in subjects with baseline NRS ≥4 at 6 months CCI [redacted]

Criteria for Evaluation – Efficacy and Pharmacodynamics (*continued*)	CCI  CCI
Criteria for Evaluation – Pharmacokinetics	Subjects participating in the PK sample collection (PK of seladelpar and its metabolites). Subjects who consent to participate in this PK sample collection will provide a predose sample (-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 to estimate the plasma concentrations of seladelpar and its metabolites.

Statistical Methods	Analysis Sets: The safety analysis set includes any subject who receives at least 1 dose of study drug. Safety analyses will be conducted on the safety analysis set according to the treatment received. The intent-to-treat analysis (ITT) analysis set includes any subject randomized into the study and receives at least 1 dose of study drug. The ITT analysis set will be the primary analysis set used for efficacy analyses, with the exception of secondary endpoints evaluated for subjects with moderate to severe pruritus. The modified intent-to-treat biopsy (mITTb) analysis set includes any subject who is in the ITT analysis set and has a baseline and Month 12/ET biopsy. The mITTb analysis set will be used to examine the histology changes or the lack thereof. The moderate to severe pruritus NRS (MSPN) analysis set includes any subject who is in the ITT analysis set and has a baseline NRS value ≥4. The MSPN analysis set will be the primary analysis set for secondary endpoints based on NRS evaluations. Subjects in the ITT and MSPN analysis sets will be analyzed according to randomized treatment assignment. The per-protocol (PP) analysis set includes any subject who is in the ITT analysis set, has at least 1 post-baseline ALP and total bilirubin evaluation, and does not have a protocol violation that is deemed to impact the primary efficacy evaluation. Selected analyses of efficacy will be conducted using the PP set. The pharmacokinetics analysis set includes any subject who participated in the PK sample collection. Unless stated otherwise, baseline values will be based on the last non-missing assessment evaluated prior to the first administration of study drug. Baseline for chemistry and hematology measures will be calculated as the arithmetic mean of multiple pretreatment measurements (Screening, Run-in, Day 1, and unscheduled assessments) preceding the first administration of study drug. Baseline pruritus NRS is defined as the mean of all daily recorded scores during the Run-in Period. Unless specified otherwise, statistical tests will be conducted at the 2-sided 0.05 significance level (alpha), and all confidence intervals (CIs) will be reported at 2-sided 95% confidence level. Descriptive statistics will be displayed by treatment group. For categorical parameters, the number and percentage of subjects in each category will be presented in data summaries. The denominators for percentages will be based on the number of subjects (n) appropriate for analysis. Continuous variables will generally be summarized based on the following: n, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized using frequency tabulations (number and percentage of subjects). Time-to-event data will be summarized using counts and Kaplan-Meier estimates with standard errors, where appropriate. All data will be listed for all patients. An independent DSMB will be convened to review the study data on a regular basis during the study conduct to ensure subjects' welfare and preserve study integrity. Details of the format, content, and frequency of these meetings will be described in a DSMB charter.

Statistical Methods (*continued)*	Primary analysis: The primary efficacy analysis for the proportion of subjects who are considered responders will be based on the proportion of subjects achieving the following composite endpoint evaluated at 12 months: • ALP <1.67× ULN • ALP decrease of ≥15% • Total bilirubin ≤1.0× ULN The treatment effect for the composite endpoint (seladelpar 10 mg versus placebo) will be evaluated at a 2-sided 0.05 significance level. Additional details, including a schematic for the testing sequence for the overall study, can be found in the statistical analysis section of the protocol. The primary efficacy analysis will be conducted on the ITT analysis set using the Cochran-Mantel-Haenszel (CMH) test. The CMH analysis will be stratified by the randomization stratum. In the primary analysis, subjects who do not provide an assessment at, or have discontinued treatment prior to, the specified time point for response evaluation or who otherwise have missing data will be considered non-responders. Additional sensitivity analyses of the primary efficacy endpoint will be detailed in the statistical analysis plan (SAP) and will assess the impact of missing data and other factors, such as protocol compliance, on robustness of study results. Key Secondary Analyses: • Normalization of ALP at 12 months (e.g., ALP ≤1.0× ULN) • Change from baseline in weekly averaged pruritus in subjects with NRS ≥4 at baseline at 6 months Type I error for the key secondary efficacy analysis will be maintained using the hierarchical fixed-sequence methodology. The fixed-sequence approach for the primary and secondary analyses is as follows: 1. If the primary efficacy analysis is positive for seladelpar 10 mg versus placebo at a 2-sided 0.05 significance level, then the 2 key secondary endpoints will be analyzed hierarchically in the following order: 2. Normalization of ALP at Month 12 (seladelpar 10 mg versus placebo): If negative at a 2-sided 0.05 significance level, no further inferential testing will be performed. Otherwise, if positive, then testing will proceed. 3. Change from baseline to Month 6 in pruritus NRS (seladelpar 10 mg versus placebo) will be tested at a 2-sided 0.05 significance level. Normalization of ALP is a responder analysis and will be conducted in the ITT analysis set using the same approach specified for the primary efficacy analysis. Change from baseline in weekly averaged pruritus NRS at 6 months will be analyzed using a mixed-effect model for repeated measures (MMRM) for subjects in the MSPN analysis set. The model will include baseline NRS, randomization stratum, treatment group, week, and treatment-by-week interaction term. Treatment by baseline interaction will be explored and added as a term if interaction is noted to be present. Least squares (LS) means for the change by treatment and the associated standard errors, the LS means for the difference between treatment groups, and associated 2-sided 95% CIs and 2-sided p-values, based on t-tests, will be derived from the MMRM model. Specifically, efficacy endpoints will be evaluated using the estimated treatment difference in mean change from baseline NRS for the week associated with their specified month. An unstructured covariance matrix will be tried first. If the model fails to converge, compound symmetry will be used in place of an unstructured covariance. The Kenward-Roger correction for the denominator degrees of freedom will be applied.

Statistical Methods (*continued)*	Sensitivity analyses for key secondary endpoint analyses will be described in the study SAP and will include the methodologies proposed for the primary endpoint where appropriate (e.g., additional methods for missing data handling and alternate population analyses). Secondary efficacy endpoint proportions will be evaluated based on the method described for the primary efficacy analysis. Continuous secondary endpoints will be evaluated based on an MMRM model with baseline value, randomization stratum, treatment group, visit (or week of evaluation, if appropriate), and treatment-by-visit (or week) interaction term. Treatment by baseline interaction will be explored and added as a term if interaction is noted to be present as fixed effects. LS means for the change by treatment and their associated standard errors, the LS means for the difference between treatment groups, and associated 2-sided 95% CIs and 2-sided p-values, based on t-tests, will be derived from the MMRM model. Secondary endpoints will initially be analyzed based on the MMRM through Month 12. Exploratory endpoints will be summarized primarily with descriptive statistics. Further details will be provided in the SAP. Safety data, including AEs, safety laboratory results, physical examination results, vital signs, and ECG will be summarized by treatment group and/or listed. <u>Pharmacokinetic Analysis</u>: Descriptive statistics will be provided for the concentration-versus-time data per visit number for seladelpar and metabolites. Further, pooling of the concentration data from this study with data from other studies will be done to facilitate development and/or updating of a population PK model and will be reported separately.
Sample Size Determination:	The planned sample size is approximately 180 subjects (120 subjects in seladelpar 10 mg, 60 subjects in the placebo group). The placebo group response rate is estimated as 20%. The seladelpar 10-mg dose group response rate is estimated as 55%. With the use of a 2-sided test of equality of binomial proportions based on a Fisher's exact test at the 0.05 level of significance, a sample size of 180 randomized subjects will provide >90% power to detect a difference between the 10 mg seladelpar group and the placebo group. Normalization of ALP is estimated to have a placebo response rate and seladelpar response rate of 2.5% and 25.5%, respectively. A sample size of 180 randomized subjects will provide >90% power to detect a difference between the seladelpar and placebo groups, based on a Fisher's exact test at a 0.05 level of significance. Change from baseline in weekly averaged pruritus NRS at Month 6 sample size is based on a 2-sample 2-sided t-test at a significance level of 0.05. The standard deviation is estimated as 2. Under these assumptions, as well as a total of 48 randomized subjects having a baseline NRS ≥4, this test provides ≥80% power to detect a treatment difference of ≥2 between the 10 mg seladelpar and placebo groups.

Table 1: Schedule of Assessments

Visit	Screening[a]	Run-in	Random-ization	Month 1	Month 3	Month 6	Month 9	Month 12/ EOT[a]	Follow-up	ET	UNS
Target Day	**W-5 to -2 (Day -35 to -15)**	**W -2 (Day -14) ±3 days**	**Day 1**	**W 4 (Day 29) ±3 days**	**W 12 (Day 85) ±7 days**	**W 26 (Day 183) ±7 days**	**W 39 (Day 274) ±7 days**	**W 52 (Day 365) ±7 days**	**2W (14 days) After W 52 +3 days**		
Informed consent	X										
Demographics	X										
Eligibility	X	X									
Randomization			X								
Medical history[b]	X										
AE		X	X	X	X	X	X	X	X	X	X
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Vital signs and weight	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Physical examination	X	X[c]	X	X[c]	X[c]	X	X[c]	X	X	X	X[c]
ECG	X		X			X		X	X	X	
Hematology[d, e]	X	X	X	X	X	X	X	X	X	X	X
Biochemistry[d]	X	X	X	X	X	X	X	X	X	X	X
Exploratory measures[d]	X[f]	X	X[f]	X	X	X	X	X[f]	X	X[f]	
PK sample[g]					X			X[g]			X[g]
Hepatitis B, C and HIV	X										
Pregnancy test[h]	X	X	X	X	X	X	X	X	X	X	
Back-up blood sample[d]		X	X	X	X	X	X	X	X	X	
Urine drug screen	X										
COVID-19 testing[i]	X	X	X	X	X	X	X	X	X	X	X
Pruritus NRS[j]	X	X	X	X	X	X	X	X		X	
5-D Itch[j]		X	X	X	X	X	X	X		X	
PBC-40 QoL[j]		X	X	X	X	X	X	X		X	
PGI-S[j]		X	X	X	X	X	X	X		X	
PGI-C[j]				X	X	X	X	X		X	
PBC clinical outcome[k]				X	X	X	X	X	X[K]	X[K]	
Abdominal ultrasound		X						X		X	
FibroScan (selected sites)		X				X		X		X	
Liver biopsy[l]		X						X		X	
Concomitant Procedures[m]			X	X	X	X	X	X	X	X	X
Study drug dispense			X		X	X	X				
Study drug compliance and accountability				X	X	X	X	X		X	
UDCA compliance		X	X	X	X	X	X	X		X	

AE=adverse event; AMA=antimitochondrial antibodies; e-diary=electronic diary; ECG=electrocardiogram; EOT=End of Treatment; ET=Early Termination; HIV=human immunodeficiency virus; INR=international normalized ratio; LTS=long-term study; NRS=numerical rating scale; PBC=primary biliary cholangitis; PBC-40 QoL=QoL measure for use in PBC; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PK=pharmacokinetic(s); PT=prothrombin time; QoL=quality of life; UDCA=ursodeoxycholic acid; UNS=Unscheduled visit; W=week.

[a] Screening: screening evaluations can be completed in up to 3 weeks. When all Screening evaluations are completed, subjects who are deemed to be eligible will move into the Run-in period; Month 12/EOT: Subjects will be invited to enter the LTS at the Month 12 Visit.

[b] Including PBC medical history, liver biopsy, FibroScan, alcohol consumption, evidence of liver cirrhosis and other forms of liver disease, and HIV.

[c] Symptom-directed (brief) physical examination.

[d] Blood will be collected after at least an 8-hour overnight fast and prior to dosing. If the subject forgets to fast prior to the blood collection, the site will record it in the source document, continue to draw laboratory tests, and proceed with the visit.

[e] PT, INR, and platelets can be performed locally at the Screening Visit, at the Run-in Period, and during the Treatment Period if deemed necessary by the investigator after consultation with the medical monitor, in cases where centrally read samples are deemed invalid.

[f] Screening Visit: Only AMA will be performed. Treatment Period: Fat-soluble vitamins will be performed at Day 1, Month 12, or ET only.

[g] PK sampling will be performed once predose (-30 minutes prior to dosing) and twice postdose (1 hour±30 minutes and 3 hours±30 minutes after dosing) at Month 3 and Month 12. Prior to the visit, subjects will be reminded to not take the study drug at home. The time of PK blood collection and dosing will be documented. When possible, a PK sample should be drawn at the onset of SAEs or clinically meaningful AEs.

[h] Applicable for women of child-bearing potential only: a serum pregnancy test will be performed at each visit. After Month 1, a urine pregnancy test will be performed at home monthly (every 30±3 days). Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.

[i] COVID-19 testing will be performed locally and only if deemed necessary per local requirements. Subjects with a positive COVID-19 test during Screening may be eligible to re-screen after recovery.

[j] Pruritus NRS, 5-D Itch, PBC-40, and PGI-S and PGI-C data will be collected via an e-diary. Subjects will be asked to complete (1) pruritus NRS: on a daily basis from the Run-in Visit and through the first 6 months of treatment. After 6 months, NRS will be collected for 7 consecutive days during each month up to EOT; (2) 5-D Itch will be collected biweekly from the Run-in Visit up until the Month 6 Visit; after Month 6, 5-D Itch will be collected once per month; and (3) The PGI-S and PBC-40 will start at Run-In and will continue at Randomization, then Month 1, then every 3 months through Month 12/ study participation. (4) PGI-C will start at Month 1 and will continue every 3 months through Month 12/ study participation. (5) Pruritus NRS, 5-D Itch, PBC40, PGI-S, and PGI-C are expected at Early Termination. (6) Pruritus NRS, 5-D Itch, PBC40, PGI-S, and PGI-C are available on the eDiary for Unscheduled Visit if deemed necessary.

[k] PBC clinical outcomes will be evaluated per Section 11. Subjects who terminate study participation for any reason other than a defined PBC clinical outcome will be asked to stay in the study without study drug intake. Subjects who decline to stay in the study without study drug intake, or who do not participate in the long-term study, a phone call will be performed for PBC clinical outcomes on an annual basis (per Section 8.1.7).

[l] Baseline liver biopsy can be performed anytime between Screening and Day 1, but only after confirmation of subject's eligibility. PT, INR, and platelets must be performed within 2 weeks prior to liver biopsy. For subjects who had a baseline liver biopsy and discontinued the study between 6 and 12 months of treatment, a follow-up liver biopsy will be performed at either the EOT or the ET visit.

[m] A concomitant procedure is any therapeutic intervention (e.g., surgery, biopsy, or physical therapy) or diagnostic assessment (e.g., blood gas measurement or bacterial cultures) performed during subjects' participation in this study. If a concomitant procedure is performed, document the procedure on the subject's 'Concomitant Procedures' eCRF. AEs related to the administration of these procedures must also be documented on the subject's AE eCRF.

2. INTRODUCTION

2.1. Primary Biliary Cholangitis

Primary biliary cholangitis (PBC, formerly known as primary biliary cirrhosis) is a serious, rare, slowly progressive and potentially life-limiting autoimmune liver disease characterized by impaired bile flow (cholestasis) and accumulation of toxic bile acids. The disease occurs more frequently in women and presents most often in middle age. The disease course is usually slow but frequently impactful; patients at the greatest risk of future poor outcomes are identifiable based on patterns of presentation, including biochemical markers of disease at baseline and on treatment.

The hallmark of PBC is cholestasis secondary to hepatobiliary injury and bile acid accumulation, with an accompanying elevation in disease-associated serum biomarkers, including alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), and depending on the severity of the disease, bilirubin and liver transaminases. Serologically, PBC is characterized by the presence of antimitochondrial antibodies (AMA) in nearly all patients (1). Clinical symptoms of PBC include pruritus and fatigue, which can be disabling for many patients. PBC peak incidence occurs in the fifth decade of life and is uncommon in persons younger than 25 years old (2). The liver histopathology of patients with PBC is characterized by portal inflammation and immune-mediated destruction of intrahepatic bile ducts. These changes occur at different rates and with varying degrees of severity. The loss of bile ducts leads to decreased bile secretion and the retention hydrophobic bile acids within the liver, resulting in hepatocellular injury, fibrosis, cirrhosis, and, eventually, liver failure (3, 4, 5).

The diagnosis of PBC often occurs at an early stage when following up on abnormal serum liver tests, especially elevated ALP. After excluding extra-hepatic biliary obstruction, the presence of either AMA (or less often, the histological confirmation by liver biopsy) establishes the diagnosis (6). Fifty to 60% of patients are asymptomatic at diagnosis. Overt symptoms develop within 2 to 4 years in most asymptomatic patients, although one-third may remain symptom-free for years (3). Fatigue and pruritus are the most common presenting symptoms (3). Fatigue has been noted in up to 78% of patients and can be a clinically important cause of disability. The severity of fatigue is independent of the severity of the liver disease, and there is no proven treatment (3). Cholestatic pruritus, the precise cause of which is uncertain, occurs in 20% to 70% of patients and can be extremely debilitating (7). Perturbation in bile acid homeostasis is a likely factor in choleatic pruritus. Lysophosphatidic acid, for example, has been suggested as a potential pruritogen in cholestasis (8), whereas rapid relief in itch can be seen in patients with treatment-resistant cholestatic pruritus if they have an endoscopic nasobiliary drain placed (9).

Other findings in patients with PBC can include jaundice, hypercholesterolemia, osteopenia, osteoporosis, and coexisting autoimmune diseases (3, 4). Portal hypertension is a late complication of the disease (3, 10). Generally, patients with untreated PBC progress to liver failure, transplant, or death. A meta-analysis of 4845 subjects in North American and European long-term studies demonstrated that subjects with untreated PBC had transplant-free survival of 79% at 5 years, 59% at 10 years, and 32% at 15 years (11). Despite being a rare disease, PBC is 1 of the top 6 indications for liver transplantation in the United States (US) and European Union (12). The recurrence of PBC following liver transplantation is reported in 11% to 45% of

transplantations, with an estimated prevalence of 30% at 10 years following transplantation, further demonstrating a need for effective therapies (13). A reported feature of PBC can be the development of esophageal varices prior to the onset of cirrhosis. Approximately 6% of early histological stage subjects with PBC have varices, and one-third of subjects with stage III to stage IV disease develop varices over a median of 5 to 6 years (6, 14). The 3-year survival following an initial variceal bleed is 46% (10).

The first-line therapy for PBC is ursodeoxycholic acid (UDCA), a noncytotoxic bile acid that has been the mainstay of treatment for more than 20 years (15). However, up to 40% of patients have persistent elevation of ALP and/or bilirubin despite UDCA and are considered inadequate responders (16).

