PROTOCOL TITLE:	The Effect of Hepatic Impairment on The Pharmacokinetics of Seladelpar: An Open-Label Study Following Oral Dosing of Seladelpar to Subjects with Primary Biliary Cholangitis (PBC) and Hepatic Impairment
PROTOCOL NUMBER:	CB8025-21838
VERSION NUMBER:	5.0
DATE:	06 March 2023
SPONSOR:	CymaBay Therapeutics, Inc. 7575 Gateway Blvd, Suite 110 Newark, CA 94560 United States of America
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IND: 125,795
EudraCT Number: 2020-005925-10
NCT Number: NCT04950764

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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
Ae	amount excreted in urine
ALP	alkaline phosphatase
ALT	alanine transaminase
AMA	anti-mitochondrial antibodies
AST	aspartate aminotransferase
AUC	area under the concentration curve
$AUC_{0\text{-}inf}$	area under the concentration-time curve from time 0 to infinity
$AUC_{0\text{-}t}$	area under the concentration-time curve from 0 to the last measurable concentration
BA	bile acid(s)
BLM	baseline measurement
BUN	blood urea nitrogen
C4	7-α-hydroxy-4-cholesten-3-one
CL_R	renal clearance
CL/F	apparent total body clearance
CK	creatine kinase
C_{max}	maximum observed plasma concentration
CP	Child-Pugh
Cr	creatinine
CTCAE	common terminology criteria for adverse events
Cum Ae	cumulative amount excreted in urine
Cum Fe	cumulative percentage excreted in urine
DB	direct bilirubin
DILI	drug induced liver injury
DMP	Data Management Plan
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
Fe	percentage excreted in urine
Fu	average fraction of unbound seladelpar
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus

HCV-RNA	hepatitis C virus – ribonucleic acid
HDL-C	high-density lipoprotein-cholesterol
HI	hepatic impairment
HIV	human immunodeficiency virus
HoFH	homozygous familial hypercholesterolemia
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
K_{el}	elimination rate constant
MCV	mean corpuscular volume
MDMA	3,4-methylenedioxymethamphetamine (ecstasy)
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NASH	nonalcoholic steatohepatitis
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect-level
OCA	obeticholic acid
PBC	primary biliary cholangitis
PCP	phencyclidine
PHT	portal hypertension
PI	principal investigator
PK	pharmacokinetic(s)
PPAR	peroxisome proliferator-activated receptor
PPARα	peroxisome proliferator receptor alpha
PPAR α/δ	peroxisome proliferator receptor alpha/delta
PT	prothrombin time
QD	once a day
QOD	every other day
RBC	red blood cell
RI	renal impairment
Rsq	adjusted R^2 value for regression estimation of K_{el}
SAE	serious adverse event
SAP	statistical analysis plan
sCr	serum creatinine
SD	standard deviation

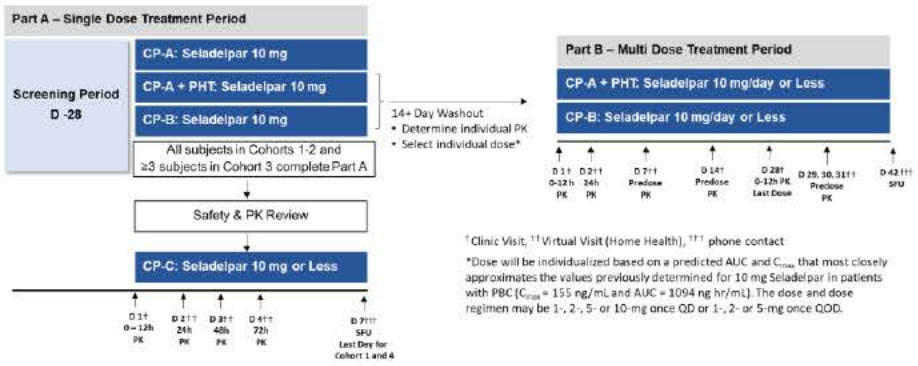
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TB	total bilirubin
TCA	tricyclic anti-depressants
TE	transient elastography
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum observed plasma concentration
TMF	trial master file
TSH	thyroid stimulating hormone
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
unbound $AUC_{0\text{-}inf}$	area under the concentration-time curve of unbound seladelpar from time 0 to infinity
unbound $AUC_{0\text{-}t}$	area under the concentration-time curve of unbound seladelpar from 0 to the last measurable concentration
unbound C_{max}	maximum observed plasma concentration of unbound seladelpar
UNS	unscheduled
Vz/F	apparent volume of distribution
WBC	white blood cell

1. SYNOPSIS

<table>
<tr><td>Title of Study:</td><td>The Effect of Hepatic Impairment on The Pharmacokinetics of Seladelpar: An Open-Label Study Following Oral Dosing of Seladelpar to Subjects with Primary Biliary Cholangitis (PBC) and Hepatic Impairment</td></tr>
<tr><td>Protocol Number:</td><td>CB8025-21838</td></tr>
<tr><td>Phase:</td><td>1b</td></tr>
<tr><td>Investigational Product:</td><td>Seladelpar</td></tr>
<tr><td>Objectives:</td><td>Primary Objectives:
Evaluate the pharmacokinetic (PK) profiles of seladelpar and major metabolites: M1, M2 and M3 after a single and multiple oral doses in PBC subjects with hepatic impairment (HI)
Evaluate the safety and tolerability of seladelpar after a single dose and multiple oral doses in PBC subjects with HI
Secondary Objectives:
Evaluate the urinary PK of seladelpar and its major metabolites: M1, M2 and M3 in PBC subjects with HI
Evaluate the relationship between plasma seladelpar PK parameters (C_{max}, AUC_{0-t}, and AUC_{0-inf}) and albumin, bilirubin, prothrombin time (PT), and Child-Pugh score.
Exploratory Objectives:
Evaluate the effect of multiple dose treatment of seladelpar on biomarkers of cholestasis and liver function (Cohorts 2 and 3 only)</td></tr>
<tr><td>Methodology/ Study Design:</td><td>This study is designed as a two-part open-label, non-randomized, single (Part A) and multiple (Part B) oral dose(s) of 10 mg seladelpar or less in PBC subjects with HI. Hepatic impairment will be based on Child-Pugh (CP) classification: A (with and without portal hypertension [PHT]), B or C subjects. Subjects will be assigned to the appropriate cohort based on their CP score at screening.
It is planned to enroll at least 24 subjects in this study in order to complete with at least six subjects per cohort.
<table>
<tr><td>Child Pugh Classification</td><td>CP-A</td><td>CP-A + PHT</td><td>CP-B</td><td>CP- C</td></tr>
<tr><td>Cohort</td><td>Cohort 1</td><td>Cohort 2</td><td>Cohort 3</td><td>Cohort 4</td></tr>
</table>
</td></tr>
</table>

Methodology/ Study Design: (***continued***)	Part A: Part A of the study will use staggered enrollment with Cohorts 1-3 to be completed before commencing enrollment of subjects in Cohort 4. Cohorts 1-3 (N = 6 per cohort) will be concurrently open for enrollment and dosing with a single oral dose of 10 mg seladelpar. Cohorts 2 and 3 may remain open and continue to enroll until enough subjects are enrolled in Part B. Once all subjects in Cohorts 1-2 and at least 3 subjects in Cohort 3 have completed Part A, safety and PK will be evaluated by the Safety Review Committee (SRC) to determine whether to enroll Cohort 4 (CP-C subjects) and to confirm that the 10 mg dose is appropriate for the first two subjects in this cohort. The first two subjects from Cohort 4 (out of a total of N = 6) will be treated with a single dose of 10 mg seladelpar; however, a lower dose may instead be selected after the PK and safety review of Cohorts 1-3. The SRC will review the safety and PK data for the first two subjects from Cohort 4 prior to dosing the remaining four subjects; an additional adjustment to their dose may be made if deemed prudent for reasons of safety or exposure. All study subjects will initially have a Screening visit followed by a Screening period of up to 28 days. Upon completion of all Screening activities, subjects will report to the Study Site on Day -1 for baseline measurements and laboratory assessments on Day -1. All subjects will remain on-site through the first 12-hour post-dose (Day 1) PK collection. For Study Sites able to house for multiple days, subjects may optionally remain on-site until the 24-hour post-dose (Day 2) PK collection and assessments are complete. For subjects at sites who are not able to house through Day 2, or for subjects who prefer to not to stay on site, they may return home after the 12 hour post-dose (Day 1) collection and assessment are complete and either return to the clinic the next day to have the 24 hour post-dose (Day 2) collection performed or have the 24 hour post-dose (Day 2) collection performed at home by a home health service or the subject may return to the site for these procedures. The 48 hours ± 30 minutes post-dose (Day 3), and 72 hours ± 30 minutes post-dose (Day 4) assessments may be performed at home by a home health service or the subject may return to the site for these procedures. All subjects will be contacted by telephone on Day 7 ± 1 day. This will be the end of study visit for Cohort 1 (CP-A) and Cohort 4 (CP-C) as they will not participate in Part B. Part A PK sample collection: PK blood samples will be taken starting on Day 1 at: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 (Day 2), 48 (Day 3) and 72 hours post-dose (Day 4). Blood sampling for unbound seladelpar will be collected on Day 1 at 2.5 and 12 hours post dose. Urine will also be collected over the following intervals: pre-dose (spot) and 0-6 hours, and 6-12 hours post-dose on Day 1 to measure seladelpar and major metabolites. Part B: Participation in Part B is limited to subjects from Cohort 2 (CP-A + PHT) and Cohort 3 (CP-B) who have completed Part A. Subjects will have a washout period of at least 14 days following last study drug administration in Part A during which each subject's individualized dose for Part B will be based on their exposure in Part A. Each subject's

Methodology/ Study Design: (***continued***)	dose will be individualized based on a predicted AUC and C_{max} that most closely approximates the values previously determined for 10 mg seladelpar in patients with PBC (C_{max} = 155 ng/mL and AUC = 1094 ng hr/mL) (Study CB8025-21629). The dose and dose regimen may be 1-, 2-, 5- or 10-mg once a day (QD) or 1-, 2- or 5-mg once every other day (QOD). Subjects will return to the Study Site between Day -6 and Day -4 for laboratory testing for Part B following their washout period. Subjects will then return to the Study Site on Day 1 for review of lab results, CP status, AEs, and concomitant medications. Any changes in these criteria should be discussed with the medical monitor before dosing. Subjects will receive seladelpar QD or QOD for 28 days beginning on Day 1 through Day 28. Except during clinic visits, study drug will be self-administered by subjects using instructions provided to ensure consistent dosing. A paper diary will be used to record dosing information. The SRC will perform a safety and PK review of the first two (sentinel) subjects in Cohort 3 (CP-B) after 28 days of treatment to assess whether it is safe to proceed with the current dosing or if a dose adjustment is necessary for the remaining subjects in this cohort. On Day 1 and Day 28, subjects will remain on-site through at least the first 12 hour post-dose (Day 1) PK collection. For Study Sites capable of housing for multiple days, subjects may optionally remain on-site until the 24-hour post-dose (Day 2) PK collection and assessments are complete. For subjects at sites who are not able to house through Day 2, or for subjects who prefer to not to stay on site, they may return home after the 12 hour post-dose (Day 1) collection and assessment are complete and either return to the clinic the next day to have the 24 hour post-dose (Day 2) collection performed or have the 24 hour post-dose (Day 2) collection performed at home by a home health service or the subject may return to the site for these procedures. On Day 2, 7, 29, 30 and 31 of Part B, pre-dose collections and safety assessments may be performed on site or at home by a home health service or the subject may return to the site for these procedures. All subjects will return to the Study Site on Day 14 for a safety assessment and pre-dose collection. The end of study (or follow-up) for Cohorts 2 and 3 will occur 14 (+3) days after the last dose as a telephone call. The last day of dosing will occur on Day 28. Part B PK sample collection: Blood samples will be taken on Day 1 at: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 hours post-dose and on Day 28 at: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 (Day 29), 48 (Day 30) and 72 hours post-dose (Day 31). Pre-dose PK will also be collected approximately on Day 7 and Day 14.

Study Design Schema:	
Subjects:	At least 24 subjects
Study Sites	Approximately 20 sites world-wide
Test Product:	Seladelpar capsules in strengths of 1 mg, 5 mg or 10 mg
Study Duration:	Part A: Total study duration for each subject is approximately 5 weeks (including a screening period of up to 28 days) Screening: Up to 28 days Baseline Visit: Day -1 Dosing Day: Day 1 Study Period: Days 1 through 4 Follow-up telephone call: Day 7 ± 1 Part B: Total Part B study duration for each subject is approximately 8 weeks (including a wash out period of at least 14 days and a follow up period of up to 17 days) Wash out: at least 14 days Baseline Visit: Day 1 Dosing Day: Day 1 through 28 Study Period: Day 1 through 31 Follow-up telephone call: 14 to 17 days after the last dose
Safety and Tolerability:	Safety and tolerability will be assessed by monitoring AEs. Additional assessments will include conducting safety physical exams, 12-lead electrocardiograms (ECGs), measuring vital signs, and collecting clinical blood and urine laboratory assessments.

Pharmacokinetic Parameters:	PK parameters to be analyzed for seladelpar and major metabolites M1, M2, and M3. Part A PK parameters include: maximum observed plasma concentration (C_{max}), time to reach maximum observed plasma concentration (T_{max}), area under the concentration-time curve from time 0 to the last measurable concentration (AUC_{0-t}), area under the concentration-time curve from time 0 extrapolated to infinity (AUC_{0-inf}), percentage area under the concentration-time curve from time 0 to infinity that is extrapolated (%extrapAUC_{0-inf}) terminal elimination half-life ($t_{½}$), elimination rate constant (K_{el}), adjusted R^2 value for regression estimation of K_{el} (Rsq), apparent total body clearance (CL/F; seladelpar only), apparent volume of distribution (Vz/F; seladelpar only), renal clearance (CL_R), amount excreted in urine (Ae), cumulative Ae (Cum Ae), percentage excreted in urine (Fe; seladelpar only), and cumulative Fe (Cum Fe; seladelpar only). Unbound AUC_{0-t}, unbound AUC_{0-inf}, unbound C_{max}, and average fraction of unbound seladelpar (Fu) will also be measured. Part B PK parameters include: Day 1, 24hour collection (Days 1 and 2): C_{max}, T_{max}, AUC_{0-t}, AUC_{0-24}, $t_{½}$, K_{el}, Rsq, CL/F (seladelpar only), Vz/F (seladelpar only) Day 28, 72-hour collection (Days 28, 29, 30 and 31): C_{max}, C_{min}, T_{max}, AUC_{0-t}, AUC_{0-24}, AUC_{0-tau}, $t_{½}$, K_{el}, Rsq, CL/F (seladelpar only), Vz/F (seladelpar only), accumulation ratio (AR): C_{max} or AUC_{0-tau} on Day 28 divided by the C_{max} or AUC_{0-24} on Day 1, respectively. Pre-dose concentrations on Day 7 and Day 14
Efficacy Parameters (Cohorts 2 and 3, Part B only):	Biomarkers of cholestasis and liver function, including alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin (TB), direct bilirubin (DB), alanine aminotransferase (ALT), aspartate amino transferase (AST), albumin and platelets, will be assessed at baseline (Day 1, Part B), Day 7, 14, and 28. Treatment effects will be evaluated by change and relative change of the biomarkers from baseline to Day 28.
Statistical Methods:	**Analysis Sets:** Three analysis sets are used and are defined as follows: Safety Analysis Set: comprises all study subjects who receive any amount of seladelpar. This analysis set will be used for all analysis of safety data and for summarization of demographics and baseline characteristics. • PK Analysis Set: comprises all study subjects who undergo plasma PK sampling with assay results. This analysis set will be used for the PK analyses and for summarization of concentration/parameter data. • Efficacy Analysis Set: comprises all study subjects who receive any amount of seladelpar in Part B and have at least one biochemistry assessment post Part B baseline. This analysis set will be used for analyzing efficacy parameters (Cohorts 2 and 3, Part B only)

	Statistical Analysis Descriptive statistics will be displayed by cohort and overall to provide an overview of the study results. Missing data will not be imputed generally. PK parameters will be summarized by cohort. Safety measures will be summarized descriptively. Efficacy parameters, and their change and relative change will be summarized descriptively. Interim analyses may be performed per Sponsor's decision. Further details on statistical methodology and data handling for this study will be provided separately in the statistical analysis plan (SAP).
Sample Size Determination:	At least 24 subjects, male or female, are planned for enrollment in the study. A minimum of six subjects per cohort are to complete the PK evaluation and expected to provide sufficient data to adequately assess the PK for seladelpar in the HI population with PBC.

