CLINICAL STUDY PROTOCOL

Unique Protocol ID: CB8025-31735

Official Title: A 52-week, placebo-controlled, randomized, Phase 3 study to evaluate the safety and efficacy of seladelpar in subjects with primary biliary cholangitis (PBC) and an inadequate response to or an intolerance to ursodeoxycholic acid (UDCA)

NCT number: NCT03602560

Protocol Version Number: Version 1.0

Date: 3-JUL-2018

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

SPONSOR CONTACT: [redacted]

EudraCT number: 2018-001171-20

CONFIDENTIALITY STATEMENT

PROTOCOL CB8025-31735

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AE	Adverse event
ALT	Alanine aminotransferase
AMA	Anti-mitochondrial antibodies
ANCOVA	Analysis of covariance
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BA	Bile acids
BMI	Body mass index
BUN	Blood urea nitrogen
C4	7α-hydroxy-4-cholesten-3-one
CDCA	Chenodeoxycholic acid
CERC	Critical Event Review Committee
CFR	Code of Federal Regulations
CK	Creatine kinase
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ELF	Enhanced liver fibrosis
ELISA	Enzyme linked immunosorbent assay
FGF19	Fibroblast growth factor 19
FIB-4	Fibrosis-4
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HA	Hyaluronic acid
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HDL-C	High density lipoprotein cholesterol
HoFH	Homozygous familial hypercholesterolemia
hs-CRP	High sensitivity C-reactive protein
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
IgM	Immunoglobulin M
INR	International normalized ratio

ITT	Intent to treat
IXRS	Interactive voice/web response system
LDH	Lactate dehydrogenase
LDL-C	Low density lipoprotein cholesterol
LOCF	Last observation carried forward
M1, M2, M3	Seladelpar (MBX-8025) metabolites
MBX-8025	Seladelpar
MedRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
mITT	Modified intent to treat
MMRM	Mixed models repeated measures
NAFLD	Non-alcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NCI	National Cancer Institute
NRS	Numerical rating scale
OCA	Obeticholic acid
PBC	Primary biliary cholangitis
PD	Pharmacodynamics
PK	Pharmacokinetics
PMM	Pattern-mixture model
PP	Per protocol
PPAR	Peroxisome proliferator-activated receptor
Pro-C3	N-terminal type III collagen propeptide
PT	Prothrombin time
QoL	Quality of life
RBC	Erythrocyte count
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
VAS	Visual analogue scale
WBC	Leukocyte count
WHO	World Health Organization

2 LIST OF SPONSOR CONTACTS

Sponsor Contact:

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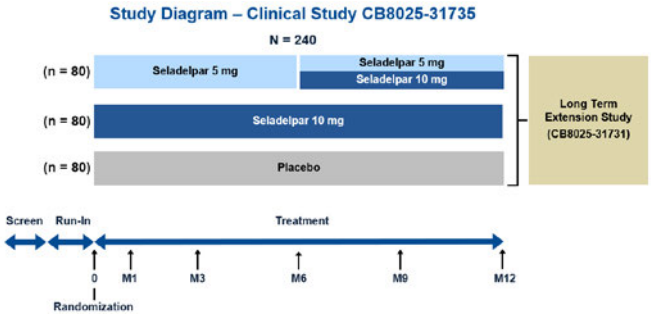
The Sponsor will notify the investigator(s) in writing with any change to the above information.

3 SYNOPSIS

Study Number	CB8025-31735
Title	A 52-week, placebo-controlled, randomized, Phase 3 study to evaluate the safety and efficacy of seladelpar in subjects with primary biliary cholangitis (PBC) and an inadequate response to or intolerance to ursodeoxycholic acid (UDCA)
Phase	3
Objectives	Primary: • To evaluate the safety and effect on cholestasis of two seladelpar regimens (5 mg/day titrated to 10 mg/day and 10 mg/day) over 52 weeks of treatment compared to placebo Key Secondary: • To evaluate the effect of seladelpar on normalization of alkaline phosphatase (AP) levels • To evaluate the effect of seladelpar on pruritus Other Secondary: • To evaluate the effect of seladelpar on quality of life (QoL) • To evaluate the effect of seladelpar on other measures of cholestasis, metabolic outcomes, and PBC prognosis criteria • To evaluate the effect of seladelpar on PBC clinical outcomes Exploratory: • To evaluate the effect of seladelpar on markers of inflammation, bile acid synthesis, levels of autotaxin, and markers of liver fibrosis
Study Outcome Measures	Primary Measures: • Response on the composite endpoint of AP and total bilirubin at 12 months: o AP < 1.67 × upper limit of normal (ULN), and o ≥ 15% decrease in AP, and o Total bilirubin ≤ ULN • Assessment of treatment-emergent AEs (TEAEs) (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 4.0), biochemistry and hematology 1. Key Secondary: • Proportion of subjects with AP ≤ 1.0 × ULN at 12 months • Change from baseline in pruritus numerical rating scale (NRS) at 6 months Other Secondary: • PBC-40 QoL at 6 and 12 months • PBC-40 QoL itch domain, and 5-D itch questionnaire

	• Response on the composite endpoint at 6 months • Proportion of subjects with AP < 1.67 × ULN and AP < 1.5 × ULN at 6 and 12 months • Proportion of subjects with AP ≤ 1.0 × ULN at 6 months and 12 months • Change from baseline in pruritus NRS at 12 months • Absolute and relative changes in AP • Proportion of subjects with PBC response criteria (Barcelona, Paris I and II, Toronto I and II, Rotterdam) • Change in UK-PBC and GLOBE risk scores • Absolute and relative changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), bilirubin (total, direct, and indirect), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL- C), triglycerides, and total cholesterol • The first occurrence of any of the following events: o Overall Death o Liver transplantation o MELD score ≥15 o Uncontrolled ascites (diuretic resistant) o Hospitalization for new onset or recurrence of any of the following: ▪ variceal bleeding ▪ hepatic encephalopathy (as defined by a West Haven score ≥ 2) ▪ spontaneous bacterial peritonitis (confirmed by culture from diagnostic paracentesis) o Hepatocellular carcinoma o Advanced PBC as defined by the Rotterdam criteria (albumin below low limit of normal (LLN) AND total bilirubin above ULN) <u>Exploratory Measures:</u> • C4 (7α-hydroxy-4-cholesten-3-one), fibroblast growth factor 19 (FGF19), N-terminal type III collagen propeptide (Pro-C3) • Haptoglobin, fibrinogen and high-sensitivity C-reactive protein (hs-CRP), homocysteine, immunoglobulin M (IgM) • Autotaxin • Enhanced liver fibrosis (ELF) score, fibrosis-4 (FIB-4) score, Lok-Index, non-alcoholic fatty liver disease (NAFLD) fibrosis score • Liver elastography (at selected centers)

Design	Double-blind, randomized, placebo controlled, 52 weeks dose ranging (placebo, 5/10 mg/day, and 10 mg/day), parallel treatment groups Subjects on 5/10 mg who are tolerating study drug but who are not responding to the therapy based on composite endpoint, will have dose adjustment performed after 6 months of treatment. 
Treatment Groups	• Seladelpar 5/10 mg • Seladelpar 10 mg • Placebo
Number of Subjects	Approximately 240 subjects total with approximately 80 subjects per group
Number of Investigational Sites	Approximately 140 worldwide
Randomization	1:1:1
Stratification	Randomization will be stratified by the following factors: • AP < 350 U/L and ≥ 350 U/L • Pruritus NRS < 4 and NRS ≥ 4
Duration	Screening: up to 2 weeks Run-In: 2 weeks Treatment: 52 weeks with an option to enter a long-term study (CB8025-31731) Follow-up: 4 weeks (if not enrolled in the long-term study) Total Duration: up to 60 weeks
Test Product, Formulation, Dose, Frequency, Administration Route	Seladelpar: Capsules; 5 and 10 mg; Once a day; Oral Placebo: Identical-looking capsules; NA; Once a day; Oral
Population	PBC subjects with an inadequate response to UDCA or intolerance to UDCA

Criteria for Eligibility	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, by at least two of the following criteria: • History of AP above ULN for at least six months • Positive anti-mitochondrial antibody (AMA) titers (>1/40 on immunofluorescence or M2 positive by enzyme linked immunosorbent assay [ELISA]) or positive PBC-specific antinuclear antibodies • Documented liver biopsy result consistent with PBC 4. On a stable and recommended dose of UDCA for the past twelve months OR intolerant to UDCA (last dose of UDCA > 3 months prior to Screening) 5. AP ≥ 1.67 × ULN 6. Females of reproductive potential must use at least one 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 or confound its results (e.g., cancer) 3. AST above 3 × ULN 4. ALT above 3 × ULN 5. Total bilirubin above 2.0 × ULN 6. Advanced PBC as defined by the Rotterdam criteria (albumin below LLN AND total bilirubin above 1 × ULN) 7. Creatine kinase (CK) above 1.0 × ULN 8. eGFR below 60 mL/min/1.73 m^2 (calculated by MDRD formula) 9. International normalized ratio (INR) above 1.0 × ULN 10. Platelet count below 100 × $10^3/\mu L$ 11. Presence of clinically significant hepatic decompensation, including:

	- History of liver transplantation, current placement on liver transplantation list, or current MELD score ≥ 15 - Complications of portal hypertension, including known esophageal varices, history of variceal bleeds or related interventions (e.g., transjugular intrahepatic portosystemic shunt placement), relevant ascites, hepatic encephalopathy - Cirrhosis with complications, including history or presence of spontaneous bacterial peritonitis 12. Other chronic liver diseases: a. Current features of auto-immune hepatitis as determined by the investigator based on immunoserology, liver biochemistry and histology b. Primary sclerosing cholangitis determined by 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. Biopsy confirmed nonalcoholic steatohepatitis f. History or evidence of Gilbert' Syndrome with elevated total bilirubin g. History or evidence of hemochromatosis h. Hepatitis B defined as presence of hepatitis B surface antigen (HBsAg) i. Hepatitis C defined as presence of HCV RNA 13. Known history of HIV 14. Evidence of significant alcohol consumption 15. Evidence of drug abuse 16. Subjects with inadequate response to obeticholic acid (OCA) or intolerance to OCA: OCA must be discontinued 30 days prior to Screening 17. Use of colchicine, methotrexate, azathioprine, or long-term systemic corticosteroids (> 2 weeks) within two months prior to Screening 18. Use of fibrates within 30 days prior to Screening 19. Use of simvastatin within 7 days prior to Screening 20. Use of an experimental or unapproved treatment for PBC within 30 days prior to Screening 21. Use of experimental or unapproved immunosuppressant within 30 days prior to Screening 22. Treatment with any other investigational therapy or device within 30 days or within five half-lives, whatever is longer, prior to Screening 23. For females, pregnancy or breast-feeding 24. 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

Procedures	Screening (Week -4): After signing an informed consent form (ICF), subjects will enter the Screening period to confirm eligibility. Demographics will be collected. A medical history will be taken, including PBC history, results of prior liver biopsy and liver elastography (FibroScan), and alcohol consumption. The subject's medical chart will be reviewed for evidence of other forms of chronic liver disease as well as for HIV infection. Detailed treatment history will be collected, including previous exposure to UDCA, OCA as well as other medications taken for PBC and its symptoms. Vital signs will be collected. Height and weight will be collected. Complete physical examination will be performed as well as a 12-lead electrocardiogram (ECG). Blood samples will be taken for hematology, biochemistry, AMA, Hepatitis B and C. If unexpected elevation of CK or INR is noted, re-test will be allowed. Women of child-bearing potential will have a serum pregnancy test performed. Urine drug screen will be performed. E-diary training will be performed, and subjects will complete the pruritus NRS. UDCA will be dispensed, and subjects will be instructed to switch their pre-study UDCA to study supply UDCA. Subjects will be instructed to continue UDCA regimen (dose and frequency) as close as possible to regimen taken prior to the study participation and as recommended per investigator's clinical judgment. Run-In (Week -2): Subjects who have been deemed eligible during the Screening period will return for Run-In period. AEs since the last visit will be evaluated. Medication history including medications since the last visit will be reviewed. Vital signs and weight will be collected. Symptom-directed physical examination will be performed. Blood samples will be taken for hematology, biochemistry, and exploratory measures. Women of child-bearing potential will have a serum pregnancy test performed. Back-up blood sample will be collected. E-diary will be dispensed and re-training will be performed, if needed. The subject will complete the pruritus NRS, 5-D itch, PBC-40 QoL, and patient global impression of severity (PGI-S) using 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 bi-weekly basis from the Run-In visit through the first six month of study drug treatment. UDCA accountability will be performed. Baseline liver biopsy will be performed on subjects willing to undergo the procedure to evaluate PBC stage and activity. PT and INR must be performed within 2 weeks prior to liver biopsy. If liver biopsy was performed within 1 year from Day 1, Baseline liver biopsy can be waived. For these instances sites will attempt to collect biopsy material. A follow up liver biopsy will be performed after at least 3 years (± 3 months) of treatment during the long-term study (CB8025-31731).

	Day 1: Subjects will be randomized into the study. AEs since the last visit will be evaluated. Medication history including medications since the last visit will be reviewed. Vital signs and weight will be collected. A complete physical examination and ECG will be performed. Blood samples will be taken for hematology, biochemistry, exploratory measures (including fat-soluble vitamins). Back-up blood sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. PBC-40 and PGI-S questionnaires will be performed. A review of pruritus NRS and 5-D itch data collected via e-diary since the previous visit will be performed. Subjects will be reminded to use e-diary to evaluate pruritus NRS on a daily basis. Liver elastrography (e.g., FibroScan) will be performed at selected sites. Subjects will be dispensed with the study drug to be taken orally once a day. Study drug dosing will be initiated immediately. UDCA will be dispensed. UDCA accountability will be performed. If a subject terminates study participation at any point after Day 1, an Early Termination visit will be completed. Month 1 (Week 4 ± 3 days): AEs since the last visit will be evaluated. Concomitant medication history since the last visit will be reviewed. Vital signs and weight will be collected. Brief symptom-directed physical examination will be performed. Blood samples will be taken for hematology, biochemistry, exploratory measures. Back-up blood sample will be collected. Women of child-bearing potential will have a serum pregnancy test. Subjects will complete PBC-40 QoL, PGI-S and patient global impression of change (PGI-C). A review of pruritus NRS and 5-D itch data collected via e-diary since the previous visit will be performed. Study drug and UDCA accountability will be evaluated. Month 3 (Week 12 ± 7 days): AEs since the last visit will be evaluated. Concomitant medication history since the last visit will be reviewed. Vital signs and weight will be collected. Brief symptom-directed physical examination will be performed. Blood sample will be taken for hematology, biochemistry, exploratory measures. Back-up blood sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. The subject will complete PBC-40 QoL, PGI-S and PGI-C. A review of pruritus NRS and 5-D itch data collected via e-diary since the previous visit will be performed. Study drug and UDCA accountability will be evaluated. Study drug and UDCA will be dispensed. Contact 1 (Week 19 ± 7 days): Subjects will be contacted by phone or email for the following: AEs will be evaluated, concomitant medications and procedures since last visit will be reviewed. Compliance with study drug administration will be evaluated. Unscheduled visit might be scheduled, if deemed necessary by investigator.