Obeticholic acid (OCA), a synthetic analogue of chenodeoxycholic acid, was conditionally approved by the Food and Drug Administration and the European Medicines Agency in 2016 based on clinically notable decreases in ALP levels while maintaining normal total bilirubin levels in subjects with PBC who are inadequate responders to UDCA or as a monotherapy in subjects with PBC who are intolerant to UDCA (17). OCA is associated with dose-dependent pruritus.

In summary, despite the previously mentioned therapeutic interventions and recent conditional approval of OCA, it is evident that many patients with PBC do not respond adequately to therapy and continue to have a progression of their disease (3, 4, 10, 18) and that additional treatments are needed.

2.2. Seladelpar

2.2.1. Overview

Seladelpar (MBX-8025) is an oral, once-daily administered, potent, and selective peroxisome proliferator-activated receptors (PPAR)δ agonist (19, 20). Seladelpar is being developed herein for the treatment of PBC in subjects with inadequate response to UDCA or intolerance to UDCA.

2.2.2. Mechanism of Action

PPARδ agonists have been shown to affect the transport, storage, and metabolism of lipids (21). Seladelpar improves cholestasis notably by decreasing the synthesis of bile acids in hepatocytes, thus preventing their toxic accumulation. The decreased synthesis results in part from the down-regulation of the gene for CYP7A1, the key enzyme for the synthesis of bile acids. Seladelpar also decreases the synthesis of cholesterol and inhibits its dietary absorption; these effects decrease the amount of cholesterol available as substrate for bile acid synthesis, thereby enhancing its effect on CYP7A1 in reducing total bile acid pools. Each of the above actions of seladelpar have been demonstrated in patients with PBC (20). In addition, seladelpar exerts anti-inflammatory effects (20) that are of potential benefit in the treatment of PBC.

For more detailed information, see the Investigator's Brochure (IB).

2.3. Nonclinical Studies

Please see the IB for details on the nonclinical studies conducted with seladelpar.

2.4. Human Experience

Seladelpar has been evaluated in 16 clinical studies across healthy volunteers and subjects with hepatic impairment, mixed dyslipidemia, homozygous familial hypercholesterolemia (HoFH), nonalcoholic steatohepatitis (NASH), and PBC. Across these studies, seladelpar tested doses have ranged from single-dose studies in healthy volunteers (1, 5, 15, 60, 120, and 360 mg) to daily long-term dosing in Phase 2 and Phase 3 studies in subjects with mixed dyslipidemia (50 and 100 mg once daily), HoFH (ascending doses 50, 100, and 200 mg once daily), and PBC (2, 5, 10, 50, and 200 mg once daily) that have ranged from 8 weeks to over 2 years.

These studies are supportive of the clinical development of seladelpar in patients with PBC.

Please refer to the IB for additional detailed information on these studies.

2.4.1. Studies in Patients With PBC

As of 2020, CymaBay conducted 4 clinical studies with seladelpar in subjects with PBC who either have had an inadequate response to UDCA or are intolerant to UDCA.

Study CB8025-21528 was the first clinical study of the seladelpar for the treatment of PBC (20). It was a double-blind, randomized, placebo-controlled, 12-week, dose-ranging study (referred to as the "high-dose" study) in adult subjects with PBC who had an inadequate response to UDCA. Subjects were randomly assigned to receive seladelpar 50 mg/day, seladelpar 200 mg/day, or placebo in a 1:1:1 ratio. The study was terminated approximately midway through enrollment (41 subjects had enrolled) after 3 subjects experienced rapid, asymptomatic, and reversible Grade 3 elevations in alanine aminotransferase (ALT) (1 subject on 50 mg and 2 subjects on 200 mg). Although CymaBay elected to terminate the study early when a transaminase elevation signal was observed, all subjects receiving seladelpar, including subjects with transaminase elevation, exhibited a pronounced decrease in ALP that was evident after the first 2 weeks and was sustained for the duration of the study (Figure 1, Panel A). Subjects who received seladelpar beyond 2 weeks showed a consistent and continual decrease in ALP. All subjects who received seladelpar for 12 weeks normalized their ALP levels (20). This study also provided important information supporting the mechanism of action of seladelpar for the treatment of PBC. Treatment with seladelpar was associated with a decrease in 7α-hydroxy-4-cholesten-3-one (C4), which represents a serum marker for hepatic bile acid synthesis. C4 reflects the activity of CYP7A1, the rate-limiting enzyme for the synthesis of bile acids.

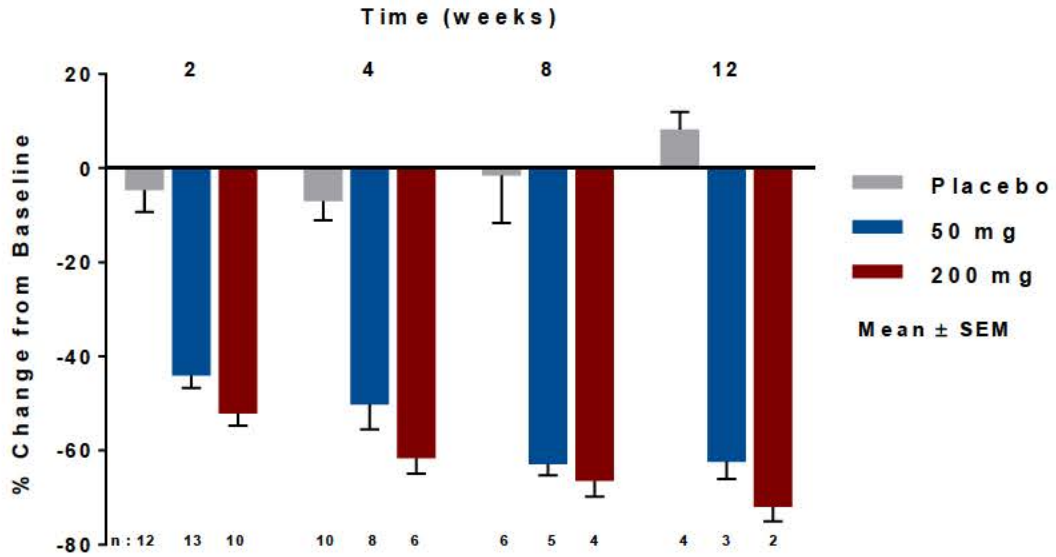
Study CB8025-21629 was the second Phase 2 study in PBC. This study was an international, multicenter, open-label, randomized, parallel-group, 8-week, dose-ranging study with a 44-week extension period in adult subjects with PBC with an inadequate response or intolerance to UDCA. Subjects received oral doses of 2, 5, or 10 mg seladelpar once daily. Subjects were randomized to receive 5 or 10 mg seladelpar, whereas those in the 2-mg seladelpar group entered after being sequentially assigned their dose. After 12 weeks, subjects on 2 or 5 mg could escalate the dose if their ALP treatment goal were not achieved. By Week 52, 10 of 11 subjects in the 2-mg dose group were up-titrated to 5 or 10 mg, and 30 of 49 subjects in the 5-mg dose group were up-titrated to 10 mg.

A total of 119 subjects were enrolled into the study; of these, 112 subjects (94.1%) were analyzed for efficacy. The 5- and 10-mg doses showed consistent, meaningful, and reproducible decreases in ALP levels (Figure 1, Panel B). At baseline, the mean ALP was 300, 345, and

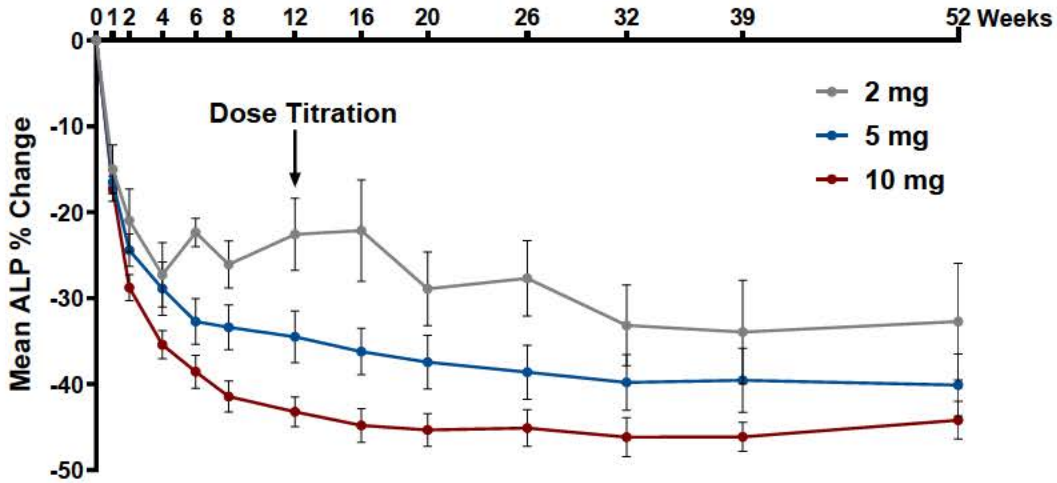
295 U/L in the 2-, 5-, and 10-mg dose groups, respectively. After 12 weeks of dosing, mean percent changes from baseline in ALP were -22.6%, -34.5%, and -43.2% for the 2-, 5-, and 10-mg dose groups, respectively. Furthermore, 31% of subjects with PBC in the 10-mg dose group achieved normalization of ALP by Week 12. After 52 weeks of dosing, mean percent changes from baseline in ALP were -32.7%, -40.1%, and -44.2% for the 2-, 5-, and 10-mg dose groups, respectively.

Figure 1: Mean Percent Changes in ALP in PBC Phase 2 Studies

Panel A: Study CB8025-21528



Panel B: Study CB8025-21629



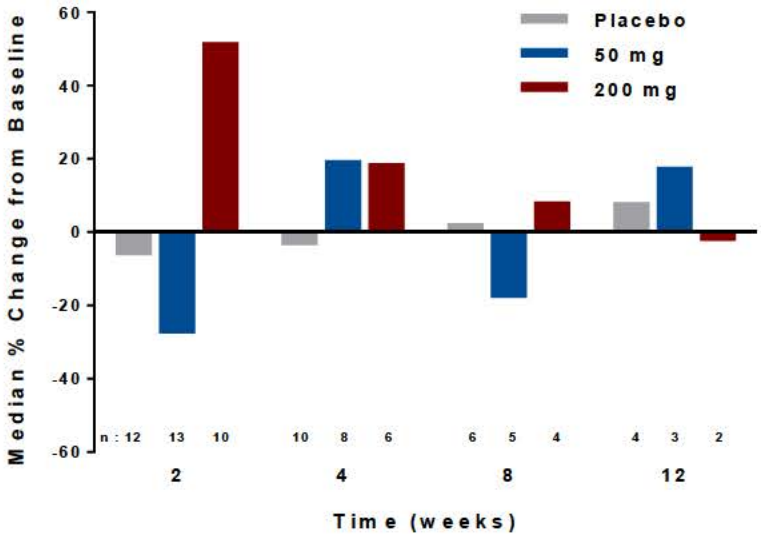
ALP=alkaline phosphatase; PBC=primary biliary cholangitis; SEM=standard error of the means.
Source: Table 14.2.1.2.1

The increases in transaminases observed with seladelpar 50- and 200-mg doses in the high-dose study (Study CB8025-21528; Figure 2, Panel A) have not been observed with seladelpar 5- and

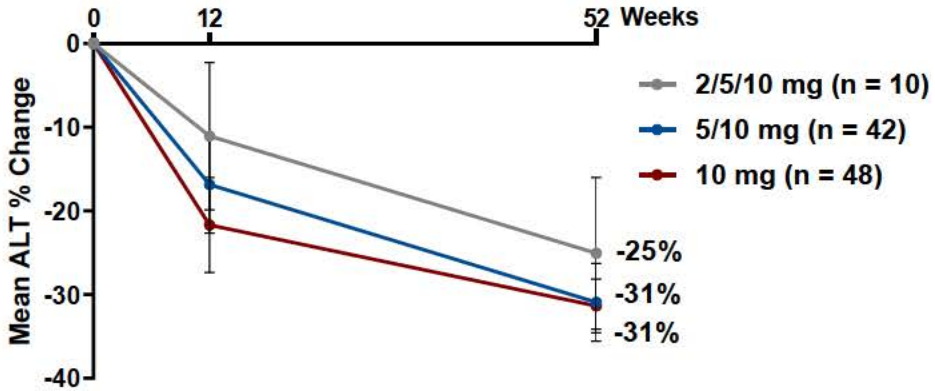
10-mg doses. As seen in Figure 2, Panel B, a decrease in median ALT levels over 12 weeks is observed in the subjects who had completed 12 weeks of seladelpar treatment (up to 12 weeks, subjects maintained their assigned dose with no dose adjustment). This indicates that, instead of elevations in transaminases at higher doses, lower doses produce reductions in transaminase levels and an indication of decreased liver injury. Decreases in transaminases likely reflect reduced hepatocellular stress accompanying reductions in cholestasis and inflammation. This is consistent with seladelpar exerting an anti-inflammatory effect that contributes to decreases in interface hepatitis and portal inflammation. Further, this result confirms that the transaminase elevation is a dose-related phenomenon.

Figure 2: Percent Change in ALT in PBC Phase 2 Studies

Panel A: Study CB8025-21528



Panel B: Study CB8025-21629



ALT=alanine aminotransferase; PBC=primary biliary cholangitis.
January 2018 data cutoff.
Values shown in Panel B are mean±standard error.
Source: Tables 14.2.4.6

Seladelpar did not increase pruritus. The baseline median pruritus visual analogue scale (VAS) was 10 and 40 in the 5- and 10-mg group, respectively. Substantial improvement in pruritus was

observed at 1 year in subjects with moderate to severe/very severe baseline pruritus (58% and 93% of subjects in the 5-mg dose group who up-titrated to 10 mg during the study [the 5/10 mg cohort] and 10-mg dose group, respectively).

Seladelpar was generally safe and well tolerated, with no transaminase elevation safety signal. There were 6 serious adverse events (SAEs), and none was deemed related to seladelpar. The results of this study concluded that seladelpar doses of 10 mg, or 5 mg adjusted to 10 mg, demonstrate potent anticholestatic efficacy that is maintained over 52 weeks.

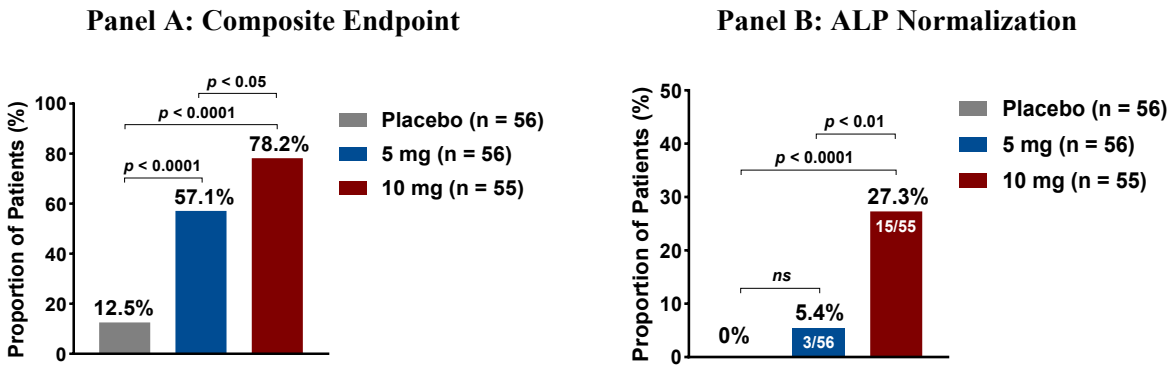
Study CB8025-31735 (ENHANCE) was designed as a Phase 3, international, double blind, randomized, placebo-controlled study in adults subjects with PBC with an inadequate response or intolerance to UDCA. Subjects were randomly assigned to receive 5 mg/day seladelpar, 10 mg/day seladelpar, or placebo in a 1:1:1 ratio. The primary efficacy analysis was planned to evaluate the response to the composite endpoint (ALP <1.67× upper limit of normal [ULN], ALP decrease of ≥15%, and total bilirubin ≤1.0× ULN) after 52 weeks of treatment. Key secondary analyses included normalization of ALP at 12 months (e.g., ALP ≤1.0× ULN) and change from baseline in the weekly averaged peak pruritus numerical rating scale (NRS) over 6 months.

The study was terminated shortly after completion of enrollment (N=265) due to histology observations in an ongoing study in subjects with NASH (Study CB8025-21730; refer to the IB for details). Although the study was still blinded, the statistical analysis plan (SAP) was adjusted to move the primary and secondary endpoints from 12 to 3 months.

As shown in Figure 3, Panel A, 57.1% and 78.2% subjects in the seladelpar 5- and 10-mg groups, respectively, met the composite endpoint versus 12.5% of subjects in the placebo group ($p<0.0001$) after 12 weeks of treatment, with seladelpar 10 mg demonstrating a statistically significant higher response than seladelpar 5 mg ($p<0.05$). Normalization of ALP (Figure 3, Panel B) was achieved in 27.3% of subjects in the 10-mg dose group versus 5.4% and 0% in the seladelpar 5-mg and placebo groups, respectively.

After 3 months of treatment, the mean relative decreases in ALP of 36% (-106 U/L) and 44% (-122 U/L) for the seladelpar 5- and 10-mg groups, respectively, were highly significant from a mean relative decrease in the placebo group (3.7% [-12 U/L]; $p<0.0001$). These are consistent with results from the Phase 2 studies.

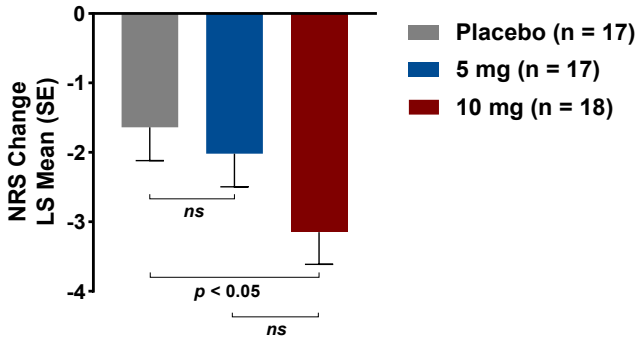
Figure 3: Study CB8025-31735: Seladelpar Effects on ALP



ALP=alkaline phosphatase; CMH=Cochran-Mantel-Haenszel; ns=not significant.
p-values by CMH test.
Source: Table 14.2.1.1 and Table 14.2.3

Seladelpar effects on pruritus after 12 weeks of treatments are presented in Figure 4. The key secondary pruritus endpoint measured change from baseline in the weekly averaged peak pruritus NRS at Month 3 in subjects with PBC with moderate to severe baseline pruritus, defined as an NRS ≥4. The NRS is a scale used for self-reported itch that goes from 0 to 10, with 0 being no itch and 10 being the worst imaginable itch. Approximately 30% of subjects completing 3 months of treatment had a mean baseline NRS of 6.2. A least squares (LS) mean decrease in NRS of 3.15 was observed for subjects in the seladelpar 10-mg group versus 1.64 for subjects in the placebo group (p=0.026). An LS mean decrease of 2.0 observed in subjects in the seladelpar 5-mg group was not significantly different from placebo.