Table 1: Part A Schedule of Study Procedures

Study Procedures	Day -28 to Day -1 (± 5 days): Screening	Day -1: Baseline	Day 1: Dosing	Day 2	Day 3	Day 4/ET[1]	Day 7 (± 1 day): Follow-Up Telephone Call
Informed consent	X						
Demographics	X						
Medical history	X	X	X				
Prior and current concomitant medications	X	X	X	X	X	X	X
Adverse events [2]	X	X	X	X	X	X	X
Inclusion/Exclusion criteria	X	X					
Physical examination	X	X[3]	X			X	
Vital signs	X	X	X	X	X	X	
Height	X						
Weight	X						
12-lead electrocardiogram[4]	X		X			X	
Child-Pugh assessment	X	X					
Pregnancy Test[5]	X	X				X	
Viral Screen	X						
Drug Screen	X	X					
Chemistry, Hematology, Coagulation, and Urinalysis	X	X				X	
Backup Blood Sample	X	X				X	
Genotyping – blood sampling		X[12]					
Confinement[6]		X	X				
Onsite visit[7]	X	X	X		X	X	
Optional Home Health Visit				X	X		
Concomitant Procedures			X	X	X	X	X
Seladelpar administration			X				
PK blood sampling[8]			X	X	X	X	
PK blood sampling for unbound Seladelpar[9]			X				

Study Procedures	Day -28 to Day -1 (± 5 days): Screening	Day -1: Baseline	Day 1: Dosing	Day 2	Day 3	Day 4/ET[1]	Day 7 (± 1 day): Follow-Up Telephone Call
PK urine sampling[10]			X				
COVID-19 Testing[11]	X	X					

1 ET = early termination. If the subject withdraws early from the study, all efforts should be made to complete Day 4 study procedures.
2 AEs will be evaluated and recorded starting from the time the subject signs the ICF.
3 The physical examination will include any changes in Child Pugh classification since the Screening Visit by assessment of clinical features such as hepatic encephalopathy, and ascites. Symptom-directed physicals may also be performed as needed at other time points.
4 A 12-lead ECG will be obtained pre-dose in supine position after at least 5 minutes of rest.
5 A serum pregnancy test will be performed on all female subjects of child-bearing potential at Screening. A urine pregnancy test will be performed on all female subjects on Day -1 or Day 1 prior to dosing, and on Day 4/Early termination.
6 All subjects will remain on-site through the first 12-hour post-dose (Day 1) PK collection. For Study Sites capable of housing for multiple days, subjects may optionally remain on-site until the 24 hour post-dose (Day 2) PK collection and assessments are complete. For subjects at sites who are not able to house through Day 2, or for subjects who prefer to not to stay on site, they may return home after the 12 hour post-dose (Day 1) collection and assessment are complete and either return to the clinic the next day to have the 24 hour post-dose (Day 2) collection performed or have the 24 hour post-dose (Day 2) collection performed at home by a home health service or the subject may return to the site for these procedures .
7 Subjects will return to the study site approximately 48 hours ±30 minutes post-dose (Day 3) and approximately 72 hours ±30 minutes post-dose.
8 Blood collection for PK analysis of seladelpar and metabolites M1, M2, and M3: pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 (Day 2), 48 (Day 3) and 72 (Day 4) hours post-dose.
9 Blood collection for PK analysis of unbound seladelpar: 2.5 and 12 hours post-dose.
10 Urine for PK analysis will be collected over the following intervals: pre-dose (spot) and 0-6 hours, and 6-12 hours.
11 COVID-19 testing will be performed locally and only if deemed necessary per local requirements.
12 Up to 15 mL from subjects who consent to the Genotyping ICF.

Table 2: Part B Schedule of Study Procedures

Study Procedure	Pre-dosing Safety Visit (between Day -6 – Day -4)	Day 1: Dosing	Day 2	Day 7	Day 14	Day 28	Day 29	Day 30	Day 31/ET[18]	Follow-up Telephone Call 14 (+3) days after last dose[7]
Medical history		X								
Prior and current concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events[1]	X	X	X	X	X	X	X	X	X	X
Abbreviated Inclusion/Exclusion criteria[19]		X								
Physical examination[2]		X[3]			X	X				
Vital signs	X	X	X	X	X	X	X	X	X	
Weight		X			X	X				
12-lead electrocardiogram[3]		X			X	X				
Pregnancy Test[4]	X	X		X	X	X			X	
Chemistry, Hematology, Coagulation, and Urinalysis	X		X	X	X	X	X	X	X	
Backup Sample	X		X	X	X	X	X	X	X	
Drug Screen	X									
Onsite visit[5]		X			X	X				
Optional Home Health visit[6]	X		X	X			X	X	X	
Concomitant Procedures		X	X	X	X	X	X	X	X	X
Seladelpar administration		X	X	X	X	X				
PK blood sampling[16]		X[8]	X[9]	X[10]	X[11]	X[12]	X[13]	X[14]	X[15]	
COVID-19 Testing[17]		X								

1 AEs will be evaluated and recorded starting from the time the subject signs the ICF.

2 The physical examination will include any changes in Child Pugh classification since the Screening Visit by assessment of clinical features such as hepatic encephalopathy, and ascites. Symptom-directed physicals may also be performed as needed at other time points.

3 A 12-lead ECG will be obtained in supine position after at least 5 minutes of rest.

4 A serum pregnancy test will be performed on all female subjects of child-bearing potential at the Pre-dosing Safety Visit. A urine pregnancy test will be performed on all female subjects on Day 1, Day 7, Day 14 and Day 28 prior to dosing, and at Day 31/Early Termination.

5 Subjects will return to the study site for indicated study procedures.

6 Scheduled study procedures will be conducted with Home Health visits or the subject may return to the site for these procedures.

7 End-of-study follow-up visit for Part B subjects will be conducted via a phone call on Follow-up

8 Blood collection for PK analysis of seladelpar and metabolites M1, M2, and M3: pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 hours

9 Blood collection for PK at 24 hours (pre-dose on Day 2) with Home Health visit or the subject may return to the site for these procedures.

10 Blood collection for PK (pre-dose on Day 7) with Home Health visit or the subject may return to the site for these procedures.

11 Blood collection for PK (pre-dose on Day 14) during on-site visit

12 Blood collection for PK analysis (Day 28) of seladelpar and metabolites M1, M2, and M3: pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 hours

13 Blood collection for PK 24 hours (Day 29) with Home Health visit or the subject may return to the site for these procedures.

14 Blood collection for PK 48 hours (Day 30) with Home Health visit or the subject may return to the site for these procedures.

15 Blood collection for PK 72 hours (Day 31) with Home Health visit or the subject may return to the site for these procedures.

16 For those subjects who may be receiving alternate dosing based on their PK results from Part A, the days for PK draws in Part B will be determined so as to coordinate with their dosing regimen.

17 COVID-19 testing will be performed locally and only if deemed necessary per local requirements.

18 ET = early termination. If the subject withdraws early from the study, all efforts should be made to complete the Day 31 study procedures through either on-site or Home Health visit.

19 Subjects will return to the Study site on Day 1 for review of lab results, CP status, AEs and concomitant medications. Any changes in these criteria should be discussed with the medical monitor before dosing.

2. DISEASE BACKGROUND

2.1. Primary Biliary Cholangitis (PBC)

Primary biliary cholangitis is a serious and potentially life-threatening autoimmune disease of the liver characterized by cholestasis and accumulation of toxic bile acids (BA). The hallmark of PBC is cholestasis with an accompanying elevation in serum biomarkers including alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and, depending on the severity of the disease, bilirubin, and liver transaminases (Lleo, 2020). 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 of 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 ALP. 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, for which there is no proven treatment, is independent of the severity of the liver disease (Kaplan, 2005). Pruritus, the cause of which is uncertain, occurs in 20 to 70% of patients and can also 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).

Generally, untreated PBC patients progress to liver failure, transplant, or death. A meta-analysis of 4,845 patients in North American and European long-term studies demonstrated that untreated PBC patients had transplant-free survival of 79% at 5 years, 59% at 10 years, and 32% at 15 years (Lammers, 2014). Despite being a rare disease, PBC is one of the top six indications for liver transplantation in the United States and European Union (Silveira, 2010). Recurrence of PBC following liver transplantation is reported in 11 to 45% of transplantations, with an estimated prevalence of 30% at 10 years following transplantation, further demonstrating a need for effective therapies (Levy, 2018). A distinct feature of PBC is the development of esophageal varices prior to the onset of cirrhosis. Approximately 6% of early histological stage PBC patients have varices, and one-third of patients with stage III-IV disease develop varices over a median of

5 to 6 years (Lindor, 2009; Huang, 2016). The three-year survival following an initial variceal bleed is 46% (Lindor, 2009).

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 ALP and/or bilirubin despite UDCA treatment and are considered inadequate responders (Corpechot, 2008). Obeticholic acid (OCA), a synthetic analogue of chenodeoxycholic acid, was approved by the FDA and EMA in 2016 based on significant decreases in ALP levels while maintaining normal total bilirubin levels in PBC patients who are inadequate responders to UDCA or, as a monotherapy in PBC patients who are intolerant to UDCA (Ocaliva, 2016). Despite the previously mentioned therapeutic interventions, many PBC patients do not respond adequately to therapy and additional treatment options are needed.

2.2. Seladelpar

2.2.1. Mechanism of Action

Seladelpar is an oral, once daily, potent, and highly selective agonist of PPARδ (Bays, 2011). The PPARδ receptor is expressed in hepatocytes (Iwaisako, 2012), where it controls genes involved in BA homoeostasis. The PPARδ receptor is also expressed in cholangiocytes, Kupffer cells, and hepatic stellate cells, all of which have a potential role in the pathophysiology of PBC (Xia, 2012; Iwaisako, 2012). Cholangiocytes use the PPARδ receptor to regulate transporters involved in the absorption and secretion of bile components (Xia, 2012). Activation of the PPARδ receptor also results in anti-inflammatory effects in macrophages and Kupffer cells in the liver (Mukundan, 2009; Odegaard, 2008). Seladelpar also decreases established fibrosis and stellate cell activity, as well as reducing macrophage infiltration in two separate nonalcoholic steatohepatitis (NASH) mouse models. (Haczeyni, 2017; Choi, 2018). Seladelpar down regulates the expression of CYP7A1 in PBC which encodes cholesterol 7α-hydroxylase, the enzyme that hydroxylates cholesterol in the first step in BA synthesis (Jones, 2017). In summary, these pre-clinical data provide a foundation for the potential biologic activity of seladelpar in PBC based on the demonstrated impact on BA synthesis, cholangiocyte function, inflammation and fibrogenesis.

2.2.2. Therapeutic Rationale for Seladelpar in PBC

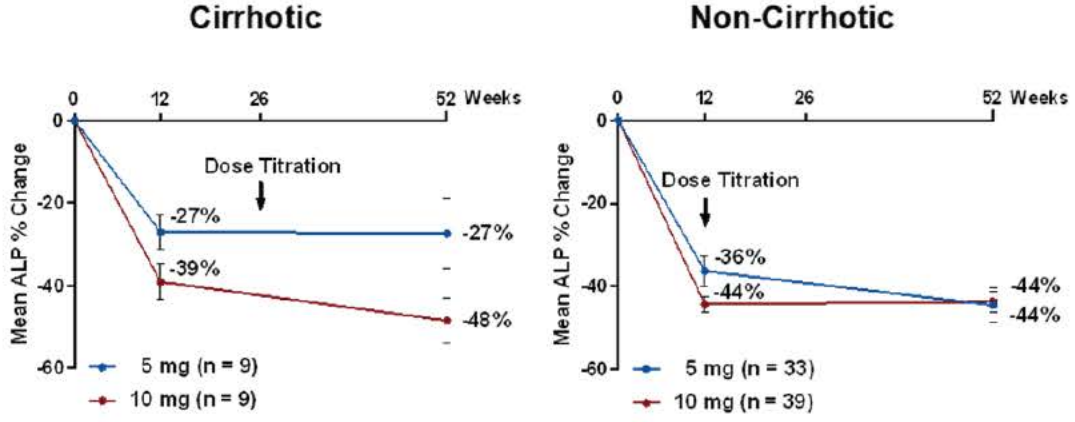
The preliminary clinical evidence supporting the development of seladelpar in PBC include two clinical Phase 2 studies and one Phase 3 study in PBC subjects: CB8025-21528 (50 and 200 mg of seladelpar), CB8025-21629 (2, 5 and 10 mg of seladelpar), and CB8025-31735 (5 and 10 mg of seladelpar).

CB8205-21528 was a double-blind, randomized, 12-week placebo-controlled dose ranging (50 mg or 200 mg/day), Phase 2 study in PBC subjects who were inadequate responders to UDCA (Jones, 2017). Seladelpar exhibited rapid, pronounced ALP decreases with no significant differences between 50 mg and 200 mg (mean reduction of 53% vs. 63%) compared with a mean reduction of 2% in the placebo group. Other biochemical markers of cholestasis, including GGT and total bilirubin, were also decreased with seladelpar versus no significant changes with placebo. BA synthesis, as measured by the biomarker C4, was suppressed by 55% and 77% at doses of 50 mg and 200 mg, respectively.

Study CB8025-21629 was an open-label, randomized, dose ranging Phase 2 study in PBC subjects who either have had an inadequate response to UDCA or are intolerant to UDCA. Subjects received oral doses of 2, 5, or 10 mg seladelpar once daily. Subjects were randomized to receive 5 or 10 mg seladelpar, whereas those in the 2-mg seladelpar group entered after being sequentially assigned their dose. After 12 weeks, subjects on 2 or 5 mg could escalate the dose if their ALP treatment goal was not achieved. By Week 52, 10 of 11 subjects in the 2-mg dose group were up-titrated to 5 or 10 mg, and 30 of 49 subjects in the 5-mg dose group were up-titrated to 10 mg. A total of 119 subjects were enrolled into the study; of these, 112 subjects (94.1%) were analyzed for efficacy. The 5- and 10-mg doses showed consistent, meaningful, and reproducible decreases in ALP levels. At baseline, the mean ALP was 300, 345, and 295 U/L in the 2-, 5-, and 10-mg dose groups, respectively. After 12 weeks of dosing, mean percent changes from baseline in ALP were -22.6%, -34.5%, and -43.2% for the 2-, 5-, and 10-mg dose groups, respectively. Furthermore, 31% of subjects with PBC in the 10-mg dose group achieved normalization of ALP by Week 12. After 52 weeks of dosing, mean percent changes from baseline in ALP were -32.7%, -40.1%, and -44.2% for the 2-, 5-, and 10-mg dose groups, respectively.