Month 6 (Week 26 ± 7 days):

AEs will be evaluated. Concomitant Medications will be reviewed. Vital signs and weight will be collected. Complete physical examination will be performed. A 12-lead ECG will be performed. Blood samples will be taken for hematology, biochemistry, exploratory measures. Back-up blood sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. The subject will complete 5-D itch, PBC-40 QoL, PGI-S and PGI-C. A review of pruritus NRS and 5-D itch data collected via e-diary since the previous visit will be performed. Starting from this visit, the subject will be instructed to fill out the NRS questionnaire via e-diary for 7 consecutive days every month through the Month 12 visit; 5-D itch will be collected at the clinic visits only. Study drug and UDCA accountability will be evaluated. Liver elastography (e.g. FibroScan) will be performed at selected sites. Study drug and UDCA will be dispensed.

Double-blind evaluation for dose up-titration will be performed. Dose up-titration will be requested if the following criteria are met:

No safety concerns limiting up-titration	AND	One of the following criteria: o AP ≥ 1.67 × ULN, OR o < 15% decrease in AP comparing to baseline value, OR o Total bilirubin > 1 × ULN

Dose Adjustment Visit (2 weeks after Month 6 ± 3 days)

All subjects will return to the clinic in two weeks after Month 6 visit for dose adjustment. For subjects who have safety concerns limiting up-titration, Dose Adjustment visit will still occur to evaluate subjects' status. Subjects will be instructed to not to take study drug at home prior to the clinic visit. TEAEs will be evaluated. Concomitant medications will be reviewed. Vital signs and weight will be collected. A brief symptom-directed physical examination will be performed. A blood sample will be taken for hematology, biochemistry, and exploratory biochemistry. A back-up serum sample will be collected. Study drug accountability will be evaluated. Additional assessments as determined by the Investigator. Dose up-titration will be performed, and the new dose of study drug will be administered.

For subjects who meet the up-titration criteria: subjects on 5 mg will be dispensed seladelpar10 mg; subjects on 10 mg will be dispensed seladelpar 10 mg, and subjects on placebo will be dispensed matched placebo. Study drug will be dispensed in a blinded manner. Subjects will immediately start dosing.

Contact 2 (Week 32 ± 7 days):

Subjects will be contacted by phone or email for the following: AEs will be evaluated, concomitant medications and procedures since last visit will be reviewed. Compliance with study drug administration will be evaluated. Unscheduled visit might be scheduled, if deemed necessary by investigator.

	Month 9 (Week 39 ± 7 days): AEs will be evaluated. Concomitant Medications will be reviewed. Vital signs and weight will be collected. Brief symptom-directed physical examination will be performed. Blood sample will be taken for hematology, biochemistry, exploratory measures. Back-up blood sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. The subject will complete 5-D itch, PBC-40 QoL, PGI-S and PGI-C. A review of pruritus NRS data collected via e-diary since the previous visit will be performed. Study drug and UDCA accountability will be evaluated. Study drug and UDCA will be dispensed. Contact 3 (Week 45 ± 7 days): Subjects will be contacted by phone or email for the following: AEs will be evaluated, concomitant medications and procedures since last visit will be reviewed. Compliance with study drug administration will be evaluated. Unscheduled visit might be scheduled, if deemed necessary by investigator. Month 12 (Week 52 ± 7 days): AEs will be evaluated. Concomitant Medications will be reviewed. Vital signs and weight will be collected. Complete physical examination will be performed. A 12-lead ECG will be performed. Blood sample will be taken for hematology, biochemistry, exploratory measures (including fat-soluble vitamins). Back-up blood sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. The subject will complete 5-D itch, PBC-40 QoL, PGI-S and PGI-C. A review of pruritus NRS data collected via e-diary since the previous visit will be performed. E- diary will be collected. Study drug and UDCA accountability will be evaluated. Study supply of UDCA will be switched to pre-study supply UDCA. Liver elastography (e.g. FibroScan) will be performed at selected sites. At the end of the visit, all subjects will be invited to participate in the long-term study (CB8025-31731). Subjects who consent to participate in CB8025-31731 will have the Month 12 visit combined with the Day 1 visit of CB8025-31731. Subjects on seladelpar will continue dosing; subjects on placebo will initiate seladelpar (5 or 10 mg). Subjects who do not consent to participate in CB8025-31731 will stop study drug and enter the four-week follow-up period. Post-Treatment Follow-up: Four weeks post-treatment, subjects will return to the clinic for a follow-up visit. This will be the subject's last visit. AEs will be evaluated. Concomitant medications will be reviewed. Vital signs and weight will be collected. Complete physical examination will be performed, as well as a 12-lead ECG. Blood sample will be taken for hematology, biochemistry, and exploratory measures. Back-up serum sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed.

<table>
<tr><td></td><td>Early Termination Visit:

AEs will be evaluated. Concomitant Medications will be reviewed. Vital signs and weight will be collected. Complete physical examination will be performed as well as a 12-lead ECG. Blood sample will be taken for hematology, biochemistry, and exploratory measures (including fat-soluble vitamins). Back-up serum sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. The subject will complete pruritus NRS, 5-D itch, PBC-40 QoL, PGI-S and PGI-C. A review of pruritus NRS data collected via e-diary since the previous visit will be performed. E-diary will be collected. Liver elastography (e.g. FibroScan) will be performed at selected sites. Study drug and UDCA accountability will be evaluated. Study supply of UDCA will be switched to pre-study supply of UDCA

Unscheduled Visit:

AEs will be evaluated. Concomitant Medications will be reviewed. Brief symptom-directed physical examination will be performed. Blood samples will be taken for biochemistry and hematology. Additional assessments as determined by the investigator.</td></tr>
<tr><td>UDCA</td><td>Subjects with inadequate response to UDCA will continue their UDCA intake in approximately the same dose as prior to the study participation and as recommended per investigator’s clinical judgment.</td></tr>
<tr><td>Concomitant Treatment</td><td>Subjects will be allowed to receive required medication to treat new or existing medical conditions.</td></tr>
<tr><td>Prohibited Treatment</td><td>Obeticholic acid
Fibrates (e.g. fenofibrate, bezafibrate)
Simvastatin
Colchicine, methotrexate, azathioprine
Systemic corticosteroids (> 2 weeks)</td></tr>
<tr><td>Dose titration</td><td>Subject will have a dose evaluation performed at the Month 6 visit to determine if dose up-titration is necessary. Dose evaluation will be done in a double-blind manner.
Dose up-titration will occur if the following criteria are met:
<table>
<tr><td>No safety concerns limiting up-titration</td><td>AND</td><td>One of the following criteria:
o AP ≥ 1.67 × ULN, OR
o < 15% decrease in AP comparing to baseline value, OR
o Total bilirubin > 1 × ULN</td></tr>
</table>
Subjects who meet the criteria will receive the up-titrated dose at the Dose Adjustment visit (2 weeks after Month 6 visit). Subjects on 5 mg will be up-titrated to 10 mg; subjects on 10 mg will continue 10 mg; and subjects on placebo will continue placebo.
Subjects who do not meet the up-titration criteria will continue the study at the initially assigned dose.</td></tr>
</table>

Safety Monitoring and Drug Interruption	Liver Safety Monitoring 1. Elevation of ALT/AST *Normal ALT/AST at baseline* • ALT/AST > 5 × ULN and total bilirubin ≤ 1 × ULN: **Interrupt study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B). Study medication can be restarted only if a firm competing etiology is identified, and liver tests return to baseline. • ALT/AST > 5 × ULN and total bilirubin > 1 × ULN: ○ Subjects with normal total bilirubin at baseline: **Stop study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B). ○ Subjects with elevated total bilirubin at baseline: ▪ Total bilirubin > 1.5 × baseline: **Stop study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B). ▪ Total bilirubin ≤ 1.5 × baseline: **Interrupt study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B). Study medication can be restarted only if a firm competing etiology is identified, and liver tests return to baseline. *Elevated ALT/AST at baseline:* • ALT/AST > 3 × baseline AND INR ≤ 1.5 × ULN AND no liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice): **Continue study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days. Closely follow the subject (see Appendix B). • ALT/AST > 3 × baseline AND INR > 1.5 × ULN AND no liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice): **Interrupt study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B). Study drug can be restarted only if a firm competing etiology is identified, and liver tests return to baseline. 2. Liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice) AND ALT/AST > 3 × baseline (irrespective of baseline levels): **Interrupt study drug**. Repeat AST, ALT, total bilirubin, and INR within 3 days. Closely follow the subject (see Appendix B). Study drug can be restarted only if a firm competing etiology is identified, and liver tests return to baseline. 3. Elevation of total bilirubin > 1.5 × baseline, regardless of ALT or AST levels, AND indicators of immunological reaction (e.g., rash, eosinophilia > 5%) OR liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice):

	Interrupt study drug. Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B). Study medication can be restarted only if a firm competing etiology is identified and liver tests return to baseline. 4. Hepatic decompensation (e.g., decompensated cirrhosis with gastro-esophageal variceal bleeding, ascites, or hepatic encephalopathy) during the study: **Stop study drug** and closely follow the subject (see Appendix B). 5. Close monitoring of a subject is not possible (see Appendix B): **Stop study drug**. Muscle Safety Monitoring I. CK > 5 × ULN with musculoskeletal symptoms: **Stop study drug**. Repeat the test within 3 days. Follow the subject weekly until resolution or stabilization. II. CK > 5 × ULN without musculoskeletal symptoms: repeat the test within 3 days. If on repeat test CK is > 2.5 × ULN, **stop study drug**. Follow the subject weekly until the event resolution or stabilization. III. CK > 2.5 × ULN and ≤ 5 × ULN regardless to musculoskeletal symptoms: repeat the test within 3 days. If the test is confirmed, **study drug will be continued at a decreased dose**. For subjects on 5 mg, the study drug will be switched to placebo. Serum Creatinine Monitoring I. Serum Creatinine > 2.0 × ULN: **Stop study drug**. The subject should be monitored weekly until resolution or stabilization. II. Serum Creatinine > 1.5 × ULN and ≤ 2.0 × ULN: **interrupt study drug**. Repeat the test within 3 days. If the test is confirmed and no alternative etiology is identified, **stop study drug**. If alternative etiology is identified, study drug may be restarted after serum creatinine returns to baseline values. The subject should be monitored weekly until event resolution or stabilization. Pancreatic Safety Monitoring I. Amylase > 3 × ULN and/or lipase > 3 × ULN without clinical symptoms of acute pancreatitis: repeat the test within 3 days. If the test confirms suspicion, **interrupt study drug**. Abdominal imaging is to be performed to exclude an alternative cause for the event. **Study drug** might be restarted only if a firm competing etiology of acute pancreatitis is identified. II. Amylase > 3 × ULN and/or lipase > 3 × ULN with clinical symptoms of acute pancreatitis: **Interrupt study drug**. Repeat the test within 3 days. Abdominal imaging is to be performed to exclude an alternative cause for the event. **Study drug** might be restarted only if a firm competing etiology of acute pancreatitis is identified

Statistics	Study Populations: The Safety population includes any subject who receives at least one dose of study drug. The Intent to Treat (ITT) population includes any subject randomized into the study. The Modified Intent to Treat (mITT) population includes any subject who is randomized into the study and receives at least one dose of study drug. The Per-Protocol (PP) population includes any subject who receives at least one dose of study drug, has at least one post baseline AP and total bilirubin evaluation, and does not have a protocol violation that is deemed to impact the efficacy analysis. Subjects will be analyzed according to randomized treatment assignment. Analysis Sets: Safety analysis will be conducted on the safety analysis set. Efficacy analysis will be conducted on the mITT analysis set and the PP analysis set. The mITT analysis set will be used for the primary efficacy analysis. Baseline is defined as the arithmetic mean of multiple pre-treatment measurements (Screening, Run-In, Day 1, and UNS if applicable) preceding the first administration of study drug, or as the last measurement prior to the first administration of study drug if only single value is available. Descriptive statistics such as means, medians, minimum, maximum and measures of dispersion will be presented. Primary analysis: The primary efficacy analysis will be based on the following composite endpoint evaluated after 52 weeks of treatment: • AP < 1.67x ULN, • AP decrease of ≥ 15%, and • Total bilirubin ≤ ULN Treatment comparisons of the primary efficacy endpoint will be tested using a gateway method. A hierarchical "fixed-sequence" approach will be used to evaluate the primary endpoint as follows: 1. The composite endpoint and seladelpar 10 mg vs placebo if negative stop 2. If positive, then: 3. The composite endpoint and for seladelpar 5/10 mg vs placebo, if negative stop This testing procedure maintains the overall Type I error for the primary efficacy endpoint at 5%. Additional details including a schematic for the testing sequence can be found in the statistical analysis section of the protocol.

	All inferential tests will be performed at the 5% alpha level. Response rates will be calculated based on the observed case analysis (i.e., [n=observed responder]/[N=modified Intention to Treat (mITT) population]) The primary efficacy analysis will be conducted on the mITT analysis set using the Cochran-Mantel-Haenszel (CMH) General Association test. The CMH analysis will be stratified by baseline AP randomization (AP level < 350 U/L and ≥ 350 U/L) and pruritis NRS < 4 and NRS ≥ 4. In the primary analysis, subjects who discontinue treatment will be considered non-responders. Sensitivity analyses will be performed on the primary efficacy endpoint using observed data only. The robustness of the primary analysis will be explored using several sensitivity analyses based on different subject populations including treating subjects who discontinue study treatment: • As responders • Same as primary analysis except based on the ITT Set. • Same as primary analysis except based on the PP Set. • Same as primary analysis except impute dropouts as non-responders in the seladelpar arm and as responders in the placebo arm (i.e. worst-case analysis). • Same as primary analysis except impute missing data using a pattern-mixture model (PMM) which considers different mechanisms for missing data. • Same as primary analysis except specify the proportion of patients achieving a decrease in AP as at least 10%, 20%, and 40%. • Using Medians instead of arithmetic means for baseline values Key Secondary Analyses: • normalization of AP at 12 months (i.e. AP ≤ ULN), and • change from baseline in the weekly averaged peak pruritus NRS over 6 months Type I error for key secondary efficacy analysis will be maintained using the hierarchical fixed-sequence. The fixed sequence approach for the primary and secondary analyses is as follows: • If the primary efficacy analysis is positive for 10 mg vs placebo and 5/10 mg vs placebo, then the two key secondary endpoints will be analysed hierarchically in the following order: 1. Normalization of AP at month 12: seladelpar 10 mg vs placebo, if negative stop, if positive then; 2. Normalization of AP at month 12: seladelpar 5/10 mg vs placebo if negative stop, if positive then; 3. Absolute change from baseline to month 6 in pruritus NRS: seladelpar 10 mg vs placebo if negative stop, if positive then;

	4. Absolute change from baseline to month 6 in pruritus NRS: seladelpar 5/10 mg vs placebo, stop Normalization of AP is a responder analysis and will be conducted in the mITT set using the same approach specified for the primary efficacy analysis. Additional analyses of pruritus, including durability of response to Month 12, will be described in SAP. Other Analyses: • The first occurrence any of the following events: o Overall Death o Liver transplantation o MELD score ≥ 15 o Uncontrolled ascites (diuretic resistant) o Hospitalization for new onset or recurrence of any of the following: ▪ variceal bleeding ▪ hepatic encephalopathy (as defined by a West Haven score ≥ 2) ▪ spontaneous bacterial peritonitis (confirmed by culture from diagnostic paracentesis) o Hepatocellular carcinoma o Advanced PBC as defined by the Rotterdam criteria (low serum albumin AND total bilirubin above 1 × ULN) Clinical events will be validated by a Critical Event Review Committee (CERC) composed of independent clinical experts familiar with hepatic diseases. <u>Sample size:</u> The planned sample size is 240 subjects (80 subjects in each of the 3 groups). The placebo group responder rate is estimated at less than 15%. The seladelpar 10 mg dose group responder rate is estimated at 40%. With the use of a 2-sided test of equality of binomial proportions based on Pearson chi-square test at the 5% level of significance, a sample size of 80 subjects per group will provide greater than 90% power to detect a difference between the 10 mg seladelpar group and the placebo group. Normalization of AP is estimated to have a placebo response rate of 5%. A 2-sided test of equality of binomial proportions based on Pearson chi-square test at the 5% level of significance yields a sample size of 80 subjects per group. This sample size provides more than 90% power to detect a difference of 30% between the seladelpar and placebo groups. Change in pruritus NRS sample size calculation was based on a 2-sample 2-sided t-test at the 5% alpha level. The standard deviation is 3. Under these assumptions, a total of 23 subjects per group provides ≥90% power to detect a treatment difference of ≥ 3 between the 10 mg seladelpar and placebo groups.