Figure 4: Study CB8025-31735: Seladelpar Effect on Pruritus



LS=least squares; NRS=numerical rating scale; ns=not significant; SE=standard error.
Source: Table 14.2.4.1

Similar to what was seen in the Phase 2 study CB8025-21629, 23%, 17%, and 4% decreases in LS mean ALT levels were observed in the seladelpar 5-mg, seladelpar 10-mg, and placebo groups, respectively.

Seladelpar was well tolerated during the study, with balance in the incidence of adverse events (AEs) being reported across the dose groups: 63%, 65%, and 74% in the seladelpar 5-mg, seladelpar 10-mg, and placebo groups, respectively. There were no treatment-related AEs of Grade 3 or greater, including transaminase elevations. In addition, there were no treatment-related SAEs, and 2 AEs in the 10-mg group and 1 in the placebo group led to study drug discontinuation. The only treatment-emergent AE (TEAE) occurring in ≤10% of subjects in any treatment group was pruritus, which was lower for subjects on seladelpar than on placebo.

Study CB8025-31731 was a Phase 2/3, open-label, long-term study to evaluate the safety and tolerability of seladelpar (2, 5, and 10 mg) in subjects who participated in the previous PBC studies with seladelpar. Similar to Study CB8025-31735, this study was terminated early. The safety and efficacy profile were consistent with other PBC studies. Please refer to the IB for additional detailed information on these studies.

3. STUDY OBJECTIVES

3.1. Primary Objectives

The primary objective of this study is to evaluate the treatment effect of seladelpar on composite biochemical improvement in cholestasis markers based on ALP and total bilirubin and to evaluate the safety of seladelpar over 12 months of treatment compared to placebo.

3.2. Secondary Objectives

The key secondary objectives of this study are to evaluate the effect of seladelpar on the normalization of ALP values at 12 months of treatment compared to placebo and to evaluate the effect of seladelpar on pruritus at 6 months of treatment compared to placebo in subjects with baseline moderate to severe pruritus.

CCI [redacted]

3.3. Exploratory Objectives

CCI [redacted]

4. STUDY POPULATION

Patients with PBC with an inadequate response to UDCA or intolerance to UDCA who meet the following inclusion and exclusion criteria may be included in the study.

4.1. Inclusion Criteria

Subjects must 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. 18 to 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 above 1.0× ULN for at least 6 months.
   b. Positive AMA titer (>1:40 on immunofluorescence or M2 positive by enzyme linked immunosorbent assay [ELISA]) or positive PBC-specific antinuclear antibodies (ANAs).
   c. Documented liver biopsy results consistent with PBC.

4. UDCA 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. ALT ≤3× ULN.
   d. Total bilirubin ≤2× ULN.
   e. Estimated glomerular filtration rate (eGFR) >45 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease study equation).
   f. International normalized ratio (INR) below 1.1× ULN.

      For subjects on anticoagulation therapy, INR must be maintained in the range required for prophylaxis for their specific disease.
   g. Platelet count ≥100×10^3/μL.

   NOTE: PT, INR, and platelets can be performed locally at the Screening Visit, if deemed necessary by the investigator after consultation with the medical monitor, in cases where centrally read samples are deemed invalid.
6. Females of reproductive potential (refer to Section 8.1.1) must 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 dose. Male subjects who are sexually active with female partners of reproductive potential must use barrier contraception, and their female partners must use a second effective birth control method during the study and for at least 90 days after the last dose.

4.2. Exclusion Criteria

Subjects must not meet 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 (e.g., cancer) or confound its results (e.g., 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, will be taken into account when calculating the MELD score. This will be done in consultation with the medical monitor.

b. Complications of portal hypertension, including known esophageal varices, history of variceal bleeds or related interventions (e.g., 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 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 (HBsAg).

   i. Hepatitis C, defined as the presence of hepatitis C virus (HCV) ribonucleic acid (RNA).

   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 is allowed if appropriately treated prior to screening.

9. Treatment with obeticholic acid (OCA), and fibrates (e.g., bezafibrate, fenofibrate, elafibranor, lanifibranor, pemafibrate, 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 for additional medications that may be excluded.

11. Treatment with anti-pruritic drugs (e.g., cholestyramine, naltrexone, rifampicin, sertraline, or any experimental approach) must be 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 is 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 (e.g., cyclosporine, tacrolimus, anti-TNF or other immunosuppressive biologics).
16. Other medications that effect liver or GI functions, such as absorption of medications or the roux-en-y gastric bypass procedure, may be prohibited and should be discussed with the medical monitor on a case-by-case basis.
17. Active COVID-19 infection during Screening.

5. STUDY DESIGN

5.1. Study Overview

This is a Phase 3, international, multicenter evaluation of seladelpar in a randomized, double-blind, placebo-controlled, parallel-group study when administered for up to 12 months as a daily oral capsule in patients with PBC. Approximately 180 subjects will be randomized across approximately 180 sites worldwide.

Enrolled subjects will have confirmed PBC as defined by having any 2 of the following 3 diagnostic criteria at screening: (1) history of ALP above 1.0× ULN for at least 6 months; (2) positive AMA titers (>1:40 on immunofluorescence or M2 positive by ELISA) or positive PBC-specific ANAs; and (3) documented liver biopsy results consistent with PBC. Please refer to Section 4 for the complete listing of the Inclusion and Exclusion Criteria.

This study is a pivotal study to evaluate the safety of seladelpar and its effect (±UDCA) on cholestasis markers and on pruritus in subjects with inadequate response to UDCA or intolerance to UDCA. Enrolled subjects must have received UDCA for at least 12 months (>3 months of stable dose) or have intolerance to UDCA (no UDCA dose in the past >3 months). During the study, the study drug will be administered as an add-on to standard-of-care UDCA therapy for subjects who tolerate UDCA; for subjects with UDCA intolerance, the study drug will be administered as a monotherapy. The study population can also include subjects with an inadequate response to UDCA+OCA or who are intolerant to OCA.

Subjects will be randomly assigned to receive placebo or seladelpar 10 mg. Subjects will be stratified by ALP (ALP level <350 U/L versus ALP level ≥350 U/L) and the presence of clinically important pruritus (pruritus NRS <4 versus NRS ≥4) to ensure even distribution across treatment groups. Subjects will be considered as formally enrolled in the study at the time of randomization.

Study drug (placebo or seladelpar) will be taken in a blinded manner orally once daily for a period of up to 12 months. Subjects with an inadequate response to UDCA will continue on UDCA throughout the study.

Subjects will be asked to use an electronic diary (e-diary) to evaluate pruritus and QoL during the study participation. E-diaries will be dispensed at the Run-in Visit and will include 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. Subjects will perform 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 will be evaluated on a monthly basis until the Month 12/End of Treatment (EOT) Visit using pruritus NRS for 7 consecutive days each month. 5-D Itch will be evaluated biweekly from the Run-in Visit for the first 6 months of treatment and on a monthly basis after that until the Month 12/EOT Visit. PBC-40, PGI-S, and PGI-C will be evaluated after 1 month and every 3 months after treatment initiation over the whole study duration.

The total duration of participation in the study for each subject will be up to ~14 months. The Screening Period will be up to 3 weeks, the Run-in Period will be 2 weeks, and the Treatment Period will be up to 12 months. During the Treatment Period, subjects will be seen every 3 months, except for the first on-treatment visit, which will be performed after 1 month after the

initiation of the study drug. After the completion of the Treatment Period, the subjects will be invited to enroll into an open-label, long-term study (Study CB8025-31731-RE) in which each subject will be administered seladelpar and subjects on placebo will initiate seladelpar treatment. Subjects who do not want to continue seladelpar treatment beyond this study and decline long-term study participation will have a safety follow-up visit performed 2 weeks (14 days +3) after the last dose of the study drug. Subjects who discontinue study drug treatment for any reason other than a PBC clinical outcome will be asked to stay in the study without study drug intake.

Subjects who discontinue study drug treatment anytime, and do not stay in the study, will be terminated from the study, and complete an Early Termination Visit. For subjects who decline to stay in the study without study drug intake, or who do not participate in the long-term study, a phone call will be performed for PBC outcomes on an annual basis (Section 8.1.7).

Study visits may occur in clinic, with the assistance of a home health service, or using virtual technologies.

In order to establish the histological status of their liver before and after treatment, all subjects will be encouraged to have a liver biopsy during the Screening Period (unless a historical biopsy meeting quality standards can be supplied) to evaluate PBC stage and histology changes at baseline and after 1 year of treatment. Subjects willing to undergo a procedure will have liver biopsy performed during the Screening Period. The follow-up liver biopsy will be performed at the Month 12 Visit or at Early Termination if the subject withdraws from the study, provided they have had at least 6 months of treatment. A follow-up liver biopsy will be performed only in subjects with baseline liver biopsy. Histology will be evaluated by a pathology review committee (PRC) as specified in a histopathology plan.

During the study, subjects will be evaluated for the progression of their disease by collecting information about PBC clinical outcomes. All PBC clinical outcomes will be adjudicated by a critical event review committee (CERC).

The study design implements safety criteria to monitor subjects with potential drug-induced liver injury, muscle injury, renal injury, and acute pancreatitis with actions to stop the study drug, to interrupt the study drug, to down-titrate the study drug, or to investigate the case prior to actions with the study drug.

Subjects will be asked to participate in a pharmacokinetic (PK) sample collection to evaluate plasma concentrations of seladelpar and its metabolites. Subjects who consent to participate in this PK sample collection will provide a predose sample (-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 per the assigned schedule.

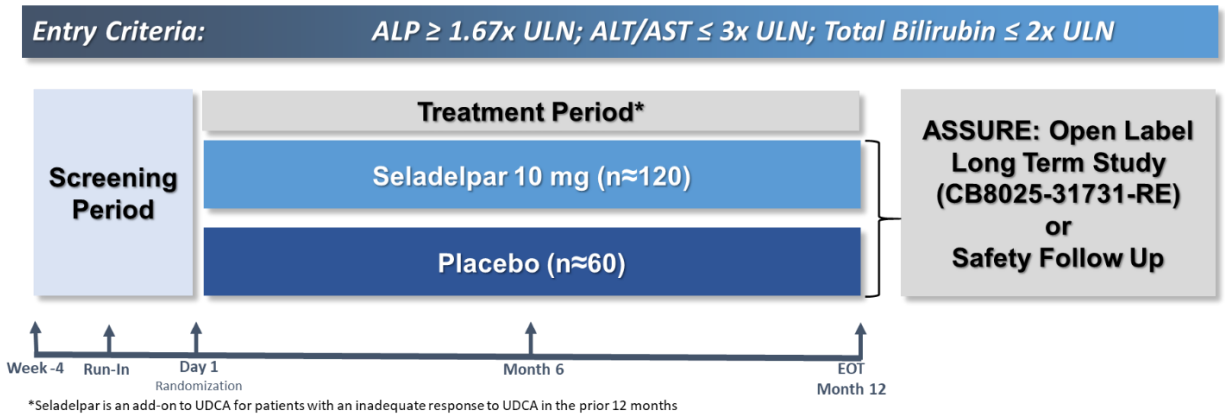
An independent data safety monitoring board (DSMB) will be convened to review the study data on a regular basis during the study conduct to ensure subjects' welfare and preserve study integrity.

A CERC will be established to analyze and adjudicate clinical events that occur during the study.

A PRC will be established to evaluate the biopsies in accordance with a defined histopathology plan.

The primary efficacy analysis will be a responder analysis of a composite of biochemical measures after 12 months of treatment with the study drug. Details of the conduct of the primary analysis will be provided in the SAP.

Figure 5: Study CB8025-32048: Study Diagram



ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; EOT=End of Treatment; UDCA=ursodeoxycholic acid; ULN=upper limit of normal.

[a] Seladelpar is an add-on to UDCA for patients with an inadequate response to UDCA in the prior 12 months.

5.2. Treatment and Allocation of Subjects

Approximately 180 subjects with PBC will be enrolled into the study.

Subjects will be randomized to seladelpar 10 mg or placebo in 2:1 ratio (approximately 120 subjects in the seladelpar 10-mg group and 60 subjects in the placebo group). Subjects will be stratified by ALP level <350 U/L versus ALP level ≥350 U/L and by the presence of clinically important pruritus (pruritus NRS <4 versus NRS ≥4).

5.3. Study Duration

The study will be up to ~14 months of duration and consists of the following periods:

- Screening Period: up to 3 weeks
- Run-in Period: 2 weeks
- Treatment Period: a maximum of 12 months with an option to enter an open-label long-term study (Study CB8025-31731-RE)
- Safety Follow-up Period: Up to 2 weeks (14 days +3) (only for subjects who are not enrolled in the long-term study)

5.4. Study Outcome Measurements

5.4.1. Primary Measures

1. Proportion of subjects who are 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 TEAEs (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0), biochemistry, and hematology

5.4.2. Key Secondary Measures

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

5.4.3. Other Secondary Measures

[redacted]

5.4.4. Exploratory Measures

[redacted]

5.5. Rationale for Dose Selection

In a double-blind, placebo-controlled study in subjects with PBC randomized to placebo, seladelpar 5 mg, or seladelpar 10 mg, the seladelpar 10-mg dose (n=55) demonstrated superior efficacy ($p<0.05$) with comparable safety compared to seladelpar 5 mg (n=56) in the composite endpoint (78.2% versus 57.1%). Further, 10 mg was superior to 5 mg ($p<0.01$) in normalizing ALP (27.3% versus 5.4%), and in subjects with baseline NRS ≥4, seladelpar 10 mg showed improvement in pruritus (LS mean decrease in NRS of 3.15 versus 1.64 in placebo, $p<0.03$), whereas the seladelpar 5-mg effect was not statistically significant. AEs were reported in 74%, 63%, and 65% of subjects receiving placebo, seladelpar 5 mg, and seladelpar 10 mg, respectively.

In Phase 2 PBC studies, dose-dependent improvements in markers of cholestasis and inflammation as well as metabolic markers (e.g., decrease in triglycerides and LDL-C) have been established for seladelpar 2-, 5-, and 10-mg doses. However, in the Phase 2 dose-ranging study, by Week 52, 10 of 11 subjects receiving seladelpar 2 mg up-titrated to 5 or 10 mg, and 30 of 53 subjects receiving seladelpar 5 mg up-titrated to 10 mg to improve clinical response.

Seladelpar 10 mg has been well tolerated to date, with no meaningful differences in the safety profile compared to lower doses of seladelpar and placebo and is not associated with drug-induced pruritus. Refer to the IB for details.

For all of the abovementioned reasons, a seladelpar dose of 10 mg/day is optimal and has been selected for this Phase 3 study.

5.6. Rationale for Placebo Arm

This study incorporates the use of a placebo comparator arm on top of the first-line standard-of-care therapy UDCA, as it is the most rigorous test of treatment efficacy and safety profile for evaluating an experimental therapy in complex patient populations.

A placebo-controlled, double-blinded pivotal study allows an unbiased estimate of the seladelpar treatment effect and full characterization of seladelpar's safety. A placebo-controlled methodology is essential to provide sufficient efficacy and safety data to support widespread use in non-study settings.

Subjects will continue to receive UDCA as the background therapy unless UDCA intolerance was diagnosed. UDCA has been the mainstay of therapy for PBC, has been studied in multiple prospective clinical studies, and has proved its beneficial effect.

Enrolled subjects will be randomized into the study in seladelpar versus placebo group in a 2:1 ratio to increase the subject's chance to receive an active drug during the study participation.

Although OCA is authorized in the US and European Union, its authorization is conditional, pending confirmation of benefit on clinical outcomes; its safety profile is not fully understood; and it is not available in all countries where the proposed clinical study is being conducted.

The effects of seladelpar on pruritus is being evaluated in this study as a key secondary endpoint; an active control study with OCA would require the exclusion of patients with severe pruritus due to the warning and dosing limitation in its label. Further, because OCA is known to cause and/or worsen pruritus, the use of OCA as a comparator would make it infeasible to establish the effect of seladelpar on pruritus.

This study includes biopsy to characterize histology in subjects with PBC treated with seladelpar and placebo, an important requirement for regulators. Coadministration with other PBC treatments such as OCA would confound the interpretation of histology, as well as the overall safety profile of seladelpar.

5.7. Benefit/Risk Assessment

The study being proposed is a placebo-controlled, double-blind, randomized study to evaluate safety and treatment effect of seladelpar with or without UDCA, the first-line standard of care, in subjects with PBC who either have an inadequate response after 12 months of receiving UDCA or are intolerant to UDCA.

5.7.1. Potential Benefit

In two placebo-controlled, PBC studies with seladelpar, subjects receiving placebo showed no relevant change in biochemical markers of cholestasis, whereas subjects receiving seladelpar exhibited a pronounced decrease in ALP. ALP is a biochemical marker for which lower values have been shown to be predictive of longer transplant-free survival for patients with PBC. After 12 weeks of treatment with seladelpar 10 mg, 82% of subjects reached ALP <1.67× ULN versus 18% of subjects with placebo ($p<0.0001$), and 27% of subjects had a normal ALP versus 0%, respectively. Importantly, 78% of subjects treated with 10 mg seladelpar met the composite responder endpoint compared to 12.5% of subjects receiving placebo ($p<0.0001$). Additional biochemical markers of cholestasis, such as GGT and 5'-nucleotidase, were also reduced by

seladelpar. Seladelpar also produced potentially beneficial metabolic and anti-inflammatory effects. These effects were sustained with long-term, open-label treatment with seladelpar.

Seladelpar's effect on quality-of-life measures such a pruritus, an important clinical outcome for patients, has been demonstrated in 2 clinical studies. In these studies, seladelpar improved pruritus when measured with either VAS or NRS. In an open-label setting, a decrease in the pruritus VAS was noted in the 10-mg group, in which approximately half of subjects had a substantial level of itching at baseline (VAS ≥40 mm or moderate to severe itch). These data were confirmed in placebo-controlled study where subjects with PBC with moderate to severe pruritus at baseline (defined as an NRS of ≥4) had a LS mean decrease in NRS of 3.15 when treated with seladelpar 10 mg, which was statistically significant compared to placebo (p=0.026). These data suggest that seladelpar treatment could improve PBC-associated itch.