A subgroup analysis was performed for subjects with and without clinically documented cirrhosis at baseline to examine the treatment effects on ALP in these sub-populations. Cirrhosis was diagnosed based on the Investigator's clinical judgment with the support of liver biopsy, elastography, or imaging testing (ultrasound, computed tomography [CT], magnetic resonance imaging [MRI]). In the analysis of cirrhotic subjects, ALP at baseline in subjects with cirrhosis was 280.6 and 309.1 U/L in the 5 and 10 mg dose groups, respectively, and 379.6 and 298.8 U/L in subjects without cirrhosis, respectively. Mean ALP values at baseline were similar between 10 mg dose groups of subjects with and without cirrhosis. At 52 weeks, the mean percent change in ALP in subjects with cirrhosis was -26.3% and -48.5% in the 5 and 10 mg dose groups, respectively; the mean percent change in subjects without cirrhosis was -44.0% and -43.2%, respectively. Mean percent changes in ALP after 12 and 52 weeks of seladelpar treatment were smaller in subjects with cirrhosis in the 5 mg dose group compared to subjects without cirrhosis, which might be attributed to the difference in the baseline values. The mean percent changes in ALP for cirrhotic and non-cirrhotic subjects in the 5 mg and 10 mg dose groups are shown in Figure 1.

Figure 1: Mean Percent Change in ALP Over Time in Subjects With and Without Cirrhosis (mITT Population)



ALP = alkaline phosphatase; mITT = modified intent-to-treat; SE = standard error. Values shown are mean ± SE

A decrease in median ALT levels over 12 weeks is observed in the subjects who had completed 12 weeks of seladelpar treatment (up to 12 weeks, subjects maintained their assigned dose with no dose adjustment). This indicates that, instead of elevations in transaminases at higher doses, lower doses produce reductions in transaminase levels and an indication of decreased liver injury. Decreases in transaminases likely reflect reduced hepatocellular stress accompanying reductions in cholestasis and inflammation. This is consistent with seladelpar exerting an anti-inflammatory effect that contributes to decreases in interface hepatitis and portal inflammation. The results of this study concluded that seladelpar doses of 10 mg, or 5 mg adjusted to 10 mg, demonstrate potent anticholestatic efficacy that is maintained over 52 weeks.

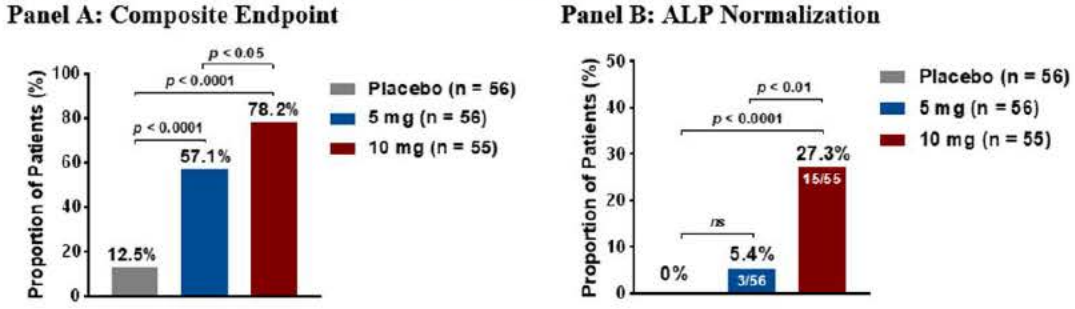
Study CB8025-31735 (ENHANCE) was designed as a Phase 3, international, double-blind, randomized, placebo-controlled study in adult subjects with PBC with an inadequate response or intolerance to UDCA. Subjects were randomly assigned to receive 5 mg/day seladelpar, 10 mg/day seladelpar, or placebo in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

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

As shown in Figure 2, Panel A, 57.1% and 78.2% subjects in the seladelpar 5- and 10-mg groups, respectively, met the composite endpoint versus 12.5% of subjects in the placebo group ($p<0.0001$) after 12 weeks of treatment, with seladelpar 10 mg demonstrating a statistically significant higher response than seladelpar 5 mg ($p<0.05$). Normalization of ALP (Figure 2, Panel B) was achieved in 27.3% of subjects in the 10-mg dose group versus 5.4% and 0% in the seladelpar 5-mg and placebo groups, respectively.

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

Figure 2: Study CB8025-31735: Seladelpar Effects on ALP



Abbreviations: ALP=alkaline phosphatase; CMH=Cochran-Mantel-Haenszel; ns=not significant.
P values by CMH test
Source: CB8025-31735 CSR, Table 14.2.1.1, Table 14.2.3

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

Based on its pharmacologic actions *in vitro*, in animals, and in humans, as well as the favorable safety and tolerability profiles at doses less than 50 mg per day, seladelpar represents a potentially important therapeutic option for the treatment of PBC.

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

2.2.3. Nonclinical Safety Assessment

The proposed seladelpar dose to be studied in this study is a dose of 10 mg for Cohorts 1-2 (Child Pugh [CP] -A and CP-A+PHT) and a dose of 10 mg or less for Cohorts 3 and 4 (CP-B and CP-C). This duration of exposure is supported by the repeat dose toxicity studies of 26 weeks in Sprague-Dawley rats and 52 weeks in cynomolgus monkeys. As shown in Table 3, there are adequate safety margins based on AUC in both sexes in all species for the 10 mg dose proposed for this study.

Further details of these chronic toxicology studies in both species are described in the IB.

Table 3: Estimated Safety Exposure Margin of Seladelpar

Species	**Rat (26-week)**		**Monkey (52-week)**	
	M	**F**	**M**	**F**
NOAEL (mg/kg/day)	15	80	1	5
AUC (ng*h/mL)	26,900	77,300	2,450	12,000
Margin (AUC) PBC – 10 mg	23X	66X	2.1X	10X

2.3. Clinical Studies

As of December 2022, seladelpar had been evaluated in 20 completed or terminated clinical studies across healthy volunteers and subjects with hepatic impairment, renal impairment, mixed dyslipidemia, homozygous familial hypercholesterolemia (HoFH), NASH, PSC, and PBC.

Across the clinical development program, seladelpar studies have ranged from single-dose studies in healthy subjects (1, 5, 15, 60, 120, and 360 mg) to long-term dosing in Phase 2 studies in subjects with mixed dyslipidemia (50 and 100 mg), HoFH (ascending doses of 50, 100, and 200 mg), PBC (2, 5, 10, 50, and 200 mg), and NASH (10, 20, and 50 mg once a day). Seladelpar dosing duration has ranged from 8 weeks to >2 years.

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

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

2.3.1. Phase 1 Study in Patients with Hepatic Impairment (CB8025-11732)

CB8025-11732 was a completed Phase 1, open-label, multicenter study to evaluate the PK, safety, and tolerability of a single oral dose of 10 mg seladelpar in subjects with varying degrees of hepatic function. Subjects were defined as having normal hepatic function (ALT, AST and total bilirubin within ULN) or characterized as having HI classified as mild, moderate, or severe based on Child-Pugh score (CDER, 2003). Two mild HI subjects had PBC and two mild HI

subjects had NASH at study entry. A total of 32 subjects were enrolled (8 per cohort), with all subjects receiving a single dose of 10 mg seladelpar according to the protocol. All subjects completed the study, except for 1 subject in the moderate HI group (Cohort 3) who withdrew from the study due to a family emergency. In summary, a single dose of seladelpar 10 mg was rapidly absorbed with individual T_{max} ranging from 0.5 to 4.0 hours across the cohorts. After reaching C_{max}, seladelpar plasma levels steadily declined with mean $t_{1/2}$ ranging from 6.19 to 7.21 hours across the cohorts. Seladelpar exposure (AUC_{0-t} or AUC_{0-inf} values) and exposure to M2 (the most abundant metabolite) more than doubled in subjects with moderate or severe HI compared to subjects with normal hepatic function. A summary of the key PK parameters is presented in Table 4.

Table 4: Summary (Mean ± SD) of PK Parameters for Seladelpar in Subjects with Varying Degrees of Hepatic Impairment

PK Parameter	Normal (Cohort 1)	Mild (Cohort 2)	Moderate (Cohort 3)	Severe (Cohort 4)
C_{max} (ng/mL)	71.9 ± 28.0	101 ± 58.7	398 ± 199	379 ± 180
T_{max} (hr)	2.0 (0.50, 4.0)	1.5 (0.50, 4.0)	1.0 (0.50, 1.5)	0.50 (0.50, 4.0)
AUC_{0-t} (hr*ng/mL)	668 ± 217	785 ± 423	1763 ± 606	1570 ± 886
AUC_{0-inf} (hr*ng/mL)	705 ± 227	815 ± 432	1807 ± 612	1616 ± 879
$t_{1/2}$ (hr)	6.66 ± 1.57	6.20 ± 1.75	6.19 ± 1.37	7.21 ± 1.58
CL/F (L/hr)	15.4 ± 4.45	14.3 ± 4.92	6.34 ± 3.00	7.78 ± 3.52
Vz/F (L)	141 ± 29.0	120 ± 36.5	54.6 ± 21.2	78.7 ± 30.6

Seladelpar metabolites M1, M2, and M3 steadily appeared in plasma and were steadily eliminated. The overall mean $t_{1/2}$ for the three metabolites ranged from 7.81 to 11.0 and did not appear to be impacted by the degree of HI. Exposure to M2 increased with the degree of HI, with the most apparent difference in the moderate and severe cohorts. A greater than 2-fold increase in M2 C_{max} and AUC_{0-t} values was observed in subjects with moderate and severe impairment compared to normal subjects. Changes in exposure to M1 and M3 were less pronounced in subjects with different degrees of hepatic impairment as compared to normal subjects.

Single doses of 10 mg seladelpar were well-tolerated by both healthy subjects and those with differing degrees of HI. Three treatment emergent adverse events (TEAEs) in 3 subjects in the mild HI group (diarrhea, gastroesophageal reflux disease, and arthralgia) were considered related to study treatment by the Investigator. All TEAEs were non-serious and mild in severity, except for 1 severe SAE of esophageal varices hemorrhage in a subject who had a history of intermittent bleeding from esophageal varices. There were no deaths or TEAEs that led to withdrawal during the study. No clinically important mean changes in vital signs, physical examination findings, or laboratory values were observed.

2.3.2. Phase 1 Study in Patients with Renal Impairment (CB8025-11942)

CB8025-11942 was a completed Phase 1, open-label, non-randomized, parallel-group study to determine the effect of renal impairment (RI) on the PK, safety, tolerability, of a single oral dose of 10-mg seladelpar compared to matched healthy subjects with normal renal function. Subjects were enrolled based on their renal function at study entry, as defined by estimated eGFR

calculated using the Modification of Diet in Renal Disease (MDRD) equation: normal renal function, mild RI, moderate RI, and severe RI.

A total of 36 subjects were enrolled and administered a single 10-mg dose of seladelpar: 12 with normal renal function, 8 with mild RI, 8 with moderate RI, and 8 with severe RI. Overall, seladelpar plasma exposures did not meaningfully increase with worsening renal function. Administration of seladelpar to subjects with mild and severe RI resulted in marginal differences in AUC and C_{max} values compared to matched normal subjects. An increase of 59% in seladelpar AUC was observed in the moderate RI group with no increase in C_{max}. The relationship between eGFR versus seladelpar plasma exposure and urine PK parameters did not show a clear correlation. Lack of effect of progressive RI on seladelpar exposure supports the conclusion that renal function does not affect seladelpar exposure in subjects with mild, moderate, or severe RI.

For seladelpar metabolites, there were minimal increases in AUC or C_{max} in the setting of mild RI; for subjects with moderate or severe renal impairment, exposures increased to varying extents. A regression analyses of seladelpar metabolite plasma PK parameters versus eGFR showed that there was a trend towards increased metabolite exposure with decreasing eGFR, as well as a trend toward decrease in renal clearance and amount of metabolites excreted in the urine with worsening renal function.

Safety of seladelpar in subjects with the varying degrees of RI was consistent with the known safety profile of seladelpar, and no new safety signal was identified. The proportion of subjects who reported TEAEs was low, with no notable trend by RI group. All TEAEs were each reported by no more than 1 subject across all treatment groups. All TEAEs were mild in severity and considered unrelated to seladelpar by the Investigator. The majority of the TEAEs recovered/resolved by the end of the study. No deaths or SAEs were reported, and no subject was discontinued due to a TEAE during this study. No TEAEs related to vital signs or ECGs were reported during the study.

In Study CB8025-21838, participation in Part B is limited to subjects from Cohort 2 (CP-A + PHT) and Cohort 3 (CP-B) who have completed Part A. Subjects will have a washout period of at least 14 days following last study drug administration in Part A during which each subject's individualized dose for Part B will be based on their exposure in Part A. Each subject's dose will be individualized based on a modeled steady-state AUC and C_{max} using a non-compartmental analysis of their Part A PK data. The dose will be selected to approximate the safe range of steady-state exposures (after 2 to 12 weeks of dosing) previously determined for 10 mg seladelpar in patients with PBC (C_{max} = 155 ng/ml [min/max, 47/227 ng/ml] and AUC = 1094 ng hr/ml [min/max, 518/1609 ng hr/ml; Table 14.7.3.1, Study CB8025-21629). The expected doses and dose regimen include 1-, 2-, 5- or 10-mg once a day (QD) or 1-, 2- or 5-mg once every other day (QOD). Further details on Study CB8025-21629 may be found in the IB.

In summary, these results support the assessment that the exposures of seladelpar and its major metabolites are comparable between healthy volunteers and subjects with mild HI, including subjects with compensated cirrhosis (Child-Pugh A). In patients with a greater degree of HI (moderate and severe), the increases in exposure are unlikely to warrant the need for a dose reduction from 10 mg for administration of a single dose. Dose modification for repeat dose administration to patients with moderate or severe HI may be appropriate to consider in the future. The safety and tolerability of a single dose of 10 mg of seladelpar was acceptable across

all degrees of hepatic impairment. Data also suggest that renal function does not affect seladelpar exposure in subjects with mild, moderate, or severe RI.

2.3.3. Phase 1 Mass-Balance Study in Healthy Male and Female Subjects (CB8025-11734)

CB8025-11734 was a Phase 1, open-label, non-randomized study to determine the absorption, metabolism, and excretion of [^{14}C]-seladelpar and to characterize and determine the metabolites present in plasma, urine, and feces in healthy male and female subjects following a single oral administration of seladelpar. Preliminary PK and urinary excretion data of radiolabeled parent compound and primary metabolites (M1, M2 and M3) are available.

In this study, four male and four healthy female subjects each received a single 10 mg dose of [^{14}C]-seladelpar (containing approximately 100 µCi). Maximum overall mean concentrations of drug-derived radioactivity in blood and plasma were observed 4 hours post-dose for females and males with overall mean values of 144 µCi (females:178; males 109) and 252 µCi (females 299; males: 205) ng/equivalents/g, respectively).