Table 1 Schedule of Assessments

Visit	Screening	Run-In	Randomi-zation	Month 1	Month 3	Contact 1[1]	Month 6	Dose Adjust	Contact 2[1]	Month 9	Contact 3[1]	Month 12[12]	Follow Up	ET	UNS
Target Day	**W-4 to -2**	**W -2**	**Day 1**	**W 4**	**W 12**	**W 19**	**W 26**	**W28**	**W 32**	**W 39**	**W 45**	**W 52**	**4W after W52**		
Informed Consent	X														
Demographics															
Eligibility	X														
Randomization			X												
Dose Evaluation[2]							X								
Up-Titration								X							
Medical History[3]	X														
AE		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	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 Exam	X	X[4]	X	X[4]	X[4]		X	X[4]		X[4]		X	X	X	X[4]
ECG	X		X				X					X	X	X	
Hematology[5, 6]	X	X	X	X	X		X	X		X		X	X	X	X
Biochemistry[5]	X[7]	X	X	X	X		X	X		X		X	X	X	X
Exploratory Measures[5]	X[8]	X	X[8]	X	X		X	X		X		X[8]	X	X[8]	
Hepatitis B and C	X														
Serum Pregnancy Test[9]	X	X	X	X	X		X			X		X	X	X	
Back-up Blood Sample[5]		X	X	X	X		X			X		X	X	X	
Urine Drug Screen	X														
Pruritus NRS[10]	X	X	X	X	X		X			X		X		X	
5-D itch[10]		X	X	X	X		X			X		X		X	
PBC-40 QoL[10]		X	X	X	X		X			X		X		X	
PGI-S[10]		X	X	X	X		X			X		X		X	
PGI-C[10]				X	X		X			X		X		X	
Liver Elastography (selected sites)			X				X					X		X	
Liver Biopsy[11]		X													
UDCA Dispense	X		X		X		X			X					
Study Drug Dispense			X		X		X	X		X					
Study Drug Compliance and Accountability				X	X	X[13]	X	X	X[13]	X	X[13]	X		X	
UDCA Accountability		X	X	X	X		X			X		X		X	

Abbreviations: AE=adverse event; AMA=anti-mitrochondrial antibodies; ECG=electrocardiogram; ET=Early Termination; NRS=numerical rating scale; PBC=primary biliary cholangitis; PGI-C=patient global impression of change; PGI-S; patient global impression of severity; QoL=quality of life; UDCA=ursodeoxycholic acid; UNS=Unscheduled visit; W=week.

1. Subject contact will be performed by phone or email communication.
2. All subjects will be evaluated for dose up-titration in a blinded manner. For subjects who met the up-titration criteria, dose up-titration will be requested. Dose up-titration will occur at Dose Adjustment visit.
3. Including PBC history, liver biopsy, liver elastography, alcohol consumption, evidence of other form of liver disease, and HIV.
4. Symptoms-directed (brief) physical examination.
5. Blood will be collected after at least an 8-hour overnight fast. If the subject forgets to fast prior to the blood collection, the site will record it in the source document and continue to draw labs.
6. PT and INR will also be performed locally at the Screening visit, Run-In, and during the treatment period if deemed necessary by the Investigator.
7. If at Screening an unexpected abnormal CK level is observed, re-test the subject to confirm eligibility.
8. Screening visit: only AMA will be performed. Fat-soluble vitamins will be performed at Day 1, Week 52 and ET (if applicable) only.
9. Serum pregnancy test will be performed in women of childbearing potential only. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.
10. Pruritus NRS, 5-D itch, PBC-40, and PGI-S and PGI-C data will be collected via 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 six months NRS will be collected for seven consecutive days during each month up to the Month 12 visit. (2) 5-D itch will be collected bi-weekly from the Run-In Visit up until the Month 6 visit; after Month 6 5-D itch will be collected at clinic visit only. 3) PBC-40, PGI-S, PGI-C will be collected during the clinic visits only.
11. Only subjects willing to undergo liver biopsy. PT and INR must be performed within 2 weeks prior to liver biopsy. If a subject had liver biopsy performed within 1 year from Day 1, sites will attempt to collect biopsy material. A follow up liver biopsy will be performed after 3 years (± 3 months) of treatment during long-term study (CB8025-31731).
12. Subjects will be invited to participate in the long-term study (CB8025-31731). Subjects who consent to participate in CB8025-31731 will have the Month 12 visit combined with the Day 1 visit in the CB8025-31731 study and continue dosing.
13. Only study drug compliance to be evaluated

4 INTRODUCTION

4.1 Primary Biliary Cholangitis (PBC)

Primary biliary cholangitis (PBC, formerly known as primary biliary cirrhosis) is a serious and potentially life threatening autoimmune disease of the liver characterized by impaired bile flow (cholestasis) and accumulation of toxic bile acids (BA).

The hallmark of PBC is cholestasis with an accompanying elevation in serum biomarkers including alkaline phosphatase (AP), gamma glutamyl transferase (GGT) and, depending on the severity of the disease, bilirubin and liver transaminases. Serologically, PBC is characterized by the presence of anti-mitochondrial antibodies (AMA) in nearly all patients (Selmi, 2010). Clinical symptoms of PBC include pruritus and fatigue, which can be quite disabling for some patients. PBC peak incidence occurs in the fifth decade of life and is uncommon in persons under 25 years of age (Kaplan, 2005). The histopathology in the livers of PBC patients 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 BA within the liver, resulting in hepatocellular injury, fibrosis, cirrhosis and eventually liver failure (Kaplan, 2005; Kumagi, 2008; Lindor, 2007). PBC is a chronic debilitating disease whose progression is associated with an increased risk of hepatocellular carcinoma and liver related mortality (Kaplan, 2005; Kumagi, 2008; Lindor, 2007).

The diagnosis of PBC often occurs at an early stage when following up on abnormal liver tests, especially elevated AP. After excluding extra-hepatic biliary obstruction, the presence of either AMA, or less often, the histological confirmation by liver biopsy establishes the diagnosis (Lindor, 2009). Fifty to 60% of patients are asymptomatic at diagnosis. Overt symptoms develop within two to four years in most asymptomatic patients, although one-third may remain symptom-free for years (Kaplan, 2005). Fatigue and pruritus are the most common presenting symptoms (Kaplan, 2005). Fatigue has been noted in up to 78% of patients and can be a significant cause of disability. The severity of fatigue is independent of the severity of the liver disease and there is no proven treatment (Kaplan, 2005). Pruritus, whose cause is uncertain, occurs in 20 to 70% of patients and can be extremely debilitating (Rishe, 2008). Other findings of PBC include jaundice, hypercholesterolemia, osteopenia and osteoporosis and coexisting autoimmune diseases (Kaplan, 2005; Kumagi, 2008). Portal hypertension is a late complication of the disease (Kaplan, 2005).

The first line therapy for PBC is ursodeoxycholic acid (UDCA), a non-cytotoxic BA that has been the mainstay of treatment for more than twenty years (Poupon, 1997). However, up to 40 percent of patients have persistent elevation of AP and/or bilirubin despite UDCA and are considered inadequate responders (Corpechot, 2008).

Obeticholic acid (OCA), a synthetic analogue of chenodeoxycholic acid (CDCA), was approved under the provisions of accelerated approval regulations (21 Code of Federal Regulations [CFR] 314.500) in the United States and European Union on 27 May 2016 and 12 December 2016, respectively. The approval was based on OCA's ability to significantly decrease AP levels and maintain a normal total bilirubin when, used as an add-on therapy in

PBC patients who are inadequate responders to UDCA or, as a monotherapy in PBC patients who are intolerant to UDCA (Ocaliva, 2016).

In summary, despite the previously mentioned therapeutic interventions and recent approval of OCA, it is evident that many PBC patients do not respond adequately to therapy and continues to have a progression of their disease (Kaplan, 2005; Kumagi, 2008; Momah, 2014) and additional treatments are needed.

4.2 Seladelpar

4.2.1 Overview

Seladelpar (MBX-8025) is an oral, once-daily administered, potent and selective peroxisome proliferator-activated receptors (PPAR) δ agonist (Bays, 2011; Jones, 2017). Seladelpar is being developed for the treatment of PBC in subjects with inadequate response to UDCA or intolerance to UDCA and in nonalcoholic steatohepatitis (NASH).

4.2.2 Mechanism of Action

PPARδ agonists have been shown to affect the transport, storage and metabolism of lipids (Barish, 2006). 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 as well as inhibiting 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 PBC patients (Jones, 2017). In addition, seladelpar exerts anti-inflammatory effects (Jones, 2017) that are of potential benefit in the treatment of PBC.

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

4.3 Nonclinical Investigations with Seladelpar

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

4.4 Human Experience

Across the clinical development program, seladelpar was evaluated in 6 Phase 1 studies and 4 Phase 2 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 studies in patients with mixed dyslipidemia (50 and 100 mg once a day), homozygous familial hypercholesterolemia (HoFH; ascending doses 50, 100, and 200 mg once a day), and PBC (2, 5, 10, 50, and 200 mg once a day). In these Phase 2 studies, treatment ranged from 8 to 12 weeks. In the ongoing Phase 2 PBC study, seladelpar is now being tested for 52 weeks at the end of which subjects are entering long-term extension study and continue dosing beyond 52 weeks.

4.4.1 Phase 1 Studies

Six Phase 1 clinical studies have been conducted in healthy subjects. The aims of these studies were to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of seladelpar. A total of 147 healthy subjects have been dosed with either seladelpar, seladelpar in combination with other agents, or placebo in the 6 completed clinical studies. Seladelpar was administered as a solution in sterile water, or as a hard gelatin capsule. In the 6 Phase 1 clinical studies, seladelpar was generally well tolerated. There were no deaths or serious adverse events (SAEs) recorded. All adverse events (AEs) were mild or moderate in severity. The type and incidence of AEs were generally similar across the various seladelpar and placebo dose groups. Please see the IB for more complete details on the Phase 1 studies conducted with seladelpar.

4.4.2 Phase 2 Studies in PBC Patients

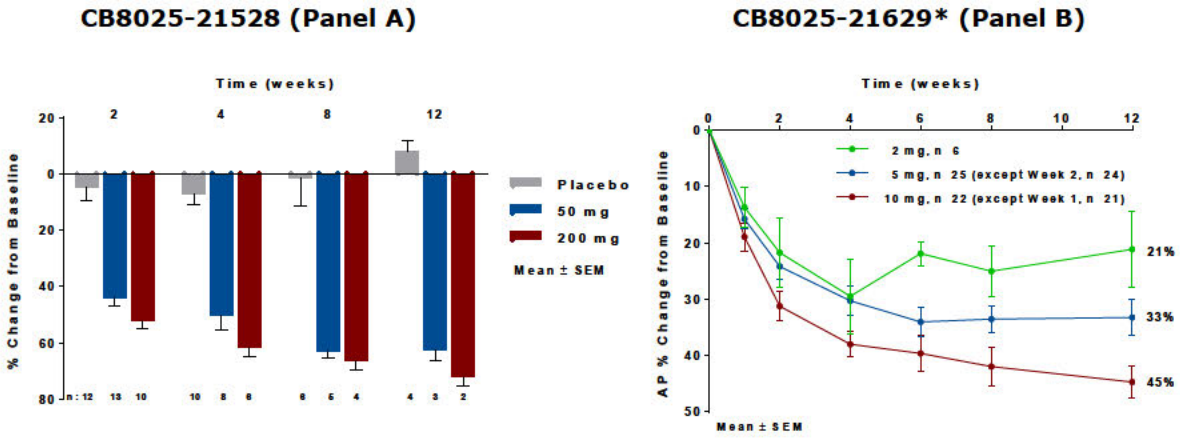
As of 2018, CymaBay conducted 3 clinical studies with seladelpar in PBC subjects.

Study CB8025-21528 was the first clinical study of the seladelpar for the treatment of PBC (Jones, 2017). It was a double-blind, randomized, placebo-controlled, 12-week dose-ranging study (referred to as the "high dose" study) in adult PBC patients who had an inadequate response to UDCA. Subjects were randomly assigned to receive 50 mg/day seladelpar, 200 mg/day seladelpar, or placebo in a 1:1:1 ratio. The study was terminated approximately mid-way through enrollment (41 subjects had enrolled) after 3 patients experienced, rapid, asymptomatic and reversible Grade 3 elevations in alanine aminotransferase (ALT) (one case at 50 mg and two cases at 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 AP 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 AP. All subjects who received seladelpar for 12 weeks normalized their AP levels (Jones, 2017). 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 C4, which represents a serum marker for the rate of hepatic BA synthesis. C4 reflects the activity of CYP7A1, the rate limiting enzyme for the synthesis of BA.