Subjects who will successfully complete this study will be offered open-label treatment in a long-term study (Study CB8025-31731-RE); subjects receiving placebo will be switched to the active treatment with seladelpar.

5.7.2. Potential Risks

Across the clinical development program, the doses of seladelpar tested have included single-dose studies in healthy volunteers (1, 5, 15, 60, 120, and 360 mg), to daily long-term dose in Phase 2 studies in subjects with mixed dyslipidemia (50 and 100 mg once daily), HoFH (ascending doses 50, 100, and 200 mg once daily), NASH (10, 20, and 50 mg once daily), and PBC (2, 5, 10, 50, and 200 mg once daily). In these studies, dosing durations have ranged from 8 weeks to over 2 years.

Seladelpar has been associated with increases in liver transaminases (ALT and AST) in subjects with PBC treated with seladelpar at doses of 50 and 200 mg. The transaminase increases appear to be dose and population dependent and were fully reversible upon treatment discontinuation. A single PBC subject taking seladelpar 200 mg/day discontinued treatment for acute muscle pain associated with increased muscle enzymes. This event was considered possibly related to treatment and was reversible upon treatment discontinuation. Mild increases in serum creatinine have been noted, similar to observations with PPARα or pan-PPAR class of medications. However, there are no concurrent change in cystatin-C or other markers of renal injury, supporting that the increase is not associated with renal toxicity.

5.7.3. Summary

Seladelpar has demonstrated the potent and rapid decrease in biochemical markers of cholestasis (ALP, GGT, and total bilirubin), a decrease in a marker of inflammation (hs-CRP) and decreases in LDL-C in subjects with PBC who had an inadequate response or intolerance to UDCA. In addition, the current data showed that seladelpar improves PBC-related pruritus. Seladelpar doses 10 mg and below were generally safe and well tolerated. There was no evidence that seladelpar was associated with transaminase elevations at these doses. There was also no evidence that seladelpar induced or worsened pruritus. Appropriate precautions have been incorporated into this protocol, with careful monitoring of potential drug-induced liver, renal, or pancreatic injury and muscle toxicity.

In summary, the benefit/risk of seladelpar in patients with PBC at doses up to 10 mg is acceptable based on the aggregate safety and treatment effect data to date.

6. STUDY MEDICATIONS

6.1. Investigational Product

6.1.1. Dose and Mode of Administration

Dose: Subjects will receive seladelpar 10 mg, seladelpar 5 mg (if down-titrated), or matching placebo in a blinded fashion.

Seladelpar, as well as matched placebo, will be supplied in a blinded fashion as 5- and 10-mg capsules.

Administration: The study drug (seladelpar or placebo) will be administered orally, once daily, for a duration of up to 12 months. The subject will take 1 capsule every day, approximately at the same time each day.

Down-Titration: Subjects who meet specific safety monitoring criteria in Section 10 or have tolerability issues may have a dose down-titration. Subjects who are initially assigned to 10 mg will be down-titrated to 5 mg in a blinded manner. Subjects initially assigned to placebo will have a blinded down-titration and will remain in the placebo group.

Subjects who experience a clinically important AE that, in the investigator's clinical judgment, warrants a dose reduction are also eligible for a similar dose down-titration. Dose down-titration must be approved by the medical monitor and will be performed in a blinded manner. Subjects who have a temporary interruption from study drug due to an AE may resume their originally assigned dose if the AE of interest has resolved and was determined to be unrelated to study drug. Study drug may be held temporarily for appropriate medical procedures, illness, travel restrictions, or other activities that may hinder the subject's ability to dose per protocol. The medical monitor should be advised of any interruption as soon as possible and consulted if study drug is to be restarted.

6.1.2. Packaging, Labeling, and Shipping

Blinded study drug will be supplied in bottles containing 5-mg, 10-mg, or placebo capsules.

The sponsor will provide the investigator with packaged study drug labeled in accordance with specific country regulatory requirements.

The supplies will be shipped in accordance with the pharmacy manual. To ensure continuity of treatment, the option of delivering the investigational product directly from each site to the subject may be considered. Additional replacement study drug will be available as required. All replacement shipments must be accounted for in the same manner as the initial drug supply.

6.1.3. Storage of Study Drug

All supplies of study medication must be stored as defined in the pharmacy manual.

6.2. Accountability of Clinical Supplies

Study drug will be dispensed at Day 1 and quarterly thereafter (e.g., Months 3, 6, and 9) and will be reconciled at all visits.

The principal investigator is responsible for ensuring that a current record of inventory/drug accountability is maintained. Inventory records must be readily available for inspection by the study monitor and are open to inspection by regulatory authorities at any time. Each shipment of drug supply for the study will contain a shipping manifest to assist the principal investigator in maintaining current and accurate inventory records.

6.3. Ursodeoxycholic Acid

UDCA will be taken as a background therapy as part of participation in the study.

UDCA will be administered orally, 1 or multiple times per day at the prestudy dose and as recommended per investigator's clinical judgment.

The UDCA dose, compliance with UDCA, and any changes in dose during the study will be documented and monitored. Compliance will be evaluated by asking the subjects if they missed any doses of UDCA between the visits; the number of doses missed should be recorded.

6.4. Randomization and Stratification

Subjects will be randomized in a blinded manner to placebo or seladelpar 10 mg in a 2:1 scheme (seladelpar 10 mg: placebo). In addition, randomized subjects will be stratified by ALP level <350 U/L versus ALP level ≥350 U/L and by the presence of clinically important pruritus (pruritus NRS <4 versus NRS ≥4).

The randomization procedure will be performed centrally via an interactive web response system (IWRS) at the Day 1 Visit. A subject will be considered formally enrolled in the study at the time of randomization and begin study drug dosing.

6.5. Emergency Unblinding

The unblinding must be clearly justified and explained by a comment in the source documentation, along with the date on which the code was broken and the identity of the person authorizing the unblinding. The date and time when the investigator removed the study blind for an individual subject will be documented by the IWRS, and an automated notification will be sent to the sponsor. The contract research organization's pharmacovigilance team may also be required to break the blind for regulatory reporting purposes.

6.6. Compliance

Compliance to the study drug will be assessed through drug accountability evaluation. Study drug accountability will be evaluated at the Month 3 through Month 12 Visits and the Early Termination Visit.

7. CONCOMITANT MEDICATIONS AND PROCEDURES

The use of concomitant medications or procedures must be documented on the subject's electronic Case Report Form (eCRF). AEs related to the administration of these medications or procedures must also be documented on the appropriate section in the eCRF.

All subjects will be instructed to remain on their optimal or best possible diet and lifestyle, including drinking habits, specifically alcoholic beverages, throughout the study.

7.1. Concomitant Medications

A concomitant medication is any drug of substance other than study drug and UDCA, including over-the-counter medications, herbal medications, and vitamin supplements, administered during subjects' participation in this study.

Any medication taken within 3 months prior to Screening and during the study period, as well as the indication, will be recorded in the source documents and the eCRFs. Any AEs related to the administration of these medications or procedures must also be documented on the appropriate section in the eCRF.

7.2. Allowed Concomitant Medication

Subjects will be allowed to receive required medication to treat new or existing medical conditions.

Subjects will continue UDCA intake in accordance with their prescribed dose. Dose adjustments or interruption in UDCA during the study will be documented.

PBC symptomatic treatment (e.g., antipruritic drugs) should be discussed with the medical monitor. Guidelines about PBC symptom management will be defined in a study manual.

7.3. Prohibited Concomitant Medication

The following medications are prohibited from use during the study:

- Obeticholic acid (OCA)
- Fibrates (e.g., bezafibrate, fenofibrate, elafibranor, lanifibranor, pemafibrate, saroglitazar)
- Colchicine, methotrexate, or azathioprine
- Long-term systemic steroids (e.g., prednisone, prednisolone, budesonide) for >2 weeks
- Experimental or unapproved treatment for PBC or related autoimmune disease
- Immunosuppressant therapies (e.g., cyclosporine, tacrolimus, anti-TNF or other immunosuppressive biologics)
- Other medications that effect liver or GI functions, such as absorption of medications, may be prohibited and should be discussed with the medical monitor on a case-by-case basis.

7.4. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery, biopsy, or physical therapy) or diagnostic assessment (e.g., blood gas measurement or bacterial cultures) performed during subjects' participation in this study. Subjects will be allowed to receive required procedures to treat new or existing medical conditions.

All concomitant procedures must be documented on the participant's eCRF. AEs related to the administration of these procedures must also be documented on the appropriate section in the eCRF.

8. STUDY PROCEDURES

8.1. Study Schedule

The schedule of study procedures is presented in Table 1.

The study for an individual subject consists of the following periods:

- Screening Period: Week -5 to Week -2 (up to 3 weeks)
- Run-in Period: Week -2 to Day 1
- Treatment Initiation: Day 1
- Treatment Period: Day 1 through up to Month 12
- Safety Follow-up Period: 2 weeks (14 days +3) after the last dose of the study drug (only applicable for subjects who are not willing to roll over to long-term study, Study CB8025-31731-RE).

Additional visits may be scheduled to evaluate an abnormal laboratory value or reported AE.

Study visits should be performed in the clinic. If study visits cannot be performed in the clinic, for example, due to COVID-19 restrictions, a plan will be detailed according to the guidance of the Food and Drug Administration, European Medicines Agency, other regulatory agencies, and local ethics committees. If needed and whenever possible, study visits may be performed through home health service or using virtual technologies (e.g., phone calls or video calls). Central laboratory must be used whenever possible, but if not feasible, local laboratory use can be considered after discussion with the medical monitor.

8.1.1. Screening Period (W -5 to -2 [Day -35 to -15])

Subjects will review and sign the informed consent form (ICF) prior to any study-related procedures. Screening period begins on the date of signing the Informed Consent. The screening period can be completed in up to 3 weeks, between days -35 and -15 prior to Day1/Randomization. When all Screening evaluations are completed, subjects who are deemed to be eligible will move into the Run-in period.

Subjects who cannot complete the Screening assessments in time due to logistical or COVID-related reasons may be eligible to continue in Screening. However, these instances should be discussed with the medical monitor and will be evaluated on a case-by-case basis.

The evaluations of eligibility will consist of the following:

- Demographic information.
- Assessment of all inclusion and exclusion criteria.
- Review of medical history, including PBC medical history, results of prior liver biopsy, FibroScan, and alcohol consumption. The subject's medical chart will be reviewed for evidence of liver cirrhosis and other forms of chronic liver disease, as well as for HIV infection.
- Documentation of prior and concomitant medications including, but not limited to, previous exposure to UDCA, OCA, fibrates (e.g., bezafibrate, fenofibrate,

elafibranor, lanifibranor, pemafibrate, and saroglitizar), and other medications taken for PBC and its symptoms (including supplements and vitamins).

- Vital signs (as described in Section 8.2.3). This will include temperature, heart rate, respiratory rate, and blood pressure.
- Height and weight measurements will be performed.
- Complete physical examination (as described in Section 8.2.2). This will include a full review of the following systems: general, skin, eyes, nose/sinuses, ears, mouth/throat, neck, breasts, respiratory, cardiac, gastrointestinal, peripheral vascular, genitourinary, musculoskeletal, neurologic, mental health, endocrine, and hematologic.
- 12-lead electrocardiogram (ECG) after at least 5 minutes of rest.
- Blood drawn for hematology, biochemistry, AMA, hepatitis B, hepatitis C and HIV as outlined in Section 8.2.5 and Appendix A. Prothrombin time (PT), INR, and platelets will also be performed locally. If unexpected elevation in INR is noted, re-test is allowed.
- COVID-19 testing will be performed locally and only if deemed necessary per local requirements. Subjects with a positive COVID-19 test during Screening may be eligible to re-screen after recovery.
- Women of child-bearing potential will have a serum pregnancy test performed. Women of child-bearing potential will be provided with urine pregnancy tests in between visits for monthly testing. Results must be relayed to the clinical staff during the next visit/contact. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.

  Note: for the purpose of this document, a woman is considered of childbearing potential, e.g., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.[24]

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient ([24]).
- Urine drug screen.
- E-diary training.
- Pruritus NRS evaluation.
- UDCA dose will be recorded. Subjects will be instructed to continue UDCA regimen (dose and frequency) at dose as close as possible to prestudy dose and as recommended per investigator's clinical judgment.

- Subjects who meet all inclusion criteria and do not meet any exclusion criteria will be invited for the Run-in Visit.

If an untoward event occurs at any time after the ICF is signed, it will be recorded as AE. Any laboratory abnormality deemed clinically important by the investigator will be considered an AE.

Subjects will be reminded of the following restrictions:

- To comply with diet and lifestyle, including drinking habits.
- Not to use prohibited concomitant medications.
- Females of reproductive potential will be reminded 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 dose.
- Male subjects who are sexually active with female partners of reproductive potential will be reminded to use barrier contraception, and their female partners must use a second effective birth control method during the study and for at least 90 days after the last dose.

8.1.2. Run-in Period (W -2 [Day -14])

Subjects who have been deemed eligible during the Screening Period will return for the Run-in Visit. The visit will occur 14 days ±3 days prior to Day1/Randomization.

Subjects who cannot complete the run-in period in time for logistical or COVID-related reasons may be eligible to continue in Run-in. However, these instances should be discussed with the medical monitor and will be evaluated on a case-by-case basis.

All subjects will have the following evaluations performed:

- Documentation of AEs that occurred since the signing of the ICF.
- Documentation of medications (including supplements and vitamins) since the last visit.
- Vital signs and weight (as described at Section 8.2.3).
- Symptom-directed (brief) physical examination (as described at Section 8.2.2).
- Blood drawn for hematology, biochemistry, and exploratory measures as outlined in Appendix A.
- Women of child-bearing potential will have a serum pregnancy test performed. Women of child-bearing potential will be provided with urine pregnancy tests in between visits for monthly testing. Results must be relayed to the clinical staff during the next visit/contact. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.
- Back-up blood sample will be collected.
- COVID-19 testing will be performed locally and only if deemed necessary. Subjects with a positive COVID-19 test during Screening may be eligible to re-screen after recovery.

- E-diary will be dispensed. Re-training will be performed, if needed.
- Pruritus NRS, 5-D Itch, PBC-40, and PGI-S questionnaires will be performed via e-diary. The subject will be instructed to use e-diary to evaluate pruritus NRS on a daily basis and 5-D Itch on a biweekly basis at approximately same time during the day from the Run-in Visit through the first 6 months of study drug treatment.
- FibroScan at selected sites.
- Abdominal ultrasound focusing on the liver, gallbladder, common bile duct, portal vein, and spleen will be performed.
- UDCA compliance.
- Baseline liver biopsy: All subjects will be encouraged to undergo the procedure to evaluate PBC stage and activity. Liver biopsy might be performed anytime between Screening and Day 1 but only after confirmation of the subject's eligibility. PT and INR must be performed within 2 weeks prior to liver biopsy.

8.1.3. Treatment Period

8.1.3.1. Day 1 (Randomization)

Day 1 begins the Treatment Period and is the date against which all subsequent visits will be timed except for the Safety Follow-up Period. At this visit, subjects will be randomized into the study. A subject will be considered formally enrolled in the study at the time of randomization. On the scheduled visit days, subjects will be in the fasted state for laboratory assessments. If subjects forget to fast, this should be noted, and the blood sample should still be collected.

The following evaluations will be performed:

- Randomization.
- Documentation of AEs that occurred since the signing of the ICF.
- Documentation of medications (including supplements and vitamins) since the last visit.
- Vital signs and weight (as described at Section 8.2.3).
- Complete physical examination (as described at Section 8.2.2) and liver-related symptoms, including cirrhosis evaluation.
- 12-lead ECG after at least 5 minutes of rest.
- Blood drawn for hematology, biochemistry, and exploratory measures (including fat-soluble vitamins) as outlined in Appendix A.
- Back-up blood sample will be collected.
- Women of child-bearing potential will have a serum pregnancy test performed. Women of child-bearing potential will be provided with urine pregnancy tests in between visits for monthly testing. Results must be relayed to the clinical staff during the next visit/contact. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.

- COVID-19 testing will be performed locally and only if deemed necessary.
- PBC-40 and PGI-S questionnaires via ediary.
- Pruritus NRS: review of previously collected data. Subjects will be reminded to use e-diary to evaluate pruritus on a daily basis during the first 6 months of treatment.
- 5-D Itch scale via e-diary: review of previously collected data. Subjects will be reminded to use e-diary to evaluate pruritus on a biweekly basis up until the Month 6 Visit.
- UDCA compliance.
- Study drug will be dispensed per the subject's randomization with interactions to take orally once daily. The first dose of the study drug will be administered on site.

If a subject terminates study participation at any point after Day 1, an Early Termination Visit will be completed.

8.1.3.2. Month 1 (W4 [Day 29])

The visit will occur 4 weeks±3 days after Day 1, and the following evaluations will be performed:

- Documentation of AEs that occurred since the signing of the ICF.
- Documentation of concomitant medications (including supplements and vitamins) since the last visit.
- Vital signs and weight (as described at Section 8.2.3).
- Symptom-directed (brief) physical examination (as described at Section 8.2.2), including ascites and encephalopathy information in support of the Child-Pugh score calculation.
- Liver-related symptoms, including cirrhosis evaluation and PBC clinical outcomes, will be monitored based on the subject's clinical evaluation, available medical history/AEs and concomitant medications, and available tests results (Section 11 and Appendix I). Unscheduled visit (UNS) might be scheduled if needed per the investigator's clinical judgment.
- Blood drawn for hematology, biochemistry, and exploratory measures as outlined in Appendix A.
- Back-up blood sample will be collected.
- COVID-19 testing will be performed locally and only if deemed necessary.
- Women of child-bearing potential will have a serum pregnancy test performed. Women of child-bearing potential will be provided with urine pregnancy tests in between visits for monthly testing. Results must be relayed to the clinical staff during the next visit/contact. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.
- PBC-40, PGI-S, and PGI-C questionnaires via e-diary.

- Pruritus NRS: review of previously collected data. Subjects will be reminded to use e-diary to evaluate pruritus on a daily basis during the first 6 months of treatment.
- 5-D Itch: review of previously collected data. Subjects will be reminded to use e-diary to evaluate pruritus on a biweekly basis up until the Month 6 Visit.
- Study drug compliance and accountability.
- UDCA compliance.