The overall mean recovery of radioactivity in urine and feces was 92.9% (female: 94.1%; male: 91.8%) over the 216-hour study with recovery in individual subjects that ranged from 78.0 to 96.7%. An overall mean of 73.4% (female: 75.1%; male: 71.8%) of the dose was recovered in urine and 19.5% (female: 19.0%; male: 20.0%) of the dose was recovered in feces through the last collection interval. Most of the administered radioactivity was recovered in the first 72 hours post-dose (85.6%).

Less than 1% of the administered dose is excreted unchanged in urine. M3 accounted for most of urinary excretion, followed by M1, then M2 (% excreted: M3 > M1 > M2 > seladelpar) indicating that seladelpar is extensively metabolized. In summary, these data support that both biliary and renal excretion contribute significantly to the overall clearance of seladelpar and its major metabolites.

Further details may be found in the IB.

2.3.4. Safety Information in Patients with PBC

Subjects in a pooled safety analysis of the PBC studies (Studies CB8025-21528, CB8025-21629, CB8025-31731, and CB8025-31735) 58.1% vs 74.0% of seladelpar and placebo treated subjects, respectively, experienced at least 1 TEAE, where patients' exposure to study drug ranged from ≤1 week to ≤3 years.

In this analysis, the most common TEAEs that occurred in seladelpar treated subjects, regardless of dose and duration, were pruritus (16.2%), nausea (14.0%), urinary tract infection (10.8%), abdominal pain upper (10.5%), and fatigue (10.5%). Pruritus and fatigue, a common underlying symptom associated with PBC, occurred at a comparable rate in the placebo treated subjects (12.0% and 8.0%, respectively). The TEAEs not occurring in placebo treated subjects were urinary tract infection and dry mouth. Instances of increases in transaminases such as those observed in some subjects with seladelpar 50- and 200-mg doses were not observed at doses up to 10 mg per day with long term dosing. Overall, seladelpar appears to be safe and well tolerated at doses up to 10 mg for up to 52 weeks of treatment.

Further details may be found in the IB.

2.4. Study Objectives

2.4.1. Primary Objectives

- Evaluate the PK profiles of seladelpar and major metabolites: M1, M2 and M3 after a single and multiple oral doses in PBC subjects with HI
- Evaluate the safety and tolerability of seladelpar after a single dose and multiple oral doses in PBC subjects with HI

2.4.2. Secondary Objectives

- Evaluate the urinary PK of seladelpar and major metabolites: M1, M2, and M3 after a single oral administration in PBC subjects with HI
- Evaluate the relationship between plasma seladelpar PK parameters (C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$) and albumin, bilirubin, PT, and Child-Pugh score.

2.4.3. Exploratory Objectives

- Evaluate the effect of multiple dose treatment of seladelpar on biochemical markers of cholestasis and liver function (Cohorts 2 and 3 only)

3. STUDY DESIGN

3.1. Study Overview

This study is designed as a two-part open-label, non-randomized, single (Part A) and multiple (Part B) oral dose of 10 mg or less seladelpar in PBC subjects with HI. Hepatic impairment will be based on CP classification (CP-A with and without portal hypertension [PHT], CP-B, or CP-C), and subjects will be designated into the appropriate cohort by CP score. It is planned to enroll at least 24 subjects in this study in order to complete at least six subjects per cohort. Subjects will be assigned to the appropriate cohort based on their CP score at screening (Appendix B) as shown below.

Child Pugh Classification	CP-A	CP-A + PHT	CP-B	CP- C
Cohort	Cohort 1	Cohort 2	Cohort 3	Cohort 4

Part A: Part A of the study will use staggered enrollment with Cohorts 1-3 to be completed before commencing enrollment of subjects in Cohort 4. Cohorts 1-3 (N = 6 per cohort) will be concurrently open for enrollment and dosing with a single oral dose of 10 mg seladelpar. Cohorts 2 and 3 may remain open and continue to enroll until enough subjects are enrolled in Part B. Once all subjects in Cohorts 1-2 and at least 3 subjects in Cohort 3 have completed Part A, safety and PK will be evaluated to determine whether to enroll Cohort 4 (CP-C subjects) and to confirm that the 10 mg dose is appropriate for the first two subjects in this cohort. The first two subjects from Cohort 4 (out of a total of N = 6) will be treated with a single dose of 10 mg seladelpar; however, a lower dose may instead be selected after the PK and safety review of Cohorts 1-3. An additional review of the safety and PK data for the first two subjects from Cohort 4 will be completed prior to dosing the remaining four subjects; an additional adjustment to their dose may be made if deemed prudent for reasons of safety or exposure.

All study subjects will initially have a Screening visit followed by a Screening period of up to 28 days. Upon completion of all Screening activities, subjects will report to the Study Site on Day -1 for baseline measurements and laboratory assessments on Day 1. All subjects will remain on-site through the first 12-hour post-dose (Day 1) PK collection. For Study Sites able to house for multiple days, subjects may optionally remain on-site until the 24 hour post-dose (Day 2) PK collection and assessments are complete; for subjects at sites who are not able to house through Day 2, or for subjects who prefer to not to stay on site, they may return home after the 12 hour post-dose (Day 1) collection and assessment are complete and have the 24 hour post-dose (Day 2) collection performed at home by a home health service. The 48 hours ± 30 minutes post-dose (Day 3), and 72 hours ± 30 minutes post-dose (Day 4) assessments may be performed at home by a home health service, or the subject may return to the site for these procedures, or the subject may return to the site for these procedures. All subjects will be contacted by telephone on Day 7 ± 1 day. This will be the end of study visit for CP-A and CP-C as they will not participate in Part B.

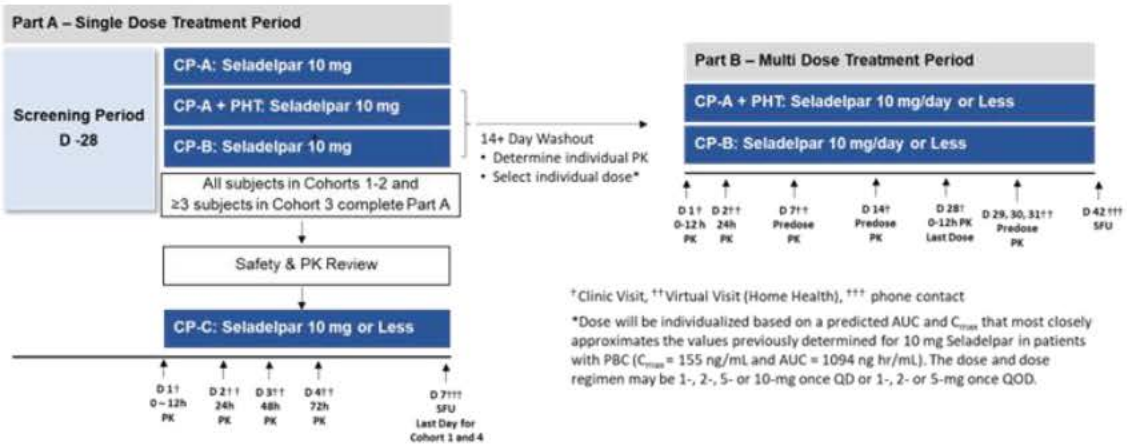
For Part A PK sample collection, blood samples will be taken starting on Day 1 at: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 (Day 2), 48 (Day 3) and 72 hours post-dose (Day 4). Blood sampling for unbound seladelpar will be collected on Day 1 at 2.5- and 12-hours post dose. Urine will also be collected over the following intervals: pre-dose (spot) and 0-6 hours, and 6-12 hours post-dose on Day 1 to measure seladelpar and major metabolites.

Part B: Participation in Part B is limited to subjects from Cohort 2 (CP-A + PHT) and Cohort 3 (CP-B) who have completed Part A. Subjects will have a washout period of at least 14 days following last study drug administration in Part A during which each subject's individualized dose for Part B will be based on their exposure in Part A. Each subject's dose will be individualized based on a modeled steady-state AUC and C_{max} using a non-compartmental analysis of their Part A PK data. The dose will be selected to approximate the safe range of steady-state exposures (after 2 to 12 weeks of dosing) previously determined for 10 mg seladelpar in patients with PBC (C_{max} = 155 ng/ml [min/max, 47/227 ng/ml] and AUC = 1094 ng hr/ml [min/max, 518/1609 ng hr/ml; Table 14.7.3.1, Study CB8025-21629). The expected doses and dose regimen include 1-, 2-, 5- or 10-mg QD or 1-, 2- or 5-mg once every other day (QOD).

Subjects will return to the Study Site between Day -6 and Day -4 for laboratory testing for Part B following their washout period. Subjects will then return to the Study Site on Day 1 for review of lab results, CP status, AEs, and concomitant medications. Any changes in these criteria should be discussed with the medical monitor before dosing.

Subjects will receive seladelpar QD or QOD for 28 days beginning on Day 1 through Day 28. On Day 1 and Day 28 subjects who prefer not to stay on site may return home after the 12 hour post-dose (Day 1) collection and assessment are complete. Their 24-hour post-dose (Day 2 and Day 29) collection can be performed at home by a home health service, or the subject may return to the site for these procedures. After the 12-hour collection on each of these days, the subject may return home. On Day 2, 7, 29, 30 and 31 of Part B, pre-dose collections and safety assessment may be performed on site or at home by a home health service. All subjects will return to the Study Site on Day 14 for a safety assessment and pre-dose collection. The end of study (or follow-up) for Cohorts 2 and 3 will occur 14 (+3) days after the last dose as a telephone call. The last day of dosing will occur on Day 28. For Part B PK sample collection, blood samples will be taken on Day 1 at: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 hours post-dose and on Day 28 at: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 (Day 29), 48 (Day 30) and 72 hours post-dose (Day 31). Pre-dose PK will also be collected on approximately Day 7 and Day 14.

Figure 3: Study Design Schema



3.2. Study Outcomes Measures

3.2.1. Primary Measures

- PK parameters of seladelpar and major metabolites: M1, M2 and M3

Plasma: C_{max}, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, %extrap$AUC_{0\text{-}inf}$, $t_{1/2}$, K_{el}, Rsq, CL/F, Vz/F

Urine: Ae and Cum Ae, Fe (seladelpar only) and Cum Fe (seladelpar only), and CL_R (seladelpar only)

- Safety & Tolerability

Type, frequency, severity, and relationship of TEAEs to seladelpar including the assessment of the following TEAEs of special interest (AESI):

- CTCAE Grade 2 increases in ALT, AST, bilirubin, CK, lipase or sCr, as defined by the Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0 (Appendix A)
- Hepatic decompensation clinical events (ascites, jaundice, esophageal variceal bleeding, hepatic encephalopathy)
- Physical examination, 12-lead ECG, and vital signs
- Biochemistry, hematology, coagulation, and urinalysis
- Efficacy (Part B, Cohorts 2 and 3 only)
- Change and relative change from baseline to Day 28 in ALP, GGT, ALT, AST, TB, DB, albumin and platelets.

3.2.2. Secondary Outcomes Measures

PK parameters of unbound seladelpar

Plasma: unbound $AUC_{0\text{-}t}$, unbound $AUC_{0\text{-}inf}$, unbound C_{max}, and Fu

3.3. Rationale for Dose Selection of Seladelpar in PBC Subjects

The proposed dose of seladelpar to be evaluated in this study is 10 mg or less given as a single or multiple oral dose(s). The dose selected for this Phase 1b trial in PBC is supported by both the nonclinical and clinical data generated to date. The proposed dose is within the current safety margins established in the chronic toxicology studies (Section 2.2.3). The dose range for the first-in-human Phase 1 clinical trial (1, 5, 15, 60, 120, and 360 mg) was based on a dose calculation considering the pharmacology of seladelpar and the NOAEL in the toxicology program. All doses were safe and well-tolerated, thus establishing the initial clinical safety of this dose range.

Chronic dosing of seladelpar is being tested and has been tested in a broad range of patient populations, including patients with mixed dyslipidemia (50 mg and 100 mg once a day for eight weeks), homozygous familial hypercholesterolemia (50 mg, 100 mg, and 200 mg once a day over 12 weeks), NASH (10 mg, 20 mg and 50 mg once a day for 52 weeks), and PBC (2 mg, 5 mg, 10 mg once a day for more than 52 weeks, and 50 mg and 200 mg once a day for up to

12 weeks). PBC patients with cirrhosis have also been dosed with 5 mg and 10 mg for over 52 weeks. Results from a hepatic impairment study (CB8025-11732) identified no safety concerns for Child-Pugh A, B, and C subjects given a single 10 mg oral dose of seladelpar. PBC patients are expected to have comparable seladelpar exposures based on the similar underlying cholestatic conditions. Additional studies (CB8025-21629, CB8025-31731, and CB8025-31735) have examined seladelpar dosing at up to 10 mg in over 50 subjects with compensated CP-A cirrhosis. Seladelpar efficacy and safety in cirrhotic subjects was comparable to non-cirrhotic subjects in these studies. Therefore, a single dose of 10 mg was selected for Part A CP-A with and without PHT and CP-B cohorts because this dose is being evaluated in phase 3 and in long-term safety studies, and a similar dose was evaluated in the prior HI study in subjects with a predominantly different etiology. The doses for Cohort 4 (CP-C) will be based on the PK and safety results of Cohorts 1-3 in Part A. The doses for subjects in Cohorts 2 and 3 in Part B will be determined based on their individual PK and safety results in Part A. In addition, after Day 28 of Part B for the first two (sentinel) subjects in Cohort 3 (CP-B), a safety review will be conducted by the SRC to assess if it is safe to proceed with the current dosing or if a dose adjustment is necessary for the remaining subjects in Part B for this cohort.

CYP2C9 is one of the major enzymes involved in the metabolism of seladelpar. This enzyme is polymorphic, and its resulting activities may vary within the potential patient population. Therefore, genotyping will allow evaluating the relationship between CYP2C9 genotype and plasma concentrations of seladelpar. Subjects will not be excluded from the study based on genotype.

3.4. Benefit/Risk Assessment

3.4.1. Potential Benefit

Subjects in Cohort 1 (CP-A without PHT) and Cohort 4 (CP-C) are limited to Part A and will only receive a single dose of seladelpar with limited or no benefit to be expected. Subjects in Cohort 2 (CP-A with PHT) and Cohort 3 (CP-B) will receive up to 28 days of seladelpar and be evaluated for their ability to have a biochemical response on markers of cholestasis and liver injury (transaminases), a time period in which seladelpar has shown favorable responses in other studies of patients with PBC; thus, subjects may gain an indication if there is reason for them to consider receiving future treatment with seladelpar. Should the safety and PK results of this study demonstrate that it is safe to administer seladelpar in cholestatic patients with hepatic insufficiency, subjects who complete participation in this study, may have the opportunity to receive study drug in a longer-term clinical study setting if medically eligible.

3.4.2. Potential Risks

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

Seladelpar has been associated with increases in liver transaminases (ALT and AST) in subjects with PBC treated with seladelpar at doses 50 mg and 200 mg. The transaminase increases appear

to be dose and population-dependent and were fully reversible upon treatment discontinuation. A single PBC subject taking seladelpar 200 mg per day discontinued treatment for acute muscle pain associated with increased muscle enzymes. This was considered possibly related to treatment and was reversible upon treatment discontinuation. Mild increases in serum creatinine have been noted, consistent with those observed with other PPARα or mixed PPARα/δ class of medications. It should be noted that there have been no similar changes in cystatin-c or other markers of renal injury, supporting that the increase is not associated with renal toxicity or decreasing glomerular filtration rate (GFR). All three of these potential toxicities are easily monitored in the study, appear to be dose and population dependent, and are rapidly reversible upon discontinuation of seladelpar treatment.