A second Phase 2 study (CB8025-21629) is currently underway in PBC patients who either have had an inadequate response to UDCA or are intolerant to UDCA. The aim of this study is to further evaluate the safety and efficacy of seladelpar at lower doses. The interim analysis was performed to evaluate the data up to 12 weeks evaluated seladelpar doses of 2, 5 and 10 mg/day. Data up to 26 weeks evaluated doses of 5 and 10 mg/day. After 12 weeks, patients on 5 mg could escalate to 10 mg if their AP treatment goal was not achieved. As of January 2018, 71 patients were exposed to at least one dose of seladelpar, of whom 53 received 12 weeks of treatment and 42 received 26 weeks of treatment. The 5 and 10 mg doses show consistent, meaningful, and reproducible decreases in AP levels (Figure 1; Panel B). At baseline, mean AP was 358, 333, and 262 IU/L in the 2, 5, and 10 mg groups, respectively. At 12 weeks, changes in AP were -21%, -33%, and -45% in the 2 (N=6), 5 (N=25), and 10 (N=22) mg groups, respectively. At 26 weeks, 69%, 67%, and 79% of

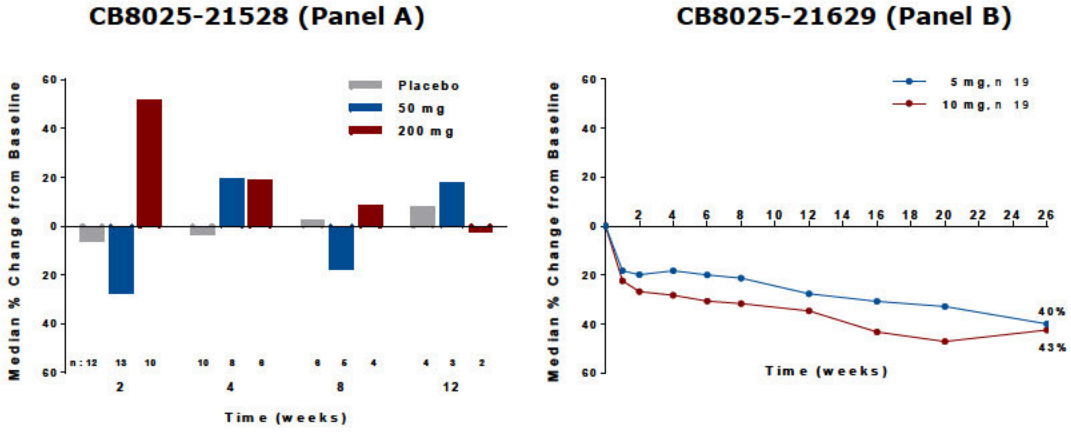
patients had an AP <1.67 × the upper limit of normal (ULN) in the 5 (N=13), 5 to 10 (N=6), and 10 mg (N=19) groups, respectively, and falls in AP were equal across regimen: -43%, -45%, and -43%, respectively, and overall, 29% had a normal AP.

Figure 1 Mean Percent Changes in AP in PBC Phase 2 Studies



The increases in transaminases observed with seladelpar 50 and 200 mg doses in the high dose study (CB8025-21528) have not been observed with 5 and 10 mg seladelpar doses. As seen in Figure 2, 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 maintain their assigned dose with no dose adjustment). This indicates that the safety signal previously manifested by an elevation in transaminases at higher doses, is replaced, at lower doses, by an efficacy signal in the form of reductions in transaminase levels. 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 Median Percent Change in ALT in PBC Phase 2 Studies



* January 2018 data cut

Seladelpar did not increase pruritus. Baseline median pruritus visual analogue scale (VAS) was 10 and 40 in the 5 and 10 mg group, respectively, and patients in the 10 mg group experienced consistent decreases during follow up (-24% at week 26). Seladelpar was generally safe and well tolerated, with no transaminase elevation safety signal. There were 6 serious AEs and none were deemed related to seladelpar. As a result of interim analysis, it was concluded that seladelpar doses of 10 mg, or 5 mg adjusted to 10 mg, demonstrates potent anti-cholestatic efficacy that is maintained over 26 weeks.

A third study (CB8025-31731) is also underway in PBC patients who completed CB8025-21629 study and willing to continue the treatment with seladelpar beyond 52 weeks.

4.4.3 Phase 2 Studies in Non-PBC Patients

Study M8025-20711 was a multicenter randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK and efficacy of seladelpar at doses 10 and 100 mg in moderately obese hyperlipidemic subjects with or without concomitant atorvastatin (Bays, 2011; Choi, 2012).

Study CB8025-21427 was a pilot study of seladelpar in the treatment of HoFH. The study was a 12-week, open label, multicenter, non-controlled, monthly dose escalation study (seladelpar: 50, 100, and 200 mg; p.o. daily) in adults with genetically confirmed HoFH.

For more details about the studies, please refer to the IB.

4.5 Risk/Benefit Assessment

The study being proposed is a placebo-controlled, double-blind randomized study to evaluate safety and efficacy of seladelpar in PBC subjects.

4.5.1 Potential Benefits

In previous PBC studies, subjects receiving placebo showed no relevant change, while subjects receiving seladelpar exhibited a pronounced decrease in AP. After 26 weeks of treatment with seladelpar 10 mg and 5/10 mg, 78% and 68% reached AP <1.67 × ULN, and 32% and 26% of subjects had a normal AP, respectively. 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.

Previous studies in PBC subjects also suggested the potential of seladelpar to improve pruritus, an important clinical outcome in PBC patients. A decrease in the pruritus VAS was noted in the 10 mg group in which approximately half of patients had a substantial level of itching at baseline (VAS ≥ 40 mm, or moderate to severe itch). This suggests that seladelpar treatment could be associated with an improvement in PBC-associated itch.

Subjects who will successfully complete this study can be rolled over into the long-term study (CB8025-31731) and can continue their seladelpar treatment until seladelpar is commercially available or the program is discontinued; subjects on placebo will be switched to the active treatment with seladelpar.

4.5.2 Potential Risks

4.5.2.1 Non-clinical Safety Findings

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

4.5.2.2 Human Safety

Currently, seladelpar has been used for a maximum of 21 days in healthy volunteers at a maximum dose of 200 mg per day; in overweight subjects with mixed dyslipidemia, with and without atorvastatin, for a maximum of eight weeks and with a maximum dose of 100 mg per day; in subjects with HoFH, on concomitant ezetimibe and maximum statin therapy (± low density lipoprotein cholesterol [LDL-C] apheresis), with dose escalation from 50 mg to a maximum of 200 mg per day; and in subjects with PBC on concomitant UDCA for 12 weeks with a maximum dose of 200 mg per day and for 52 weeks and beyond with a maximum dose of 10 mg per day.

Seladelpar has been associated with increases in transaminases (ALT and aspartate aminotransferase [AST]), particularly in subjects with PBC treated with seladelpar at doses 50 mg and 200 mg. The increases appear to be dose dependent and population dependent. The increases were fully reversible upon treatment discontinuation. No clear transaminase elevation signal was seen in PBC subject treated with seladelpar at doses 5 and 10 mg.

Seladelpar has been associated with a pre-clinical muscle toxicity signal. One PBC subject taking 200 mg per day discontinued seladelpar for acute muscle pain associated with increased muscle enzymes. The AE was reversible upon treatment discontinuation and was considered possibly related to treatment. Muscle toxicity signal was not seen in PBC subject treated with seladelpar at doses 5 and 10 mg.

Seladelpar has been associated with increases in serum creatinine. These increases are generally mild (in the 10% range) and serum creatinine shifts are within the normal range. Similar increases have been observed with drugs of the PPARα class or the mixed PPARα/δ class. In the short term, these increases in serum creatinine have not been associated with relevant decreases in measured glomerular filtration rate. In the long run, data from controlled clinical trials do not support that PPARα or mixed PPARα/δ are associated with a degradation of renal function. It is hypothesized that the increase in serum creatinine is of muscle origin (with an increase in creatine synthesis, which is later metabolized into creatinine). However, caution must be exercised. One subject with HoFH and a chronic renal insufficiency, treated with seladelpar 100 mg and one subject with PBC treated with seladelpar 200 mg had serum creatinine elevation above the normal range that were reversible upon treatment discontinuation and considered possibly related to seladelpar. No subjects treated with low doses of seladelpar (up to 10 mg) experienced Grade 2 or Grade 3 increases in serum creatinine. Therefore, it was concluded that the seladelpar at doses up to 10 mg had no clinically relevant impact on serum creatinine levels.

4.6 Rationale for Dose Selection

In PBC studies seladelpar at dose of 2, 5, and 10 mg, retains a relevant clinical activity to improve markers of cholestasis and inflammation as well as metabolic markers (e.g., decrease in triglycerides and LDL-C). There was a dose ranging activity from 2 to 10 mg/day with 10 mg/day demonstrating the best risk/benefit profile. For these reasons, a seladelpar a dose of 10 mg/day and dose titration regimen of 5 mg with a potential to increase to 10 mg have been selected for the proposed Phase 3 study. These doses were well tolerated, appeared safe and were not associated with drug-induced pruritus.

4.7 Conclusions

In conclusion, seladelpar demonstrated the potent and rapid decrease in biochemical markers of cholestasis (AP, GGT, and total bilirubin), decrease a marker of inflammation (hs-CRP) and decrease LDL-C in PBC subjects who had an inadequate response or intolerance to UDCA. In addition, the current data suggest that seladelpar has a potential to improve PBC-related pruritus. Lower doses of seladelpar (up to 10 mg) 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. The clinical experience with seladelpar is nonetheless limited, and appropriate precautions are incorporated into this protocol, with careful monitoring of potential transaminase elevations.

5 STUDY OBJECTIVES

5.1 Primary Objectives

The primary objective of this study is to evaluate the safety and effect on cholestasis of 2 seladelpar dose regimens (5 mg/day titrated to 10 mg/day and 10 mg/day) over 52 weeks of treatment compared to placebo.

5.2 Secondary Objectives

The key secondary objectives of this study are to evaluate the effect of seladelpar on normalization of AP levels and to evaluate the effect of seladelpar on pruritus.

Other secondary objectives of the study are to evaluate the effect of seladelpar on quality of life (QoL), to evaluate the effect of seladelpar on other measures of cholestasis, metabolic outcomes, PBC prognosis criteria, and the effect on PBC clinical outcomes.

5.3 Exploratory Objectives

The exploratory objectives of the study are to evaluate the effect of seladelpar on markers of inflammation, bile acid synthesis, levels of autotaxin, and markers of liver fibrosis.

6 STUDY POPULATION

PBC subjects with an inadequate response to UDCA or intolerance to UDCA.

6.1 Selection Criteria

6.1.1 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, by at least 2 of the following criteria:
   - History of AP above ULN for at least 6 months
   - Positive AMA titers (>1/40 on immunofluorescence or M2 positive by enzyme linked immunosorbent assay [ELISA]) or positive PBC-specific antinuclear antibodies
   - Documented liver biopsy result consistent with PBC
4. On a stable and recommended dose of UDCA for the past twelve months OR intolerant to UDCA (last dose of UDCA > 3 months prior to Screening)
5. AP ≥ 1.67 × ULN
6. Females of reproductive potential must use at least one 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

6.1.2 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 or confound its results (e.g., cancer)
3. AST above 3 × ULN
4. ALT above 3 × ULN
5. Total bilirubin above 2.0 × ULN
6. Advanced PBC as defined by the Rotterdam criteria (albumin below LLN AND total bilirubin above 1 × ULN)
7. Creatine kinase (CK) above 1.0 × ULN
8. eGFR below 60 mL/min/1.73 m2 (calculated by MDRD formula)

9. International normalized ratio (INR) above 1.0 × ULN
10. Platelet count below 100 × 103/μL
11. Presence of clinically significant hepatic decompensation, including:
    - History of liver transplantation, current placement on liver transplantation list, or current MELD score ≥ 15
    - Complications of portal hypertension, including known esophageal varices, history of variceal bleeds or related interventions (e.g., transjugular intrahepatic portosystemic shunt placement), relevant ascites, hepatic encephalopathy
    - Cirrhosis with complications, including history or presence of spontaneous bacterial peritonitis
12. Other chronic liver diseases:
    a. Current features of auto-immune hepatitis as determined by the investigator based on immunoserology, liver biochemistry and histology
    b. Primary sclerosing cholangitis determined by 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. Biopsy confirmed nonalcoholic steatohepatitis
    f. History or evidence of Gilbert' Syndrome with elevated total bilirubin
    g. History or evidence of hemochromatosis
    h. Hepatitis B defined as presence of hepatitis B surface antigen (HbsAg)
    a. Hepatitis C defined as presence of HCV RNA
13. Known history of HIV
14. Evidence of significant alcohol consumption
15. Evidence of drug abuse
16. Subjects with inadequate response to OCA or intolerance to OCA: obeticholic acid must be discontinued 30 days prior to Screening
17. Use of colchicine, methotrexate, azathioprine, or long-term systemic corticosteroids (> 2 weeks) within two months prior to Screening
18. Use of fibrates within 30 days prior to Screening
19. Use of simvastatin within 7 days prior to Screening
20. Use of an experimental or unapproved treatment for PBC within 30 days prior to Screening
21. Use of experimental or unapproved immunosuppressant within 30 days prior to Screening
22. Treatment with any other investigational therapy or device within 30 days or within five half-lives, whatever is longer, prior to Screening
23. For females, pregnancy or breast-feeding
24. 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

7 STUDY DESIGN

This Phase 3 study will utilize an international, multicenter, double-blind, randomized, placebo-controlled 52-week dose-ranging (placebo, 5/10 mg/day, and 10 mg/day), parallel treatment groups design.

This study is a pivotal study to evaluate the safety of seladelpar and its effect (± UDCA) on cholestasis and on pruritus in subjects with inadequate response to UDCA or intolerance to UDCA. The study population can also include subjects with an inadequate response to UDCA + OCA, or who are intolerant to OCA.

The study is planned to enroll approximately 240 subjects. Subjects will be randomly assigned to receive placebo, seladelpar 5 mg titrated to 10 mg, or seladelpar 10 mg. Subjects will be stratified by AP level (AP < 350 U/L and ≥ 350 U/L) and presence of significant pruritus (pruritus numerical rating scale [NRS] < 4 and NRS ≥ 4). Subjects will be considered as formally entered the study at the time of randomization.

Study drug (placebo or seladelpar) will be taken in a blinded manner orally once a day for a period of 52 weeks. After first 6 months of treatment, evaluation of the initially assigned dose will be performed in a blinded manner. Subjects assigned to the seladelpar 5/10 mg group who are not responders based on composite endpoint at Month 6, and are tolerating study drug, will be up titrated from seladelpar 5 to 10 mg for the remainder of the study. Those patients initially assigned to placebo or 10 mg will not have their dose changed. To avoid unblinding, all subjects will be invited to Dose Adjustment visit which will occur two weeks after Month 6 visit.

Subjects with an inadequate response to UDCA will continue to receive UDCA throughout the study. Study specific UDCA supply will be provided and taken during the study participation. UDCA supply will be switched from pre-study supply to the study supply at the Screening visit and continue through the Week 52 visit. At the Week 52 visit, UDCA will be switched to pre-study supply.