8.1.3.3. Month 3 (W12 [Day85])

The visit will occur 12 weeks±7 days after Day 1, and the following evaluations will be performed:

- Documentation of AEs that occurred since the signing of the ICF.
- Documentation of concomitant medications (including supplements and vitamins) since the last visit.
- Vital signs and weight (as described at Section 8.2.3).
- Symptom-directed (brief) physical examination (as described at Section 8.2.2), including ascites and encephalopathy information in support of the Child-Pugh score calculation.
- Liver-related symptoms, including cirrhosis evaluation and PBC clinical outcomes, will be monitored based on the subject's clinical evaluation, available medical history/AEs and concomitant medications, and available tests results (Section 11 and Appendix I). UNS visit might be scheduled if needed per the investigator's clinical judgment.
- Blood drawn for hematology, biochemistry, and exploratory measures as outlined in Appendix A.
- PK sample collection: Prior to the visit, subjects will be reminded not to take the study drug at home. Time of PK blood collection and dosing will be documented. PK sampling will be performed once predose (-30 min prior to dosing) and twice postdose (1 hour±30 minutes and 3 hours±30 minutes after dosing).
- Back-up blood sample will be collected.
- COVID-19 testing will be performed locally and only if deemed necessary.
- Women of child-bearing potential will have a serum pregnancy test performed. Women of child-bearing potential will be provided with urine pregnancy tests in between visits for monthly testing. Results must be relayed to the clinical staff during the next visit/contact. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.
- PBC-40, PGI-S, and PGI-C questionnaires via e-diary.
- Pruritus NRS: review of previously collected data. Subjects will be reminded to use e-diary to evaluate pruritus on a daily basis during the first 6 months of treatment.

- 5-D Itch: review of previously collected data. Subjects will be reminded to use e-diary to evaluate pruritus on a biweekly basis up until the Month 6 Visit.
- Study drug compliance and accountability.
- UDCA compliance.
- Dispense study drug.

8.1.3.4. Month 6 (W26 [Day183])

The visit will occur 26 weeks±7 days after Day 1, and the following evaluations will be performed:

- Documentation of AEs that occurred since the signing of the ICF.
- Documentation of concomitant medications (including supplements and vitamins) since the last visit.
- Vital signs and weight (as described in Section 8.2.3).
- Complete physical examination (as described at Section 8.2.2), including ascites and encephalopathy information in support of the Child-Pugh score calculation.
- Liver-related symptoms, including cirrhosis evaluation and PBC clinical outcomes, will be monitored based on the subject's clinical evaluation, available medical history/AEs and concomitant medications, and available tests results (Section 11 and Appendix I). UNS visit might be scheduled if needed per the investigator's clinical judgment.
- 12-lead ECG after at least 5 minutes of rest.
- Blood drawn for hematology, biochemistry, and exploratory measures as outlined in Appendix A.
- Back-up blood sample collection.
- COVID-19 testing will be performed locally and only if deemed necessary.
- Women of child-bearing potential will have a serum pregnancy test performed. Women of child-bearing potential will be provided with urine pregnancy tests in between visits for monthly testing. Results must be relayed to the clinical staff during the next visit/contact. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.
- PBC-40, PGI-S, and PGI-C questionnaires via e-diary.
- Pruritus NRS: review of previously collected data. Subjects will be instructed to use e-diary on a monthly basis for 7 consecutive days each month until Month 12.
- 5-D Itch: review of previously collected data. Subjects will be instructed to evaluate pruritus via 5-D Itch in a monthly basis until Month 12.
- FibroScan at the selected sites.
- Study drug compliance and accountability.

- UDCA compliance.
- Dispense study drug.

8.1.3.5. Month 9 (W39 [Day 274])

The visit will occur 39 weeks±7 days after Day 1, and the following evaluations will be performed:

- Documentation of AEs that occurred since the signing of the ICF.
- Documentation of concomitant medications (including supplements and vitamins) since the last visit.
- Vital signs and weight (as described at Section 8.2.3).
- Brief symptom-directed physical examination (as described at Section 8.2.2), including ascites and encephalopathy information in support of the Child-Pugh score calculation.
- Liver-related symptoms, including cirrhosis evaluation and PBC clinical outcomes, will be monitored based on the subject's clinical evaluation, available medical history/AEs and concomitant medications, and available tests results (Section 11 and Appendix I). UNS visit might be scheduled if needed per the investigator's clinical judgment.
- Blood drawn for hematology, biochemistry, and exploratory measures as outlined in Appendix A.
- Back-up blood sample collection.
- COVID-19 testing will be performed locally and only if deemed necessary.
- Women of child-bearing potential will have a serum pregnancy test performed. Women of child-bearing potential will be provided with urine pregnancy tests in between visits for monthly testing. Results must be relayed to the clinical staff during the next visit/contact. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.
- PBC-40, PGI-C, and PGI-S questionnaires via e-diary.
- Pruritus NRS: review of previously collected data. Subjects will be instructed to continue to use e-diary on a monthly basis for 7 consecutive days each month through EOT visit.
- 5-D Itch: review of previously collected data. Subjects will be instructed to evaluate pruritus via 5-D Itch in a monthly basis until Month 12.
- Study drug compliance and accountability.
- UDCA compliance.
- Dispense study drug.

8.1.3.6. Month 12/End of Treatment (W52 [Day 365])

The visit will occur 52 weeks±7 days after Day 1, and the following evaluations will be performed:

- Documentation of AEs that occurred since the signing of the ICF.
- Documentation of concomitant medications (including supplements and vitamins) since the last visit.
- Vital signs and weight (as described at Section 8.2.3).
- Complete physical examination (as described at Section 8.2.2), including ascites and encephalopathy information in support of the Child-Pugh score calculation.
- Liver-related symptoms, including cirrhosis evaluation and PBC clinical outcomes, will be evaluated based on the subject's clinical evaluation, available medical history/AEs and concomitant medications, and available tests results (Section 11 and Appendix I). UNS visit might be scheduled if needed per the investigator's clinical judgment.
- 12-lead ECG after at least 5 minutes of rest.
- Blood drawn for hematology, biochemistry, and exploratory measures (including fat-soluble vitamins) as outlined in Appendix A.
- PK sample collection: Prior to the visit, subjects will be reminded not to take the study drug at home. Time of PK blood collection and dosing will be documented. PK sampling will be performed once predose (-30 min prior to dosing) and twice postdose (1 hour±30 minutes and 3 hours±30 minutes after dosing).
- Back-up blood sample collection.
- COVID-19 testing will be performed locally and only if deemed necessary.
- Women of child-bearing potential will have a serum pregnancy test performed. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.
- PBC-40, PGI-S, and PGI-C questionnaires via e-diary.
- Pruritus NRS and 5-D Itch: review of previously collected data.
- E-diary will be collected.
- FibroScan at the selected sites.
- Abdominal ultrasound focusing on the liver, gallbladder, common bile duct, portal vein, and spleen will be performed.
- Study drug compliance and accountability.
- UDCA compliance.
- Subjects who had baseline liver biopsy: Liver biopsy will be performed approximately 12 months after baseline liver biopsy (window: 48 to 56 weeks after

baseline liver biopsy). PT, INR, and platelets must be performed within 2 weeks prior to liver biopsy.

At the end of the visit, subjects will be invited to participate in the long-term study (Study CB8025-31731-RE).

8.1.4. Post-Treatment Safety Follow-up (2W [14 Days after W52])

The visit will occur 2 weeks (14 days +3 days) after the last dose of the study drug and is applicable only to subjects who do not participate in the long-term study. The following evaluations will be performed:

- Documentation of AEs that occurred since the signing of the ICF.
- Documentation of concomitant medications (including supplements and vitamins) since the last visit.
- Vital signs and weight (as described at Section 8.2.3).
- Complete physical examination (as described at Section 8.2.2), including ascites and encephalopathy information in support of the Child-Pugh score calculation.
- Liver-related symptoms, including cirrhosis evaluation and PBC clinical outcomes, will be evaluated based on the subject's clinical evaluation, available medical history/AEs and concomitant medications, and available tests results (Section 11 and Appendix I). UNS visit might be scheduled if needed per the investigator's clinical judgment.
- 12-lead ECG after at least 5 minutes of rest.
- Blood drawn for hematology, biochemistry, and exploratory measures as outlined in Appendix A.
- Back-up blood sample collection.
- COVID-19 testing will be performed locally and only if deemed necessary.
- Women of child-bearing potential will have a serum pregnancy test performed.

This will be the subject's last visit. Any clinically important abnormalities should be followed up by the investigator, until resolution or stabilization of those abnormalities.

Subjects who decline participation in the long-term study will be asked to be followed to collect information about PBC clinical outcomes (Section 8.1.7).

8.1.5. Early Termination

Subjects who discontinued study drug treatment for any reason other than a defined PBC clinical outcome will be asked to stay in the study without study drug intake. Subjects who decline to stay in the study without study drug intake should return for an Early Termination Visit, and the following evaluations should be performed:

- Documentation of AEs that occurred since the signing of the ICF.

- Review and documentation of concomitant medications (including supplements and vitamins) since the last visit.
- Vital signs and weight (as described at Section 8.2.3).
- Complete physical examination (as described at Section 8.2.2), including ascites and encephalopathy information in support of the Child-Pugh score calculation.
- Liver-related symptoms, including evaluation for cirrhosis and PBC clinical outcomes, will be monitored based the on subject's clinical status, available medical history/AEs and concomitant medications, and available tests results (Section 11 and Appendix I). UNS visit might be scheduled if needed per the investigator's clinical judgment.
- 12-lead ECG after at least 5 minutes of rest.
- Blood drawn for hematology, biochemistry, and exploratory measures (including fat-soluble vitamins) as outlined in Appendix A.
- Back-up blood sample will be collected.
- COVID-19 testing will be performed locally and only if deemed necessary,
- Women of reproductive status will have serum pregnancy test performed.
- Pruritus NRS, 5-D Itch, PBC-40, PGI-S, and PGI-C questionnaires via e-diary,
- Pruritus NRS and 5-D Itch: review of previously collected data,
- E-diary will be collected.
- FibroScan at the selected sites.
- Abdominal ultrasound focusing on the liver, gallbladder, common bile duct, portal vein, and spleen will be performed.
- Study drug compliance and accountability.
- UDCA compliance.
- Subjects who had baseline liver biopsy and discontinued the study between 6 and 12 months of treatment: Follow-up liver biopsy will be performed. PT, INR, and platelets must be performed within 2 weeks prior to liver biopsy.

Any clinically important abnormalities should be followed up by the investigator until resolution or stabilization of those abnormalities.

Subjects who discontinue from the study for any reason other than a defined PBC clinical outcome and decline to stay in study without study drug intake, or who do not participate in the long-term study will be followed to collect information about PBC clinical outcomes on an annual basis per Section 8.1.7.

8.1.6. Unscheduled Visit

A UNS visit must be scheduled if safety monitoring criteria are met within the timeline outlined in Section 10 and if the dose is adjusted for safety reason. A UNS visit might be scheduled at any time during the study participation if deemed necessary per the investigator's clinical judgment.

At any UNS visit, the following evaluations will be performed:

- Documentation of AEs that occurred since the signing of the ICF.
- Review and documentation of concomitant medications (including supplements and vitamins) since the last visit.
- Symptom-directed (brief) physical examination (as described at Section 8.2.2).
- Vital signs and weight (as described at Section 8.2.3).
- COVID-19 testing will be performed locally and only if deemed necessary.
- Blood drawn for biochemistry and hematology.
- Blood sample for PK. When possible a PK sample should be drawn at the onset of SAEs or clinically meaningful AEs. In these instances, document subject's time of last dose.

Additional assessments or study-required follow-up (e.g., unscheduled study drug dispensation and e-diary management) as determined by the investigator.

8.1.7. Annual Follow-Up for PBC outcomes Assessment

Subjects who discontinue study drug treatment for any reason other than a defined PBC clinical outcome will be asked to stay in the study without study drug intake. Subjects who decline to stay in the study without study drug intake, or who do not participate in the long-term study, a phone call will be performed annually (52 weeks ±45 days) after the subject's last visit, or at the time of the study last patient last visit (LPLV), whichever is earlier. This does not apply to subjects who discontinue treatment but remain on study.

During this phone call, the following information will be collected:

- PBC clinical outcomes that have occurred in the previous year.
- New PBC treatments that the subject may have been exposed to in the previous year.

If the site becomes aware of a PBC clinical outcome event before the time of the Annual Follow-up Call, the event should be communicated to the site and will be recorded, and the Annual Follow-up Phone call will not occur. Otherwise, the Annual Follow-up Phone calls will be expected until the time of the study LPLV.

8.2. Study Assessments

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying study manual and other administrative guides, which will provide the study site personnel with administrative and detailed technical information that does not impact subject safety.

8.2.1. Demographics

Demographic information will be collected and will include the subject's date of birth, age, sex, child-bearing status, race, and ethnicity.

8.2.2. Medical History and Physical Examination

A detailed medical history and PBC medical history will be taken at Screening. Information about prior medications and concomitant medications will be collected, including information about prior UDCA use or UDCA intolerance.

Complete physical examinations will be performed at Screening, Day 1, Month 6, Month 12, Follow-up, and Early Termination (if applicable) Visits. These will include a full review of the following systems: general, skin, eyes, nose/sinuses, ears, mouth/throat, neck, breasts (optional, per clinical judgment only), respiratory, cardiac, gastrointestinal, peripheral vascular, genitourinary (optional, per clinical judgment only), musculoskeletal, neurologic, mental health, endocrine, and hematologic.

Symptom-directed (brief) physical examinations will be performed at Run-in, Month 1, Month 3, Month 9, and UNS Visits. Brief physical examinations will be performed for a condition that warrants the examination as determined by the investigator. Subjects with platelet level above $500\times10^3/\mu L$ on hematology panel will be evaluated for thrombolytic events.

Ascites and Encephalopathy information will be requested as part of the physical examination at Month 1, Month 3, Month 6, Month 9, Month 12, Follow-up, and Early Termination (if applicable) Visits in support of the Child-Pugh score calculation.

Liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain and tenderness, fatigue, loss of appetite, dark urine, or jaundice) will be evaluated at each visit from Screening through Month 12 Visit or until the Follow-up Visit or Early Termination Visit (if applicable).

Subjects will be regularly evaluated for cirrhosis status per Appendix I and for PBC clinical outcomes as outlined in Section 11.

Subjects with symptoms consistent with acute pancreatitis will be educated to seek immediate medical care for evaluation for suspected acute pancreatitis.

Any clinically important change in physical examination findings that occurs after signing the ICF will be recorded as an AE.

8.2.3. Vital Signs and Weight/Height

Vital sign measurements include temperature, heart rate, respiratory rate, and blood pressure, recorded in the sitting position after at least 5 minutes of rest.

Vital signs and weight will be assessed on all in-clinic visits, from Screening through Month 12 Visit, or until the Follow-up Visit or Early Termination Visit (if applicable). Height measurement will be performed only at Screening.

Vital signs may be obtained more frequently if a condition that warrants additional monitoring develops.

8.2.4. Electrocardiograms

A 12-lead ECG will be obtained in supine position after at least 5 minutes of rest at Screening, Day 1, Month 6, Month 12, and Follow-up or Early Termination (if applicable) Visits.

8.2.5. Laboratory Tests

Blood samples for laboratory testing from Screening and onward will be collected at study visits after at least an 8-hour overnight fast and prior to dosing. If the subject forgets to fast, the site will record it in the source document, continue to draw laboratory tests, and proceed with the visit. Additional details about sample collection, processing, and handling and laboratory determination techniques are provided in the laboratory manual.

Laboratory tests will be collected at each study visit per the Schedule of Assessments (Table 1) and will include the following parameters (Appendix A).

Biochemistry:

ALP, AST, ALT, GGT, protein, albumin, total bilirubin, direct bilirubin, indirect bilirubin, 5'-nucliotidase, aldolase, sodium, potassium, chloride, bicarbonate, blood urea nitrogen/urea, serum creatinine, eGFR, creatine kinase (CK), venous blood glucose, lactate dehydrogenase, triglycerides, total cholesterol, HDL-C, LDL-C, cystatin C, troponin I, lipase, and amylase.

Hematology:

Erythrocyte count, hemoglobin, hematocrit, leukocyte count (WBC), WBC differential (absolute and percentage), platelets, PT, and INR.

PT and INR will also be performed locally at the Screening Visit, at the Run-in Visit, and during the Treatment Period if deemed necessary by the investigator.

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Other Testing: HBsAg, HCV RNA and HIV; vitamin A, vitamin D, vitamin E, and vitamin K; serum pregnancy testing (β-HCG) and urine pregnancy testing; and PK blood sample.

Back-up Blood Sample:

Blood samples collected during the study will be archived as back-up samples. These samples can be stored for up to 5 years following completion of the study and can be used to measure drug level and future research purposes related to the study drug and/or cholestatic liver diseases.

Urine Drug Screen:

Amphetamine, THC (11-nor-9-carboxy-delta-9-THC), cocaine, opiates, and phencyclidine.

Plasma concentrations testing:

Subjects will be invited to participate in a PK sample collection to evaluate plasma concentrations of seladelpar and its metabolites. Subjects who consent to participate in this PK sample collection will provide 1 predose (-30 minutes prior to dosing) and 2 postdose samples at 1 hour±30 minutes and 3 hours±30 minutes at Month 3 and Month 12, per the assigned schedule. For each sample collection timepoint, a total of 3 blood samples will be collected.

Time of PK blood collection and time of dosing will be recorded in the source document.

Sample collection, processing, and handling details are provided in the laboratory manual.

8.2.6. Abdominal Ultrasound

Abdominal ultrasound examination will be used to visualize the liver, gallbladder, common bile duct, portal vein, and spleen to detect anatomical structures and abnormalities. Ultrasound is a standard clinical procedure for subjects with liver diseases and uses transmission and reflection of ultrasound waves to visual internal organs through abdominal wall. Abdominal ultrasound will be used to determine changes in the examined organs over the study duration.

Abdominal Ultrasound Examination Schedule and Timing: Subjects will undergo 3 abdominal ultrasound examinations as follows: at the Run-in and Month 12/EOT Visits or at the Early Termination Visit (if applicable). Clinical sites will determine the logistics of scheduling the abdominal ultrasound and will complete the examination within the study visit window.

Abdominal Ultrasound Examination Instructions: Subjects will be instructed to fast for 8 or more hours (if possible) prior to the scheduled abdominal ultrasound examination but will be allowed to take necessary medications and small quantities of water.