In the single dose portion of the study (Part A), the single low dose level (10 mg or less) of study drug is expected be associated with a minimal risk. In the multiple dose portion of the study (Part B), the dose will be individually decreased to provide an exposure that approximately match exposures that already have had good safety experience. Moreover, subjects will be closely evaluated at regular intervals (Days 7, 14, and 28) through exams and laboratory assessments so that study drug interruption and follow up can be quickly instituted. In light of the above, the degree of risk is expected to be minimal.

4. SUBJECT SELECTION

4.1. Inclusion Criteria

PBC patients who meet the following criteria may be included in the study:

1. Males and females between 18 and 80 years of age (inclusive) who are able to comprehend instructions and follow the study procedures and are willing to sign an Informed Consent Form (ICF)
2. Females of childbearing potential who are sexually active with a non-sterile male partner (sterile male partners are defined as men vasectomized since at least 6 months) must be willing to use the contraceptive methods described in Section 8.2.1 throughout the study and for 30 days after study drug administration.
3. Male subjects who have not been vasectomized for at least 6 months prior, and who are sexually active with a female partner of childbearing potential must be willing to use the contraceptive methods described in Section 8.2.1 from study drug administration until at least 90 days after study drug administration.
4. Male subjects (including men who have had a vasectomy) with a pregnant partner must agree to use a condom from study drug administration until at least 90 days after study drug administration.
5. Male subjects must be willing not to donate sperm until 90 days following study drug completion of administration.
6. Willing to abstain from consuming grapefruit, pomelo, star fruit, or Seville orange containing products from 7 days prior to dose of study medication through day of discharge.
7. Confirmed diagnosis of PBC based on any **two** of the following three criteria:
    - History of elevated ALP, GGT or conjugated bilirubin levels for at least 6 months
    - Positive AMA titer or if AMA negative or low titer (≤ 1:80), PBC specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)
    - Documented liver histology results consistent with PBC
8. Evidence at Screening of cirrhosis including at least one of the following:
    - Biopsy results consistent with cirrhosis in PBC
    - Liver stiffness as assessed by transient elastography (TE) ≥ 16.9 kPa
    - Radiological evidence of cirrhosis (nodular liver or enlargement of portal vein and splenomegaly)
    - Clinical evidence in the absence of acute liver failure consistent with cirrhosis, which may include:
        - gastroesophageal varices
        - ascites

- Low platelet count (< 140 × 10^3/μL)
- Albumin < 3.5 g/dL
- INR > 1.3
- Total bilirubin > ULN

9. Subjects must have the following specific additional laboratory parameters that is measured by the Central Laboratory at Screening:
    - ALP, ALT, and AST < 10 × ULN
    - Total bilirubin ≤ 5 × ULN
    - Estimated glomerular filtration rate (eGFR) >45 mL/min/1.73 m^2 (calculated by the MDRD study equation).
10. Patients taking UDCA will be allowed to enroll if meeting the following criteria:
    - A minimum of 12 weeks of treatment prior to Day 1
11. One of the following should be met for CP-A subjects with PHT:
    - Cross sectional abdominal imaging with evidence of venous collaterals, within the past 2 years from screening
    - EGD with non-bleeding varices, within the past 2 years from screening
    - Spleen length >13 cm by imaging within the past 6 months
12. MELD-Na scores of 6 to 24 at Screening
13. Subjects must be able to comply with the instructions for study drug administration and be able to complete the study schedule of procedures.

4.2. Exclusion Criteria

PBC subjects meeting any of the following exclusion criteria are not eligible for study enrollment:

1. Clinically significant or history of acute or chronic liver disease of an etiology other than PBC
2. Patients with a diagnosis of overlapping PBC and autoimmune hepatitis
3. History, evidence, or high suspicion of hepatobiliary malignancy based on imaging, screening laboratory values, and/or clinical symptoms.
4. Presumptive or diagnosed infection that requires systemic therapy within 12 weeks of Screening and through Day 1
5. Female subjects who are pregnant or nursing

Specific criteria for defining child-bearing potential, acceptable methods of birth control, and male partner recommendations are outlined in detail in Section 8.2.1 of the protocol.

6. Screening ECG that demonstrates a QT interval ≥ 500 msec, or any other significant ECG finding with clinically significant abnormalities as determined by the Investigator.

7. Positive for HBsAg, HCV-RNA, or anti-HIV antibody
8. Presence of any conditions (e.g., geographic, or social), actual or projected, that the Investigator feels would restrict or limit the patient's participation for the duration of the study.
9. Any clinically significant abnormalities in laboratory test results at Screening that would, in the opinion of the Investigator, increase the subject's risk, jeopardize complete participation in the study, or compromise interpretation of study data or subject safety.
10. Any non-hepatic acute or chronic condition that, in the opinion of the Investigator, would limit the patient's ability to complete and/or participate in the study or compromise the integrity of the data.
11. Has experienced an illness that is considered by the Investigator to be clinically significant within 2 weeks before administration of investigational product.
12. Clinically-relevant drug or alcohol abuse within 6 months of Screening. A positive drug screen will exclude subjects unless it can be explained by a prescribed medication.
13. Any prohibited medication as listed in Section 5.3.3 of the study protocol.
14. Known sensitivity or idiosyncratic reaction to any compound present in seladelpar capsule, its related compounds, or any compound listed as being present in the formulation of the investigational product.
15. Use of OCALIVA®, any drug of the same class, or fibrates (e.g., bezafibrate, fenofibrate, elafibranor, lanifibranor, pemafibrate, saroglitizar) within 30 days of Baseline
16. Use of an experimental or unapproved treatment for PBC within 30 days of Baseline
17. Clinically evident complication(s) of cirrhosis and portal hypertension that required either emergency room visit, hospital admission or both during the 2-week period prior to investigational product administration, including but not limited to variceal hemorrhage, grade ≥3 hepatic encephalopathy in the Investigator's clinical judgement, and new onset / worsening large volume ascites formation. Subjects with hospitalization or emergency room visit occurring > 2 weeks - ≤ 12 weeks prior to investigational product administration will be discussed with the Sponsor's Medical Monitor on a case-by-case basis.

5. SCHEDULE OF STUDY PROCEDURES

The Schedule of Study Procedures are outlined in Table 1 for Part A and Table 2 for Part B. For the purpose of study procedures, Study Days for Part A (Section 5.1) and Part B (Section 5.2) are specified separately.

5.1. Part A Study Visit Procedures

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

- Screening Period: Up to 28 days
- Baseline Visit on Day -1 and Dosing on Day 1
- Study Period: Days 1 through 4
- Follow-up Telephone Call: Day 7 ± 1 day

5.1.1. Day –28 to Day –1 (Screening) Procedures

The following Screening procedures will be performed for all potential subjects at a visit (or visits) conducted within 28 days prior to dosing:

- Obtain informed consent
- Collect demographic data
- Review and record medical history
- Record prior and concomitant medications
- Record AEs (starting from the time the subject signs the informed consent)
- Assess inclusion/exclusion criteria
- Conduct a complete physical examination
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Measure height
- Measure weight
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes)
- Child-Pugh Assessment
- Obtain blood specimens for:
    - Serum pregnancy test
    - Viral Screen
    - Chemistry
    - Hematology
    - Coagulation

    - Back up blood sample
- Obtain urine specimens for:
    - Drug Screen (cannabinoids are excluded)
    - Urinalysis

COVID-19 testing will be performed locally and only if deemed necessary per local requirements, and in the judgement of the Investigator.

The Investigator has discretion to repeat Screening assessments/procedures if he/she believes the results were spurious and do not reflect accurate values. Repeat assessments/procedures must be conducted within the 28-day Screening Period, prior to the Baseline Visit. The repeat lab or assessment must be at least 7 days apart and recorded as an unscheduled visit. Subjects who fail a Screening Visit may be rescreened once with prior approval from the Sponsor.

5.1.2. Day -1 (Baseline) Procedures

Subjects will report to this visit fasted for a minimum of 2 hours. The following procedures will be performed at the Day -1 visit:

- Review and record medical history
- Assess for concomitant medications
- Reassess inclusion/exclusion criteria
- Record AEs
- Conduct a complete physical examination
- Re-assess Child-Pugh score by assessment of clinical features such as hepatic encephalopathy and ascites
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Obtain blood specimens for:
    - Chemistry
    - Hematology
    - Coagulation
    - Back up blood sample
- Obtain urine specimens for:
    - Pregnancy test (result reviewed prior to dosing)
    - Urinalysis

An optional blood sample (up to 15 mL) will be collected from subjects who consent to the genotyping test and will be kept for possible exploratory CYP2C9, CYP2C8, CYP3A4, and UGT genotyping following the results of the study.

COVID-19 testing will be performed locally and only if deemed necessary per local requirements and in the judgement of the Investigator

5.1.3. Day 1 Dosing Day Procedures

- Review and record medical history
- Assess for concomitant medications
- Assess for concomitant procedures
- Record AEs
- Conduct a complete physical examination
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Seladelpar administration
- Obtain blood specimens at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 hours for:
    - Plasma PK
- Obtain 12-lead pre-dose ECG (after subject has been supine for at least 5 minutes)
- Obtain urine specimens (spot) and 0-6 hours, 6-12 hours post-dose for:
    - Urine PK

5.1.4. Day 2 Procedures

The following procedures will be performed at the Day 2 visit:

- Assess for concomitant medications.
- Assess for concomitant procedures
- Assess for AEs.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Obtain blood specimens pre-dose for:
    - Plasma PK

5.1.5. Day 3 Procedures

The following procedures will be performed at the Day 3 visit:

- Assess for concomitant medications
- Assess for concomitant procedures
- Assess for AEs

- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Obtain blood specimens for:
    - PK samples

5.1.6. Day 4/ET Procedures

The following procedures will be performed at the Day 4/ET visit

- Assess for concomitant medications
- Assess for concomitant procedures
- Assess for AEs
- Conduct a complete physical examination
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Obtain 12lead ECG (after subject has been supine for at least 5 minutes)
- Obtain blood specimens for:
    - Chemistry
    - Hematology
    - Coagulation
    - Back up blood sample
    - PK sample
- Obtain urine specimens for:
    - Urinalysis
    - Pregnancy Test

5.1.7. Day 7 ± 1 day (Follow Up) Procedures

The following procedures will be performed at the Day 7± 1 follow up by telephone call:

- Assess for concomitant medications
- Assess for concomitant procedures
- Assess for AEs

5.1.8. Unscheduled (UNS) Visits

Unscheduled visits may be conducted at the Investigator's discretion and/or when repeat of laboratory assessments is needed.

5.2. Part B Study Visit Procedures

5.2.1. Pre-dosing Safety Visit (between Day -6 – Day -4) (Optional Home Health Visit)

- Assess for concomitant medications.
- Assess for concomitant procedures
- Assess for AEs.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Obtain blood specimens for:
    - Serum Pregnancy Test
    - Chemistry
    - Hematology
    - Coagulation
    - Back up blood sample
- Obtain urine specimens for:
    - Urinalysis
    - Drug Screen (cannabinoids are excluded)

5.2.2. Day 1 Dosing Day Procedures

- Review and record medical history
- Assess for concomitant medications
- Assess for concomitant procedures
- Record AEs
- Assess abbreviated inclusion/exclusion criteria per study procedures
- Conduct a complete physical examination
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Seladelpar administration
- Measure weight
- Obtain urine specimens for:
    - Pregnancy test (result reviewed prior to dosing)
- Obtain blood specimens for PK samples at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 hours for:
    - Plasma PK

- Obtain 12 lead ECG pre-dose (after subject has been supine for at least 5 minutes)

COVID-19 testing will be performed locally and only if deemed necessary per local requirements, and in the judgement of the Investigator.

5.2.3. Day 2 Procedures

The following procedures for the Day 2 visit will be performed onsite or at home, by a home health service:

- Assess for concomitant medications.
- Assess for concomitant procedures
- Assess for AEs.
- Seladelpar administration
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Obtain blood specimens for:
    - Chemistry
    - Hematology
    - Coagulation
    - Back up blood sample
- Obtain urine specimens for:
    - Urinalysis
- Obtain blood specimens pre-dose for:
    - 24-hour PK and safety labs

5.2.4. Day 7 Procedures

The following procedures for the Day 7 visit will be performed onsite or at home, by a home health service or by the PI or qualified medical staff:

- Assess for concomitant medications
- Assess for concomitant procedures
- Assess for AEs
- Seladelpar administration
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Obtain blood specimens pre-dose for:
    - Chemistry
    - Hematology

  - Coagulation
  - Back up blood sample
  - PK Samples
- Obtain urine specimens for:
  - Urine pregnancy Test, pre-dose
  - Urinalysis

5.2.5. Day 14 Procedures

Subjects will return to the study site for the following Day 14 procedures:

- Assess for concomitant medications
- Assess for concomitant procedures
- Assess for AEs
- Conduct a complete physical examination
- Seladelpar administration
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Measure weight
- Obtain 12 lead ECG pre-dose (after subject has been supine for at least 5 minutes)
- Obtain blood specimens pre-dose for:
  - Chemistry
  - Hematology
  - Coagulation
  - Back up blood sample
  - PK samples
- Obtain urine specimens for:
  - Urine pregnancy test, pre-dose
  - Urinalysis

5.2.6. Day 28 Procedures

The following procedures will be performed at the Day 28/ET visit

- Assess for concomitant medications
- Assess for concomitant procedures
- Assess for AEs
- Conduct a complete physical examination

- Seladelpar administration
- Measure weight
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Obtain 12-lead ECG pre-dose (after subject has been supine for at least 5 minutes)
- Obtain blood specimens for:
    - Chemistry
    - Hematology
    - Coagulation
    - Back up blood sample
    - PK samples at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 hours
- Obtain urine specimens for:
    - Urine pregnancy test, pre-dose
    - Urinalysis

5.2.7. Day 29 Procedures

The following procedures for the Day 29 visit will be performed onsite or at home, by a home health service:

- Assess for concomitant medications
- Assess for concomitant procedures
- Assess for AEs
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Obtain blood specimens for:
    - Chemistry
    - Hematology
    - Coagulation
    - Back up blood sample
    - 24 hour PK
- Obtain urine specimens for:
    - Urinalysis

5.2.8. Day 30 Procedures

The following procedures for the Day 30 visit will be performed onsite or at home, by a home health service:

- Assess for concomitant medications
- Assess for concomitant procedures
- Assess for AEs
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Obtain blood specimens for:
    - Chemistry
    - Hematology
    - Coagulation
    - Back up blood sample
    - 48 hour PK
- Obtain urine specimens for:
    - Urinalysis

5.2.9. Day 31/ET Procedures

The following procedures for the Day 31 visit will be performed onsite or at home, by a home health service:

- Assess for concomitant medications
- Assess for concomitant procedures
- Assess for AEs
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Obtain blood specimens for:
    - Chemistry
    - Hematology
    - Coagulation
    - Back up blood sample
    - 72-hour PK
- Obtain urine specimens for:
    - Urinalysis
    - Pregnancy Test

5.2.10. Follow Up Procedures after Last Dose

The following procedures will be performed 14 (+3) days after the last dose by telephone call:

- Assess for concomitant medications
- Assess for concomitant procedures
- Assess for AEs

5.2.11. Unscheduled (UNS) Visits

Unscheduled visits may be conducted at the Investigator's discretion and/or when repeat of laboratory assessments is needed.

5.3. Concomitant and Prohibited Medications

5.3.1. Concomitant Medications

Any medication (including herbal medications and vitamin supplements) taken within 28 days prior to Day 1, as well as the reason for use, will be recorded in the source documents and the electronic Case Report Forms (eCRF). Any AEs related to the administration of these medications or procedures must also be documented on the appropriate section in the eCRF.

The COVID-19 vaccine will be allowed within a minimum of a 2-week window before the screening visit. It should be documented as a concomitant medication according to protocol requirements.

If possible, subjects enrolled in the trial should get their vaccine after their end of study follow up visit; however, if it is in the opinion of the investigator that the subject should not wait, they can receive the vaccine during the trial, and it should be documented as a concomitant medication and any adverse events should be documented.

Subjects should refrain from the use of any new prescription medications or products or change in the dose or frequency of existing therapies within 28 days prior to Day 1 and until the end of the study. The Sponsor's Medical Monitor should be informed of any changes or addition of medications during this time period.

Concomitant medications will be coded using WHO Drug dictionary.

5.3.2. Permitted Concomitant Medications

- Hormonal contraception for female subjects of child-bearing potential
- Acetaminophen for subjects not more than 1 gram per 24 hours for no more than 5 days in succession, following approval by the study Investigators and the Sponsor
- Low-dose aspirin for subjects

Other concomitant medication deemed necessary for the well-being of the subject during the study may be given at the discretion of the Investigator after agreement with the Sponsor. In the setting of a medical emergency, treatment should not be delayed; however, the Sponsor should be notified in a timely manner, e.g., within 6-12 hours.

The Investigator is responsible to ensure that details regarding concomitant medication use are recorded in the eCRF.

Permitted medications will include those necessary to treat hepatic disease and its complications including UDCA as prescribed by the subject's treating physician. Stable medications to treat other chronic conditions are permitted at the discretion of the investigator and in agreement with the Sponsor.

5.3.3. Prohibited Medications

The following medications are prohibited from 28 days prior to Day 1 and through the end of the study:

- Investigational agents, other than seladelpar
- Investigational devices for any indication
- OCALIVA® (30 days prior to Day 1)
- Fibrates (30 days prior to Day 1, e.g., bezafibrate, fenofibrate, elafibranor, lanifibranor, pemafibrate, saroglitazar)

Use or intend to use any medications/products known to be transported by breast cancer resistance protein, moderate or strong inducers or inhibitors of CYP3A4, and/or CYP2C8 and 2C9 inhibitors, including St. John's wort, within 14 days prior to check-in, unless deemed acceptable by the PI or Sub-Investigator.

5.4. 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. All concomitant procedures must be documented on the subject's eCRF. Adverse events related to the administration of these medications or procedures must also be documented on the appropriate section in the eCRF.

Concomitant procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

5.5. Diet and Activity Control

Subjects should maintain their normal level of physical activity, diet, and lifestyle throughout the entire study (i.e., will not begin a new exercise program or participate in any unusually strenuous physical exertion).

During Part A, all subjects will be required to fast for at least 8 hours before and 2 hours after dosing after which standard meals will be provided. Subjects who are diabetic and/or who require food for health reasons will be allowed to have an optional snack either 2 hours before or 2 hours after dose administration at the discretion of the Investigator.

During Part B, subjects will be required to fast for at least 8 hours before and 2 hours after dosing on Study Days 1 and 28. Standard meals will be provided after the fasting period. Accommodations for subjects who are diabetic and/or who require food for health reasons will be allowed as described above.

During both Part A and B, unaccustomed strenuous exercise is prohibited from 48 hours before Day 1, throughout the study period and the follow-up visit.

5.6. Clinical Evaluations

5.6.1. Medical History and Physical Examinations

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

Complete physical examinations will be performed as outlined in Table 1 and Table 2. Complete physical examinations 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 (optional or as indicated), musculoskeletal, neurologic, mental health, endocrine and hematologic. Complete physical examinations will be performed at all visits.

Any clinically significant change in physical examination findings that occurs after signing the ICF will be recorded as an AE. The physical examination may be performed by a physician, trained physician's assistant, or a nurse practitioner, as acceptable according to local regulation.

5.6.2. Height and Weight

Height measurement (cm) will be performed without shoes at Screening only. Weight (kg) without shoes and empty pockets will be taken at each study visit per the Schedule of Study Procedures (Table 1 and Table 2).

5.6.3. Vital Signs

Vital signs (including oral temperature, respiratory rate, and seated blood pressure [diastolic and systolic] and heart rate) will be obtained at Screening and at all study visits as outlined in the Schedule of Study Procedures (Table 1 and Table 2).

Seated blood pressure and heart rate will be measured after the subject has been seated for at least 5 minutes. For all subjects, blood pressure and heart rate will be measured with a sphygmomanometer.

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

If other procedures are scheduled at the same time point, vital signs will be obtained first, before an ECG and/or collection of blood samples.

5.6.4. Electrocardiograms

Electrocardiogram parameters of ventricular rate, PR interval, QRS duration, QT interval (uncorrected), and QT interval corrected for heart rate according to Fridericia's formula (QTcF) will be performed during Part A at Screening and Day 1. These procedures will be conducted in Part B on Day 1, Day 14 and Day 28. If other procedures are scheduled at the same time point, the ECG will be obtained after vital sign measurements and before the collection of blood samples.

A 12-lead ECG will be obtained in supine position after at least 5 minutes of rest at Screening and at all study visits as outlined in the Schedule of Study Procedures (Table 1 and Table 2). For all subjects, the ECG will be reviewed, signed, and dated by the Investigator or qualified designee. Any significant ECG findings will be reported to the Medical Monitor. The ECGs will be classified in 1 of 3 categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. All clinically significant findings will be reported as AEs.

5.6.5. Child-Pugh Assignment

Child-Pugh assignment will be allocated at Screening. Subjects will be allocated into the appropriate cohort based on their Child-Pugh score (Appendix B). Subjects may be reassigned to the appropriate cohort based on their Child Pugh score on Day -1, if the score changes from Screening.

5.6.6. Laboratory Assessments

Blood samples for laboratory testing from Screening visit and onward will be collected at study visits after at least a 2-hour fast. If the subject forgets to fast, the site or home health visit personnel will document, continue to draw labs and proceed with the visit. Additional details about sample collection, processing, handling and laboratory determination techniques are provided in the Laboratory Manual.

Instructions regarding the collection, processing, and shipment of laboratory samples are detailed in the Laboratory Manual. All samples will be given a unique identifier. The exact timing of dosing, as well as actual date and time (24-hour time clock) will be entered on the eCRF.

Laboratory tests will be collected be taken at each study visit per the Schedule of Study Procedures (Table 1 and Table 2) and will include the following parameters.

Biochemistry: Albumin, ALT, ALP, Amylase, AST, Bicarbonate, Blood Urea Nitrogen (BUN)/Urea, Chloride, CK, Bilirubin (total, direct, indirect), Creatinine, Cystatin-C, eGFR, Free Fatty Acid, GGT, Glucose, Lipase, non-HDL-C, Potassium, Total Protein, Sodium, Uric Acid, Thyroid Stimulating Hormone (TSH)

Hematology: Erythrocyte Count (RBC), Mean Corpuscular Volume (MCV), Hemoglobin, Hematocrit, Leukocyte Count (white blood cell count [WBC]), WBC Differential (absolute and percentage)

Coagulation: Platelets, prothrombin time (PT), international normalized ratio (INR)

Back-Up Blood Sample: One additional serum sample will be collected at each study visit. These samples can be stored for up to 5 years following completion of the study and used for additional safety assessments, measure drug levels, potential new biochemical markers, and/or to replace any missing or discarded samples.

Pregnancy Tests: Serum pregnancy test will be tested in female subjects of child-bearing potential at Screening.

In Part A, urine pregnancy test will be conducted on Day -1 and Day 4/Early Termination. In Part B, urine pregnancy test will be conducted on Day 1, Day 7, Day 14, and Day 28 prior to dosing, and Day 31/Early Termination. The Investigator may check pregnancy at other timepoints per local requirements.

HIV Antibody, Hepatitis B and C Testing: Part A Screening only. The hepatitis tests will include HBsAg and HCV antibody (HCV-RNA only if HCV antibody is positive).

Urinalysis: Urine color and appearance, specific gravity, pH, glucose, protein, occult blood, bilirubin, urobilinogen, nitrite, ketones, WBC, RBC, epithelial cells, WBC esterase, bacteria, mucus threads.

Urine Drug Screen: Amphetamine, barbiturates, benzodiazepines, cocaine, ecstasy (MDMA), methadone, opiates, oxycodone, phencyclidine (PCP), propoxyphene, tricyclic anti-depressants (TCA). Cannabinoids are not included in this drug screen.

5.6.7. Pharmacokinetic Assessments

PK samples will be obtained from blood and urine (Part A only). Plasma and urine concentrations of seladelpar and metabolites (M1, M2 and M3) will be determined.

Procedures for collection, processing, storage, and shipping instructions for these PK blood and urine samples will be presented in a separate lab manual.

An optional blood sample (up to 15 mL) will be collected upon admission on Day -1 from subjects who consent to the genotyping test and will be kept for possible exploratory CYP2C9, CYP2C8, CYP3A4, and UGT genotyping following the results of the study. No analysis or Summary Table is required for genotyping tests results; only Genotype Listing is to be provided.

No other genotyping tests will be performed using this blood sample.

5.6.7.1. Part A Pharmacokinetic Assessments

Individual PK parameters will be calculated from concentration versus time data with noncompartmental methods (C_{max}, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $\%extrapAUC_{0\text{-}inf}$, $t_{½}$, K_{el}, Rsq, CL/F [seladelpar only], Vz/F [seladelpar only], CL_R, Ae, Cum Ae, Fe [seladelpar only], Cum Fe [seladelpar only]; unbound $AUC_{0\text{-}t}$, unbound $AUC_{0\text{-}inf}$, unbound C_{max}, and Fu).

Blood samples for plasma PK of seladelpar and metabolites M1, M2 and M3 will be obtained at the following times:

- Day 1: pre-dose sample (≈ 10 minutes before seladelpar administration), ±5 minutes for 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, and 5 hours post-dose, and ±10 minutes for 6, 8 and 12 hours post-dose, ±15 minutes for 24 hours post-dose and ±30 min for 48 and 72 hours post-dose.

Blood samples for plasma PK of unbound seladelpar will be obtained at the following times:

- Day 1: ±5 minutes for 2.5 hours post-dose, and ±10 minutes for 12 hours post-dose.

When multiple assessments are scheduled at any given timepoint, clinical assessments should precede all blood collection, including ECGs.

Urine samples for PK analysis will be collected at the following times:

- Day 1: For 24-hour urine collection, subjects will be instructed to empty their bladder before seladelpar administration. Urine will be collected over the following intervals: pre-dose (spot) and 0-6 hours, and 6-12 hours.

5.6.7.2. Part B Pharmacokinetic Assessments

Individual PK parameters will be calculated from concentration versus time data with noncompartmental methods.

Part B PK parameters include:

- Day 1, 24 hour collection (Days 1 and 2): C_{max}, T_{max}, AUC_{0-t}, AUC_{0-24}, $t_{½}$, K_{el}, Rsq, CL/F (seladelpar only), Vz/F (seladelpar only).
- Day 28, 72-hour collection (Days 28, 29, 30 and 31): C_{max}, C_{min}, T_{max}, AUC_{0-t}, AUC_{0-24}, AUC_{0-tau}, $t_{½}$, K_{el}, Rsq, CL/F (seladelpar only), Vz/F (seladelpar only), accumulation ratio (AR): C_{max} or AUC_{0-tau} on Day 28 divided by the C_{max} or AUC_{0-24} on Day 1, respectively.

Blood samples will be taken on:

- Day 1: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and (Day 2 pre-dose) 24 hours post-dose
- Day 28: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 (Day 29), 48 (Day 30) and 72 hours post-dose (Day 31).
- Day 7 and Day 14: Pre-dose.

6. CLINICAL SUPPLIES

6.1. Investigational Product

Seladelpar will be administered in an open-label manner as oral capsules containing 10 mg or less at the study site.

- Part A: Subjects will be administered one seladelpar 10 mg capsule.
- Part B: Subjects may be administered one seladelpar 10 mg capsule, or potentially a lesser strength capsule depending on evaluation of PK and safety results for subjects from Part A and sentinel subjects from Part B. Dose frequency will be either QD or QOD depending on each subjects individualized dosing.

The drug product is manufactured for CymaBay Therapeutics, Inc. (CymaBay) under current Good Manufacturing Practice regulations at a contract manufacturing facility that has undergone FDA inspection.

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

6.2. Study Drug Accountability

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

Upon receipt of the investigational drug, the designated site personnel will visually inspect the shipment, verify the number and condition of study drug received, and confirm receipt of study drug. Study drug reconciliation will be performed based on assessing the single dose study-drug container.

At the completion of the study, all unused study-drug supplies will be returned to the Sponsor (or designee) or disposed of by the clinic, per the Sponsor's (or designee's) written instructions. A more detailed description of these processes is outlined in a separate study specific Pharmacy Manual.

6.3. Study Drug Storage

Seladelpar is stored between 15°C and 25°C in a tightly closed container, protected from light.

7. ADVERSE EVENTS

7.1. 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 TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity after initiation of the study drug.

7.1.1. Events Meeting the Adverse Event Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after seladelpar administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

7.1.2. Events Not Meeting the Adverse Event Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject’s condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

7.2. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

Adverse events of special interest for this study have been identified as AEs that meet CTCAE Version 5.0 or the most recent version (Appendix A) Grade 2 criteria (Section 7.4.1) or higher for AEs of elevated ALT, AST, bilirubin, CK, lipase, or sCr. Hepatic decompensation clinical events including ascites, jaundice, esophageal variceal bleeding, and hepatic encephalopathy, are also defined as AESI for this study.

7.3. Definition of Serious Adverse Events

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.

7.4. Assessment of Adverse Events

7.4.1. Severity

The severity of an AE will be graded from 1 to 5 according to NCI CTCAE criteria (Appendix A).

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

7.4.2. 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 investigator's clinical judgment. One of the 6 outcomes listed below must be recorded:

- **Recovered/Resolved** –The subject has fully recovered from the event with no residual effects observable or returned to baseline status.
- **Recovered/Resolved with sequelae** – The subject has recovered from the event with some residual side effects observable.
- **Not Recovered/Not Resolved** – The subject or event has not recovered or resolved or shown further improvement after an appropriate time of follow-up.
- **Recovering/Resolving** – The subject or event is still improving but has not fully recovered.
- **Fatal** – Death.
- **Unknown** – Subject lost to follow-up.

7.4.3. Relationship to Study Drug

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

7.4.4. Action Taken with Study Medication

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

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

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

7.4.5.1. Non-Serious Adverse Events

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.

7.4.5.2. Serious Adverse Events

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 (ICH) of Technical Requirements for Pharmaceuticals for Human Use 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 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, United BioSource Corporation (UBC) by e-mail (CymaBayPV@ubc.com) or fax (+1-866-750-9110) to UBC Pharmacovigilance department, 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 7.3.

The outcome for the event will be listed on the SAE Report Form as defined in Section 7.4.2.

If additional information regarding a previously submitted SAE is obtained, a follow-up SAE must be sent to the Sponsor's representative (safety vendor). The Sponsor and/or its designee will identify and report to regulatory authorities within the required timeframes, all SUSARs and clinically important increases in rate of serious suspected adverse reactions.

SAEs must be collected and reported by the Investigator for the whole period from the signing of ICF until the last study visit. An SAE deemed related to study drug even if it occurs after last visit should be reported to the Sponsor.

The Investigator will document all available information 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 minimally include sufficient information to permit identification of the following:

- Subject's study number
- Time and date of study drug administrations
- Time and date of the start of the event and either the date and time of the resolution of the event or a statement that the event is ongoing
- A brief description of the event and countermeasures 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. 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. Details about the distribution of safety responsibilities are presented in the Safety Reporting Plan.

8. SAFETY MONITORING

The safety and tolerability of seladelpar will be assessed by evaluation of AEs, physical examinations, vital sign measurements, ECGs, and clinical laboratory parameters (hematology, clinical chemistry, and urinalysis). Safety assessments will be performed at scheduled intervals from Screening to the end of study assessments as presented in the Schedule of Study Procedures.

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

8.1.1. Liver Safety Monitoring

Any subjects with increase in liver enzymes should be evaluated for drug induced liver injury (DILI) as well as for natural progression of their PBC. Liver safety criteria will be monitored using two different approaches depending on the subject's liver status as baseline. Subjects with CP-A cirrhosis at Baseline will be monitored per Section 8.1.1.1 which is in line with the recently published guideline (Palmer, 2020). Subjects with CP-B cirrhosis will be monitored per Section 8.1.1.2.

8.1.1.1. Liver Safety Monitoring for Subjects with Child-Pugh A Cirrhosis at Baseline

Table 5, Table 6, and Table 7 provide the algorithms that will be followed to assess potential DILI (Palmer, 2020). These algorithms are applicable to subjects with baseline CP-A status only; liver safety monitoring for subjects with CP-B status is described in Section 8.1.1.2.

Subjects with suggested DILI should be initially queried for a possible clinical explanation of liver enzyme increases, associated symptoms, and relationship to the study drug. Liver enzymes must be repeated within 3 days with appropriate discussion with the medical monitor and the subject should be closely observed as per Appendix C. Evaluating potential cholestatic DILI should follow the algorithm in Table 7 from recently published in consensus guidelines (Palmer, 2020).

Table 5: DILI Criteria for Subjects With Normal Baseline ALT and AST

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

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

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

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

Table 6: DILI Criteria for Subjects With Abnormal Baseline ALT and AST

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

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BLM=baseline measurement; DILI=drug-induced liver injury; INR=international normalized ratio; ULN=upper limit of normal.
[a] Clinical symptoms associated with the study drug: appearance of fatigue, nausea, right upper quadrant pain or tenderness, fever, rash, jaundice, and/or eosinophilia (absolute count >1×ULN).
[b] Repeat AST, ALT, total bilirubin, and PT/INR within 3 days and closely observe the subject (see Appendix C)

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

Table 7: Algorithm for Monitoring and Interrupting Study Drug for Cholestatic DILI Signals for Patients with PBC Without Advanced[a] Cirrhosis

Treatment emergent Alkaline phosphatase (ALP)	Bilirubin	Symptoms[b]	Action
ALP ≥2× baseline without alternative explanation	Normal	None	Repeat Blood tests in 7-10 days[c] Follow-up for symptoms
ALP ≥2× baseline without alternative explanation	Total bilirubin ≥2× baseline	None or present	Interrupt study drug. Blood tests should be repeated within 7-10 days[c] Initiate close monitoring and workup for competing aetiologies. Study drug can be restarted only if another aetiology is identified, and liver abnormalities return to baseline. Drug cannot be restarted if hepatic decompensation occurs.[d]

Treatment emergent Alkaline phosphatase (ALP)	Bilirubin	Symptoms[b]	Action
ALP ≥ 2× baseline without alternative explanation	Normal or elevated	Present	Interrupt study drug. Repeat blood tests in 7-10 days[c] Initiate close monitoring and workup for competing aetiologies. Study drug can be restarted only if another aetiology is identified and liver abnormalities return to baseline. Drug cannot be restarted if hepatic decompensation occurs.[d]
ALP ≥ 3× baseline without alternative explanation	Normal or elevated	None or present	Interrupt study drug. Blood tests should be repeated within 7-10 days[c] Initiate close monitoring and workup for competing aetiologies. Study drug can be restarted only if another aetiology is identified, and liver abnormalities return to baseline. Drug cannot be restarted if hepatic decompensation occurred.[d]

Note: Some variance should be allowed to this algorithm to take into consideration the drug under evaluation and the stage of liver disease being studied. Abbreviations: ALP, Alkaline Phosphatase; ULN, upper limit of normal.
[a] Advanced Cirrhosis indicates Child Pugh B and C
[b] Liver-related symptoms (eg, severe fatigue, nausea, new onset of or worsening or pruritus, right upper quadrant pain); Immunologic reaction (eg, rash, >5% eosinophilia); New onset of or increase of pruritus; or hepatic decompensation
[c] The specific interval between tests should also be determined based on the patient's clinical condition.
[d] The study subject will require close follow-up monitoring to exclude recurrence of liver injury after restarting the study drug

8.1.1.2. Liver Safety Monitoring for Subjects With Child-Pugh B Cirrhosis at Baseline

Subjects with CP-B cirrhosis at Baseline and suggested DILI will be discussed with medical monitor on a case-by-case basis.

- Subjects with suggested DILI should be initially queried for a possible clinical explanation of liver enzyme increases, associated symptoms, and relationship to the study drug.
- Liver enzymes must be repeated within 2-5 days.
- Subjects with Total Bilirubin elevation Grade 2 and above per CTCAE Version 5.0 (defined as >1.5×ULN if baseline was normal and >1.5× baseline if baseline was abnormal): the subject will be evaluated for DILI versus natural progression of the disease.
- If DILI is suspected, study drug must be interrupted. Study drug can be restarted only if a firm competing etiology is identified; down titration to a lower dose may be considered.

Table 8 provides the algorithm that will be followed to assess potential drug-induced muscle injury.

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

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

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

Table 8: Muscle Injury Safety Criteria for Study Drug Interruption or Stopping Rules

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

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

8.1.2. Renal Safety Monitoring

Table 9 provides the algorithm that should be applied to assess potential drug-induced renal injury. Repeat serum creatinine level measurements within 3 days of initial serum creatinine elevation.

Table 9: Renal Safety Criteria for Study Drug Interruption or Stopping Rules

sCr During Study Treatment	**Repeat sCr Test Results**	**Alternative Etiology Identified?**	**Study Action**
sCr >1.5×ULN but ≤2.0×ULN	sCr <1.5×ULN	N/A	**Continue study drug.**
	sCr >1.5×ULN	Yes	**Interrupt study drug.** Subject should be monitored weekly until event resolution. **Study drug may be reinitiated** after serum creatinine returns to baseline levels.
	sCr >1.5×ULN	No	**Interrupt study drug.** Subject should be monitored weekly until event stabilization or resolution. **Study drug may be**

sCr During Study Treatment	Repeat sCr Test Results	Alternative Etiology Identified?	Study Action
			reinitiated after serum creatinine returns to baseline levels. If serum creatinine increases after re-initiation of study drug, **stop study drug permanently**
sCr >2.0×ULN	sCr >2.0×ULN	N/A	**Stop study drug permanently.** Subject should be monitored weekly until event stabilization or resolution.

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

8.1.3. Pancreatic Safety Monitoring

As shown in Table 10, subjects with elevated amylase and/or lipase >3×ULN should be initially queried for symptoms of acute pancreatitis, possible clinical explanation (such as chronic pancreatitis), and relationship to study drug. Repeat amylase and lipase within 3 days of initial elevation.

Table 10: Pancreatic Safety Criteria for Drug Interruption or Stopping Rules

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

ULN=upper limit of normal.

8.1.4. Additional Withdrawal Criteria and Replacement of Subjects

Subjects may be discontinued from the study for the reasons listed below. Subjects will be asked to continue their participation in the study without the study drug intake, if feasible for the site and the subject.

- Enrolled into the study in violation of this protocol.
- CTCAE grade 3 or above possibly or probably related to study drug.
- The subject should be informed of a 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 with the reason to be provided.
- At the discretion of the investigator for medical reasons.
- Female subjects who become pregnant.
- At the discretion of the investigator or sponsor for noncompliance.

Additional subjects may be added to replace subjects who have prematurely discontinued investigational product in order to complete the study with at least six subjects per cohort at the discretion of the sponsor.

8.2. Precautions

8.2.1. Pregnancy

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

A woman is considered of child-bearing potential, i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile.

Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Post-menopausal female is defined as absence of menses for 12 months without an alternative medical cause (such as bilateral oophorectomy or hysterectomy with bilateral oophorectomy).

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 30 days after the last study drug administration. 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 study drug administration. 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, or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion or salpingectomy
- vasectomized partner for at least 6 months

9. SAFETY REVIEW COMMITTEE

An SRC will be established to oversee subject's safety. The SRC will be composed of an independent external liver disease clinical expert, the Sponsor's lead clinical pharmacologist, and the Sponsor's lead Medical Monitor. Other members of the investigational team may participate as deemed appropriate. Additional details will be provided in an SRC charter including details of the voting members.

Formal minutes and recommendations will be provided by the SRC to the sponsor regarding additional data requests and the continuation of the conduct of the study as outlined in the current protocol.

Part A (Single Dosing, Cohorts 1-4)

The SRC will perform a safety and PK review once all subjects in Cohorts 1-2 and at least 3 subjects in Cohort 3 have completed Part A, to determine whether to proceed with Cohort 4 and determine if the 10 mg or lower dose is appropriate for the first two subjects in Cohort 4.

Upon completion of dosing of the first two subjects in Cohort 4, the SRC will make a decision to continue enrolling Cohort 4 and determine if dose level should be maintained or adjusted on the basis of available safety and PK data.

Part B (28-Day Dosing, Cohort 3)

The SRC will perform a safety and PK review after the first two subjects in Cohort 3 (CP-B) have completed 28 days of treatment to determine whether it is safe to proceed with the current dosing for the remaining subjects in this cohort or if the approach to individualizing dose levels should be adjusted. If the SRC agrees that both the available PK and safety data are consistent with an acceptable safety profile, the remainder of subjects in Cohort 3 will be enrolled and dosed according to the protocol, subject to any adjustment to dose levels specified by the SRC.

The SRC review of data from Cohort 3 will include available PK, adverse events, SAEs, vital signs and ECGs, liver-related safety events, and elevations in ALT/AST, serum creatinine, CK, and lipase that meet safety monitoring criteria.

The SRC will consider if the study should continue, or the dose adjusted when any of the following occur:

- 5 subjects develop any Grade 3 CTCAE related to study drug
- 3 subjects develop any Grade 4 CTCAE related to study drug

10. STUDY WITHDRAWAL OF AN INDIVIDUAL SUBJECTS

Subjects may be withdrawn from the study for any of the following reasons:

- Study subject unable or unwilling to continue participation in the study
- Adverse event (regardless of relationship to investigational product) that precludes further participation in the study in the judgment of the Investigator and/or sponsor
- Informed consent withdrawn
- Lost to follow-up (after 3 documented attempts to contact the subject)
- The Investigator considers that it is in the best interest of the subject to discontinue participation in the study
- Enrolled into the study in violation of this protocol
- Female subjects who become pregnant
- Vomiting within 5 hours post-dose seladelpar

A subject may withdraw consent to participate in this study at any time without penalty or loss of benefits to which the individual is otherwise entitled. Every reasonable effort should be made to determine the reason for early study withdrawal, and this information should be recorded on the appropriate page(s) of the eCRF.

For study subjects who prematurely discontinue treatment, reasonable efforts should be made to obtain all protocol-specified assessments to avoid losing data that are needed to evaluate safety. The study Investigator /designated staff should strongly encourage subjects who prematurely discontinue treatment to comply with performance of all follow-up assessments as planned in the Schedule of Study Procedures (Section 5).

For Part A, if the study subject elects to permanently withdraw from the study, assessments scheduled at the Day 4 must be performed as soon as possible after discontinuation of treatment. The Day 7 follow up telephone call will be performed for adverse events, concomitant medications and concomitant procedures.

For Part B the study subject should have their end of treatment procedures done at the time of withdrawal or as soon as possible after withdrawal. The follow up telephone call will be performed 14 (+3) days after last dose for adverse events, concomitant medications, and concomitant procedures.

The Sponsor's Medical Monitor must be notified within 24 hours in the event of investigational product withdrawal after the occurrence of an AE. Subjects withdrawn secondary to an ongoing AE or SAE, regardless of relationship to investigational product, must be followed clinically until resolution or stabilization of the AE or SAE.

11. INDIVIDUAL AND STUDY STOPPING CRITERIA

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

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

If based on review of available safety and/or PK data, that risk to the study subjects is such that the subjects' safety cannot be adequately guarded within the confines of the study protocol, it is within the remit of CymaBay to stop further conduct of the study.

For Part B, individual safety monitoring criteria (Section 8) will be used for renal, muscle and pancreatic toxicity. These are similar to those used in other studies of seladelpar in patients with PBC. Liver safety monitoring will employ criteria appropriate to studies in patients with advanced liver disease.

12. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Formal statistical hypothesis testing is not planned. Descriptive statistics will be displayed to provide an overview of the study results. Statistical analysis will be performed using SAS unless otherwise stated.

All continuous variables will be summarized with the following descriptive statistics: number of non-missing observations (n), arithmetic and geometric means, standard deviation (SD), coefficient of variation [CV(%)], median, minimum, maximum, unless otherwise specified. Categorical variables will be summarized using the following descriptive statistics: frequency counts and percentages. The denominator for percentages will be based on the number of subjects appropriate for analysis. Data will be presented by cohort. All data will be listed in data listings. Generally, missing data will not be imputed.

Further details of the statistical analyses, methods, and data conventions are described in the SAP. This document may modify the plans outlined in the protocol; however, any major modifications of the primary analysis will also be reflected in a protocol amendment.

12.1. Sample Size

At least 24 subjects, male or female, are planned for enrollment in the study in order to complete with at least six subjects per cohort. The sample size is based upon clinical considerations. Six subjects per cohort are expected to provide sufficient data to adequately assess the PK for seladelpar in populations with PBC.

12.2. Analysis Sets

12.2.1. Safety Analysis Set

The safety analysis set comprises all study subjects who receive any amount of seladelpar. This analysis set will be used for all analysis of safety data and for summarization of demographic and baseline characteristics.

12.2.2. Pharmacokinetic Analysis Set

The PK analysis set will consist of all study subjects who undergo plasma PK sampling and have assay results. This analysis set will be used for the PK analyses and for summarization of concentration/parameter data.

12.2.3. Efficacy Analysis Set

The Efficacy Analysis Set will consist of all study subjects who receive any amount of seladelpar in Part B and have at least one biochemistry assessment post Part B baseline. This analysis set will be used for analyzing efficacy parameters (Cohorts 2 and 3, Part B only).

12.3. Pharmacokinetic Analysis

The parameters describing the PK will be derived from plasma/urine concentrations and actual sample draw times from the noncompartmental analysis.

Plasma concentration data and urine data for seladelpar and major metabolites: M1, M2, and M3 will be displayed graphically on the linear and semi-logarithmic scales. The following graphs will be presented for the concentration-time data:

- Individual subject plasma/urine concentration profile versus time
- Mean concentration (± SD) versus time, designated by cohort

Pharmacokinetic parameters for seladelpar, M1, M2, and M3 will be calculated, listed, and summarized with descriptive statistics as detailed in the SAP. Pharmacokinetic parameter listings and statistical summaries will be generated separately for each cohort. A statistical analysis of PK parameters for seladelpar, M1, M2, and M3 will be carried out with an analysis of variance model on log-transformed PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf}, as response variables, with cohort as fixed effect. Correlation between plasma seladelpar PK parameters and albumin, bilirubin, PT, and Child-Pugh score will be evaluated.

All PK summaries will be prepared with the PK analysis set.

12.4. Safety Analysis

12.4.1. Vital Signs

Changes from baseline in vital signs at each scheduled timepoint will be summarized by cohort descriptively for the safety analysis set. The baseline value is defined as the last value observed before the administration of seladelpar. All vital sign data will be listed individually by each subject based on the safety analysis set.

12.4.2. Electrocardiograms

Continuous ECG parameters including heart rate, ventricular rate, PR interval, QRS duration, QT interval (uncorrected), and QTcF interval will be summarized by cohort and scheduled timepoint in terms of absolute values and changes from baseline with descriptive statistics. A listing will be provided for investigator-identified ECG abnormalities from safety ECGs. Overall evaluation of safety ECGs will be summarized by cohort with frequency counts and percentage of subjects as normal or abnormal, and the relevance of the abnormality will be summarized by clinically significant or not clinically significant. In addition, a summary shift table comparing baseline interpretation (normal, abnormal – not clinically significant, abnormal – clinically significant) to the Investigator interpretation at each time point will also be presented.

12.4.3. Adverse Events

All TEAEs will be summarized by MedDRA system organ class and preferred term by severity and by causal relationship to seladelpar. The severity of TEAEs will be graded based on CTCAE, Version 5.0 or later (Appendix A), when possible. An overall summary of AEs will present the numbers and percentages of subjects with at least 1 TEAE, with a serious TEAE, with a drug-related TEAE, with a drug-related serious TEAE, and an AESI. The number and percentage of subjects with TEAEs leading to discontinuation and the number and percentage of subjects with AEs leading to death (if applicable), will also be summarized. A summary of TEAEs by maximum CTCAE Grade will be provided.

All summaries will be provided for the safety analysis set.

All AE data will be listed for subjects.

12.4.4. Clinical Laboratory Parameters

Each individual baseline value is the last value observed before the administration of seladelpar and any data obtained after administration of investigation product is regarded as post-baseline data.

Safety laboratory parameters will be summarized by cohort with descriptive statistics at baseline and at each post-baseline visit. All continuous laboratory data will be summarized by cohort, and at each scheduled timepoint with descriptive statistics. Categorical data will be summarized with frequency and percentage at each scheduled timepoint by cohort. For all continuous laboratory variables, a shift table comparing the baseline value relative to the normal reference range (normal, low, and high) to last observation on treatment will be presented. For urinalysis, a shift table comparing the baseline value to the maximum value will be presented by cohort (number of subjects with results of negative, trace, or positive).

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.

Individual data listings of laboratory results will be presented for each subject. Values outside of the laboratory's reference range (i.e., those with low or high values) will be flagged in the laboratory listings.

12.5. Efficacy Analysis

Efficacy parameters will be analyzed descriptively by cohorts on Efficacy Analysis Set.

The effect of multiple dose treatment of seladelpar on biochemical markers of cholestasis and liver function (Cohorts 2 and 3 only) will be presented by descriptive statistics.

12.6. Protocol Deviations

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

Deviations from the protocol will be noted in the source documentation, in the trial master file (TMF) and database. The sponsor will assess the protocol deviations to determine whether the deviation is reported to regulatory authorities as a serious breach of ICH Good Clinical Practice and the protocol. Moreover, all protocol deviations will be included in the final listing outputs.

12.7. Handling of Dropouts and Missing Data

In general, missing data will not be imputed. Detailed descriptions of handling dropouts and missing data are contained in the SAP. All efforts will be made to prevent data from being missed.

12.8. Interim Analyses

Interim analyses may be performed per Sponsor's decision.

13. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

13.1. Data Management

A Data Management Plan (DMP) will specify all relevant aspects of data processing and handling for the study, including how data will be managed and cleaned. Relevant sections of the DMP includes the following: standard operating procedures to be followed; eCRF data entry and flow, tracking and filing; coding and coding review plan; reconciliation of SAEs; external and vendor data integration, import, and reconciliation; and general listing review.

13.2. Electronic Systems

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

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

14. ADMINISTRATIVE ASPECTS

14.1. Protocol Adherence

The PI must adhere to the protocol as detailed in this document and agree that the Sponsor must approve any changes to the protocol prior to seeking approval from the EC. No alterations in the protocol will occur without agreement between the Sponsor and the PI. No alterations in the protocol affecting subject safety will occur without the express written approvals of the Sponsor, PI, and EC.

14.2. Study Monitoring

The Sponsor's or designee's monitor (i.e., "the monitor") will be responsible for monitoring this clinical trial. The monitor 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.

The monitor will specifically review the study conduct, proper eCRF and source documentation completion and retention, and accurate study-drug accountability. To this end, the monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. The PI will grant access to all documents (related to the study and the individual subjects) at any time these are requested by the sponsor or designee. In turn, the monitor will adhere to all requirements for subject confidentiality as outlined in the ICF. The PI and PI's staff will be expected to cooperate with the monitor, to be available during a portion of the monitoring visit to answer questions, to resolve discrepancies, and to provide any missing information.

14.2.1. 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.

14.2.2. Electronic Case Report Forms

Subjects who have signed the ICF will be assigned a subject number and will have trial data entered in an eCRF. The eCRF completion is important to the medical monitoring of the trial and should be completed promptly after each patient visit.

14.3. Audits and Inspections

14.3.1. 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 or remote audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

14.3.2. Trial Monitoring

A Sponsor representative will monitor the site (in person or remotely) to initiate the study, before the administration of the treatment to 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. All subject -specific information is confidential and no documentation that can link study information to the individual subject will be collected or retained by the Sponsor.

14.4. Ethics

14.4.1. Ethics Review

This protocol, the informed consent document, recruitment advertisements and all relevant supporting data, as well as amendments to any of these documents, must be submitted to the IRB/EC for approval. IRB/EC approval of these documents must be obtained before the study may be initiated. The study will not start before written approval by IRB/EC has been obtained and the local regulatory requirements have been complied with.

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

The PI is responsible for keeping the IRB/EC advised of the progress of the study and of any changes made to the protocol as deemed appropriate but, in any case, at least once a year. The PI is also responsible for notifying the IRB/EC of any reportable AEs that occur during the study.

14.4.2. 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.

14.4.3. Informed Consent

This study will be conducted in compliance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice: Consolidated Guidelines pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, patients must give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits. 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 informed consent document must be signed and dated by the patient and PI, or designee, prior to study participation. A copy of the informed consent document must be provided to the subject. Signed consent forms must remain in the subject's study file and be available for verification by Sponsor or its representative at any time.

14.5. Records

The results from Screening and data collected during the study will be recorded in the subject's eCRF. To maintain confidentiality, the subjects will be identified only by numbers and initials. The completed eCRFs will be transferred to the Sponsor or designee. Copies of each eCRF will be retained by the PI. All source documents, records, and reports will be retained by the clinic.

All primary source data or copies thereof (e.g., laboratory records, eCRFs, data sheets, correspondence, photographs, and computer records) that are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report will be retained in the clinic archives.

Sponsor will inform the PI of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest (longest) standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Sponsor standards/procedures; otherwise, the retention period will default to the retention period of 15 years following completion of the clinical trial.

14.6. Quality Control and Quality Assurance

Standard operating procedures are available for all activities performed at the study sites relevant to the quality of this study. Designated study site personnel will be responsible for maintaining quality assurance and quality control to ensure that the study conduct as well as data collection and documentation are performed in compliance with the study protocol, Good Clinical Practice (GCP) requirements, and applicable regulatory requirements.

All clinical data will undergo source document verification by the clinical research associate and data review by data management before the database is locked. Programmed edit checks are also implemented to check for missing data, data inconsistencies, data ranges, etc. Corrections will be made before the database is locked. The eCRFs can be printed directly from the database. Each eCRF will be reviewed and signed electronically by the investigator.

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. For example, source documents may include laboratory reports, ECGs, etc.

14.7. Disclosure

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.

14.8. Financing and Insurance

The financing and insurance for this study are outlined in the Clinical Trial Research Agreement.

SPONSOR PROTOCOL APPROVAL AND SIGNATURE PAGE

Protocol Title: The Effect of Hepatic Impairment on The Pharmacokinetics of Seladelpar: An Open-Label Study Following Oral Dosing of Seladelpar to Subjects with Primary Biliary Cholangitis (PBC) and Hepatic Impairment

Protocol Number: CB8025-21838

Version Number: 5.0

Date of Protocol: 06-MAR-2023

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

I have read the above-mentioned amended Protocol.

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

PPD

PPD
Vice President of Clinical Development
CymaBay Therapeutics, Inc.

_____PPD_____
Date

INVESTIGATOR PROTOCOL REVIEW AND SIGNATURE FORM

Protocol Title: The Effect of Hepatic Impairment on The Pharmacokinetics of Seladelpar: An Open-Label Study Following Oral Dosing of Seladelpar to Subjects with Primary Biliary Cholangitis (PBC) and Hepatic Impairment

Protocol Number: CB8025-21838

Version Number: 5.0

Date of Protocol: 03-MAR-2023

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.

I have read the above-mentioned amended Protocol.

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Principal Investigator (Please PRINT)

_____ _____

Principal Investigator (Signature) **Date**

_____

Name of Institution (Please PRINT)

REFERENCES

1. Bays HE, Schwartz S, Littlejohn T III, et al. MBX-8025, a novel peroxisome proliferator receptor-delta agonist: lipid and other metabolic effects in dyslipidemic overweight patients treated with and without atorvastatin. J Clin Endocrinol Metab. 2011;96(9):2889-97.
2. CDER FDA Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function – Study Design, Data Analysis, and Impact on Dosing and Labeling – May 2003
3. Choi Y, Song J, Johnson JD, et al. Seladelpar Improves Hepatic Steatohepatitis and Fibrosis in a Diet-Induced and Biopsy-Confirmed Mouse Model of NASH. Abstract #1311. Presented at: The Liver Meeting; Nov 9-13, 2018; San Francisco, CA, USA
4. Corpechot C, Abenavoli L, Rabahi N, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology 2008;48(3):871-877.
5. Haczeyni F, Wang H, Barn V, et al. The Selective Peroxisome Proliferator–Activated Receptor-Delta Agonist Seladelpar Reverses Nonalcoholic Steatohepatitis Pathology by Abrogating Lipotoxicity in Diabetic Obese Mice. Hepatology 2017;1(7):663-674.
6. Iwaisako K, Haimer M, Paik YH, et al. Protection from liver fibrosis by a peroxisome proliferator-activated receptor δ agonist. 2012;109(21):E1369-76.
7. Huang YQ. Recent advances in the diagnosis and treatment of primary biliary cholangitis. World J Hepatol 2016 November 28;8(33):1419-1441.
8. Jones D, Boudes PF, Swain MG, et al. Seladelpar (MBX-8025), a selective PPARδ agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study. Lancet Gastroenterol Hepatol 2017;2(10):716-726.
9. Kaplan MM, Gershwin ME. Primary Biliary Cirrhosis. N Engl J Med. 2005;353(12):1261-1273.
10. Kumagi T and Heathcote EJ. Review. Primary biliary cirrhosis. Orphanet Journal of Rare Diseases. 2008;3:1.doi:10.1186/1750-1172-3-1.
11. Lammer WJ, van Burren HR, Hirschfield GM, et al. Levels of Alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology 2014;147:1338-1349.
12. Levy C. Primary biliary cholangitis guidance update: implications for liver transplantation. Liver Transplantation 2018;24(11):1508-1511.
13. Lindor K. Ursodeoxycholic acid for the treatment of primary biliary cirrhosis. N Engl J Med 2007;357:1524-1529.
14. Lindor KD, Gershwin ME, Poupon R, et al. Primary biliary cirrhosis. Hepatology 2009;50(1):291-308.
15. Lleo A, Wang GQ, Gershwin ME, Hirschfield GM. Primary biliary cholangitis. Lancet 2020;396:1915-1926.

16. Mukundan L, Odegaard J, Morel CR, et al. PPAR-δ senses and orchestrates clearance of apoptotic cells to promote tolerance. Nature Medicine 2009;15(11):1266-1273.

17. Obeticholic Acid Package Insert. Ocaliva 2016.

18. Odegaard J, Ricardo-Gonzalez RR, Eagle AR, et al. Alternative M2 Activation of Kupffer Cells by PPARd Ameliorates Obesity-Induced Insulin Resistance. Cell Metab 2008 Jun;7(6):496-507.

19. Palmer M, Regev A, Lindor K, Avigan MI, Dimick-Santos L, Treem W, et al. Consensus guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury occurring during clinical trials in adults with chronic cholestatic liver disease. Aliment Pharmacol Ther. 2020 Jan;51(1):90-109.

20. Poupon RE, Lindor KD, Cauch-Dudek K, et al. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology 1997;113:884-890.

21. Rishe E, Azarm A, Bergasa NV. Itch in primary biliary cirrhosis: a patients' perspective. Acta Derm Venereol 2008;88:34-37.

22. Selmi C, Meda F, Kasangian A, et al. Experimental evidence on the immunopathogenesis of primary biliary cirrhosis. Cellular & Molecular Immunology 2010;7:1-10.

23. Silveira MG, Talwalkar JA, Lindor KD, et al. Recurrent primary biliary cirrhosis after liver transplantation. American Journal of Transplantation 2010;10:720-726.

24. Xia X, Jung D, Webb P, et al. Liver X Receptor /J and Peroxisome Proliferator-Activated Receptor J Regulate Cholesterol Transport in Murine Cholangiocytes. Hepatology 2012;56:2288-2296.

25. Greenberg JA, Hsu J, Bawazeer M, et al. Clinical practice guideline: management of acute pancreatitis. Can J Surg. 2016;59(2):128-140. doi:10.1503/cjs.015015

APPENDICES

APPENDIX A – National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

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

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

The NCI CTCAE may also be accessed here:

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

APPENDIX B – Assessment of Liver Function

Child-Pugh Classification Criteria

	Points Scored for Observed Findings		
	1	**2**	**3**
Encephalopathy Grade [a]	none	1 or 2	3 or 4
Ascites	absent	slight	moderate
Serum bilirubin mg/dL	< 2	2 to 3	> 3
Serum albumin, g/dL	> 3.5	2.8 to 3.5	< 2.8
Prothrombin time, sec prolonged	< 4	4 to 6	> 6

[a] Grade: 0 = normal consciousness, personality, neurological examination, electroencephalogram
1 = restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
2 = lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
3 = somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
4 = unarousable coma, no personality/behavior, decerebrate, slow 2-3 cycles per second delta activity

Source: FDA Guidance for Industry: Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis, and impact on dosing and labeling (2003)

Total Score	**Classification**	**Hepatic Impairment Severity**
5 to 6	A	Mild
7 to 9	B	Moderate
10 to 12	C	Severe

Source: FDA Guidance for Industry: Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis, and impact on dosing and labeling (2003)

APPENDIX C – Close Observation Criteria

The "close observation" will be performed on subjects meeting liver safety monitoring criteria per Section 8.1.1.1. 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 laboratory abnormality stabilization.
    c. After laboratory 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.