Subjects will be asked to use an e-diary to evaluate pruritus and quality of life 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 evaluation of their pruritus in a daily basis via pruritus NRS starting from the Run-In visit through the first 6 months of treatment. After six months, pruritus will be evaluated in a monthly basis using pruritus NRS for 7 consecutive days each month. 5-D itch will be evaluated bi-weekly from the Run-In visit up until the Month 6 visit and at each clinic visit from Month 6 till Month 12 visit. PBC-40, PGI-S and PGI-C will be evaluated at each clinic visit over the whole study duration.

The total duration of the study for each subject will be up to 60 weeks. The Screening period will be up to 2 weeks, the run-in period will be 2 weeks, and treatment period will be 52 weeks. During the treatment period, subjects will be seen in the clinic every 3 months with an exception of first on treatment visit which will be performed after one month after initiation

of the study drug. Subjects will also return 2 weeks after Month 6 visit for blinded dose-adjustment visit. In addition, subjects will have contact visits performed over phone or email every 12 weeks between on-site visits. At the end of 52 weeks of treatment, subjects will be invited to participate in the long-term study (CB8025-31731) and continue their treatment with seladelpar; subjects on placebo will be switched to seladelpar. Subjects who do not want to continue seladelpar treatment beyond 52 weeks and decline long-term study participation will have a follow-up visit performed 4 weeks after the last dose of the study drug.

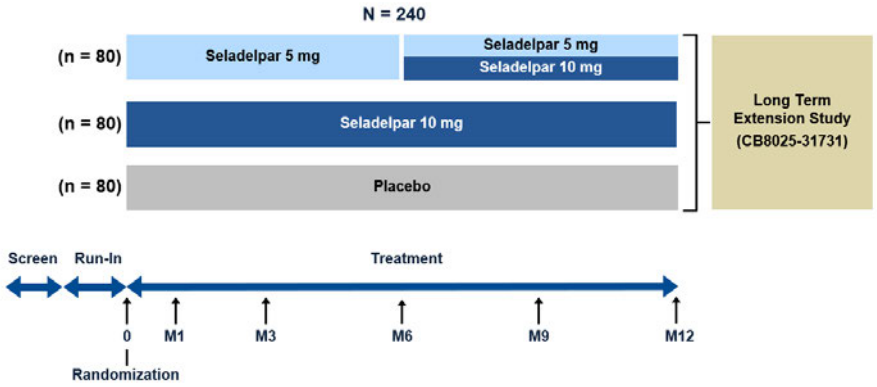
Subjects will be asked to go through liver biopsy to evaluate PBC stage and activity. Subjects willing to undergo a procedure will have liver biopsy performed during the Run-In period. If liver biopsy was performed within 1 year prior to Day 1, Baseline liver biopsy can be waived. For these instances sites will attempt to collect biopsy material. The follow-up liver biopsy will be performed at least 3 years after initiation of treatment, during the long-term study (CB8025-31731).

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 either 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.

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

The primary efficacy analysis will be a responder analysis (composite point) after 12 months of treatment with seladelpar. The study will be blinded for the study drug until the data base lock.

Figure 3 Study Diagram – Clinical Study CB8025-31735



7.1 Treatment and Allocation of Subjects

Approximately 240 PBC patients will be enrolled into the study.

Subjects will be randomized to placebo, seladelpar 5/10 mg or seladelpar 10 mg in 1:1:1 ratio (approximately 80 subjects per group). Subject will be stratified by AP level (AP < 350 U/L

and ≥ 350 U/L) and pruritus status (pruritus NRS < 4 and NRS ≥ 4). Subjects randomized to 5/10 mg will start treatment with seladelpar daily dose of 5 mg/day and after 6 months of treatment might up-titrate their dose to 10 mg/day.

7.2 Study Duration

The study will be up to 60 weeks of duration and consists of the following periods:

- Screening period: up to 2 weeks
- Run-In: 2 weeks
- Treatment Period: 52 weeks with an option to enter long-term study (CB8025-31731)
- Follow-up period: 4 weeks (if not enrolled in long-term study)

7.3 Study Outcome Measurements

7.3.1 Primary Measures

- Response on the composite endpoint of AP and total bilirubin at 12 months:
  - AP < 1.67 × ULN,
  - ≥ 15% decrease in AP, and
  - Total bilirubin ≤ ULN
- Assessment of treatment-emergent AEs (TEAEs) (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 4.0), biochemistry and hematology

7.3.2 Key Secondary Measures

- Proportion of patients with AP ≤1.0 × ULN at 12 months
- Change from baseline in pruritus NRS at 6 months

7.3.3 Other Secondary Measures

- PBC-40 QoL at 6 and 12 months
- PBC-40 QoL itch domain, and 5-D itch questionnaire
- Response on the composite endpoint at 6 months
- Proportion of subjects with AP <1.67 × ULN and AP < 1.5 × ULN at 6 and 12 months
- Proportion of subjects with AP ≤ 1.0 × ULN at 6 months
- Change from baseline in pruritus NRS at 12 months
- Absolute and relative changes in AP
- Proportion of patients with PBC response criteria (Barcelona, Paris I and II, Toronto I and II, Rotterdam)
- Change in UK-PBC and GLOBE risk scores

- Absolute and relative changes in ALT, AST, GGT, bilirubin (total, direct, and indirect), LDL-C, high density lipoprotein cholesterol (HDL-C), triglycerides, and total cholesterol
- The first occurrence of any of the following:
  - Overall death
  - Liver transplantation
  - MELD score ≥15
  - Uncontrolled ascites (diuretic resistant)
  - Hospitalization for new onset or recurrence of any of the following:
    - variceal bleeding
    - hepatic encephalopathy (as defined by a West Haven score ≥ 2)
    - spontaneous bacterial peritonitis (confirmed by culture from diagnostic paracentesis)
  - Hepatocellular carcinoma
  - Advanced PBC as defined by the Rotterdam criteria (albumin below LLN AND total bilirubin above 1 × ULN)

7.3.4 Exploratory Measures

- C4 (7α-hydroxy-4-cholesten-3-one)
- Fibroblast growth factor 19 (FGF19)
- N-terminal type III collagen propeptide (Pro-C3)
- Haptoglobin, fibrinogen and hs-CRP, homocysteine, immunoglobulin M (IgM)
- Autotaxin
- Enhanced liver fibrosis (ELF) score, fibrosis-4 (FIB-4) score, Lok-Index, non-alcoholic fatty liver disease (NAFLD) fibrosis score
- Liver elastography (at selected centers)

8 STUDY MEDICATIONS

8.1 Clinical Supplies

Investigational product (study drug) and UDCA will be supplied for the study.

8.1.1 Investigational Product (Study Drug), Dosage and Mode of Administration

Seladelpar will be supplied in a blinded fashion as 5 mg and 10 mg capsules. Matching placebo will be provided. The study drug (seladelpar or placebo) will be administered orally, once daily for the duration of to 52 weeks. The subject will take 1 capsule every day, approximately at the same time each day.

8.1.2 UDCA, Dosage and Mode of Administration.

The standard of care UDCA will be supplied in an unblinded fashion. UDCA will be administered orally, one or multiple times per day at the dose as close as possible to pre-study dose and as recommended per investigator's clinical judgment. Pre-study UDCA will be switched to the study supply UDCA at the Screening visit. UDCA study supply will be provided for up to 56 weeks of duration (from the Screening visit through the Month 12 visit). At the Week 52 visit, study supply UDCA will be switched to pre-study supply of UDCA.

8.1.3 Packaging, Labeling and Shipping

The Sponsor will provide the investigator with packaged study drug and UDCA labeled in accordance with specific country regulatory requirements. The supplies will be shipped in accordance with the Pharmacy Manual.

8.1.3.1 Dose Up-titration

Subjects assigned to the seladelpar 5/10 mg group who are tolerating study drug and are not responders based on composite endpoint according to Month 6 laboratory result, will be up titrated from seladelpar 5 to 10 mg. Those patients initially assigned to placebo or 10 mg will not have their dose changed. Dose up-titration will occur 2 weeks after Month 6 period, when subjects will return to the clinic for dose titration visit. Dose up-titration will be performed in a blinded manner.

8.1.3.2 Dose Down-titration

Subjects who meet muscle safety monitoring criteria per Section 10.4.2 and eligible for the dose down-titration: subject who initially assigned to 10 mg will be down-titrated to 5 mg; subjects initially assigned to 5 mg, will be down-titrated to placebo. Subjects initially assigned to placebo will stay on placebo. Dose down-titration will be performed in a blinded manner.

8.1.4 Accountability of Clinical Supplies

The investigator or a designee will keep a record of the dates and amounts of study drug and UDCA received, the amount dispensed to study subjects, and the amount returned from study subjects.

8.1.5 Replacement Study Drug and UDCA

Additional replacement study drug and UDCA will be available as required. All replacement shipments must be accounted for in the same manner as the initial drug supply.

8.1.6 Storage of Study Drug and UDCA

All supplies of study medication and UDCA must be stored as defined in the Pharmacy Manual.

8.2 Randomization

Subjects will be randomized in a blinded manner to placebo or seladelpar in a 1:1:1 scheme (placebo: seladelpar 5/10mg: seladelpar 10 mg). In addition, randomized subjects will be stratified by AP level (AP < 350 U/L and ≥ 350 U/L) and pruritus status (pruritus NRS < 4 and NRS ≥ 4).

8.2.1 Randomization Procedure

Randomization procedure will be performed centrally via interactive voice/web response system (IXRS) at Day 1 visit. A subject will be considered formally enrolled in the study at the time of randomization and begin study drug dosing.

8.3 Emergency Unblinding

In the event of a medical emergency, where knowledge of the subject's treatment assignment is necessary per the medical judgment, the investigator or the Sponsor can break the blind. 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.

8.4 Method of Administration and Compliance

Study drug will be dispensed on Day 1 and from Month 3 to Month 12 visits and will be taken orally once a day, according to the study schedule.

UDCA will be dispensed at the Screening visit and from Month 3 to Month 12 visits and will be taken orally as recommended per investigator clinical judgment.

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

8.5 Concomitant Medications and Procedures

The use of concomitant medications or procedures (defined below), 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.

8.5.1 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 trial.

All subjects will be instructed to remain on their current diet and lifestyle, including drinking habits, specifically alcoholic beverages, throughout the entire study.

8.5.1.1 Allowed Concomitant Medication:

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

8.5.1.2 Prohibited Concomitant Medication

Use of OCA, fibrates (e.g. fenofibrate, bezafibrate), simvastatin, colchicine, methotrexate, azathioprine or long-term systemic corticosteroids (> 2 weeks) will be prohibited during the study.

8.5.2 Concomitant Procedures

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

9 STUDY PROCEDURES

9.1 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 -4 to Week -2
- Run-In: Week -2 to Day 1
- Treatment Initiation: Day 1
- Treatment Period: Day 1 through Month 12
- Follow-up Period: 28 days after the last dose of the study drug (only applicable for subjects who are not willing to roll-over to long-term study (CB8025-31731).

Visits, which occur within ± 3 days of the calculated date from Run-In period through the Month 1 visit and Dose adjustment visit and within ± 7 days of the calculated date from Month 3 through Month 12 will not be considered protocol violations.

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

9.1.1 Screening (Week -4 to Week -2)

Subjects will review and sign the informed consent form (ICF) prior to any study-related procedures.

Screening evaluations will be performed within 2 weeks prior to Run-In period.

The evaluations of eligibility will consist of:

- Demographic information
- Assessment of all inclusion and exclusion criteria
- Review of medical history, including PBC medical history, results of prior liver biopsy, liver elastography (e.g., FibroScan), and alcohol consumption. The subject's medical chart will be reviewed for evidence of 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 as well as other medications taken for PBC and its symptoms (including supplements and vitamins)
- Vital signs (as described in Section 9.2.2). This will include temperature, heart rate, respiration rate and blood pressure
- Height and weight measurements will be performed
- Complete physical examination (as described in Section 9.2.1). This will include a full review of the following systems: general, skin, eyes, nose/sinuses, ears, mouth/throat,

neck, breasts, and respiratory, cardiac, gastrointestinal, peripheral vascular, genitourinary, musculoskeletal, neurologic, mental health, endocrine and hematologic

- 12-lead electrocardiogram (ECG) after at least 5 minutes rest
- Blood drawn for hematology, biochemistry, AMA, hepatitis B and hepatitis C as outlined in Section 9.2.4 and Appendix A. If unexpected elevation of CK or INR is noted, re-test is allowed.
- Women of child-bearing potential will have a serum pregnancy test performed
- Urine drug screen
- E-diary training
- Pruritus NRS evaluation.
- UDCA will be dispensed. Subjects will be instructed to switch their pre-study UDCA to study supply UDCA at the time of Screening. Subjects will be instructed to continue UDCA regimen (dose and frequency) as close as possible to regimen taken prior to the study participation 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 significant 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 one 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 to use a second effective birth control method during the study and for at least 90 days after the last dose.

9.1.2 Run-In (Week -2 to Day 1)

Subjects who have been deemed eligible during the Screening period will return for the Run-In period.

All subjects will have the following evaluations performed:

- Documentation of AEs that occurred since the signing of the ICF
- Documentation of medication (including supplements and vitamins) since the last visit
- Vital signs and weight (as described at Section 9.2.2)
- Symptom-directed (brief) physical examination (as described at Section 9.2.1)

- 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
- Back-up blood sample will be collected
- 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 bi-weekly basis at approximately same time during the day from the Run-In visit through the first six month of study drug treatment.
- UDCA accountability
- Baseline liver biopsy: Only subjects willing to undergo the procedure to evaluate PBC stage and activity. PT and INR must be performed within 2 weeks prior to liver biopsy. If liver biopsy performed within 1 year from Day 1, baseline liver biopsy can be waived. For these instances sites will attempt to collect biopsy material. A follow up liver biopsy will be performed at least 3 years (± 3 months) of treatment during the long-term study (CB8025-31731).

9.1.3 Treatment Period

Day 1 (Randomization)

Day 1 begins the treatment period and is the date against which all subsequent visits will be timed with the exception of Dose Adjustment Visit and 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 clinic visit days, subjects will arrive to the clinic in the fasted state for laboratory assessments. If subjects forget to fast, this should be noted and the lab 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 medication (including supplements and vitamins) since the last visit
- Vital signs and weight (as described at Section 9.2.2)
- Complete physical examination (as described at Section 9.2.1)
- 12-lead ECG after at least 5 minutes 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. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.
- PBC-40 and PGI-S 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 six months of treatment.
- 5-D Itch: review of previously collected data. Subjects will be reminded to use e-diary to evaluate pruritus on a bi-weekly basis up until the Month 6 visit.
- Liver elastography (e.g, FibroScan): at selected sites
- Study drug will be dispensed per the subject's randomization with interactions to take orally once a day. The first dose of the study drug will be administered on site.
- UDCA will be dispensed.
- UDCA accountability will be performed.