Abdominal Ultrasound Examination Analysis: Local reader will review and analyze the scans.

8.2.7. Liver Elastography

The FibroScan examination will be used to evaluate ELF through a noninvasive imaging technique. FibroScan is the most commonly used liver elastography method. It uses a modified ultrasound probe to measure the velocity of a shear wave. Cross-sectional elastogram images will be created, depicting the stiffness generated from the wave propagation information. FibroScan is considered a reliable, highly accurate, and precise method for assessing hepatic fibrosis.

FibroScan Examination Schedule and Timing: Subjects will undergo 3 FibroScan examinations at sites when the test is available: Run-in, Month 6, Month 12, and Early Termination (if applicable) Visits. Clinical sites will determine the logistics of scheduling the FibroScan examination and will complete within the study visit window. Predose FibroScan examinations may be performed from the Run-In Visit (Week -2) to study drug dosing at Day 1.

FibroScan Examination Instructions: Subjects will be instructed to fast for 4 or more hours (if possible) prior to the scheduled FibroScan examination but will be allowed to take necessary medications and small quantities of water.

FibroScan Examination Analysis: Local reader will review and analyze the scans.

8.2.8. Liver Biopsy

Liver biopsy will be collected in subjects who consent during Screening Period (any time between Screening and Day 1) but only after confirmation of eligibility and at Month 12 or Early Termination Visit for subjects who discontinue treatment, provided that they have had a liver biopsy performed at baseline and at least 6 months of treatment. All biopsies will be collected, processed, fully masked, and evaluated by the PRC as specified in the histopathology plan. Pathology evaluation will be done fully blinded with respect to study site, subject ID, treatment, timepoint, and other subject clinical and laboratory information.

Consenting subjects who have had biopsy tissue collected within 6 months of screening may have that liver biopsy sample used instead of that from a screening period baseline biopsy provided it meets the quality requirements described in the Laboratory Manual. The medical monitor should be consulted to confirm the suitability of the sample.

Liver biopsy will be used to determine PBC stage and activity, using appropriate central reporting.

Pre-Liver Biopsy Instructions: The subject must have PT, INR, and platelets performed within 2 weeks prior to liver biopsy. Subjects will be instructed, if possible, to fast 6 to 8 hours prior to the scheduled liver biopsy.

Liver Biopsy Analysis: The PRC will review and analyze the biopsy samples in accordance with a histology plan (Section 16).

8.2.9. Pruritus Numerical Rating Scale

Pruritus NRS will be used as a key secondary measure to evaluate pruritus in subjects with PBC.

The test will be performed based on data collected via e-diary on a daily basis from the Run-in (Week -2) Visit and for the first 6 months of study drug treatment. After 6 months of treatment, pruritus NRS will be evaluated for 7 consecutive days each month up to EOT. See Appendix D for details.

Pruritus NRS data will be collected via e-diary.

8.2.10. 5-D Itch Scale

The 5-D Itch scale will be used as a secondary measure for the multidimensional quantification of pruritus over time. The 5-D Itch scale is a measure of itching that has been validated in patients with chronic pruritus to detect changes over time. It is a brief, single-page, multiple choice or “check all boxes that apply” form (22). See Appendix E for details.

The test will be performed based on data collected via e-diary on a biweekly basis from the Run-in Visit up until the Month 6 Visit and on a monthly basis from Month 6 until Month 12 or Early Termination Visit (if applicable).

The 5-D Itch data will be collected via e-diary.

8.2.11. PBC-40 QoL

The PBC-40 questionnaire will be used as a secondary measure to evaluate health-related QoL measures, specifically fatigue. PBC-40 is a disease-specific health-related QoL tool developed to measure specifically the psychometric profile of patients with PBC. It covers 6 domains relevant to PBC including cognitive, social, emotional function, fatigue, itch, and other symptoms (23). See Appendix F for details.

It will be performed at Run-in, Day 1, and Month 1 visits, and every 3 months after initiation of treatment until the EOT Visit or Early Termination Visit (if applicable). The questionnaire will be evaluated by the site personnel, and the investigator will react to any evidence of deterioration.

PBC-40 QoL data will be collected via e-diary.

8.2.12. PGI-S and PGI-C

The PGI-S and the PGI-C questionnaires will be used as an anchor scale to help interpret within-subject change in pruritus data collected via other pruritus questionnaires. The PGI-S evaluations will be performed at Run-in, Day 1, and Month 1 visits, and every 3 months after initiation of treatment until the EOT Visit or Early Termination Visit (if applicable). The PGI-C evaluations will be performed at Month 1 and every 3 months after initiation of treatment until the EOT Visit or Early Termination Visit (if applicable). See Appendix G and Appendix H for details.

9. ADVERSE EVENTS

9.1. Definition of Adverse Events

An AE is any medical occurrence in a subject administered a pharmaceutical product in a clinical study, regardless of a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

An AE includes any condition (including a pre-existing condition) that (1) was not present prior to study treatment but appeared or reappeared following initiation of the study treatment or (2) was present prior to initiation of the study treatment but worsened during study treatment. This would include any condition resulting from concomitant illnesses, reactions to concomitant medications, or progression of disease states. Pregnancy should be documented as an AE and should be immediately reported to the clinical monitor and to the sponsor upon learning of the event. Pregnancies will be followed up through delivery or termination of the pregnancy.

A TEAE will be defined as any AE that newly appeared, increased in frequency, or worsened in severity after initiation of the study drug until up to 17 days after the last study medication administration.

9.2. Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death.
- Is life threatening (was at risk of death) at the time of the event.
- Requires in-patient hospitalization or prolongation of an existing hospitalization.
- Results in persistent or important disability/incapacity, defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event that, when based on appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above in the definition for an SAE. Examples of such events include allergic bronchospasm, requiring intensive treatment at an emergency room or at home, blood dyscrasias, convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

9.3. Assessment of Adverse Events

9.3.1. Severity

The severity of an AE will be graded from 1 to 5 according to Appendix C and NCI CTCAE Version 5.0 criteria (27 November 2017). The CTCAE general guideline will be used to assess AE severity. Not all grades are appropriate for all AEs. Therefore, some AEs listed in the CTCAE have fewer than 5 options for grade selection.

Grade	Clinical Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3	Severe or medically important but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	Death related to AE

9.3.2. Outcome

Subjects will be followed until AEs have resolved, have returned to baseline status, or are deemed stable or commensurate with ongoing disease processes, per the investigator's clinical judgment. One of the 6 outcomes listed below must be recorded:

Recovered/Resolved – The subject has fully recovered from the event with no residual effects observable or returned to baseline status.

Recovered/Resolved with sequelae – The subject has recovered from the event with some residual effect's observable.

Not Recovered/Not Resolved – The subject or event has not recovered or resolved or shown further improvement after an appropriate time of follow-up.

Recovering/Resolving – The subject or event is still improving but has not fully recovered.

Fatal – Death

Unknown – Subject lost to follow-up

9.3.3. Relationship to Study Drug

The relationship or association of the AE to a study drug will be characterized as "**unrelated**," "**unlikely**," "**possible**," "**probably**," or "**definite**."

Relationship	Attribution	Description
Unrelated to the study drug	Unrelated	The AE is **clearly not related** to the study drug.
	Unlikely	The AE is **doubtfully related** to the study drug.
Related to the study drug	Possible	The AE **maybe related** to the study drug.
	Probable	The AE is **likely related** to the study drug.
	Definite	The AE is **clearly related** to the study drug.

9.3.4. Action Taken With Study Medication

As a consequence of an AE, the action taken with study drug (based on the NCI Thesaurus) can be as follows:

- Dose not changed: An indication that a medication schedule was maintained
- Drug withdrawn: An indication that a medication schedule was modified through termination of a prescribed regimen of medication
- Drug interrupted: An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication
- Dose reduced: An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength or amount
- Not applicable: Determination of a value is not relevant in the current context
- Unknown: Not known, not observed, not recorded, or refused

9.4. Recording, Reporting, and Follow-up of Adverse Events

9.4.1. Nonserious Adverse Events

Details about the safety reporting process are presented in the safety reporting plan.

All AEs must be recorded by the investigator in the eCRF, regardless of association with the use of the study treatment. An AE will be recorded any time after the time of signed ICF and will be captured until the last study visit.

To avoid colloquial expressions, the AE should be reported in standard medical terminology. Whenever possible, the AE should be evaluated and reported as a diagnosis rather than as individual signs or symptoms. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded.

For each AE, the investigator or an adequately qualified designee will evaluate and report the onset, duration, severity, seriousness, and relationship to (association with) the study treatment and will indicate the action taken.

Abnormal laboratory findings will be determined by review of all laboratory data collected on the subjects. At each visit, the investigator is responsible for assuring that the subject is questioned regarding all potential AEs and concurrent illnesses.

Any laboratory abnormality deemed clinically important by the investigator should be reported as an AE. A clinically important abnormality is a confirmed abnormality that is changed sufficiently from baseline, so that, in the clinical judgment of the investigator, a change in management is warranted. This alteration may include further monitoring the laboratory test, initiating other diagnostic tests or procedures, or administering treatment. Whenever possible, the etiology of the abnormal findings will be documented in the eCRF. Repeated, additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

Any clinically important laboratory abnormalities that are either unexplained or considered treatment-related should be promptly reported to the sponsor. Any additional relevant laboratory results obtained by the investigator during this study will be supplied to the sponsor and recorded in the eCRF.

9.4.2. Serious Adverse Events

The sponsor or designee is responsible for regulatory submissions and reporting to the investigators of SAEs including suspected unexpected serious adverse reactions (SUSARs) per the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines E2A and E6 and per the US 21 Code of Federal Regulations § 312.32. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines. Independent Ethics Committee (IEC) will be notified of any SAE according to applicable regulations.

Any SAE, including death due to any cause, that occurred from the signing of ICF through the last study visit, regardless of relationship to the study treatment, must be reported immediately (no later than 24 hours) by the investigator to the sponsor's representative (safety vendor) using the SAE Report Form. Planned hospitalizations or procedures will not be considered as SAEs.

The criteria for seriousness will be indicated on the SAE Report Form as defined in Section 9.2.

The outcome for the event will be listed on the SAE Report Form as defined in Section 9.3.2.

If additional information regarding a previously submitted SAE is obtained, a follow-up SAE must be sent to the sponsor's representative (safety vendor).

The sponsor and/or its designee will identify and report to regulatory authorities, within the required timeframes, all SUSARs and clinically important increases in rate of serious suspected adverse reactions.

SAEs must be collected and reported by the investigator for the whole period from the signing of ICF until the last study visit. If the event of death occurs after the last study visit, the death will not have to be reported as an SAE.

The investigator will document all available information regarding the SAE on the SAE Report Form. The investigator should not wait to receive additional information to document fully the event before notifying the sponsor's representative of an SAE. The initial notification should include, as a minimum, sufficient information to permit identification of the following:

- Subject's study number
- Time and date of study drug administrations
- Time and date of the start of the event and either the date and time of the resolution of the event or a statement that the event is ongoing
- A brief description of the event and counter-measures taken
- Investigator's opinion of the relationship of the event and the investigational product

Follow-up report(s) should follow the initial report detailing relevant aspects of the AEs in question. Where applicable, information from relevant hospital case records and autopsy reports should be obtained. All source information provided to the sponsor must be appropriately anonymized.

9.4.3. Follow-up on Reported AEs

SAEs recorded during the study should be followed by the investigator until resolution or stabilization.

After the Follow-up Visit, nonserious AEs should be followed up until they resolve or stabilize, for a duration determined by the investigator.

Follow-up procedures will be determined by the nature of the event and the judgment of the investigator.

9.4.4. Distribution of Responsibilities

Details about the distribution of safety responsibilities are presented in the safety reporting plan.

10. SAFETY MONITORING

Enrolled subjects with the following laboratory abnormalities should be monitored closely, and the dose may be decreased or the study drug may be interrupted and/or discontinued if criteria are met. The sponsor's medical monitor should be contacted as soon as possible if any of these events is observed.

10.1.1. Liver Safety Monitoring

Table 2 and Table 3 provide the algorithm that will be followed to assess potential drug-induced liver injury.

Table 2: DILI Criteria for Participants With Normal Baseline ALT and AST

Baseline	ALT or AST During Study Treatment Duration	Other Concurrent Parameters Required During Study Treatment Duration	Study Action
NORMAL BASELINE ALT and AST			
ALT, AST, and total bilirubin <1.0× ULN	ALT or AST >8× ULN	--	**Stop study drug permanently**[b]
	ALT or AST >5× ULN for more than 2 weeks	--	
	ALT or AST >3× ULN	**AND** total bilirubin >2× ULN **OR** INR >1.5	
	ALT or AST >3× ULN	**AND** clinical symptoms[a]	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; DILI=drug-induced liver injury; INR=international normalized ratio; ULN=upper limit of normal.

[a] Clinical symptoms associated with the study drug: appearance of fatigue, nausea, right upper quadrant pain or tenderness, fever, rash, jaundice, and/or eosinophilia (absolute count >1× ULN)

[b] Repeat AST, ALT, total bilirubin, and PT/INR within 3 days and closely observe the subject (see Appendix B)

Table 3: DILI Criteria for Participants With Abnormal Baseline ALT and AST

Baseline	ALT or AST During Study Treatment Duration	Other Concurrent Parameters Required During Study Treatment Duration	Study Action
ABNORMAL BASELINE ALT and AST			
ALT or AST >1.0× ULN	ALT or AST >2× BLM	AND concomitant total bilirubin >2 × BLM **OR** INR increase by 0.2	**Stop study drug permanently**[b]
	Regardless of ALT or AST levels	Clinical symptoms[a] **AND** concomitant total bilirubin (>2 × BLM)	
ALT or AST <2× ULN	ALT or AST >5× BLM	--	**Interrupt study drug**[b]
ALT or AST ≥2× ULN but <5× ULN	ALT or AST >3× BLM		
ALT or AST ≥5× ULN	ALT or AST >2× BLM		

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BLM=baseline measurement; DILI=drug-induced liver injury; INR=international normalized ratio; ULN=upper limit of normal.

[a] Clinical symptoms associated with the study drug: appearance of fatigue, nausea, right upper quadrant pain or tenderness, fever, rash, jaundice, and/or eosinophilia (absolute count >1× ULN).

[b] Repeat AST, ALT, total bilirubin, and PT/INR within 3 days and closely observe the subject (see Appendix B)

- **Interrupt study drug**: Repeat AST, ALT, total bilirubin, and PT/INR within 3 days and closely observe the subject (see Appendix B). Study drug can be restarted at the same dose level only if a firm competing etiology is identified and liver tests return to baseline. Down titration to a lower dose can also be considered at this time.
- **Stop study drug permanently**: Repeat AST, ALT, total bilirubin, and PT/INR within 3 days and closely observe the subject (see Appendix B).
- If close observation of a participant is not possible, stop study drug permanently.

10.1.2. Muscle Injury Safety Monitoring

Table 4 provides the algorithm that will be followed to assess potential drug-induced muscle injury.

Subjects with elevated CK levels >2.5× ULN should be initially queried for a possible clinical explanation (such as strenuous exercise, heavy labor, or traumatic injury), associated symptoms, and relationship to the study drug. Repeat CK level measurements within 3 days of initial CK elevation.

Subjects may continue to take the study drug if (1) a clinical explanation is identified and/or (2) the event is considered unrelated to study drug.

If no alternative clinical explanation is identified, the study drug will be interrupted, and the following algorithm should be followed to assess potential drug-induced muscle injury.

Table 4: Muscle Injury Safety Criteria for Study Drug Interruption or Stopping Rules

CK During Study Treatment	**Grade 3 CTCAE Myalgia or Myopathy**	**Repeat CK Test Results**	**Study Action**
CK >2.5× ULN	Not observed	CK level is ≤2.5× ULN	**Study drug may be reinitiated** at this time at the current dose level.
CK >2.5× ULN	Not observed	CK level is >2.5× ULN	Study drug should remain held and CK testing should be performed weekly until CK ≤2.5× ULN. **Study drug may then be reinitiated** as outlined in Section 6.1.1 of the study protocol.
CK >2.5× ULN	Observed	CK level is >2.5× ULN	Study drug should remain held and CK testing should be performed weekly until CK ≤2.5× ULN. **Study drug may then be reinitiated** at as outlined in Section 6.1.1 of the study protocol. If symptoms reappear after rechallenge and there is no clinical explanation, then the **study drug should be permanently discontinued**. The participant should continue to be routinely monitored until complete resolution of symptoms or study completion, whichever comes first.

CK=creatine kinase; CTCAE=Common Terminology Criteria for Adverse Events; ULN=upper limit of normal.

10.1.3. Renal Safety Monitoring

Table 5 provide the algorithm that should be applied to assess potential drug-induced renal injury. Repeat serum creatinine level measurements within 3 days of initial serum creatinine elevation.

Table 5: Renal Safety Criteria for Study Drug Interruption or Stopping Rules

sCr During Study Treatment	**Repeat sCr Test Results**	**Alternative Etiology Identified?**	**Study Action**
sCr >1.5× ULN but ≤2.0× ULN	sCr <1.5× ULN	N/A	**Continue study drug.**
	sCr >1.5× ULN	Yes	**Interrupt study drug.** Participant should be monitored weekly until event resolution. **Study drug may be reinitiated** after serum creatinine returns to baseline levels.
	sCr >1.5× ULN	No	**Interrupt study drug.** Participant should be monitored weekly until event stabilization or resolution. **Study drug may be reinitiated** after serum creatinine returns to baseline levels. If serum creatinine increases after re-initiation of study drug, s**top study drug permanently**
sCr >2.0× ULN	sCr >2.0× ULN	N/A	**Stop study drug permanently.** Participant should be monitored weekly until event stabilization or resolution.

N/A=not applicable; sCr=serum creatinine; ULN=upper limit of normal.

10.1.4. Pancreatic Safety Monitoring

As shown in Table 6, subjects with elevated amylase and/or lipase >3× ULN should be initially queried for symptoms of acute pancreatitis, possible clinical explanation (such as chronic pancreatitis), and relationship to study drug. Repeat amylase and lipase within 3 days of initial elevation.