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

Month 1

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 medication (including supplements and vitamins) since the last visit
- Vital signs and weight (as described at Section 9.2.2)
- Symptom-directed (brief) physical examination (as described at Section 9.2.1)
- Blood drawn for hematology, biochemistry, and exploratory measures as outlined in Appendix A
- Back-up blood sample will be collected
- Women of child-bearing potential will have a serum pregnancy blood 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: review of previously collected data. Subjects will be reminded to use e-diary to evaluate pruritus on a daily basis
- 5-D Itch: review of previously collected data. Subjects will be reminded to use e-diary to evaluate pruritus on a bi-weekly basis.
- Study drug and UDCA accountability.

Month 3

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 medication (including supplements and vitamins) since the last visit
- Vital signs and weight (as described at Section 9.2.2)
- Symptom-directed (brief) physical examination (as described at Section 9.2.1)
- Blood drawn for hematology, biochemistry, and exploratory measures as outlined in Appendix A
- Back-up blood sample will be collected
- 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: review of previously collected data. Subjects will be reminded to use e-diary to evaluate pruritus on a daily basis
- 5-D Itch: review of previously collected data. Subjects will be reminded to use e-diary to evaluate pruritus on a bi-weekly basis
- Study drug and UDCA accountability
- Study drug and UDCA dispense

Contact 1

The visit will occur 19 weeks ± 7 days after Day 1 over the phone or by email contact and the following will be performed:

- Documentation of AEs that occurred since the signing of the ICF
- Documentation of concomitant medication (including supplements and vitamins) since the last visit
- Compliance with study drug
- Unscheduled visit scheduled, if deemed necessary by investigator

Month 6

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 medication (including supplements and vitamins) since the last visit
- Vital signs and weight (as described at Section 9.2.2)
- Complete physical examination (as described at Section 9.2.1)
- 12-lead ECG after at least 5 minutes rest

- Blood drawn for hematology, biochemistry, and exploratory measures as outlined in Appendix A
- Back-up blood sample collection
- 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.
- 5-D itch, 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 through the Month 12 visit.
- 5-D Itch: review of previously collected data. Subjects will be instructed to evaluate pruritus via 5-D itch at the clinic visits only.
- Liver elastography (e.g., FibroScan) - at the selected sites
- Study drug and UDCA accountability
- Study drug and UDCA dispense
- Double-blind evaluation for dose up-titration will be performed. The double-blind dose up-titration will be requested if the following criteria are met:

No safety concerns limiting up-titration	AND	One of the following criteria: ○ AP ≥ 1.67 × ULN OR ○ < 15% decrease in AP comparing to baseline value OR ○ Total bilirubin > 1 × ULN

Dose Adjustment Visit (2 weeks after Month 6 ± 3 days)

To avoid unblinding, all subjects will be invited to Dose Adjustment visit. For subjects who have safety concerns limiting up-titration, Dose Adjustment visit will still occur to evaluate subjects' status. Dose Adjustment visit will occur 2 weeks after Month 6 visit and the following evaluations will be performed. Subjects will be instructed to not to take study drug at home prior to the clinic visit.

- Documentation of AEs that occurred since the signing of the ICF
- Documentation of concomitant medication (including supplements and vitamins) since the last visit
- Vital signs and weight (as described at Section 9.2.2)
- Brief symptom-directed physical examination (as described at Section 9.2.1)
- Blood drawn for hematology, biochemistry, and exploratory measures as outlined in Appendix A
- Study drug accountability
- Additional assessments as determined by the Investigator

- Dose up-titration will be performed and study drug will be dispensed in a blinded manner:
    - Subjects who meet the up-titration criteria: subjects on 5 mg will be dispensed seladelpar 10 mg; subjects on seladelpar 10 mg will be dispensed seladelpar 10 mg, and subjects on placebo will be dispensed matching placebo. Subjects will immediately start dosing.
    - Subjects who do not meet the up-titration criteria will continue the initially assigned dose.

Contact 2

The visit will occur 32 weeks ± 7 days after Day 1 over the phone or by email contact and the following will be performed:

- Documentation of AEs that occurred since the signing of the ICF
- Documentation of concomitant medication (including supplements and vitamins) since the last visit
- Compliance with study drug
- Unscheduled visit scheduled, if deemed necessary by investigator

Month 9

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 medication (including supplements and vitamins) since the last visit
- Vital signs and weight (as described at Section 9.2.2)
- Brief symptom-directed physical examination (as described at Section 9.2.1)
- Blood drawn for hematology, biochemistry, and exploratory measures as outlined in Appendix A
- Back-up blood sample collection
- 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.
- 5-D itch, 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 the Month 12 visit.
- Study drug and UDCA accountability
- Study drug and UDCA dispense

Contact 3

The visit will occur 45 weeks ± 7 days after Day 1 over the phone or by email contact and the following will be performed:

- Documentation of AEs that occurred since the signing of the ICF
- Documentation of concomitant medication (including supplements and vitamins) since the last visit
- Compliance with study drug
- Unscheduled visit scheduled, if deemed necessary by investigator

Month 12

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 medication (including supplements and vitamins) since the last visit
- Vital signs and weight (as described at Section 9.2.2)
- Complete physical examination (as described at Section 9.2.1)
- 12-lead ECG after at least 5 minutes rest
- Blood drawn for hematology, biochemistry, and exploratory measures (including fat-soluble vitamins) as outlined in Appendix A
- Back-up blood sample collection
- 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.
- 5-D itch, PBC-40, PGI-S and PGI-C questionnaires via e-diary
- Pruritus NRS: review of previously collected data.
- E-diary will be collected
- Liver elastography (e.g., FibroScan) - at the selected sites
- Study drug and UDCA accountability
  Study supply of UDCA will be switched to pre-study supply of UDCA

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

- Subjects who consent to participate in CB8025-31731 will have the Month 12 visit combined with the Day 1 visit of the CB8025-31731. Subjects on seladelpar will continue dosing; subjects on placebo will initiate seladelpar (5 or 10 mg).

- Subjects who do not consent to participate in CB8025-31731 will stop study drug and enter the 4-week follow-up period.

9.1.4 Post-Treatment Follow-Up

The visit will occur four weeks (28 days ± 7 days) after the last dose of the study drug. The following evaluations will be performed:

- Documentation of AEs that occurred since the signing of the ICF
- Documentation of concomitant medication (including supplements and vitamins) since the last visit
- Vital signs and weight (as described at Section 9.2.2)
- Complete physical examination (as described at Section 9.2.1)
- 12-lead ECG after at least 5 minutes rest
- Blood drawn for hematology, biochemistry, and exploratory measures as outlined in Appendix A
- Back-up blood sample collection
- Women of child-bearing potential will have a serum pregnancy test performed

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

9.1.5 Early Termination Visit

Subjects who discontinue participation in the study prematurely 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 medication (including supplements and vitamins) since the last visit
- Vital signs and weight (as described at Section 9.2.2)
- Complete physical examination (as described at Section 9.2.1)
- 12-lead ECG after at least 5 minutes 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 reproductive status will have serum pregnancy test performed. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.
- Pruritus NRS, 5-D itch, PBC-40, PGI-S and PGI-C questionnaires via e-diary
- Pruritus NRS: review of previously collected data.
- E-diary will be collected

- Liver elastography (e.g., FibroScan) - at the selected sites
- Study drug and UDCA accountability
- Study supply of UDCA will be switched to pre-study supply of UDCA

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

9.1.6 Unscheduled Visit

Unscheduled visit must be scheduled if Safety Monitoring Criteria are met within the timeline outlined in Section 10.5. An unscheduled visit might be scheduled at any time during the study participation if deemed necessary per the investigator's clinical judgement.

At any Unscheduled Visit the following evaluations will be performed:

- Documentation of AE that occurred since the signing of the ICF
- Review and documentation of concomitant medication (including supplements and vitamins) since the last visit
- Symptom-directed (brief) physical examination (as described at Section 9.2.1)
- Blood drawn for biochemistry and hematology
- Additional assessments as determined by the investigator

9.2 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 center personnel with administrative and detailed technical information that does not impact subject safety.

9.2.1 Medical History and Physical Examination

A detailed medical history and PBC medical history will be taken at Screening.

Complete physical examinations will be performed at Screening, Day 1, Month 6, Month 12, Follow-up visit, and Early Termination visit (if applicable). 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, Dose Adjustment Visit, Month 9, and Unscheduled visits. Brief physical examinations will be performed for a condition that warrants the exam as determined by the investigator. Subjects with platelet level above 500×10^3 µL on hematology panel will be evaluated for thrombolytic events.

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

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

9.2.2 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 rest.

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

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

9.2.3 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 period or Early Termination (if applicable).

9.2.4 Laboratory Tests

Laboratory testing (as described below) will be performed at all clinic visits. Blood samples will be collected after at least an 8-hour overnight fast and prior to dosing. If the subject forgets to fast or takes the study drug prior to the blood collection, the site will continue to draw labs.

Hematology will be assessed at all visits.

Biochemistry will be assessed at all visits.

Exploratory Measures will be assessed at all onsite visits with the exception of Dose Adjustment Visit. At the Screening visit only AMA will be tested. Fat-soluble vitamins (vitamins A, D, E, and K) will be tested at Day 1, Week 52, and ET visit (if applicable) only.

Hepatitis B and C testing will be assessed at Screening only. Women of child-bearing potential will have a serum pregnancy test performed at each clinic visit: Screening, Run-In, Day 1, Month 1, from Month 3 through Month 12, and Follow-up visit or Early Termination (if applicable). Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.

Urine drug screen will be assessed at Screening only.

Laboratory testing will be obtained as follows:

Biochemistry:

AP, AST, ALT, GGT, protein, albumin, total bilirubin, direct bilirubin, indirect bilirubin, bone-specific AP, aldolase, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN)/urea, creatinine, estimated glomerular filtration rate (eGFR), CK, venous blood glucose, lactate dehydrogenase (LDH), triglycerides, total cholesterol, HDL-C, and LDL-C, troponin I, lipase, and amylase.

Hematology:

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

PT and INR will also be performed locally at the Screening visit, Run-In, and during the treatment period if deemed necessary by the Investigator.

Exploratory Measures:

Anti-mitochondrial antibodies, autotaxin, IgM, fibronogen, FGF19, haptoglobin, hs-CRP, homocysteine, hyaluronic acid (HA), procollagen III amino terminal peptide, Pro-C3, tissue inhibitor of metalloproteinase 1, C4 (7α-hydroxy-4-cholesten-3-one).

Other Testing:

HBsAg, HCV RNA; Vitamin A, Vitamin D, Vitamin E, and Vitamin K; serum pregnancy testing (β-HCG)

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 used to measure drug level, potential new biochemical markers, and/or to replace any missing or discarded samples.

Urine Drug Screen:

Amphetamine, THC (11-nor-9-carboxy-delta-9-THC), Cocaine, Opiates, and Phencyclidine. Sample collection, processing and handling details are provided in the Laboratory Manual.

9.2.5 Liver Elastography

Liver elastography (e.g., FibroScan) exam will be used to evaluate liver fibrosis 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 to be a reliable, highly accurate, and precise method for assessing hepatic fibrosis. Other liver elastography techniques might include shear-wave elasticity imaging, acoustic radiation force impulse imagining, supersonic shear imaging, or magnetic resonance elastography. For sites when different liver elastography techniques are available, subjects must be evaluated using the same technique over the study duration.

Liver Elastography Exam Schedule and Timing: Subjects will undergo three liver elastography exams at centers when the test is available: Day 1, Month 6, Month 12 visits, and Early Termination visit (if applicable). Clinical sites will determine the logistics of scheduling the liver elastography exam and complete within the study visit window.

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

Liver Elastography Exam Analysis: Local Reader will review and analyze scans.

9.2.6 Liver Biopsy

Subjects who are willing to evaluate their PBC stage and activity will have liver biopsy performed during Run-In period. If liver biopsy was performed within 1 year from Day 1, baseline liver biopsy can be waived. For these instances sites will attempt to collect biopsy material. This material might be used as a baseline comparison to liver biopsy that might be performed in at least 3 years (± 3 months) of treatment during the long-term study (CB8025-31731).

Liver biopsies will generally be obtained from the right lobe of the liver, however, if the Baseline biopsy is obtained from the left lobe, then the follow-up liver biopsy (in CB8025-31731) must also be obtained from the left lobe. Biopsies should be performed using a 16G or larger biopsy instrument and samples should be at least 2.0 cm in length.

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: Central reader will review and analyze the samples.

9.2.7 Pruritus Numerical Rating Scale (NRS)

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

The test will be performed via e-diary on a daily basis from the Run-In (Week -2) visit and for the first six month of study drug treatment. After six month of treatment, pruritus NRS will be evaluated on a monthly basis over 7 consecutive days. See Appendix D for details. Pruritus NRS data will be collected via e-diary.

9.2.8 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 (Elman, 2010). See Appendix E for details.

The test will be performed via e-diary on a bi-weekly basis from Run-In up up until the Month 6 visit, and at each clinic visit from Month 6 through the Month 12 visit or Early Termination Visit (if applicable). 5-D itch data will be collected via e-diary.

9.2.9 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 quality of life tool developed to specifically measure the psychometric profile of PBC patients. It covers six domains relevant to PBC including cognitive, social, emotional function, fatigue, itch, and other symptoms (Jacoby, 2005). See Appendix F for details.

It will be performed at each clinic visit from the Run-In period through the Month 12 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.

9.2.10 PGI-S and PGI-C

The PGI-S and the PGI-C questionnaires will be used as an anchor scale to help interpret within-patient change in pruritus data collected via other pruritus questionnaires. See Appendix G and Appendix H for details.

9.3 Dose Titration

During the study participation subjects might go through dose titration for efficacy reasons. For subjects who have safety concerns limiting up-titration, Dose Adjustment visit will still occur to evaluate subjects' status. Subject will have a dose evaluation performed at the Month 6 visit to determine if dose up-titration is necessary. Dose evaluation will be done in a double-blind manner.

The double-blind dose up-titration will occur if the following criteria are met:

No safety concerns limiting up-titration	AND	One of the following criteria: o AP ≥ 1.67 × upper limit of normal (ULN), OR o < 15% decrease in AP comparing to baseline value, OR o Total bilirubin > 1 × ULN

Subjects who meet the criteria will receive the up-titrated dose at the Dose Adjustment visit (2 weeks after Month 6). Subjects on 5 mg will be up-titrated to 10 mg; subjects on 10 mg will continue 10 mg; and subjects on placebo will continue placebo.

10 ADVERSE EVENTS

10.1 General

10.1.1 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 study treatment, or 2) was present prior to 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 adverse event and should be reported to the clinical monitor and to the Sponsor immediately upon learning of the event. Pregnancies will be followed up through delivery or termination of the pregnancy.

A treatment emergent adverse event (TEAE) will be defined as any AE that newly appeared, increased in frequency, or worsened in severity after initiation of the study drug. For adverse event reporting purposes, UDCA is not considered as a study drug.

10.1.2 Definition of Serious AEs (SAEs)

An SAE is any medical occurrence 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 significant 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 upon 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

10.1.3 AE Severity

The severity of an AE will be graded from 1 to 5 according to Appendix C and NCI CTCAE version 4.0 criteria (v4.03, 14 June 2010).

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 five 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 significant 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

10.1.4 Adverse Event Outcome

Subjects will be followed until AEs have either resolved, returned to baseline status, or are deemed stable or commensurate with ongoing disease processes, per the Investigational judgment.

One of the four outcomes listed below must be recorded:

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

Resolved with sequelae – The subject has recovered from the event with some residual effects observable.

Ongoing – Effects of the event are still present, regardless of whether the effect is changing or stable and persistent.

Fatal outcome (for serious adverse events only)

10.1.5 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

10.1.6 Action Taken with Study Medication

As a consequence of an AE, the action taken with study drug can be:

- None: no changes were made to study drug administration or dose
- Permanently discontinued: study drug was stopped and not restarted
- Temporarily interrupted: dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- Temporarily interrupted: dosing was temporarily interrupted or delayed due to the AE and restarted at the decreased dose
- Not applicable: e.g., in case the AE occurred after signing the ICF but before the administration of study drug was commenced

10.2 Recording, Reporting, and Follow-up of 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 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 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 AE and concurrent illnesses.

Any laboratory abnormalities deemed clinically significant by the investigator should be reported as an AE. A clinically significant abnormality is a confirmed abnormality that is

changed sufficiently from baseline, so that in the judgment of the investigator, a change in management is warranted. This alteration may include: monitoring the laboratory test further, 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 significant 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.

10.2.1 SAE Reporting Process

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 United States 21 CFR § 312.32. Country specific regulatory requirements will be followed in accordance with local country regulations and guidelines. Independent Ethics Committees (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, 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 10.1.2

The outcome for the event will be listed on the SAE Report Form as defined in Section 10.1.4.

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 serious and unexpected suspected adverse reactions (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 a Serious Adverse Event.

The investigator will document all available information regarding the SAE on the SAE form. The investigator should not wait to receive additional information to fully document 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:

- 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, using the SAE form in eCRF detailing relevant aspects of the adverse events 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.

10.2.2 Follow-up of Reported AEs

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

After the Follow-up Visit, non-serious AEs should be followed up until they resolve or have failed to resolve, 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.

10.3 Distribution of Responsibilities

Details about the distribution of safety responsibilities are presented in the Safety Reporting Plan.

10.4 Safety Monitoring Criteria and Withdrawal Criteria

10.4.1 Liver Safety Monitoring

Enrolled subjects with the following lab abnormalities should be monitored closely and may interrupt study drug or discontinue study drug if criteria are met:

1. Elevation of ALT/AST

Normal ALT/AST at baseline

- ALT/AST > 5 × ULN and total bilirubin ≤ 1 × ULN: **Interrupt study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B). Study medication can be restarted only if a firm competing etiology is identified and liver tests return to baseline.
- ALT/AST > 5 ULN and total bilirubin > 1 × ULN:
  - Subjects with normal total bilirubin at baseline: **Stop study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B).

- Subjects with elevated total bilirubin at baseline:
  - Total bilirubin > 1.5 × baseline: **Stop study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B).
  - Total bilirubin ≤ 1.5 × baseline: **Interrupt study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B). Study medication can be restarted only if a firm competing etiology is identified and liver tests return to baseline.

Elevated ALT/AST at baseline:

- ALT/AST > 3 × baseline AND INR ≤ 1.5 × ULN AND no liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice): **Continue study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days. Closely follow the subject (see Appendix B).
- ALT/AST > 3 × baseline AND INR > 1.5 × ULN AND no liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice): **Interrupt study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B). Study drug can be restarted only if a firm competing etiology is identified and liver tests return to baseline.

2. Liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice) AND ALT/AST > 3 × baseline (irrespective of baseline levels): **Interrupt study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days. Closely follow the subject (see Appendix B). Study drug can be restarted only if a firm competing etiology is identified and liver tests return to baseline.
3. Elevation of total bilirubin > 1.5 × baseline, regardless of ALT or AST levels, AND indicators of immunological reaction (e.g., rash, eosinophilia > 5%) OR liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice): **Interrupt study drug**. Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B). Study drug can be restarted only if a firm competing etiology is identified and liver tests return to baseline.
4. Hepatic decompensation (e.g., decompensated cirrhosis with gastro-esophageal variceal bleeding, ascites, or hepatic encephalopathy) during the study: **Stop study drug** and closely follow the subject (see Appendix B).
5. Close monitoring of a subject is not possible (see Appendix B): **Stop study drug**.

10.4.2 Muscle Safety Monitoring

I. CK > 5 × ULN with musculoskeletal symptoms: **Stop study drug**. Repeat the test within 3 days. Follow the subject weekly until resolution or stabilization.

II. CK > 5 × ULN without musculoskeletal symptoms: repeat the test within 3 days. If on repeat test CK is > 2.5 × ULN, **stop study drug**. Follow the subject weekly until the event resolution or stabilization.

III. CK > 2.5 × ULN and ≤ 5 × ULN regardless to musculoskeletal symptoms: repeat the test within 3 days. If the test is confirmed, **study drug will be continued at a decreased dose.** For subjects on 5 mg, the study drug will be switched to placebo.

10.4.3 Serum Creatinine Monitoring

I. Serum creatinine > 2.0 × ULN: **Stop study drug**. The subject should be monitored weekly until resolution or stabilization.

II. Serum Creatinine > 1.5 × ULN and ≤ 2.0 × ULN: I**nterrupt study drug**. Repeat the test within 3 days. If the test is confirmed and no alternative etiology is identified, **stop study drug**. If alternative etiology is identified, study drug may be restarted after serum creatinine returns to baseline values. The subject should be monitored weekly until event resolution.

10.4.4 Pancreatic Safety Monitoring

I. Amylase > 3 × ULN and/or lipase > 3 × ULN without clinical symptoms of acute pancreatitis: repeat the test within 3 days. If the test confirms suspicion, **interrupt study drug**. Abdominal imaging is to be performed to exclude an alternative cause for the event. Study drug might be restarted only if a firm competing etiology of acute pancreatitis is identified.

II. Amylase > 3 × ULN and/or lipase > 3 × ULN with clinical symptoms of acute pancreatitis: **interrupt study drug**. Repeat the test within 3 days. Abdominal imaging is to be performed to exclude an alternative cause for the event. Study drug might be restarted only if a firm competing etiology of acute pancreatitis is identified.

10.4.5 Additional Withdrawal Criteria and Replacement of Subjects

Subjects may be discontinued from the study for the following reasons:

- Enrolled into the study in violation of this protocol
- Required the use of a prohibited concomitant medication
- 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

- Significant protocol deviation
- Administrative decision by the investigator or Sponsor or designee
- Lost to follow-up

The date the subject is withdrawn and the reason for discontinuation will be recorded in the eCRF.

10.5 Precautions

10.5.1 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 one 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 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 trial and the preferred and usual lifestyle of the subject.

A second effective birth control method may include:

- 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

11 STUDY TERMINATION

CymaBay Therapeutics, Inc. reserves the right to discontinue the study if it becomes aware of information concerning the quality, safety of the trial medication (based on recommendation from Medical Monitor), as well as other important information that may affect proper conduct of the trial. Should the study be discontinued by the Sponsor, then the investigator, IEC, and competent authorities should 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, due to specific clinical observations relating to safety concerns. If the Principal Investigator intends to prematurely terminate the trial at his/her site, he/she must immediately inform the Sponsor on his/her intention as well as of the reasons why.

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

12 DATA HANDLING CONSIDERATIONS

12.1 Processing of Electronic Case Report Forms

The study will be performed using electronic data capture (EDC). 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.

12.2 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 100% 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 (WHO) Drug classification will be used to code medications.

Electronic CRFs will be available for review by the Clinical Research Associate (CRA) and Sponsor and Sponsor`s designee after completion by the site. The eCRFs will be monitored remotely and onsite by the Clinical Research Organization (CRO) after documented training and in accordance with the monitoring plan. The CRA will review the eCRF data on a regular basis and post any queries for the site to complete prior to the scheduled onsite monitoring visits. Only those individuals who are qualified and authorized by the investigator to complete eCRFs will trained and receive passwords allowing eCRF completion.

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.

12.3 Data Discrepancies

After all subjects complete the study and data discrepancies are resolved, protocol deviations during both enrollment and study execution will be reviewed. Significant protocol deviations and procedural discrepancies will be discussed. All data will be included in the safety analyses.

13 STATISTICAL ANALYSES

13.1 General Statistical Considerations

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using SAS Version 9.3.

Descriptive statistics will be displayed to provide an overview of the study results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for analysis.

Statistical tests of efficacy variables will be presented as 2-sided p-values rounded to 4 decimal places. P-values less than 0.0001 will be presented as "<0.0001" and p-values greater than 0.9999 will be presented as ">0.9999." Statistical comparison will be performed at the 0.0500 level of significance. For continuous variables, display of descriptive statistics will generally include n (number of subjects), mean, standard deviation (SD), median, minimum, and maximum.

13.2 Determination of Sample Size

The placebo group responder rate is estimated at less than 15% (Nevens, 2016). The seladelpar 10 mg dose group responder rate is estimated at 40%. With the use of a 2-sided test of equality of binomial proportions based on Pearson chi-square test at the 5% level of significance, a sample size of 80 patients per group will provide greater than 90% power to detect a difference between the 10 mg seladelpar group and the placebo group.

The key secondary efficacy analysis of normalization of AP is estimated to have a placebo response rate is of 5%. A 2-sided test of equality of binomial proportions based on Pearson chi-square test at the 5% level of significance yields a sample size of 80 patients per group. This sample size provides more than 90% power to detect a difference of 30% between the 10 mg seladelpar and placebo groups.

The key secondary efficacy analysis of change in pruritus NRS sample size calculation was based on a 2-sample 2-sided t-test at the 5% alpha level. The standard deviation is 3 (Lai, 2017). Under these assumptions, a total of 23 subjects per group provides ≥90% power to detect a treatment difference of ≥3 (Lai, 2017) between 10 mg seladelpar and placebo groups.

To account for a subject dropout rate of > 15%, the planned number of study subjects for an adequately powered study is 240 subjects, or 80 subjects per treatment group.

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

13.3 Analysis Sets

13.3.1 Safety Set

The safety set is defined by any subject who receives at least one 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 set.

13.3.2 Intent to Treat Analysis Set (ITT)

The ITT analysis set is defined as any subject randomized into the study.

13.3.3 Modified Intent to Treat Analysis Set

The Modified Intent to Treat (mITT) set includes any subject who is randomized into the study and receives at least one dose of study drug. The mITT set will be used for the primary efficacy analysis.

13.3.4 Per Protocol (PP) Analysis Set

The Per-Protocol (PP) set includes any subject who is randomized into the study, receives at least one dose of study drug, has at least one post baseline AP and total bilirubin evaluation, and does not have a protocol violation that is deemed to impact the efficacy analysis.

13.4 Analysis Time Points

Baseline is defined as the arithmetic mean of multiple pre-treatment measurements (Screening, Run-In, Day 1, and UNS if applicable) preceding the first administration of study drug, or as the last measurement prior to the first administration of study drug if only single value is available.

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

Unless otherwise noted, all references to the last dose of study drug refer to the last dose of study drug taken across all study periods.

The Last Visit for all assessments is the last non-missing assessment during the Treatment Period. All scheduled and unscheduled assessments within this time will be considered. Last Visit will be determined separately for each study procedure where Last Visit is mentioned within this document.

13.5 Handling of Drop-Outs and Missing Data

Detailed descriptions of Handling Drop-Outs and Missing Data are contained in the SAP. All efforts will be made to prevent missing data from occurring.

Sensitivity analyses will be performed on the primary efficacy endpoint using observed data only. The robustness of the primary analysis will be explored using several sensitivity analyses on a variety of patient populations including subjects who discontinue study drug.

For responder analyses, any subject who does not provide an assessment at the specified time point for the defining of response will be considered a non-responder.

For efficacy endpoints that utilized an analysis of covariance (ANCOVA) model, observed cases will serve as the primary analysis. The robustness of the primary analysis will be explored using several sensitivity analyses to assess the effect of missing data. Analysis will be conducted where missing data is imputed using a "responders," last observation carried forward (LOCF) and "worst case" methodologies. For efficacy endpoints that utilized the mixed models repeated measures (MMRM), no imputations will be made for missing values.

The following additional sensitivities will be performed:

- As responders
- Same as primary analysis except based on the ITT Set.
- Same as primary analysis except based on the PP Set.
- Same as primary analysis except impute dropouts as non-responders in the seladelpar arm and as responders in the placebo arm (i.e. worst-case analysis).
- Same as primary analysis except impute missing data using a pattern-mixture model (PMM) which considers different mechanisms for missing data.
- Same as primary analysis except specify the proportion of patients achieving a decrease in AP as at least 10%, 20%, and 40%.
- Using Medians instead of arithmetic means for baseline values

13.6 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 overall and repeated by stratification group.

Demographic 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. Values will be summarized and listed using absolute values and percentages.

Study participants that discontinued the study along with reasons for discontinuation will be summarized and listed.

13.7 Efficacy Analysis

Primary Efficacy Endpoint

The primary efficacy analysis will be based on the following composite endpoint evaluated after 52 weeks of treatment:

- AP < × 1.67 ULN,

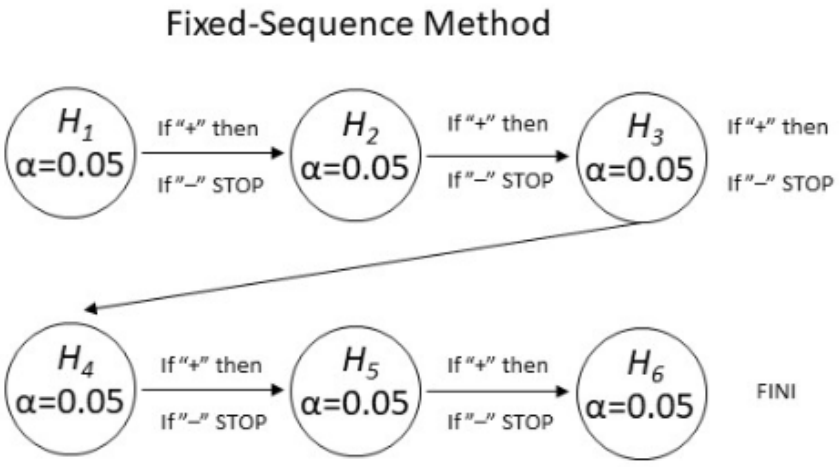
- AP decrease of ≥ 15%, and
- Total bilirubin ≤ ULN

Treatment comparisons of the primary efficacy endpoint will be tested using a gateway method. A hierarchical "fixed-sequence" approach will be used to evaluate the primary endpoint as follows:

1. The composite endpoint and seladelpar 10 mg vs placebo if negative stop
2. If seladelpar 10 mg test is positive, that test the composite endpoint for seladelpar 5/10 mg vs placebo; if negative stop

This testing procedure maintains the overall Type I error for the primary efficacy endpoint at 5%. Analyses for the composite endpoint will be completed using a Cochran–Mantel–Haenszel (CMH) test stratified by the randomization stratification factor (AP level < 350 U/L and ≥ 350 U/L) and pruritis NRS < 4 and NRS ≥ 4 and will be conducted on the mITT population. If assumptions required for the CMH test including, but not limited to, small cell counts or all responses within a stratum are the same for both treatment groups (e.g., all responders within a stratum), additional data handling and analysis methodology will be used and described within the SAP.