Table 6: Pancreatic Safety Criteria for Study Drug Interruption or Stopping Rules

Amylase or Lipase During Study Treatment	Symptoms of Acute Pancreatitis?	Repeat Amylase or Lipase Test Results	Actions to Be Taken
Amylase or lipase >3× ULN	No	Amylase or lipase ≤ 3× ULN	**Continue study drug.**
	No	Amylase or lipase >3× ULN	**Interrupt study drug.** Perform computed tomography or magnetic resonance imaging to rule out pancreatitis Monitor weekly until event resolution unless an alternative etiology is known. Study drug may be restarted if alternative etiology is identified as outlined in Section 6.1.1.
Amylase or lipase >3× ULN	Yes	Amylase or lipase	**Interrupt study drug.** Perform computed tomography or magnetic resonance imaging Monitor weekly until event resolution unless an alternative etiology is known (see Clinical practice guideline: management of acute pancreatitis for suggested management guidelines) (25) Study drug may be restarted if alternative etiology is identified, episode is resolved, and amylase and lipase are normalized as outlined in Section 6.1.1.

ULN=upper limit of normal.

10.1.5. Additional Withdrawal Criteria and Replacement of Subjects

Subjects may be discontinued from study drug intake for the following reasons. Subjects who discontinue study drug treatment anytime will be terminated from the study and will complete an Early Termination Visit. Subjects who discontinue from the study before Month 12 will be asked to be followed for PBC clinical outcomes on an annual basis unless occurrence of a PBC clinical outcome.

- Enrolled into the study in violation of this protocol.
- Required the use of a prohibited concomitant medication.
- Subject experienced a PBC clinical outcome.
- Grade 3 events and above not already described by the Safety Monitoring criteria and related to study drug: any subject will be discontinued from the study drug that experiences a CTCAE grade 3 or higher that is considered possibly or probably related to study drug.
- Grade 4 events not already described by the Safety Monitoring and not related to study drug: any subject will be considered for discontinuation from the study drug. The Investigator, in consultation with the Sponsor's medical monitor, may consider

specific medical nature of the event, the causality assessment, and possible outcome of the event. An imminent resolution or improvement in the event, so that the subject would be suitable for the clinical study and it would be both safe and in their best interest to continue or restart study drug, the study drug may be continued.

- The subject should be informed of new approved and available treatment to make an informed decision regarding continuation in the study. The availability of a new standard of care does not automatically terminate a subject from study participation.
- Withdrawal of informed consent.
- At the discretion of the investigator for medical reasons.
- Female subjects who become pregnant.
- At the discretion of the investigator or sponsor for noncompliance.

11. PBC CLINICAL OUTCOMES

Subjects will be assessed for the PBC clinical outcomes as outcomes during participation in the study. Subjects who met one of the PBC clinical outcomes will be discontinued from the study (i.e., will complete an Early Termination Visit).

All subjects who discontinued study drug treatment for any reason other than a defined PBC clinical outcome and decline to stay in the study without study drug intake before Month 12, or who do not participate in the long-term study will be followed to collect information about PBC clinical outcomes on an annual basis per Section 8.1.7.

PBC clinical outcomes will be defined as follows:

a. Overall death
b. Liver transplantation
c. MELD score ≥15 for at least 2 consecutive visits.* For subjects who are on anticoagulation medication, the effect on INR as a secondary consequence of anticoagulation therapy will be taken into account for its impact on MELD score (both at baseline and on treatment) when determining if this Outcome has been met. Subjects should be carefully monitored to ensure the adjusted INR on the anticoagulant therapy is maintained at a stable value.
d. Ascites requiring treatment
e. Hospitalization for new onset or recurrence of any of the following:
    i. Variceal bleeding
    ii. Hepatic encephalopathy (as defined by a West Haven score ≥2)
    iii. Spontaneous bacterial peritonitis (confirmed by culture from diagnostic paracentesis)

*In subjects who reach a MELD score ≥ 15, repeat laboratory tests to assess serum creatinine, total bilirubin, INR, and sodium and recalculate the MELD score should be done

within 7 days to confirm the initial findings to evaluate for decompensation and determine if therapy should be discontinued.

12. STUDY STOPPING CRITERIA

The entire study may be discontinued at the discretion of the sponsor based on the occurrence of the following:

- AEs with respect to their nature, frequency, severity, and/or duration
- Medical or ethical reasons affecting the continued performance of the study
- Cancellation of seladelpar drug development

The Data Safety Monitoring Board (DSMB, Section 14) will consider if the study should continue when any of the following occur:

- 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

13. PRECAUTIONS

13.1. Pregnancy

No specific human clinical studies have been performed to determine the reproductive and developmental toxicity of seladelpar.

As a precaution, women of child-bearing potential receiving study drug must use 1 barrier contraceptive and a second effective birth control method during the study and for at least 90 days after the last dose. Male subjects who are sexually active with female partners of reproductive potential must use barrier contraception, and their female partners must use a second effective birth control method during the study and for at least 90 days after the last dose. Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

A second effective birth control method may include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:

  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner

14. DATA SAFETY MONITORING BOARD

An independent DSMB will be established in order to protect subjects' welfare, preserve study integrity, and provide recommendations as needed regarding study conduct. The DSMB will be composed of 2 external liver disease clinical experts and a biostatistician. The DSMB will meet at predefined time points and on an as-needed basis based on enrollment, treatment milestones, and safety. The DSMB will also review all SAEs, liver-related safety events, and elevations in ALT/AST, serum creatinine, CK, and lipase that meet safety monitoring criteria. Formal minutes and recommendations will be provided by the DSMB to the sponsor regarding additional data requests and the continuation of the conduct of the study as outlined in the current protocol. The DSMB will operate under the guidance of an agreed upon charter. Details of the format, content, and frequency of these meetings will be described in a DSMB charter.

The DSMB will consider if the study should continue when any of the following occur:

- 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

15. CLINICAL EVENT REVIEW COMMITTEE

A CERC will be established to act as an expert, independent capacity to review fatal events, hepatic events, and disease progression that occur during the course of the study (Section 11) to determine if events meet the prespecified event definitions. The members of the CERC will be composed of 3 independent hepatologists and/or gastroenterologists.

A CERC charter will be developed to establish predefined critical event definitions and procedures that will be followed. The CERC members will evaluate whether critical event definitions are met during independent voting and will remain blinded to treatment assignment.

16. PATHOLOGY REVIEW COMMITTEE

The evaluation of liver biopsy tissue from subjects with PBC is intended to provide an important component of a comprehensive safety dataset to evaluate treatment effects of seladelpar in its PBC development program.

A PRC will be formed and will consist of at least 3 experienced hepatopathologists, who will serve as the blinded pathologists to read biopsies collected during the study.

The PRC will be responsible for selecting the scoring system, approving the biopsy reading process, and establishing a framework for evaluating biopsies based on scoring that may guide selection of cases for adjudication, if necessary. Collectively, these will be translated to a histopathology plan that will also outline and standardize procedural recommendations for collection of the liver biopsy, the biopsy slide preparation, and staining.

17. STUDY TERMINATION

CymaBay Therapeutics, Inc. reserves the right to discontinue the study if it becomes aware of information concerning the quality, safety of the study medication (based on recommendation from medical monitor), and other important information that may affect proper conduct of the study. Should the study be discontinued by the sponsor, then the investigator, IEC, and competent authorities will be notified by the sponsor or sponsor's delegate, in accordance with applicable regulatory regulations.

The study may be prematurely terminated by the principal investigator at his/her site, due to specific clinical observations relating to safety concerns. If the principal investigator intends to prematurely terminate the study at his/her site, he/she must immediately inform the sponsor on his/her intention and of the reasons why.

CymaBay Therapeutics, Inc. reserves the right to discontinue the study at any time for administrative reasons.

18. DATA HANDLING CONSIDERATIONS

18.1. Processing of Electronic Case Report Forms

The study will be performed using electronic data capture. The investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs. Any change or correction to the eCRF after saving must be accompanied by a reason for the change. Corrections made after the investigator's review and approval (by means of a password/electronic signature) will be reapproved by the investigator. The investigator should maintain a list of personnel authorized to enter data into the eCRF. The investigator will maintain a Site Delegation Personnel Log to document signatures and initials of all persons qualified and authorized by the investigator to make entries and/or corrections to the source documents.

18.2. Database

Data entry will be performed through username- and password-protected access to a secure database. All data will be entered using eCRFs. Internally developed programs for plausibility, consistency, and out-of-range data fields will supplement the review of the data. A manual review of AEs, drug accountability, and termination summary data will be performed by data management personnel. The Medical Dictionary for Regulatory Activities (MedDRA) coding

thesaurus will be used to classify AEs and medical history, and the World Health Organization Drug classification will be used to code medications.

eCRFs will be available for review by the sponsor and sponsor's designee after completion by the site. The eCRFs will be monitored remotely and/or onsite by the sponsor, Contract research organization (CRO), or other sponsor designee after documented training and in accordance with the monitoring plan.

The completed eCRF must be electronically reviewed, signed, and dated by a qualified physician who is designated as principal or sub-investigator for the study. The investigator must retain the original source documents. A final pdf of the eCRFs will be provided to the study site by the CRO or designee at the end of the study for archival purposes.

An electronic audit trail system will be maintained within the eCRF to track all data changes in the database once the data have been saved initially into the system or electronically loaded.

18.3. Data Discrepancies

After all subjects complete the study and data discrepancies are resolved, protocol deviations during both enrollment and study execution will be reviewed. Clinically important protocol deviations and procedural discrepancies will be discussed.

19. STATISTICAL ANALYSIS

19.1. General Statistical Considerations

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using Statistical Analysis System Version 9.4 or higher. Unless specified otherwise, statistical tests will be conducted at the 2-sided 0.05 significance level (alpha), and all confidence intervals (CIs) will be reported as 2-sided 95%.

Descriptive statistics will be displayed by treatment group to provide an overview of the study results. For categorical parameters, the number and percentage of subjects in each category will be presented in data summaries. The denominators for percentages will be based on the number of subjects (n) appropriate for analysis. Continuous variables will generally be summarized based on the following: n, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized using frequency tabulations (number and percentage of subjects). Time-to-event data will be summarized using counts and Kaplan-Meier estimates with standard errors, where appropriate. All data will be listed for all subjects.

19.2. Determination of Sample Size

For purposes of sample size estimation, the placebo group response rate is estimated as 20%. The seladelpar 10-mg dose group response rate is 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 will provide >90% power to detect a difference between the 10-mg seladelpar group and the placebo group.

The key secondary efficacy analysis of normalization of ALP is 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 will provide >90% power to detect a difference between the seladelpar and placebo groups, based on a Fisher's exact test at a 0.05 level of significance.

The key secondary efficacy analysis of change from baseline in weekly averaged pruritus NRS at Month 6 sample size calculation is based on a 2-sample 2-sided t-test with a significance level of 0.05. The standard deviation is estimated as 2. Under these assumptions, as well as a total of 48 randomized subjects having a baseline NRS ≥4, this test provides >80% power to detect a treatment difference of ≥2 between 10-mg seladelpar and placebo groups.

The stated power calculations are based on previous results from Study CB8025-31735 as well as an assumed dropout rate of approximately 10%.

Randomization will be centralized to ensure adequate blinding of the study.

19.3. Analysis Sets

19.3.1. Safety Analysis Set

The safety analysis set is defined as any subject who receives at least 1 dose of study drug. Subjects will be included in the group based on treatment received, if this should differ from the treatment assignment. All safety analyses will be completed using the safety analysis set.

19.3.2. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set is defined as any subject who is randomized into the study and receives at least 1 dose of study drug. The ITT analysis set will be the primary analysis set used for efficacy analyses, with the exception of secondary endpoints evaluated for subjects with moderate to severe pruritus.

19.3.3. Modified Intent-to-Treat Biopsy Analysis Set

The modified intent-to-treat biopsy (mITTb) analysis set includes any subject who is in ITT analysis set and has a baseline and Month 12/ET biopsy. The mITTb analysis set will be used to examine the histology changes or the lack thereof.

19.3.4. Moderate to Severe Pruritus NRS Analysis Set

The moderate to severe pruritus NRS (MSPN) analysis set includes any subjects who is in the ITT analysis set and has a baseline NRS value ≥4. The MSPN analysis set will be the primary analysis set for secondary endpoints based on NRS evaluations.

Subjects in the ITT and MSPN analysis sets will be analyzed according to randomized treatment assignment.

19.3.5. Per-Protocol Analysis Set

The per-protocol (PP) analysis set includes any subject who is in the ITT analysis set, has at least 1 postbaseline ALP and total bilirubin evaluation, and does not have a protocol violation that is deemed to impact the efficacy analysis. Selected analyses of efficacy will be conducted using the PP analysis set.

19.3.6. Pharmacokinetics Analysis Set

The pharmacokinetics analysis set includes any subject who participates in the PK sample collection.

19.4. Analysis Time Points

Unless stated otherwise, baseline values will be based on the last non-missing assessment evaluated prior to the first administration of study drug. Baseline for chemistry and hematology measures will be calculated as the arithmetic mean of multiple pretreatment measurements (Screening, Run-in, Day 1, and unscheduled assessments) preceding the first administration of study drug. Baseline pruritus NRS is defined as the mean of all daily recorded scores during the Run-in Period.

Unless otherwise noted, all references to Day 1 refer to the day of study drug initiation for analytical purpose.

The final analysis will take place after the last subject visit at Month 12 (or Early Termination).

19.5. Disposition, Demographics, and Baseline Characteristics

The number of subjects screened, and the number and percentage of those subjects who were screen failures, broken down by primary reason for Screening failure will be presented.

Demographics and baseline characteristics (medical histories, physical examinations, and concomitant medications) will be summarized using descriptive statistics for continuous variables and frequency distributions for discrete variables.

Study subjects who discontinue the study along with reasons for discontinuation will be summarized and listed.

19.6. Efficacy Analysis

All efficacy analyses will be conducted on the ITT analysis set. Analysis details for instances in which data present differently from testing assumptions will be provided in the SAP. Additional sensitivity and supplementary analyses will be performed for the primary and key secondary endpoints, as applicable. Subgroup analyses will be defined in the study SAP. Unless specified otherwise, data collected following treatment discontinuation will not be included in data summaries or inferential analyses.

19.6.1. Primary Efficacy Analysis

The primary efficacy analysis for the proportion of subjects who are considered responders will be based on the proportion of subjects achieving the following composite endpoint evaluated at 12 months:

- ALP <1.67× ULN
- ALP decrease of ≥15%
- Total bilirubin ≤1.0× ULN

Any subject who does not provide an assessment at, or has discontinued treatment prior to, the specified time point for response evaluation or who otherwise has missing data will be considered a nonresponder. Analyses for the composite endpoint will be completed using a Cochran-Mantel-Haenszel (CMH) test. The CMH analysis will be stratified by the randomization stratum and will be conducted on the ITT analysis set. The risk difference and 95% CI using Miettinen and Nurminen will also be provided. Statistical significance of the difference between placebo and seladelpar will be defined as a 2-sided $p \leq 0.05$.

19.6.2. Key Secondary Efficacy Endpoint Analysis

The key secondary efficacy analysis for the proportion of subjects who achieve normalization of ALP at 12 months will be conducted in the ITT analysis set using the same approach specified for the primary efficacy analysis.

Change from baseline in weekly averaged pruritus NRS at 6 months will be analyzed using a mixed-effect model for repeated measures (MMRM) for subjects in the MSPN analysis set. The model will include baseline NRS, randomization stratum, treatment group, week, and treatment-by-week interaction term. Treatment by baseline interaction will be explored and added as a term if interaction is noted to be present. LS means for the change by treatment and the associated standard errors, the LS means for the difference between treatment groups, and the associated 2-sided 95% CIs and 2-sided p-values, based on t-tests, will be derived from the MMRM model. Specifically, efficacy endpoints will be evaluated using the estimated treatment difference in mean change from baseline NRS for the week associated with their specified month. An

unstructured covariance matrix will be tried first. If the model fails to converge, compound symmetry will be used in place of an unstructured covariance. The Kenward-Roger correction for the denominator degrees of freedom will be applied.

Type I error for the key secondary efficacy analyses will be maintained using a hierarchical fixed-sequence methodology. The fixed-sequence approach for the primary and key secondary analyses is as follows:

10. If the primary efficacy analysis is positive for seladelpar 10 mg versus placebo at a 2-sided 0.05 significance level, then the 2 key secondary endpoints will be analyzed hierarchically in the following order:
11. Normalization of ALP at Month 12 (seladelpar 10 mg versus placebo): If negative at a 2-sided 0.05 significance level, no further inferential testing will be performed. Otherwise, if positive, then testing will proceed.
12. Change from baseline to Month 6 in pruritus NRS (seladelpar 10 mg versus placebo) will be evaluated at a 2-sided 0.05 significance level.

19.6.3. Other Secondary Efficacy Endpoint Analysis

CCI [redacted]

19.6.4. Exploratory Efficacy Endpoint Analysis

CCI [redacted]

19.6.5. Sensitivity Analysis for the Primary and Key Secondary Efficacy Endpoints

Detailed descriptions of dropouts and missing data handling will be described in the SAP. All efforts will be made to prevent missing data from occurring.

Sensitivity analyses will be performed on the primary and key secondary efficacy responder endpoints using observed data only. The robustness of the primary analysis will be explored using several sensitivity analyses on a variety of patient populations.

For efficacy endpoints that utilize MMRM, observed cases will serve as the primary analysis. The robustness of the primary and key secondary analyses will be explored using sensitivity analyses to assess the effect of missing data.

The following sensitivity analyses will also be performed, where applicable:

- Same as primary analysis except based on the PP analysis set.
- Tipping point analysis and other sensitivity approaches will be performed in the primary and key secondary efficacy endpoint analyses and will be described in the SAP.

19.7. Safety Analysis

All safety analyses will be based on the safety analysis set.

AEs will be coded based on the MedDRA. TEAE incidence will be summarized by MedDRA system organ class and preferred term by severity and by causal relationship to study drug. The severity of TEAEs will be graded based on NCI CTCAE Version 5.0.

Safety laboratory parameters, liver fibrosis scores, vital signs, body weight, and body mass index values (absolute and change from baseline) will be summarized by treatment group using descriptive statistics at baseline and at each postbaseline visit.

Further details of the safety analysis will be provided in the SAP.

19.8. Pharmacokinetic Analysis

Descriptive statistics will be provided for the concentrations-versus-time data per visit number for seladelpar and metabolites per visit. Further, pooling of the concentration data from this study with data from other studies will be done to facilitate development and/or updating of a population PK model and will be reported separately.

20. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

20.1. Study Monitoring

20.1.1. Source Documents

The investigators and institution(s) will permit study-related monitoring of the eCRF data by CymaBay Therapeutics, Inc. or their assignee by providing direct access to source data and/or documents. A study monitor will conduct onsite and/or remote monitoring visits, in accordance with the monitoring plan, to review the eCRF data against the source data/documents for completeness and accuracy. Remote access to source data will be provisioned only under approved country regulations and subject consent. Remote access to source data may include email, remote access to the electronic medical record (EMR), video calls, or teleconferences with the investigator/designee.