The fixed sequence approach is as follows:



Notes: H_1=Composite endpoint tested with 10 mg seladelpar vs. placebo, H_2=Composite endpoint tested with 5/10 mg seladelpar vs. placebo, H_3=AP Normalization tested with 10 mg seladelpar vs. placebo, H_4=AP Normalization tested with 5/10 seladelpar vs. placebo, H_5= Change from baseline in the weekly averaged peak pruritus NRS over 6 months tested with 10 mg seladelpar vs. placebo, H_6= Change from baseline in the weekly averaged peak pruritus NRS over 6 months tested with 5/10 mg seladelpar vs. placebo

Statistical significance of the difference between placebo and seladelpar will be defined as a p-value ≤ 0.05. Sensitivity analyses will be performed on the primary efficacy endpoint using

observed data only. The CMH test will also be used for AP responder analyses, disease prognostic risk responder analyses, and subgroup analyses.

Efficacy laboratory parameters

Efficacy laboratory parameters will be analyzed using an ANCOVA model with absolute change and percent change from Baseline as the dependent variable including treatment group and randomization stratification factor as fixed effects and Baseline as a covariate.

Secondary endpoints

The key secondary efficacy analysis for normalization of AP is a responder analysis and will be conducted in the mITT set using the same approach specified for the primary efficacy analysis.

Change from baseline in the weekly averaged peak pruritus NRS over 6 months will be evaluated using ANCOVA with terms for treatment factor and baseline pruritis score as covariates. The analysis will be limited to those subjects in the mITT analysis set with an NRS ≥ 4. The weekly pruritus score will be calculated by recording the daily pruritis score each day for seven days and then taking the median value of the seven days' worth of daily recorded data. If any data are available for a given week, the available NRS results will be used for the calculation of the weekly median. If no NRS results are available in a given week, the median of the prior week will be used to impute those missing results using the last observation carried forward (LOCF) method.

Sensitivity analyses will be performed using the mITT population on all responder endpoints using a logistic regression model with response as the endpoint and treatment group and randomization strata as factors.

Other Secondary endpoints will include the first occurrence of any of the following clinical events:

- Overall death
- Liver transplantation
- MELD score ≥ 15
- Uncontrolled ascites (diuretic resistant)
- Hospitalization for new onset or recurrence of any of the following:
  - variceal bleeding
  - hepatic encephalopathy (as defined by a West Haven score ≥ 2)
  - spontaneous bacterial peritonitis (confirmed by culture from diagnostic paracentesis)
- Hepatocellular carcinoma
- Advanced PBC as defined by the Rotterdam criteria (low serum albumin AND total bilirubin above 1 × ULN)

Clinical events will be validated by a Critical Event Review Committee (CERC) composed of independent clinical experts familiar with hepatic diseases.

Other secondary and exploratory analysis will be performed using ANCOVA similar to efficacy laboratory parameters where appropriate.

Tables and listing will be provided for all efficacy analysis and exploratory analysis and figures where appropriate.

13.8 Safety Analysis

All safety analyses will be based on the Safety population. TEAEs will be summarized by MedDRA System Organ Class (SOC) and preferred term by severity and by causal relationship to seladelpar. The severity of TEAEs will be graded based on NCI CTCAE, Version 4.0.

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

An overall summary of AEs will provide the overall summary of TEAEs and the numbers and percentages of subjects with at least 1 TEAE, with a serious TEAE, with a TEAE that led to permanent withdrawal of study medication, with a drug-related TEAE, with a severe TEAE, and with a drug-related serious TEAE. The number and percentage of subject discontinuations due to TEAEs, and the number and percentage of subjects with AEs leading to death (if applicable), will also be summarized.

Descriptive statistics and change from baseline will be determined for each measure of laboratory tests, at each assessment. Abnormal laboratory values will be graded by the investigator as: “clinically significant” or “not clinically significant”, where available, and all laboratory values will be reported. Clinically significant abnormal laboratory values will be reported as AEs, after study treatment has been initiated. investigators may repeat laboratory tests for any parameter that is abnormal and/or clinically significant.

Tables and listings will be provided for all safety analyses.

14 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1 Study Monitoring

14.1.1 Source Documents

The investigators and institution(s) will permit trial-related monitoring of the eCRF data by CymaBay Therapeutics Inc. or their assignee by providing direct access to source data and/or documents. The study monitor will verify the CRFs against the source documentation.

14.1.2 Case Report Forms

Patients who have signed the ICF will be assigned a patient number and will have trial data entered into a CRF. CRF completion is important to the Medical Monitoring of the trial and should be completed promptly after each patient visit.

14.1.3 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 patient 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 will be noted in the source documentation, in the eCRF and a complementary database. The Sponsor will assess any protocol deviation and decide whether any of these non-compliances should be reported to regulatory authorities as a serious breach of ICH Good Clinical Practice (GCP) and the protocol.

14.2 Audits and Inspections

14.2.1 Trial 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 on-site 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 no documentation that can link study information to the specific subject will be collected or retained by the Sponsor.

14.2.2 Trail Monitoring

A Sponsor representative will visit the site to initiate the study, prior to the first treatment of the first subject, and at agreed upon times throughout the study, including at the end of the study. Medication dispensing, and clinical drug supply records will be 100% verified at the study site by the study monitor. It is understood that all subject specific information is confidential and no documentation that can link study information to the specific subject will be collected or retained by the Sponsor.

14.3 Ethics Committees

The investigators will provide IECs with all information impacting the risk profile of the drug. The trial 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.

15 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 adverse events 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.

16 ETHICS

16.1 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 trial.

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

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

16.2 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.

16.3 Written Informed Consent

The subject must give consent to participate in the trial, only after having been fully informed by the investigator or a person designated by him/her of the nature, significance, and implications of the trial, as well as to the associated risks involved. Such meetings must be carried out on an individual basis and 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 or not to participate in the study. Written informed consent will be obtained for all subjects enrolled in the trial and before study related activities are performed on a subject. The process of obtaining written 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 personally dated and signed by both the investigator and the subject. The original will be retained by the investigator and filed in the investigator's Site File. A copy of the original must be provided to the study subject.

17 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.

18 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.

19 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 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 pre-publication manuscript prior to the submission of the manuscript, to the publisher.

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APPENDIX A – LABORATORY EVALUATIONS

Biochemistry			
AP	Direct Bilirubin Indirect Bilirubin	Bicarbonate	LDH
AST		BUN/Urea	TG
ALT	Aldolase	Serum Creatinine	Total Cholesterol
GGT	Sodium	eGFR	HDL-C
Protein	Potassium	CK	LDL-C
Albumin	Chloride	Venous Glucose	Amylase
Total Bilirubin		Troponin I	Lipase

Hematology	**Exploratory Measures**		**Other Tests**
RBC	AMA	Homocysteine	Serum Pregnancy Test
Hemoglobin	Autotoxin	Hyaluronic acid (HA)	Back-up Sample
Hematocrit	C4	Procollagen III amino terminal peptide	HBsAg (Screening only)
WBC	IgM		HCV RNA (Screening only)
WBC differentials (abs and %)	Fibrinogen	Tissue inhibitor of metalloproteinase 1	Vitamin A (D1, W52, ET only)
Platelets	FGF19	Pro-C3	Vitamin D (D1, W52, ET only)
PT/INR	Haptoglobin		Vitamin E (D1, W52, ET only)
	hs-CRP		Vitamin K (D1, W52, ET only)
			Urine Drug Screen (Screening only)

APPENDIX B – CLOSE OBSERVATION CRITERIA

The "close observation" will be performed on subjects meeting liver safety monitoring criteria per Section 10.1.4. If "close observation" is not feasible, study drug must be stopped.

1. 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
2. Laboratory Testing
    a. Repeat ALT, AST, Bilirubin (total), and PT/INR within 3 days
    b. Monitor the subject every 3 days until the lab abnormality stabilization
    c. After lab abnormality is stabilized, monitor the subject once a week until the event resolution
3. 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 (NCI CTCAE)

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:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_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

APPENDIX E – 5-D ITCH SCALE

1. **Duration**: During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree**: Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction**: Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability**: Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

APPENDIX F – PBC-40 QOL

For each statement, please circle the response that comes closest to how you feel. If any of the statements do not apply to you please circle 'does not apply'.

Can you say how often the following statements about digestion and diet applied to you IN THE LAST FOUR WEEKS?							
1	I was able to eat what I liked	Never	Rarely	Sometimes	Most of the time	Always	
2	I ate or drank only a small amount, and still felt bloated	Never	Rarely	Sometimes	Most of the time	Always	
3	I felt unwell when I drank alcohol	Never	Rarely	Sometimes	Most of the time	Always	Did not apply / never drink alcohol
And IN THE LAST FOUR WEEKS, how often did you experience any of the following?							
4	I had discomfort in my right side	Never	Rarely	Sometimes	Most of the time	Always	
5	I had dry eyes	Never	Rarely	Sometimes	Most of the time	Always	
6	My mouth was very dry	Never	Rarely	Sometimes	Most of the time	Always	
7	I had aches in the long bones of my arms and legs	Never	Rarely	Sometimes	Most of the time	Always	
Some people with PBC experience itching. How often did you experience itching IN THE LAST FOUR WEEKS? If you did not itch, please circle 'does not apply'							
8	Itching disturbed my sleep	Never	Rarely	Sometimes	Most of the time	Always	Did not apply/ no itch
9	I scratched so much I made my skin raw	Never	Rarely	Sometimes	Most of the time	Always	Did not apply/no itch
10	I felt embarrassed because of the itching	Never	Rarely	Sometimes	Most of the time	Always	Did not apply/no itch
Fatigue can also be a problem for many people with PBC. How often did the following statements apply to you IN THE LAST FOUR WEEKS?							
11	I had to force myself to get out of bed	Never	Rarely	Sometimes	Most of the time	Always	
12	I had to have a sleep during the day	Never	Rarely	Sometimes	Most of the time	Always	
13	Fatigue interfered with my daily routine	Never	Rarely	Sometimes	Most of the time	Always	
14	I felt worn out	Never	Rarely	Sometimes	Most of the time	Always	

15	I felt so tired, I had to force myself to do the things I needed	Never	Rarely	Sometimes	Most of the time	Always	
16	I felt so tired, I had to go to bed early	Never	Rarely	Sometimes	Most of the time	Always	
17	Fatigue just suddenly hit me	Never	Rarely	Sometimes	Most of the time	Always	
18	PBC drained every ounce of energy out of me	Never	Rarely	Sometimes	Most of the time	Always	
	The next section is about the effort and planning that can be involved in living with PBC. Thinking about THE LAST FOUR WEEKS, how often did the following statements apply to you?						
19	Some days it took me a long time to do anything	Never	Rarely	Sometimes	Most of the time	Always	
20	If I was busy one day I needed at least another day to recover	Never	Rarely	Sometimes	Most of the time	Always	
21	I had to pace myself for day-to-day things	Never	Rarely	Sometimes	Most of the time	Always	
	The following statements are about the effects that PBC may have on things like memory and concentration. Thinking about THE LAST FOUR WEEKS, how often did the following statements apply to you?						
22	Because of PBC I had to make a lot of effort to remember things	Never	Rarely	Sometimes	Most of the time	Always	
23	Because of PBC I had difficulty remembering things from one day to the next	Never	Rarely	Sometimes	Most of the time	Always	
24	My concentration span was short because of PBC	Never	Rarely	Sometimes	Most of the time	Always	
25	Because of PBC, I had difficulty keeping up with conversations	Never	Rarely	Sometimes	Most of the time	Always	
26	Because of PBC, I found it difficult to concentrate on anything	Never	Rarely	Sometimes	Most of the time	Always	
27	Because of PBC, I found it difficult to remember what I wanted to do	Never	Rarely	Sometimes	Most of the time	Always	
	Now some more general statements about how PBC may be affecting you as a person. How much do the following statements apply to you?						
28	Because of PBC, I get more stressed about things than I used	Not at all	A little	Somewhat	Quite a bit	Very much	
29	My sex life has been affected because of PBC	Not at all	A little	Somewhat	Quite a bit	Very much	Does not apply
30	Having PBC gets me down	Not at all	A little	Somewhat	Quite a bit	Very	
31	I feel I neglect my family because of having PBC	Not at all	A little	Somewhat	Quite a bit	Very much	Does not apply
32	I feel guilty that I can't do what I used to do because of having	Not at all	A little	Somewhat	Quite a bit	Very much	
33	I worry about how my PBC will be in the future	Not at all	A little	Somewhat	Quite a bit	Very much	

These statements relate to the possible effects of PBC on your social life. Thinking of your own situation, how much do you agree or disagree with them?

34	I sometimes feel frustrated that I can't go out and enjoy myself	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
35	I tend to keep the fact that I have PBC to myself	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
36	I can't plan holidays because of having PBC	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
37	My social life has almost stopped	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

The next section is about the impact that PBC may be having on your life overall. How much do you agree or disagree with the following statements?

38	Everything in my life is affected by PBC	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
39	PBC has reduced the quality of my life	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
40	I can still lead a normal life, despite having PBC	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

The next few questions are about your general health and well being:

A	In general, would you say your health is:	Excellent	Very good	Good	Fair	Poor
B	And how would you have rated it before you had PBC?	Excellent	Very good	Good	Fair	Poor
C	COMPARED TO ONE YEAR AGO, how would you rate your health in general now?	Much better	Somewhat better	About the same	Somewhat worse	Much worse

APPENDIX G – PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S)

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

- o None
- o Mild
- o Moderate
- o Severe

APPENDIX H – PATIENT GLOBAL IMPRESSION OF CHANGE (PGI-C)

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

- o Very Much Better
- o Moderately Better
- o A little bit better
- o No change
- o A little worse
- o Moderate Worse
- o Very much worse

APPENDIX I – NORMAL RANGES FOR SAFETY LABORATORY PARAMETERS

BIOCHEMISTRY	Conventional Units	SI Units
AP	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	25-210 U/L	25-210 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
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 J – INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

CB8025-31735

A 52-week, placebo-controlled, randomized, Phase 3 study to evaluate the safety and efficacy of seladelpar in subjects with Primary Biliary Cholangitis (PBC) and an inadequate response to or an intolerance to ursodeoxycholic acid (UDCA)

PROTOCOL VERSION NUMBER:	Version 1.0
DATE OF PROTOCOL:	3-JUL-2018

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 (DD/MMM/YYYY): _____

Site Address: _____

_____

_____