20.1.2. Case Report Forms

Subjects who have signed the ICF will be assigned a subject number and will have study data entered into a CRF. CRF completion is important to the medical monitoring of the study and should be completed promptly after each subject visit.

20.1.3. Protocol Deviations

Protocol deviations are not permitted, and protocol waivers will not be granted. Deviations to the protocol should be avoided, except when the investigator considers subject safety to be at risk if action is not taken. The sponsor is to be notified of any protocol deviations that occur.

Deviations from the protocol will be noted in the source documentation, in the eCRF, and in a complementary database. Protocol deviations related to missing protocol-specified information, missed visits or data collection, alternative visits, delays, etc., that occur in relation to COVID-19 will be designated as such and captured in the source, eCRF, and complementary database. Administrative study guidance will outline how this information will be handled. The sponsor will assess any protocol deviation and decide whether any of these noncompliance's should be reported to regulatory authorities as a serious breach of ICH Good Clinical Practice (GCP) and the protocol.

20.2. Audits and Inspections

20.2.1. Study Auditing

Regulatory authorities, IEC, and/or CymaBay Therapeutics, Inc. or its designee(s) may request access to all source documents, eCRF data, and other study documentation for onsite or remote audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

It is understood that all subject-specific information is confidential and that no documentation that can link study information to the specific subject will be collected or retained by the sponsor.

20.2.2. Study Monitoring

A sponsor representative will visit the site at regular intervals and as managed under the risk-based monitoring approach, which is considerate of onsite source document verification and remote review (no source) options. Available medication dispensing and clinical drug supply records will be verified by the study monitor. It is understood that all subject-specific information is confidential and that no documentation that can link study information to the specific subject will be collected or retained by the sponsor. Remote source document verification may only occur in business critical situations when onsite source data verification cannot occur timely (e.g., database lock and subject safety) and only under approved country regulations and subject consent. Remote source document verification solutions may include encrypted email, remote access to the EMR, video calls, or teleconferences with the investigator.

20.3. Ethics Committees

The investigators will provide IEC with all information impacting the risk profile of the drug. The study will not commence until written IEC approval for the protocol and ICF is received by the sponsor. The investigator has the responsibility to conform to all of the local requirements for periodic updates and notification to the committee.

21. QUALITY CONTROL AND QUALITY ASSURANCE

Clinical data will be recorded in eCRF. Data will be verified and confirmed by the investigators.

All data that will be used in the safety analyses and AEs will be source documents verified by the monitors. Additionally, the sponsor will conduct audit reviews of monitored eCRFs.

A final audit of the electronic database against the final eCRF will be done.

22. ETHICS

22.1. Ethics Review

The protocols, ICFs, any information provided to the subject, recruitment advertisements, and any amendments to these items must be reviewed and approved by the IEC prior to their use in the study.

The study will not start before written approval by IEC(s) has been obtained and compliance with the local regulatory requirements has been accomplished.

The IEC must meet all the appropriate ICH requirements for composition, documentation, and operational procedures.

22.2. Ethical Conduct of the Study

The study will be conducted in strict accordance with the Declaration of Helsinki, ICH GCP guidelines, applicable laws and regulations, and the procedures outlined in IEC-approved version of this protocol.

22.3. Informed Consent

Subjects must give consent to participate in the study only after having been fully informed by the investigator or a person designated by him/her of the nature, significance, and implications of the study, as well as the associated risks involved. Such meetings must be carried out on an individual basis and must be adapted to the educational background and previous knowledge of the subject. Participation in this meeting should be documented in the subject's file. The subject must be allowed ample time to inquire about details and to decide whether to participate in the study. Informed consent will be obtained from all subjects enrolled in the study and before study-related activities are performed on a subject. The process of obtaining informed consent will be documented in the source documents of the subject. Only ICFs approved by the IEC will be used.

The ICF must be dated and signed by both the investigator and the subject. Electronic signature may be provided if acceptable by local authorities.

23. RETENTION OF RECORDS

All study-related material, including source documents, eCRFs, competent authority and IEC correspondence and analyses, and any other documentation required by applicable laws and regulations will be maintained for 15 years after completion of the study or notification from the sponsor that the data can be destroyed, whichever comes first.

24. PROTOCOL AMENDMENTS

Any change or addition to this protocol will only be made when a protocol amendment has been written, approved, and signed by CymaBay Therapeutics, Inc. and the principal investigator before the change or addition can be considered effective. This amendment must also be submitted to the IEC for approval and, when necessary, competent authority approval before implementation. Protocol amendments may affect consent forms of current and future subjects. CymaBay Therapeutics, Inc. will clearly specify when a protocol amendment includes safety, procedural, and/or efficacy information that will require specific ICF text changes.

25. DISCLOSURE OF INFORMATION AND PUBLICATION POLICY

Information concerning the investigational medication and patent application processes, scientific data, or other pertinent information is confidential and remains the property of CymaBay Therapeutics, Inc. The investigator may use this information for the purposes of the study only. It is understood by the investigator that CymaBay Therapeutics, Inc. will use the information developed in this clinical study in connection with the development of the investigational medication and, therefore, may disclose it as required to other clinical investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the sponsor.

The investigator may not submit for publication or presentation the results of this study without first receiving written authorization from CymaBay Therapeutics, Inc. CymaBay Therapeutics, Inc. agrees that, before it publishes any results of the study, it shall provide the investigator with at least 30 days for review of the prepublication manuscript prior to the submission of the manuscript to the publisher.

26. REFERENCES

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APPENDIX A. LABORATORY EVALUATIONS

Biochemistry

ALP	Direct bilirubin	Bicarbonate	LDH
AST	Indirect bilirubin	BUN/urea	TG
ALT	Aldolase	Serum creatinine	Total cholesterol
GGT	Sodium	eGFR	HDL-C
Protein	Potassium	CK	LDL-C
Albumin	Chloride	Venous blood glucose	Amylase
Total bilirubin	Cystatin C	Troponin I	Lipase
5'-nucleotidase			

Hematology

RBC
Hemoglobin
Hematocrit
WBC
WBC differentials (abs and %)
Platelets
PT/INR

CCI

CCI

Other Tests

Serum pregnancy test
Back-up sample
HBsAg (Screening only)
HCV RNA (Screening only)
HIV (Screening only)
PK blood sample
Vitamin A (D1, M12, and ET only)
Vitamin D (D1, M12, and ET only)
Vitamin E (D1, M12, and ET only)
Vitamin K (D1, M12, and ET only)
Urine drug screen (Screening only)
Urine pregnancy test

APPENDIX B. CLOSE OBSERVATION CRITERIA

The "close observation" will be performed on subjects meeting liver safety monitoring criteria Section 10.1.1. If "close observation" is not feasible, study drug must be stopped.

13. Comprehensive medical history and health status review
    a. Provide detailed history of current liver-related symptoms (e.g., right upper quadrant pain or tenderness, nausea, vomiting, fatigue, loss of appetite, dark urine, or jaundice).
    b. Provide all current diagnoses, diseases, procedures, and symptoms.
    c. Provide comprehensive medical history including prior diagnoses, procedures and symptoms.
    d. Provide concomitant drug use, including prescription medications, nonprescription medications, herbal supplements, dietary supplements, alcohol use, recreational drug use, special diets, and exposure to environmental chemical agents.
    e. Provide comprehensive medication and drug use history, including nonprescription medications, herbal supplements, dietary supplements, alcohol use, recreational drug use, special diets, and exposure to environmental chemical agents.
14. Laboratory testing
    a. Repeat ALT, AST, bilirubin (total), and PT/INR within 3 days.
    b. Monitor the subject every 3 days until the laboratory abnormality stabilization.
    c. After laboratory abnormality is stabilized, monitor the subject once a week until the event resolution.
15. Rule out the following diagnoses:
    a. Acute viral hepatitis types A, B, C, D, and E.
    b. Autoimmune or alcoholic hepatitis.
    c. NASH.
    d. Hypoxic/ischemic hepatopathy.
    e. Biliary tract disease besides PBC.

APPENDIX C. NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The NCI CTCAE will be used to assess an AE severity.

The NCI CTCAE will be provided as a separate document with the study protocol.

The NCI CTCAE may also be accessed here:

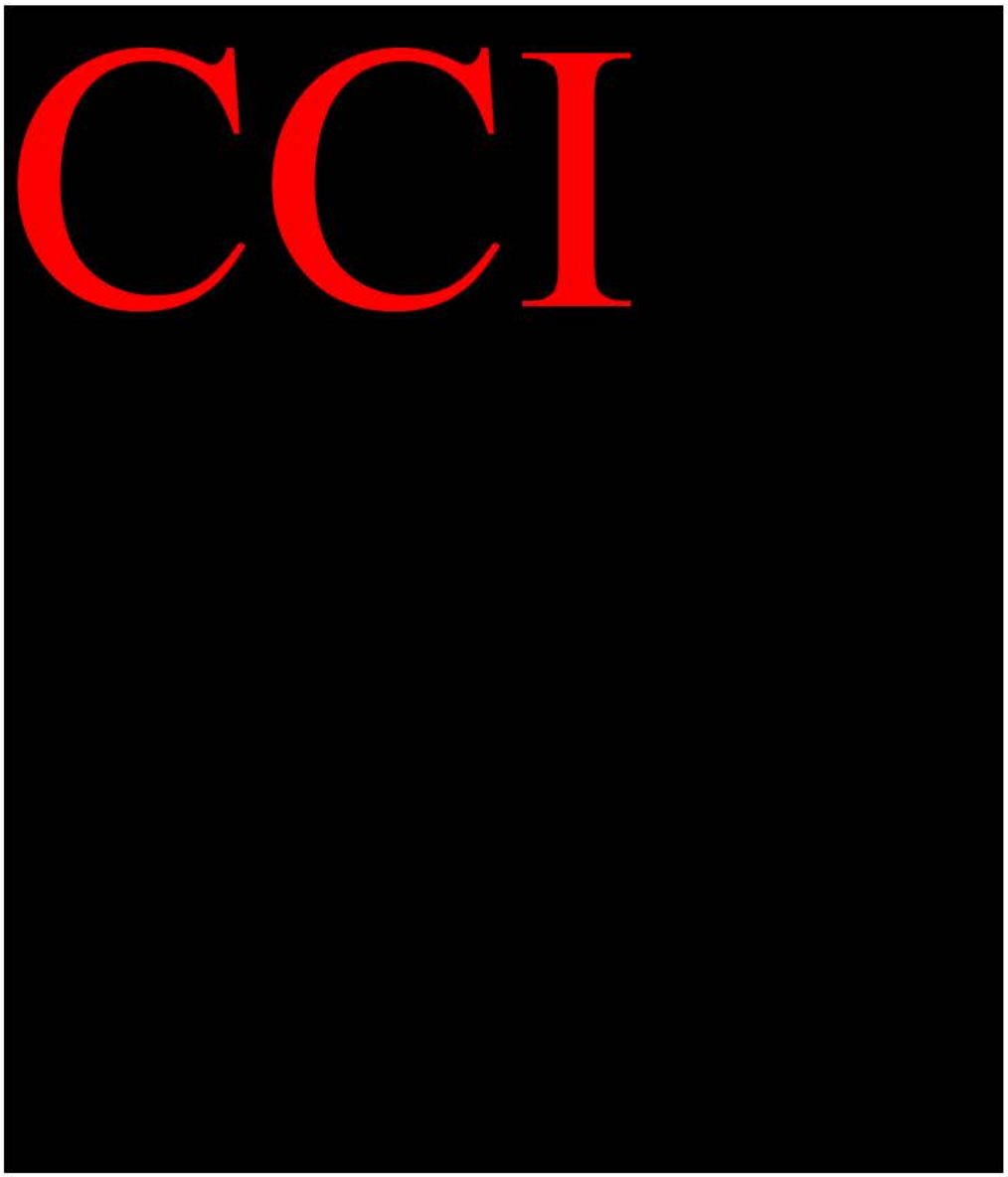
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

APPENDIX D. PRURITUS NRS

Rate the intensity of the worst itching you experienced in the past 24 hours from no itching to worst possible itching by selecting a number.

Itch Scale

0	1	2	3	4	5	6	7	8	9	10
No itching										Worst imaginable itching


CCI


CCI


CCI


CCI

APPENDIX G. PATIENT GLOBAL IMPRESSION OF SEVERITY

Please choose the response below that best describes the severity of your pruritus over the past week.

- None
- Mild
- Moderate
- Severe

APPENDIX H. PATIENT GLOBAL IMPRESSION OF CHANGE

Please choose the response below that best describes the overall change in your pruritus since you started taking the study drug.

- Very much better
- Moderately better
- A little bit better
- No change
- A little worse
- Moderate worse
- Very much worse

APPENDIX I. CIRRHOSIS DETERMINATION

For the study purposes, cirrhosis will be defined using the following criteria (one or more):

- Historical liver biopsy demonstrating cirrhosis (e.g., Ludwig Stage 4 or Ishak Stage 5)
- Current or prior history of decompensated liver disease, including ascites, hepatic encephalopathy, esophageal varices, or other clinical conditions consistent with liver cirrhosis and/or portal hypertension,
- Liver stiffness >16.9 kPa by FibroScan at screening
- Combination of platelets $<140\times10^3/\mu L$ with the following:
  - Serum albumin <3.5 g/dL
  - INR >1.3 (not due to antithrombotic agent use)
  - Total bilirubin >1.0×ULN
- The presence of radiological evidence of cirrhosis (nodular liver) with concurrent splenomegaly)
- Clinical determination by the investigator

APPENDIX J. NORMAL RANGES FOR SAFETY LABORATORY PARAMETERS

BIOCHEMISTRY	Conventional Units	SI Units
ALP	37-116 U/L	37-116 U/L
Albumin	3.5-5.5 g/dL	35-55 g/L
ALT	6-41 U/L	6-41 U/L
AST	9-34 U/L	9-34 U/L
GGT	Female : 7-38 U/L Male : 11-52 U/L	Female : 7-38 U/L Male : 11-52 U/L
Protein	6.0-8.0 g/dL	60-80 g/L
Total Bilirubin	0.10 – 1.10 mg/dL	1.7-18.8 umol/L
Direct Bilirubin	0.00-0.20 mg/dL	0.0-3.4 umol/L
Indirect Bilirubin	0.10- 1.00 mg/dL	1.7-17.1 umol/L
Aldolase	<7.7 U/L	<7.7 U/L
Sodium	134-144 mmol/L	134-144 mmol/L
Potassium	3.5-5.1 mmol/L	3.5-5.1 mmol/L
Chloride	95-110 mmol/L	95-110 mmol/L
Bicarbonate	21-33 mmol/L	21-33 mmol/L
BUN/Urea	5-22 mg/dL	1.79-7.85 mmol/L
Serum Creatinine	Female : 0.49-1.12 mg/dL Male : 0.62-1.44 mg/dL	Female : 43-99 umol/L Male : 55-127 umol/L
CK	Female : 26-192 U/L Male : 39-308 U/L	Female : 26-192 U/L Male : 39-308 U/L
Venous Glucose	60-115 mg/dL	3.3-6.4 mmol/L
Troponin I	<0.3 ng/mL	<0.3 ug/L
LDH	113-226 U/L	113-226 U/L
TG	50-150 mg/dL	0.57-1.70 mmol/L
Total Cholesterol	100-200 mg/dL	2.59-5.18 mmol/L
HDL-C	35-60 mg/dL	0.91-1.55 mmol/L
LDL-C	50-130 mg/dL	1.30-3.37 mmol/L
Amylase	22-123 U/L	22-123U/L
Lipase	11-82 U/L	11-82 U/L
5'-nucleotidase	0 - 15 U/L	0 - 15 U/L
Cystatin C	0.49-1.19 mg/L	0.49-1.19 mg/L
eGFR	18-49y : >60 mL/min/1.73m^2 >=50y : >=49 mL/min/1.73m^2	18-49y : >60 mL/min/1.73m^2 >=50y : >=49 mL/min/1.73m^2
HEMATOLOGY		
RBC	Female : 3.90 – 5.40 10^6/uL Male : 4.30 – 6.00 10^6/uL	Female : 3.90 – 5.40 10^{12}/L Male : 4.30 – 6.00 10^{12}/L
Hemoglobin	Female : 12.0-16.0 g/dL Male : 13.6-18.0 g/dL	Female : 120-160 g/L Male : 136-180 g/L
Hematocrit	Female : 35-45% Male : 40-52%	Female : 0.35-0.45 Male : 0.4-0.52
WBC	3.5-11.0 10^3/uL	3.5-11.0 10^9/L
Neutrophils, abs	1.0-8.0 10^3/uL	1.0-8.0 10^9/L
Lymphocytes, abs	1.0-5.0 10^3/uL	1.0-5.0 10^9/L
Eosinophils, abs	0.0-0.8 10^3/uL	0.0-0.8 10^9/L
Monocytes, abs	0.0-1.0 10^3/uL	0.0-1.0 10^9/L
Neutrophils, %	40.0-80.0 %	40.0-80.0 %
Lymphocytes, %	15.0-45.0 %	15.0-45.0 %
Eosinophils, %	0.0-10.0 %	0.0-10.0 %
Monocytes, %	0.0-12.0 %	0.0-12.0 %
Platelets	140-400 10^3/uL	140-400 10^9/L
PT	Reagent specific ranges	Reagent specific ranges
INR	0.8-1.2	0.8-1.2
OTHER		
Pregnancy test (β-HCG)	Female : 0-5 IU/L	Female : 0-5 IU/L
Vitamin A	24-128 ug/dL	24-128 ug/dL
Vitamin D	30-80 ng/mL	75.0-200.0 nmol/L
Vitamin E	0.51-2.88 mg/dL	0.51-2.88 mg/dL
Vitamin K	0.22-4.88 nmol/L	0.22-4.88 nmol/L
HBsAg	Non-reactive	Non-reactive
HCV RNA	Not Detected	Not Detected

APPENDIX K. INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

PROTOCOL TITLE: **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)

PROTOCOL NUMBER: CB8025-32048
VERSION NUMBER: 4.0
DATE OF PROTOCOL: 09-February-2022

SPONSOR: CymaBay Therapeutics, Inc.
7575 Gateway Blvd, Suite 110
Newark, CA 94560
United States of America

I have read all pages of this clinical study protocol for which CymaBay Therapeutics, Inc. is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and the provisions of Declaration of Helsinki. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol, and the ICH GCP guidelines and Declaration of Helsinki, to enable them to work in accordance with the provisions of these documents.

Investigator:

Printed Name:

Signature:

Date:

Site Address: