A PHASE 2, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, MULTIPLE CENTER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF SELADELPAR ADMINISTERED FOR 24 WEEKS IN ADULT PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS (PSC)

PROTOCOL NUMBER CB8025-21845

for

CymaBay Therapeutics, Inc.

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STUDY IDENTIFICATION

Sponsor:	PPD
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ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ACG	American College of Gastroenterology
AE	adverse event
AIH	autoimmune hepatitis
AP	alkaline phosphatase
ALT	alanine aminotransferase
ANCA	anti-neutrophil cytoplasmic antibody
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration–time curve
BLM	baseline measurement
BUN	blood urea nitrogen
C4	7-alpha-hydroxy-4-cholesten-3-one
CK	creatine kinase
C_{max}	maximum drug concentration
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DSMC	Data Safety Monitoring Committee
DVM	data validation manual
EASL	European Association for the Study of the Liver
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
ELF	enhanced liver fibrosis
EOS	end of study
EOT	end of treatment
ERCP	endoscopic retrograde cholangiopancreatography
ET	early treatment withdrawal
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus

HDL-C	high-density lipoprotein cholesterol
HI	hepatic impairment
HIV	human immunodeficiency virus
HoFH	homozygous familial hypercholesterolemia
hs-CRP	high-sensitivity C-reactive protein
IA	Interim Analysis
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
INR	International Normalized Ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDL-C	low-density lipoprotein cholesterol
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
MMRM	mixed-effect model repeated measures
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
NASH	nonalcoholic steatohepatitis
NOAEL	no-observed-adverse-effect level
NRS	Numeric Rating Scale
NSF	nephrogenic systemic fibrosis
OLE	Open Label Extension
p-ANCA	perinuclear anti-neutrophil cytoplasmic antibody
PBC	Primary Biliary Cirrhosis
PD	Pharmacodynamic(s)
PDK4	pyruvate dehydrogenase kinase 4
PE	physical exam
PI	Principal Investigator
PK	Pharmacokinetic(s)
PP	per protocol
PPARδ	peroxisome proliferator-activated receptor-δ
PRESTO	Primary Sclerosing Cholangitis Risk Estimate Tool

PRO	patient reported outcomes
PRO-C3	procollagen III N-terminal peptide
PRO-C5	C-terminal pro-peptide of type V collagen
PSC	primary sclerosing cholangitis
PT	prothrombin time
PTC	percutaneous transhepatic cholangiography
QoL	quality of life
RBC	red blood cell; erythrocyte
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCr	serum creatinine
SD	standard deviation
SOC	system organ class
SUSAR	suspected, unexpected serious adverse reaction
$t_{1/2}$	half-life
t_{max}	time to reach maximum plasma concentration
TE	transient elastography
TEAE	treatment-emergent adverse event
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
UNS	unscheduled
U.S.	United States
UK	United Kingdom
VAS	visual analogue score
WBC	white blood cell

1. SYNOPSIS

Title of Study:	A Phase 2, Randomized, Double Blind, Placebo Controlled, Multiple Center Study to Evaluate the Safety, Tolerability, and Efficacy of Seladelpar Administered for 24 Weeks in Adult Patients with Primary Sclerosing Cholangitis (PSC)
Protocol Number:	CB8025-21845
Phase:	2
Investigational Product:	Seladelpar

Objectives:	Primary Objective:
	• Evaluate the treatment effect of seladelpar on alkaline phosphatase (AP) in participants with PSC during the study period
	
	Secondary Objectives:
	• Assess the safety and tolerability of seladelpar in participants with PSC during the study period
	• Evaluate the effect of seladelpar on the following:
	  ○ Alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total, direct), and gamma-glutamyl transpeptidase (GGT)
	  ○ Total cholesterol, HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), and triglycerides
	  ○ 7-alpha-hydroxy-4-cholesten-3-one (C4) and serum bile acids
	  ○ High sensitivity C-reactive protein (hs-CRP) and fibrinogen
	  ○ Enhanced liver fibrosis (ELF) Score (total and individual components) and procollagen III N-terminal peptide (PRO-C3) and C-terminal pro-peptide of type V collagen (PRO-C5) levels
	• Evaluate changes in pruritus, fatigue, and quality of life (QoL)
	• Assess changes in symptoms associated with Inflammatory Bowel Disease (IBD)
	• Evaluate the incidence, frequency and severity of PSC-related symptoms and adverse events (AEs)
	• Evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of seladelpar in participants with PSC
	
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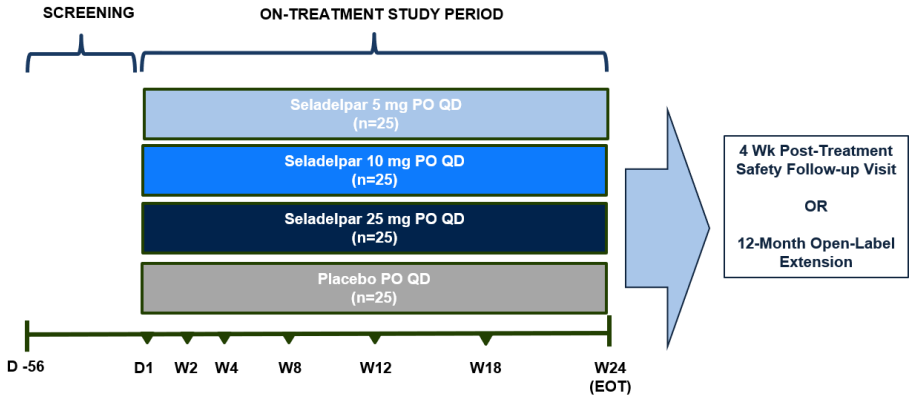
Methodology/ Study Design:	This is a multiple-center evaluation of seladelpar in a randomized, double-blind, placebo-controlled, parallel-group study when administered for 24 weeks as a daily oral capsule in patients with PSC. Approximately, 100 participants will be randomized across approximately 60 sites worldwide. Patients to be studied will have confirmed PSC as defined as having any 2 of the following 3 diagnostic criteria: historical elevated AP, abnormal cholangiography or liver histology consistent with PSC. Participants will be required to have an AP $\geq$ 1.5 × upper limit of normal (ULN) and variability $\leq$ 40% for AP, ALT, AST and total bilirubin between two visits during Screening. Ursodeoxycholic acid (UDCA) therapy will be allowed at stable doses of $\leq$ 20 mg/kg/day for at least 24 weeks. Patients with stable IBD are allowed, including those treated with a stable regimen of biologic, immunosuppressant, or systemic corticosteroid therapy. The presence or history of cirrhosis (compensated or decompensated), small duct PSC, overlapping autoimmune hepatitis (AIH), cholangiocarcinoma (diagnosed or suspected), acute cholangitis or recently placed bile duct stents or ballooning dilatation procedure will all be excluded from this study. Please refer to Section 4 of the protocol for the complete listing of the Inclusion and Exclusion Criteria. All patients with IBD will be required to have had a colonoscopy within the last 12 to 18 months of consent with no evidence of dysplasia. All participants will undergo MRCP and MRI with contrast during Screening to assess bile duct strictures and the presence of cholangiocarcinoma. Transient elastography (TE) via FibroScan® will be performed to assess liver stiffness and to exclude cirrhotic patients during Screening. On Day 1, participants will be randomized into one of four treatment arms (seladelpar 5 mg, seladelpar 10 mg, seladelpar 25 mg, or placebo) in a 1:1:1:1 ratio. Participants will be stratified at randomization, according to UDCA use (Yes/No) and by averaged Screening total bilirubin values ($\leq$ ULN vs > ULN but $\leq$ 2 × ULN) to ensure even distribution across the are treatment groups. Participants will return to the clinic at Weeks 2, 4, 8, 12, 18, and 24 for on-treatment assessments and procedures. Participants will receive study-drug bottles on Day 1 and at Weeks 4, 8, and 12. Dose reductions will be permitted based on specific safety parameters and with approval by the Sponsor Medical Monitor. MRCP and MRI with contrast will be performed at Week 24 to assess changes in bile duct strictures and volume. FibroScan® will be performed at Weeks 12 and 24 to assess changes in liver stiffness. Standardized patient reported outcomes (PRO) assessments for pruritus and other PSC symptoms, quality of life (QoL), and IBD-related symptoms will be performed at Day 1 and key visits during and after study drug treatment. Week 24 will be the End of Treatment (EOT) clinic visit. All participants eligible and willing can be enrolled into a separate 12 month open-label extension (OLE) study starting at Week 24. Participants who do not enroll in the OLE study participant will return to the clinic at Week 28 for an End of Study (EOS) follow-up visit. An interim analysis (IA) will be conducted when approximately 10 participants per treatment arm have completed the Week 12 visit. The overall safety and efficacy of seladelpar in PSC will be assessed at the IA, in addition to dose selection for the long-term OLE. Full 24-hour PK profiles will be collected in a subset of participants (at least 6 participants per treatment arm) at Day 1 and Week 12. A full listing of the study procedures and assessments by visit are listed in Section 5 of the protocol.

Study Design Schema:	
Participants:	Approximately 100 participants randomized.
Randomization	1:1:1:1 Participants will be stratified according to UDCA use (Yes/No) and averaged Screening total bilirubin values (≤ ULN vs > ULN but ≤ 2 × ULN) to ensure even distribution across the four treatment arms.
Study Sites	Approximately 60 sites in Australia, Europe, Israel, and North America
Test Product(s):	Seladelpar or placebo will be supplied as a single capsule intended to deliver 5 mg, 10 mg, 25 mg or placebo administered orally, once daily. Study drug should be administered in the fasted state, approximately 2 hours before or after a meal.
Duration of Treatment:	Total study duration is up to 36 weeks. Screening: Up to 8 weeks Treatment Period: 24 weeks CCI [redacted]
Criteria for Evaluation - *Safety:*	Safety and tolerability will be assessed by monitoring AEs and concomitant medications. Additional assessments will include conducting physical examinations (PEs), 12-lead electrocardiograms (ECGs), measuring vital signs, and collecting clinical laboratory assessments. Specific safety monitoring algorithms for liver, muscle, renal and pancreatic injury have been incorporated into the study.
Criteria for Evaluation - *Pharmacokinetics:*	PK will be analyzed to determine the single dose and repeat dose steady-state exposure. The results in PSC participants will be compared to both healthy volunteers and other seladelpar-treated study populations. Measured PK parameters will include maximum observed plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), area under the concentration-time curve from time 0 to last measurement (AUC_{last}), terminal elimination phase half-life ($t_{½}$) for seladelpar and the major metabolites (M1, M2, and M3).CCI [redacted] Urine will also be collected over the 24-hour periods to assess the renal clearance of seladelpar and primary metabolites.

Criteria for Evaluation - *Efficacy and Pharmacodynamics:*	Primary Efficacy
	• Relative (%) change in AP from Baseline to Week 24.
	
	Secondary Efficacy and Pharmacodynamics
	• Relative (%) change in AP at Week 12
	• Absolute change in AP from Baseline to Week 12 and Week 24
	• Proportion of participants achieving AP response parameters at Week 12 and Week 24
	• The absolute and percentage changes from Baseline at Week 24 of the following PD parameters:
	  • ALT, AST, bilirubin (total and direct), and GGT
	  • Total cholesterol, HDL-C, LDL-C, and triglycerides
	  • C4 and serum bile acids
	  • hs-CRP and fibrinogen
	  • ELF Score (total and individual components), PRO-C3 levels and PRO-C5
	• Changes in pruritus via the numeric rating scale (NRS), in addition to fatigue and quality of life as determined by PSC PROs and QoL tools during the study period
	• Incidence and severity of PSC-related symptoms during the study period
	• Incidence and severity of IBD-associated intestinal symptoms during the study period
	• Hepatic disease progression
	• Relationship of drug exposure and changes in efficacy, safety/tolerability and PD parameters after 24 weeks of treatment
	
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Statistical Methods:	The primary efficacy analysis will consist of comparing each seladelpar treatment arm against the placebo arm using Analysis of Covariance (ANCOVA) model. The model will have the relative change in AP from Baseline to Week 24 as the dependent variable, treatment arm, UDCA stratification group (Yes/No) and total bilirubin stratification group (≤ ULN vs > ULN but ≤ 2 × ULN) as factors, and baseline AP as a covariate. A sensitivity analysis for the primary efficacy endpoint will be performed using a mixed model for repeated measures (MMRM) approach. The secondary endpoints will be analyzed descriptively. The confidence intervals of treatment differences will be provided. The safety and tolerability endpoints will be summarized descriptively. At the planned IA, the evidence regarding the safety and efficacy of seladelpar in PSC participants will be assessed, in order to evaluate the appropriateness of continuing the study and inform dose selection for the OLE study.
Sample Size Determination:	A sample size of 25 participants randomized per treatment arm was chosen in order to gather sufficient proof-of-concept treatment response and safety data on seladelpar in this population. The sample size yields 20 completing participants per treatment arm, assuming 20% dropout rate, from randomization to Week 24. A sample size of 20 in each arm will have at least 90% power to detect a difference in means of 25% in relative (%) change of AP from baseline, assuming that the common standard deviation is 20%, using a two-sample t-test with a 0.0166 two-sided significance level, where the significance level of 0.0166 is the multiplicity-adjusted level using Bonferroni approach.

2. INTRODUCTION

2.1. PRIMARY SCLEROSING CHOLANGITIS (PSC)

2.1.1. Disease Overview

PSC is a chronic cholestatic liver disease that is characterized by diffuse inflammation and fibrosis of the bile ducts (Karlsen 2017). The intra and/or extrahepatic bile ducts can be affected with ongoing ductal destruction leading to cholestasis, advanced fibrosis, and cirrhosis. Disease progression will eventually lead to liver failure with its consequent complications such as portal hypertension and increased risk of malignancy, including hepatocellular carcinoma (HCC) and cholangiocarcinoma (Karlsen 2017). PSC is frequently associated with IBD, particularly ulcerative colitis, with an estimated prevalence of 70% of IBD in PSC patients, depending on screening programs and nationality (Mertz 2019).

The disease typically has slow progression and its course may be variable from one patient to another (Lazaridis 2016). Males are affected twice as often as females and are usually diagnosed with the disease in their fourth decade of life (Molodecky 2011). Patients are often diagnosed incidentally, and nearly 50% are asymptomatic at the time of diagnosis (Lazaridis 2016). Despite being asymptomatic, patients with PSC have a shorter average time of survival compared with matched controls from the general population.

Various review articles that consider the epidemiology of PSC on a global basis note a high degree of variability in prevalence and incidence figures (1 per 10,000 and 0.4-2.0 per 10,000, respectively) with the greatest incidence and prevalence in Scandinavia, the UK, and the United States (U.S.) (Karlsen 2017). Several studies have suggested an increasing trend in PSC incidence and prevalence rates. However, these apparent increases are more likely due to increasing awareness of the disease, greater understanding of the coincidence with IBD, and improved diagnostics revealing more patients at the asymptomatic stage of disease.

The etiology of PSC remains unclear although it is likely caused by multiple factors. These include autoimmunity, portal bacteremia, absorption of toxins, ischemic injury, viral infections, toxic bile acids, and a genetic predisposition (Karlsen 2017). The pathogenesis of PSC involves the exposure of genetically predisposed individuals to an environmental antigen that subsequently elicits an aberrant immune response, leading to development of the disease.

The diagnosis of PSC is challenging as most patients are asymptomatic or display nonspecific symptoms (Lazaridis 2016). Diagnosis is typically achieved after a complication such as cholangitis or when hepatic dysfunction occurs. The severity and symptoms can vary between individuals who suffer from PSC as it is made up of more than one disease subtype, which include classic PSC, small-duct PSC, and immunoglobulin G4 (IgG4) PSC. A diagnosis of PSC is made in patients with unexplained elevated serum AP and GGT and when MRCP or endoscopic retrograde cholangiopancreatography (ERCP) show characteristic bile duct changes with multifocal strictures and segmental dilatations, and when causes of secondary sclerosing cholangitis and other cholestatic disorders are excluded (Lazaridis 2016). At present, there is no

specific diagnostic serologic test for PSC. A marked increase in serum autoantibody levels can occur in patients with PSC, including anti-neutrophil cytoplasmic antibodies (ANCAs), anticardiolipin antibodies, and antinuclear antibodies (Sebode 2018). Patients who present with clinical, biochemical, and histological features compatible with PSC but have normal cholangiograms are classified as having small-duct PSC. Patients presenting with IBD and increased liver test values are generally suspected of having concurrent PSC. However, these abnormal values do not reflect the severity of the underlying disease.

Currently, liver biopsies are rarely performed to diagnose PSC. However, changes observed from liver biopsies in PSC patients are generally nonspecific, although periductal concentric fibrosis ("onion skinning") is a typical finding and may support the diagnosis of PSC (Lindor 2015). A liver biopsy is generally only performed in patients with a normal cholangiography assessment and suspected of having small-duct PSC, overlapping autoimmune hepatitis or suspected of being cirrhotic.

PSC has been described to progress through four stages:

- Stage 1: Lymphocyte infiltrates and bile duct epithelial cell degeneration in the portal triads
- Stage 2: Inflammatory infiltrates and early fibrogenesis in the periportal parenchyma with piecemeal necrosis and enlarged bile ducts with minimal ductopenia
- Stage 3: Portal-to-portal bridging fibrosis with severe degeneration of the ducts and ductopenia
- Stage 4: End-stage liver disease with cirrhosis

The most frequent clinical symptoms in PSC are fatigue and pruritus, with other less common symptoms such as abdominal discomfort, jaundice, and weight loss (Lindor 2015). Other symptoms may include vitamin deficiencies and bone disease and, in advanced liver disease, portal hypertension, coagulopathy, and liver failure (Fricker 2019). Secondary complications of PSC include bacterial cholangitis, gall stones, and malignancies (cholangiocarcinoma and HCC) (Lazaridis 2016).

2.1.2. Treatment of PSC

Currently, the primary therapy for PSC is endoscopic and/or radiologic dilatation or stenting of bile duct strictures targeted at reducing cholestasis and halting progression of strictures and other elements of the disease (Lindor 2015). Orthotopic liver transplantation remains the only clinically proven treatment for patients with PSC-related end stage liver disease. Patients receiving a transplant have improved survival rates, with 5-year survival rates of up to 70% (Khan 2012). However, PSC recurs in the donor liver in approximately 20%–25% of patients at 5 years. Additionally, patients with PSC have a 5–35% lifetime risk of developing cholangiocarcinoma (Khan 2012). Liver transplantation for the treatment of cholangiocarcinoma remains experimental due to significantly lower patient survival due to recurrent disease (Zamora-Valdes 2018).

Although there is no established or approved pharmacologic therapy for PSC, UDCA has been studied in multiple prospective clinical studies and is considered the only pharmacologic treatment option with a significant biochemical response. However, the data supporting a beneficial effect on clinical endpoints and long-term outcomes remains conflicting. Several prospective, randomized controlled trials have evaluated different doses of UDCA ranging from 10–15 mg/kg/day to 17–23 mg/kg/day and most recently up to 28–30 mg/kg/day (Saffioti 2017). Currently, neither the American Association for the Study of Liver Diseases (AASLD) nor the European Association for the Study of the Liver's (EASL) Clinical Guidelines make a recommendation for general use of UDCA in PSC (Beuers 2009; Chapman 2010). However, recent American College of Gastroenterology (ACG) guidelines have put a limitation on doses above 27 mg/kg/day with a suggestion that intermediate doses may offer an improved biochemical response associated with improved outcomes (Lindor 2015). AP is the traditional marker of cholestasis and biochemical response to UDCA in PSC and recent studies have demonstrated it as predictive of disease progression and outcomes of treated and untreated patients. PSC patients with very high serum AP levels treated with UDCA usually fail to adequately respond, whereas those with lower serum AP activity generally have a favorable response and excellent long-term prognosis (Stanich 2011). Guidance from clinical experts has suggested a trial of 24 weeks of UDCA and to continue treatment if the AP is reduced by 40% from baseline or < 1.5 × ULN and no significant tolerability or safety issues are observed (Tabibian 2014).

A number of immunosuppressive (prednisolone, budesonide, azathioprine, cyclosporine, methotrexate, mycophenolate, tacrolimus), anti-inflammatory (pentoxifylline, etanercept, other anti-TNF monoclonal antibodies) and anti-fibrotic (colchicine, penicillamine, pirfenidone) agents approved for other indications have been evaluated as primary or adjunctive treatments for PSC (Saffioti 2017). None of these agents have demonstrated a significant clinical benefit. Small pilot studies are currently studying the role of antibiotics in PSC, with liver enzyme reductions seen after treatment with metronidazole or oral vancomycin. However, alterations of the gut microbiome have largely been evaluated in small uncontrolled studies and is still considered experimental.

Several recent Phase 2 clinical studies have evaluated novel targets for the treatment for PSC with varying levels of treatment response. Nor-ursodeoxycholic acid, obeticholic acid and cilofexor have been studied for 12–24 weeks, demonstrating only a modest reduction in AP and other markers of hepatic injury (Fickert 2017; Kowdley 2017; Trauner 2019). The monoclonal antibodies, vedolizumab and simtuzumab, which specifically target key mechanisms hypothesized to be associated with PSC, have also been studied showing minimal or no treatment effect (Christensen 2018; Muir 2019). Most recently, the fibroblast growth factor 19 analogue, NGM282, demonstrated significant reductions in bile acid synthesis, liver transaminases, and fibrosis markers but no improvement in AP (Hirschfield 2018). None of these agents have demonstrated an impact on hepatic or biliary histology.

Therefore, a significant unmet medical need still exists for novel agents for the treatment of PSC in order to prevent disease progression and subsequent complications.

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 bile acid homoeostasis. Seladelpar down regulates the expression of *CYP7A1* which encodes cholesterol 7α-hydroxylase, the enzyme that hydroxylates cholesterol in the first step in bile acid synthesis (Jones 2017). The PPARδ receptor is also expressed in cholangiocytes, Kupffer cells, and hepatic stellate cells, all of which have implications for potential activity in PSC (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 2 separate nonalcoholic steatohepatitis (NASH) mouse models. (Haczeyni 2017, Choi 2018). In summary, these pre-clinical data provide a foundation for the potential biologic activity of seladelpar in PSC based on the demonstrated impact on bile acid synthesis, cholangiocyte function, inflammation and fibrogenesis.

2.2.2. Therapeutic Rationale for Seladelpar in PSC

The preliminary clinical evidence supporting the development of seladelpar in PSC include 2 clinical Phase 2 studies in primary biliary cirrhosis (PBC) participants; CB8025-21528 (high dose study) and CB8025-21629 (ongoing low dose study).

CB8205-21528 was a double-blind, randomized, 12-week placebo-controlled, dose ranging (50 mg/day or 200 mg/day) Phase 2 study in PBC participants who were inadequate responders to UDCA (Jones 2017). Seladelpar exhibited rapid, pronounced AP 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. Bile acid synthesis, as measured by the biomarker C4, was suppressed by 55% and 77% at doses of 50 mg and 200 mg, respectively. However, three cases of reversible Grade 3 ALT elevations, balanced with the significant treatment response, resulted in the stopping of this trial and initiating a study evaluating daily doses of 2 mg, 5 mg, and 10 mg of seladelpar (CB8025-21629).

CB8025-21629 is an ongoing open-label, randomized dose ranging Phase 2 study in PBC participants who either have had an inadequate response to UDCA or are intolerant to UDCA. The aim of this study is to further evaluate the safety and efficacy of seladelpar at lower doses. An IA was performed using available data as of January 2018. The safety and efficacy of seladelpar treatment was evaluated for subsets of participants completing 12 weeks and 26 weeks of seladelpar treatment. Analysis of the first subset comprised those completing 12 weeks of treatment on fixed daily doses of 2 mg, 5 mg and 10 mg. After 12 weeks, patients on 2 mg increased to 5 mg and those on 5 mg could escalate to 10 mg if their AP treatment goal was not achieved. At the time of this analysis, 71 patients were exposed to at least one dose of seladelpar,

of whom 53 received 12 weeks of treatment and 42 received 26 weeks of treatment. The 5 mg and 10 mg doses show consistent, meaningful, and reproducible decreases in AP levels. At 12 weeks, changes in AP were -21%, -33%, and -45% in the 2 mg (N=6), 5 mg (N=25), and 10 mg (N=22) mg groups, respectively. At 26 weeks, the decrease in AP was equivalent across dosing regimens with -43%, -45%, and -43%, in the 5 mg (N=13), 5 mg to 10 mg (N=6), and 10 mg (N=19) groups, respectively, and with an overall proportion of participant with AP normalization of 29%. The increases in transaminases observed with seladelpar 50 mg and 200 mg doses have not been observed with 2 mg, 5 mg and 10 mg seladelpar doses. Median ALT levels decreased over 12 weeks at each of the dosing levels, with no evidence to date of the previous safety signal. Seladelpar did not increase pruritus. Baseline median pruritus visual analogue scale (VAS) was 10 and 40 in the 5 mg and 10 mg group, respectively, and patients in the 10 mg group experienced consistent decreases during follow up (-24% at Week 26). Seladelpar was generally safe and well tolerated and there was no transaminase elevation safety signal. There were six serious adverse events (SAEs); none were deemed related to seladelpar. In summary, these results provide evidence that seladelpar doses of 5 mg adjusted to 10 mg and 10 mg demonstrate potent and durable anti-cholestatic effects over 26 weeks.

Based on the identified pharmacologic activities *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 PSC.

2.3. NONCLINICAL STUDIES

Please see the Investigator's Brochure (IB) for details on the nonclinical studies conducted with seladelpar.

2.3.1. Nonclinical Safety Assessment

The proposed seladelpar daily doses to be studied in the Phase 2 PSC study are 5 mg, 10 mg, and 25 mg for 24 weeks. These doses and duration of exposure are supported by the repeat dose toxicity studies of 26 weeks in Sprague-Dawley rats and 52 weeks in cynomolgus monkeys. The exposure in PSC patients is expected to be similar to those observed in PBC patients. Based on this, there are adequate safety margins based on area under the concentration–time curve (AUC) in both sexes in all species, except for male monkeys, for the 5 mg, 10 mg, and 25 mg doses proposed for this study. Further details of these chronic toxicology studies in both species are described in the IB.

Table 2.3.1-1: 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
Margin (AUC) PSC – 25 mg	9.2X	26X	0.8X	4.1X
Margin (AUC) NASH – 50 mg	9.9X	28X	0.9X	4.4X
Abbreviations: AUC=area under the plasma concentration versus time curve; NASH=nonalcoholic steatohepatitis; NOAEL=no-observed-adverse-effect-level.				

2.4. CLINICAL STUDIES

The completed studies to date in the seladelpar clinical development program include seven Phase 1 studies and three Phase 2 studies. One Phase 1 study studied seladelpar PK, safety, tolerability, and bioavailability in participants with varying hepatic impairment (HI) in addition to healthy participants (CB8025-11732). All other Phase 1 studies assessed seladelpar PK, bioavailability, drug-drug interactions, effect on the QT internal, safety, and tolerability in healthy volunteers. The three Phase 2 studies have evaluated seladelpar in three different disease populations: (1) mixed dyslipidemia participants (M8025-20711), (2) homozygous familial hypercholesterolemia (HoFH) participants (CB8025-21427), and (3) PBC participants (CB8025-21528).

Ongoing clinical studies include a Phase 1 mass balance study in healthy participants (CB8025-11734), a Phase 2 low dose study in PBC participants (CB8025-21629), a Phase 2 study in NASH participants (CB8025-21730), a Phase 3 efficacy study in PBC participants (CB8025-31735), and a Phase 2/3 long term study (CB8025-31731) to allow continued access to seladelpar for eligible and willing PBC participants completing participation in prior seladelpar PBC studies (CB8025-21629 and CB8025-31735).

These studies are supportive of the clinical development of seladelpar in patients with PSC. Please refer to the IB for additional detailed information on these studies. Additional clinical data not included in the IB is summarized in the following sections.

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

CB8025-11732 is 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 participants with varying degrees of hepatic function. Participants 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. A total of 32 participants were enrolled (8 per cohort), with all participants receiving a single dose of 10 mg seladelpar according to the protocol. All participants completed the study, except for 1 participant 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 a median T_{max} of 0.5 to 2.0 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 participants with moderate or severe HI compared to participants with normal hepatic function. A summary of the key PK parameters is presented in Table 2.4.1-1.

Table 2.4.1-1: Summary (Mean ± Standard Deviation [SD]) of PK Parameters for Seladelpar in Participants 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

The appearance of seladelpar metabolites M1, M2, and M3 in plasma was similar to the parent compound and was followed by steady elimination. The overall mean $t_{1/2}$ for the three metabolites ranged from 7.81 to 11.0 hours with no apparent effect of the degree of HI. Exposure to M2 increased with HI severity, with the most apparent difference in the moderate and severe cohorts. A greater than 2-fold increase in M2 AUC_{0-t} values was observed in participants with moderate and severe impairment compared to normal participants. Changes in exposure to M1 and M3 were less pronounced in participants with different degrees of HI as compared to healthy participants with normal hepatic function. Single doses of 10 mg seladelpar were well-tolerated by both healthy participants and those with differing degrees of HI. Twenty-five percent of participants reported at least one TEAE during study participation and no individual events were reported in more than one participant in any cohort. Three TEAEs in 3 participants 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 participant in the severe HI group who had a history of intermittent bleeding from esophageal varices. This SAE began 4 days after the single dose of study drug was administered, did not result in study discontinuation, and was considered unlikely related to study treatment by the Investigator. 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.

In summary, these results support that the exposures of seladelpar and its major metabolites are comparable between healthy participants and participants with mild HI, including patients with compensated cirrhosis. The safety and tolerability of a single dose of seladelpar was acceptable across all degrees of HI.

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

CB8025-11734 is an ongoing 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 participants following a single oral administration of seladelpar. Preliminary pharmacokinetic and urinary excretion data of radiolabeled parent compound and primary metabolites are available.

In this study, four males and four healthy female participants each received a single 10 mg dose of [^{14}C] – seladelpar (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 participants 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 suggesting 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 the identified metabolites.

2.4.3. Additional Sub-Population Data in the Phase 2 Low-Dose Study in Patients with PBC (CB8025-21629)

2.4.3.1. Patients Treated for 52-Weeks

CB8025-21629 is an on-going Phase 2 multi-center study of adult PBC patients who have an inadequate response to or intolerance of UDCA. The study protocol was initially designed as an open-label, randomized, uncontrolled, 8-week dose ranging parallel group (5, 10, and 25 mg) design with an open-label extension for up to 26 weeks of treatment. Upon a planned interim data review performed in July 2017, the study was modified to 1) add a 2 mg dose to better inform the dose range and assess a minimally effective dose; 2) limit the highest dose tested to 10 mg; 3) extend the duration to 52 weeks; and 4) increase the number of participants in the 5 and 10 mg dose arms from 12 to 49 participants each. As of 23 July 2018, a total of 34 participants who were initially assigned either 5 mg (n=17) or 10 mg (n=17) dose groups have completed 52 weeks. The 5 mg dose group includes participants who may have titrated to 10 mg (5/10 mg). The 2 mg dose group is not represented in the 52-Week Cohort due to the small number of participants reaching this timepoint as of the date of the data cut. Table 2.4.3-1 summarizes the changes in AP in the patients completing 52 weeks as compared to the 12-week response rates.

Table 2.4.3-1: CB8025-21629: Alkaline Phosphatase – Mean Percent Change, AP < 1.67 × ULN and AP Normalization

	12-Week Cohort		52-Week Cohort	
	5 mg (N=32)	10 mg (N=32)	5/10mg (N= 17)	10 mg (N=17)
Mean % Change in AP	-37.09	-42.70	-46.91	-45.88
AP < 1.67 x ULN	21 (65.6%)	26 (81.3%)	11 (64.7%)	13 (76.5%)
AP Normalized	4 (12.5%)	10 (31.3%)	4 (23.5%)	5 (29.4%)

Lower doses of seladelpar were generally safe and well-tolerated, with most AEs being mild in severity, and no reported deaths. There was no evidence that seladelpar was associated with transaminase elevations or that it induced or worsened pruritus. At the time of the data cutoff presented in this protocol, a total of 11 participants experienced 11 SAEs during the study (6 SAEs in the 5/10 mg group and 5 SAEs in the 10 mg group). All the SAEs were considered unrelated or unlikely/remotely related to seladelpar treatment. The most common AEs were pruritus (unrelated to study drug), followed by fatigue, diarrhea, and nausea. Pruritus and fatigue are expected AEs as they are the most frequent symptoms of PBC (Kaplan 2005). In summary, these data support a continued durable treatment effect with favorable safety and tolerability for up to 52 weeks.

2.4.3.2. Patients with Compensated Cirrhosis

Of the 119 participants enrolled into the study, 25 were diagnosed as having compensated cirrhosis (5/10 mg, n=14 and 10 mg, n=11) based on liver biopsy, imaging tests, and/or liver elastography. As of 23 July 2018, 15 of 25 participants received seladelpar for 3 months, 13 of 26 for 6 months, and 8 of 26 for 1 year (Mayo 2019).

Mean decreases in AP (%) were -25% and -39% at 3 months, -24% and -41% at 6 months, and -36% and -43% at 1 year in the 5/10 mg and 10 mg groups, respectively. After 1 year, all patients in 5/10 mg and 3 of 5 patients in 10 mg had AP < 1.67 × ULN; the median decreases in ALT (%) were -31% and -50%, and the median absolute changes in pruritus VAS were 0 and -25 in 5/10 mg and 10 mg groups, respectively. Three patients with cirrhosis experienced an SAE, all unrelated to seladelpar. Total bilirubin, platelets, albumin, and international normalized ratio (INR) remained stable and no liver decompensation events were observed. These preliminary data demonstrate that seladelpar treatment is safe and well-tolerated and the demonstrated anti-cholestatic and anti-inflammatory effects support the use of seladelpar in PBC patients with compensated cirrhosis.

2.5. STUDY OBJECTIVES

2.5.1. Primary Objective

- Evaluate the treatment effect of seladelpar on relative (%) change in AP in participants with PSC during the study period

2.5.2. Secondary Objectives

- Assess the safety and tolerability of seladelpar in participants with PSC during the study period
- Evaluate the effect of seladelpar on the absolute and/or relative (%) changes of the following:
  - ALT, AP, AST, bilirubin (total, direct), and GGT
  - Total cholesterol, HDL-C, LDL-C, and triglycerides
  - C4 and serum bile acids
  - hs-CRP and fibrinogen
  - ELF Score (total and individual components), PRO-C3 and PRO-C5 levels
- Evaluate changes in pruritus, fatigue, and QoL
- Assess changes in symptoms associated with IBD during the study period
- Evaluate the changes in PSC-related symptoms and AEs
- Evaluate the PK and PD of seladelpar in participants with PSC

CCI [redacted]

3. STUDY DESIGN

3.1. STUDY OVERVIEW

This is a multiple center evaluation of seladelpar in a randomized, double blind, placebo controlled, parallel group study when administered for 24 weeks as a daily oral capsule in patients with PSC. Approximately 100 participants will be randomized across approximately 60 sites worldwide.

Patients to be studied will have confirmed PSC as defined as having any two of the three following criteria: historical elevated AP, abnormal cholangiography or liver histology consistent with PSC. Participants will be required to have an AP $\geq$ 1.5 × ULN at Screening. UDCA therapy will be allowed at stable doses of $\leq$ 20 mg/kg/day for at least 24 weeks. Patients with stable IBD are allowed, including those treated with a stable regimen of biologic, immunosuppressant, or systemic corticosteroid therapy. The history or presence of cirrhosis (compensated or decompensated), small-duct PSC, overlapping AIH, cholangiocarcinoma (diagnosed or suspected), acute cholangitis or recently placed bile duct stents or ballooning dilatation procedure will all be excluded from this study. Please refer to Section 4 of the protocol for the complete listing of the Inclusion and Exclusion Criteria.

All patients with IBD will be required to have had a colonoscopy with no evidence of dysplasia within 12-18 months of consent (as defined by local country guidelines) or during the Screening period. MRCP and MRI with contrast will be performed during Screening to assess bile duct strictures and cholangiocarcinoma. FibroScan® will be performed during Screening to assess liver stiffness and to rule out cirrhosis.

On Day 1, participants will be randomized into one of four treatment arms (seladelpar 5 mg, seladelpar 10 mg, seladelpar 25 mg, or placebo) in a 1:1:1:1 ratio. Participants will be stratified at randomization, according to UDCA use (Yes/No) and by averaged Screening total bilirubin values ($\leq$ ULN vs > ULN but $\leq$ 2 × ULN) to ensure even distribution across the four treatment arms.

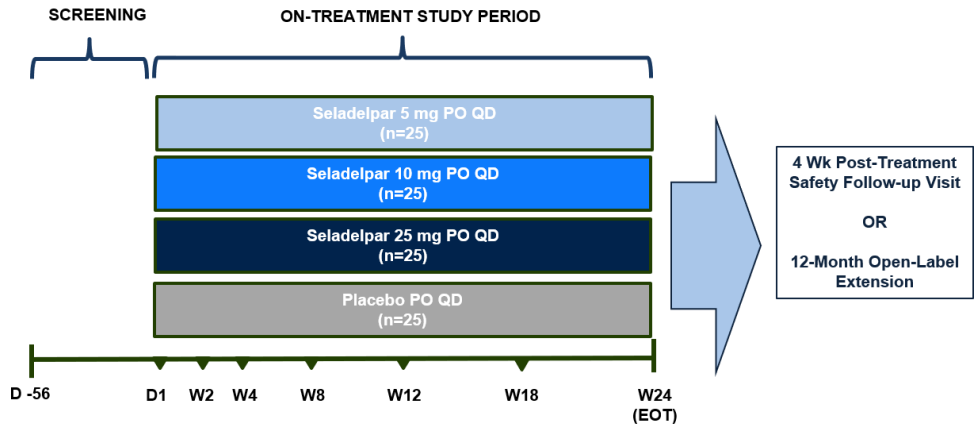
Participants will return to the clinic at Weeks 2, 4, 8, 12, 18, and 24 for on-treatment assessments and procedures. Participants will receive study-drug bottles on Day 1 and at Weeks 4, 8 and 12. Dose reductions will be permitted based on specific safety parameters and with approval by the Sponsor's Medical Monitor. MRCP and MRI with contrast will be performed at Week 24 to assess changes in bile duct strictures and volume. FibroScan® will be performed at Weeks 12 and 24 to assess changes in liver stiffness. PRO assessments for pruritus and other PSC symptoms, QoL and IBD-related symptoms will be evaluated at Day 1 and key visits during and after study drug treatment. Week 24 will be the EOT clinic visit. All participants eligible and willing can be enrolled into a separate 12-month OLE study starting at Week 24. Participants who do not enroll in the OLE study will return to the clinic at Week 28 for an EOS follow-up visit.

An IA will be conducted when approximately 10 participants per treatment arm have completed the Week 12 visit. The overall safety and efficacy of seladelpar in PSC will be assessed at the IA, in addition to dose selection for the long-term OLE. Full 24-hour PK profiles will be collected in

a subset of participants (up to 6 per arm) at Day 1 and Week 12. A full listing of the study procedures and assessments by visit are listed in Section 5 of the protocol.

Figure 3.1-1

Study Design Schema



3.2. STUDY OUTCOMES MEASURES

3.2.1. Primary Measures

- Treatment response defined as relative (%) change in AP from Baseline to Week 24

3.2.2. Secondary Measures

- Assessment of TEAEs (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0, (Appendix A), as well as biochemistry, hematology and urinalysis results
- Relative (%) change in AP at Week 12
- Absolute change in AP at Week 12 and Week 24
- Proportion of participants achieving the following AP response parameters at Week 12 and Week 24:
  - Normalization defined as $\leq$ ULN
  - $< 1.3 \times$ ULN
  - $< 1.5 \times$ ULN
  - $\geq$ 20%, 30%, and 40% relative decrease from Baseline
- Absolute and relative changes in ALT, AST, GGT, bilirubin (total and direct), C4, serum bile acids, hs-CRP, fibrinogen, ELF Score (total and components), PRO-C3, PRO-C5, total cholesterol LDL-C, HDL-C and triglycerides
- QoL
- Pruritus as measured by both the 5-D Itch Scale and a study-specific 10-point NRS

- Incidence and severity of PSC-related symptoms or procedures defined as acute cholangitis, pruritus, fatigue, stent-placement, balloon dilatation and cholangiocarcinoma
- Incidence and severity of IBD-related symptoms as defined by the Mayo Partial IBD Score
- Hepatic disease progression as defined by the first occurrence of the following events:
  - Liver transplantation
  - Model for End-Stage Liver Disease (MELD) score ≥ 15
  - Incidence and severity of hepatic decompensation events including uncontrolled ascites, variceal bleeding, hepatic encephalopathy (as defined by a West Haven score ≥ 2), spontaneous bacterial peritonitis (confirmed by culture from diagnostic paracentesis)
  - Hepatocellular carcinoma
- PK parameters to determine exposure as well as exposure-response and exposure-safety relationships

CCI [redacted]

3.3. RATIONALE FOR DOSE SELECTION OF SELADELPAR IN PSC PARTICIPANTS

The proposed doses of seladelpar to be evaluated in this study are 5, 10, and 25 mg, given as a single oral daily dose. The doses selected for the Phase 2 trial in PSC are supported by both the nonclinical and clinical data generated to date. The proposed doses are within the current safety margins established in the chronic toxicology (Section 2.3.1). 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 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), HoFH (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).

Patients with PSC are expected to have similar seladelpar exposures as PBC patients based on the similar underlying cholestatic conditions. Seladelpar has been studied in PBC participants at doses 2 mg, 5 mg, 10 mg, 50 mg and 200 mg and demonstrated rapid and significant improvements in cholestasis (AP, GGT, total bilirubin) and inflammation (liver transaminases, hs-CRP) while also demonstrating no worsening or possible improvement in pruritus. However, three cases of Grade 3 ALT elevations were observed as early as Week 2 in the high dose PBC study (CB8025-21528); one in the 50 mg dosing group and two in the 200 mg dosing group. While the transaminase elevations were not associated with clinical symptoms and were fully reversible following drug discontinuation, these events support a safety threshold at doses < 50 mg in a cholestatic populations. As of 23 July 2018, there have been no Grade 3 ALT elevations in PBC patients treated with 5 mg and 10 mg for up to 52 weeks. Additionally, seladelpar exposure in PSC patients is expected to be approximately 50–60% higher than non-cholestatic participants (healthy volunteers and NASH). Currently, doses of 10 mg, 25 mg, and 50 mg are being evaluated in an ongoing Phase 2 study in NASH participants, with no ALT elevations meeting liver safety monitoring criteria at any dose. The 25 mg maximal dose proposed in PSC remains within the safety margins based on both the PBC and NASH exposures.

Both animal and human data support that seladelpar is cleared both through biliary and renal excretion, an important factor in the setting of cholestasis. Following administration of a single oral dose of [^{14}C]-seladelpar to Sprague-Dawley rats, urine and feces were collected at designated intervals up to 166 hours post-dose for radioactivity analysis. Both Phase 1 and Phase 2 (glucuronide-conjugated) metabolites were identified in both urine and feces, supporting both hepatic and renal clearance. More recently, a Phase 1 single dose study in healthy participants (n= 4 male and 4 female) was conducted to determine the pharmacokinetics, disposition and mass balance of seladelpar and its metabolites following a single [^{14}C]-labeled oral dose. An overall mean of 73.4% of the dose was recovered in urine and 19.5% of the dose was recovered in feces through the last collection interval. Furthermore, seladelpar is extensively metabolized and the resulting metabolites are largely excreted in urine. These data suggest that in diseases with decreased biliary excretion, seladelpar and its metabolites can be cleared by renal elimination and thus, should not result in significant alterations in exposure and safety margins in the PSC population.

Additionally, a drug-induced liver injury (DILI) safety monitoring algorithm based on the Food and Drug Administration's (FDA) Guidance for Industry for DILI has been incorporated into the study. A Data Safety Monitoring Committee (DSMC) will perform ongoing safety reviews at key timepoints throughout the study. Additionally, the Week 12 interim analysis will be to review the preliminary safety and tolerability of these doses in PSC. CCI [redacted]

3.4. RATIONALE FOR A PLACEBO CONTROL ARM

This study incorporates the use of a placebo comparator arm as it is the most rigorous test of treatment efficacy and safety profile for evaluating an experimental therapy in complex patient

populations. UDCA has been studied in multiple prospective clinical studies and is considered the only pharmacologic treatment option with some degree of biochemical response. However, EASL as well as AASLD currently do not make a recommendation for general use of UDCA in PSC (Beuers 2009; Chapman 2010). Additionally, there are currently no medications approved for the treatment of patients who are unresponsive to UDCA. Therefore, most randomized, blinded studies for experimental therapies utilize placebo as the comparator arm, independent of whether UDCA is used as a background medication, as there is not an accepted standard of care in PSC.

3.5. BENEFIT/RISK ASSESSMENT

3.5.1. Potential Benefit

In a completed PBC study, participants receiving the high dose of seladelpar (50 mg and 200 mg/day) exhibited a pronounced decrease in AP. These pronounced decreases in AP were also observed with lower doses of seladelpar (5 mg and 10 mg/day), after 26 weeks; the decrease in AP was equal across regimen at -43%, -45%, and -43%, in the 5 mg (N=13), 5 mg to 10 mg (N=6), and 10 mg (N=19) groups, respectively, with overall AP normalization of 29%. Seladelpar also has demonstrated a reduction in other biochemical markers such as ALT, AST, total bilirubin and GGT with the 5 mg and 10 mg doses, in addition to producing potentially beneficial metabolic and anti-inflammatory effects.

Previous studies in PBC participants indicate the potential of seladelpar to improve pruritus, an important clinical outcome in patients with cholestatic liver diseases. PBC participants who had a substantial level of itching at Day 1 and were treated with seladelpar 10 mg had a significant decrease in pruritus VAS following treatment. These data suggest treatment with seladelpar may also be associated with an improvement in PSC-related itch, given the overlapping pathogenesis with PBC-related pruritus.

Participants who successfully complete this study will be offered the opportunity to enroll into an OLE study. The OLE study will allow participants to continue their seladelpar treatment for an additional 12 months or until the program is discontinued. Participants on placebo will be switched to the active treatment with seladelpar for a total of 12 months.

3.5.2. Potential Risk

Across the clinical development program, the 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 dose in Phase 2 studies in patients with mixed dyslipidemia (50 mg and 100 mg once a day), HoFH (ascending doses 50 mg, 100 mg, and 200 mg once a day), NASH (10 mg, 20 mg and 50 mg once a day), or PBC (2 mg, 5 mg, 10 mg, 50 mg, and 200 mg once a day). In these studies, dosing durations have ranged from 8 to 12 weeks in completed studies and up to 52 weeks in the ongoing ‘low dose’ PBC study (CB8025-21629). In an ongoing long-term safety study in PBC (CB8025-31731), designed to provide continued access to seladelpar for those PBC participants who completed a prior seladelpar study, 4 participants to date have received seladelpar for more than 2 years.

Seladelpar has been associated with increases in liver transaminases (ALT and AST) in participants 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 participant taking seladelpar 200 mg per day discontinued treatment for acute muscle pain associated with increased muscle enzymes. This event was considered possibly related to treatment and was reversible upon treatment discontinuation. Mild increases (approximately 10%) in serum creatinine have been noted, consistent with those increases observed with other PPARα or mixed PPARα/δ class of medications. However, there are no concurrent change in cystatin-c or other markers of renal injury, supporting that the increase is not associated with renal toxicity and 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. To date, there have not been any liver transaminase elevations meeting the pre-defined drug-induced liver injury criteria, serum creatinine increases > 10% or muscle toxicity in PBC participants treated with 5 mg and 10 mg or in NASH participants treated with 10 mg, 20 mg or 50 mg.

3.5.3. Procedural Risks

Participants will undergo MRI with contrast and MRCP as part of this study. The major risk from undergoing these procedures is related to gadolinium-based contrast administration. Patients with impaired renal function who receive certain gadolinium-based contrast agents are at risk for developing Nephrogenic Systemic Fibrosis (NSF). In order to mitigate this risk, study participants are required to have adequate renal function (eGFR $\geq$ 60 mL/min/1.73 m^2). Additionally, only gadoxetate disodium will be used in this study. Gadoxetate disodium has a favorable safety profile with no cases of NSF reported to date. In addition, emerging data suggest that repeated exposure to gadolinium-based contrast agents can result in gadolinium deposition in the brain and other tissues, though no distinct clinical disease has been linked with deposition to date. However, the poorly understood, but likely low risk associated with tissue deposition of gadolinium is mitigated by the direct benefit of having a contrast-enhanced MRI to the patient. Patients with PSC are at risk for developing cholangiocarcinoma, and contrast-enhanced MRI is the most sensitive technique available for detecting cholangiocarcinoma. As a result, MRIs obtained in this study will benefit the individual participant by providing them with a highly sensitive screening for cholangiocarcinoma.

3.5.4. Summary

Seladelpar has demonstrated activity to improve liver histology and decrease markers of liver fibrosis in non-clinical studies. In clinical studies, seladelpar showed the ability to decrease markers of cholestasis (AP, GGT, bilirubin), hepatic and systemic inflammation (liver transaminases, hs-CRP), and bile-acid synthesis (C4, serum bile acids) in PBC participants, a study population relevant to PSC. These data support the assessment of seladelpar as a candidate for the treatment of PSC. Appropriate precautions have been incorporated into this protocol, with careful monitoring of potential DILI and muscle toxicity. In summary, as there are no approved treatments for PSC, the benefit/risk of seladelpar in PSC patients at doses of 5 mg, 10 mg, and 25 mg is acceptable based the aggregate safety and treatment effect data to date.

4. PARTICIPANT SELECTION

4.1. INCLUSION CRITERIA

Patients who meet the following criteria may be included in the study:

1. Males and females who are 18 years of age and older and are able to comprehend instructions and follow the study procedures and are willing to sign an Informed Consent Form (ICF)
2. Confirmed diagnosis of PSC based on any **two** of the following three criteria:
   - Historical evidence of an elevated AP > ULN from any prior laboratory result
   - Liver biopsy consistent with PSC
   - Abnormal cholangiography consistent with PSC as measured by MRCP, ERCP, or PTC
3. Participants must have the following specific additional laboratory parameters measured by the Central Laboratory at Screening:
   - AP $\geq 1.5 \times$ ULN and $< 8 \times$ ULN
   - Total bilirubin $\leq 2 \times$ ULN
   - ALT and AST $\leq 5 \times$ ULN
   - eGFR ≥ 60 mL/min/1.73 m^2 by modification of diet in renal disease (MDRD) calculation
   - Platelets $\geq 140 \times 10^3/\mu L$
   - INR ≤ 1.3 (in the absence of warfarin or other anticoagulant therapy)
   - Albumin ≥ 3.5 g/dL
4. Participants taking UDCA will be allowed to enroll if meeting the following criteria:
   - Total daily dose of ≤ 20 mg/kg/day
   - A minimum of 24 weeks of stable treatment
   - A minimum of 12 weeks off treatment prior to Screening if UDCA has been recently discontinued
5. Participants with concomitant IBD may enroll upon meeting the following criteria:
   - A colonoscopy performed within 12 to 18 months (as defined by local country guidelines) of consent or during the Screening period, with no evidence of dysplasia
   - No episode of an IBD flare or IBD flare-related bloody diarrhea within 24 weeks of Screening and through Day 1

- Stable regimen of biologic treatments, immunosuppressants, or systemic corticosteroids (≤ 10 mg/day prednisone or equivalent) for ≥ 12 weeks prior to Screening and through Day 1

6. FibroScan® values ≤ 14.4 kPa
7. Participants 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

1. Clinically significant acute or chronic liver disease of an etiology other than PSC
2. A diagnosis of overlapping AIH and PSC
3. Small-duct PSC
4. Secondary or IgG4 related sclerosing cholangitis
5. Presence of a cholangiocarcinoma on MRCP or MRI at Screening as determined by the central radiologist and the Principal Investigator (PI) or Medical Monitor
6. Bile duct stent or percutaneous bile duct drain placement within 12 weeks of Screening
7. Balloon dilation procedure of a stricture within 12 weeks of Screening
8. History, evidence, or high suspicion of cholangiocarcinoma or other hepatobiliary malignancy based on imaging, screening laboratory values, and/or clinical symptoms
9. Presumptive or diagnosed acute cholangitis within 12 weeks of Screening and through Day 1
10. Evidence of compensated or decompensated cirrhosis based on histology, relevant medical complications, or laboratory parameters:
    a. Historical liver biopsy demonstrating cirrhosis (e.g., Ludwig Stage 4 or Ishak Stage ≥ 5)
    b. Current or prior history of decompensated liver disease, including ascites, hepatic encephalopathy, variceal bleeding or other clinical conditions consistent with cirrhosis and/or portal hypertension
    c. FibroScan® values > 14.4 kPa
    d. Combined low platelet count (< $140 \times 10^3/\mu L$) with one or more of the following:
        - Albumin < 3.5 g/dL,
        - INR > 1.3 (not due to antithrombotic agent use), or
        - Total bilirubin > ULN
11. Variability > 40% in any one of the following laboratory parameters: AP, ALT, AST, or total bilirubin values between at least two visits during Screening approximately 4 weeks apart
    a. If a lab value at Screening Visit 2 is > 40% higher than the lab value at Screening Visit 1, a third sample may be drawn. If the difference between the third sample and

the value from Screening Visit 1 is also > 40% higher, the participant is excluded from the study

12. Prior or actively listed for liver transplantation
13. Any contraindication or inability to obtain a MRCP, MRI with contrast, FibroScan®, or colonoscopy (if required)
14. Females 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 7.5.1 of the protocol
15. ECG with clinically significant abnormalities as determined by the Investigator
16. Positive for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) RNA, or anti-human immunodeficiency virus (HIV) antibody
17. History of malignancy diagnosed or treated within 2 years
    - Recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted
    - Cervical carcinoma in-situ is allowed if appropriately treated prior to Screening
    - Participants under active evaluation for malignancy are not eligible
18. Clinically relevant drug or alcohol abuse within 24 weeks of Screening. A positive drug screen will exclude participants unless it can be explained by a prescribed medication
19. Any prohibited medication as listed in Section 5.2.2 of the study protocol
20. Prior exposure to seladelpar
21. Use of obeticholic acid, vancomycin, minocycline, fibrates or any other experimental or unapproved agent for the treatment of PSC within 12 weeks of Screening and throughout the study period
22. Participation in a study of another investigational agent within 4 weeks of the last study visit for that study or five half-lives of the investigational drug (whichever is longer) prior to Screening
23. History of clinically significant unstable or untreated illness or any other acute or chronic medical condition that may interfere with participant treatment, assessment, or compliance with the protocol
24. Presence of any other 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

5. SCHEDULE OF STUDY PROCEDURES

The Schedule of Study Procedures are outlined in Table 5-1.

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

- **Screening Period:** Day -56 to Day -1
- **Randomization and Treatment Initiation:** Day 1
- **Study Treatment Period:** Day 1 through Week 24
- CCI [redacted]

The visits should occur as close to the intended dates as possible and within a ± 3-day window for individual scheduled visits. Participants attending any visits out of windows should be brought back into compliance with the overall study visit schedule as soon as possible thereafter.

Table 5-1: Schedule of Study Procedures

Study Procedure	D –56 to –1 (Screening)		D1	W2 (±3 days)	W4 (±3 days)	W8 (±3 days)	W12 (±3 days)	W18 (±3 days)	W24/ET (EOT)[a] (±3 days)	W28 (EOS)[b] (±3 days)
	Screening Visit 1	Screening Visit 2								
Informed consent	X									
CCI										
Adverse event evaluations[c]	X	X	X	X	X	X	X	X	X	X
Demographics, Medical Hx	X									
Prior and concomitant meds	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion criteria	X		X							
Body Weight, Vital Signs, PE	X		X	X	X	X	X	X	X	X
Height	X									
12-lead electrocardiogram[d]	X		X						X	X
Colonoscopy (if required)[e]	X									
MRCP[f]	X								X	
MRI with contrast[f]	X								X	
FibroScan®	X						X		X	
PK blood and urine samples[g]			X[g]	X	X	X	X[g]	X	X	
Chemistry and Hematology	X	X[h]	X	X	X	X	X	X	X	X
Viral Screen	X									
Prothrombin time (PT) and INR	X		X		X		X		X	X
p-ANCA	X									
Fasting lipid panel	X		X				X		X	X
Pregnancy test[i]	X		X				X		X	
ELF Panel			X		X		X		X	X
CCI										
Cystatin-C			X	X	X	X	X	X	X	X
Urinalysis	X		X				X		X	X
Drug Screen	X									
5-D Pruritus Scale	X		X	X	X	X	X	X	X	X
PSC PRO	X		X	X	X	X	X	X	X	X
Mayo Partial IBD Score	X		X	X	X	X	X	X	X	X
Dispense Pruritus NRS[k]	X				X		X	X		
Randomization			X							
Dispense study drug			X		X	X	X			
Study drug compliance				X	X	X	X	X	X	

Table 5-1 Schedule of Study Procedures (cont'd)

Abbreviations: C4 = 7 Alpha-hydroxy-4-cholesten 3 one; D = Day; ELF = Enhanced Liver Fibrosis; EOS = End of Study; EOT = End of Treatment; ET = early treatment withdrawal; hs-CRP = high sensitivity C reactive protein; IBD = Inflammatory Bowel Disease; Hx = History; MRCP = magnetic resonance cholangiopancreatography; NRS = Numeric Rating Scale; p-ANCA = perinuclear anti-neutrophil cytoplasmic antibodies; PDK4= pyruvate dehydrogenase kinase 4; PE = Physical Exam; PK = pharmacokinetic; PRO = Patient Reported Outcomes; PRO-C3 = procollagen III N-terminal peptide; PRO-C5 = C-terminal pro-peptide of type V collagen; PT/INR = Prothrombin Time/International Normalized Ratio; W = Week.

Footnotes:

[a] At Week 24 (EOT), participants will be offered enrollment into an OLE study and will be reconsented. Refer to Section 8 for Early Treatment Withdrawal (ET) procedures.

[b] Week 28 (EOS) study visit will only be performed in participants not participating in the OLE study.

[c] AEs will be evaluated and recorded starting from the time the participant signs the informed consent.

[d] A 12-lead ECG will be obtained in supine position after at least 5 minutes of rest and ECGs must be sent to the Sponsor at PPD

[e] Colonoscopy will be performed during Screening in IBD patients who do not have an available report within 12 to 18 months of consent.

[f] MRCP and MRI with contrast will be performed in all participants during Screening and at Week 24. MRCP and MRI with contrast are to be performed at the same imaging facility for a given patient during the trial. Both imaging procedures are to be scheduled and performed on the same day for a given visit. MRCP imaging is to be performed before MRI with contrast at all visits.

[g] PK blood samples will be collected before dosing the study medication in the clinic (pre-dose). In a subset of participants, full 24-hour PK will be collected at pre-dose and at 0.5, 1, 2, 4, 8, 12 and 24 hours after dosing at Day 1 and Week 12. Urine samples will also be collected over the 24 hours interval.

[h] Screening Visit 2 will occur approximately 4 weeks after Screening Visit 1 to measure serum AP, ALT, AST and total bilirubin to satisfy Exclusion Criterion #11.

i A serum pregnancy test will be performed on all female participants of child-bearing potential at Screening and Week 24. A urine pregnancy test will be performed on all female participants at Day 1 (pre dose) and Week 12 (pre-dose). Additional tests may be added as indicated.

[j] CCI [redacted]

[k] NRS will be dispensed at listed visits with the data recorded and collected by the site as outlined in Section 5.5.13 of the protocol

5.1. STUDY VISIT PROCEDURES

5.1.1. Day -56 to Day -1 Procedures (Screening Visits 1 and 2)

5.1.1.1 Screening Visit 1

The following Screening Visit 1 procedures will be performed for all potential participants at a visit (or visits) conducted within 56 days prior to dosing.

- Obtain informed consent.
- CCI [redacted]
- Record AEs (starting from the time the participant signs the informed consent).
- Register participant in Interactive Web Response System (IWRS).
- Collect demographic data.
- Review and record medical history.
- Obtain historical AP results, MRI, MRCP, ERCP, PTC and/or liver biopsy reports as required for PSC diagnosis and dominant stricture assessment.
- Record prior and concomitant medications.
- Assess inclusion/exclusion criteria.
- Measure body weight.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Conduct a complete physical examination (PE).
- Measure height.
- Obtain 12-lead ECG (after participant has been supine for at least 5 minutes).
- In patients with concomitant IBD, obtain colonoscopy report from eligible historical colonoscopy or undergo a colonoscopy procedure to obtain a new report if outside the 48- to 72-week window.
- Obtain new MRCP.
- Obtain new MRI with contrast.
- Perform FibroScan® assessment.
- Obtain clinical laboratory samples for the following:
    - Chemistry
    - Hematology
    - HIV antibody and hepatitis B and C screening tests
    - PT/INR
    - Perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA)

  - Lipids
  - Serum pregnancy test as indicated
- Obtain urine samples for the following:
  - Urinalysis
  - Selected drugs of abuse, excluding cannabinoids
- Perform 5-D Pruritus Scale (See Appendix D).
- Perform the PSC PRO (See Appendix C).
- Perform Mayo Partial IBD Score (See Appendix B).
- Dispense Pruritus NRS diary with instructions to initiate approximately 7 days **prior** to their Day 1 visit.

For all Screening laboratory assessments or procedures, the PI has the discretion to repeat them if he/she believes there is a good chance the results were spurious and do not accurately represent the participant's true values. Repeat laboratory assessments or procedures must be performed within the 8-week Screening Period, prior to randomization, and a participant may only have these laboratory assessments or procedures repeated once for an individual lab or procedure at least two weeks from the previous testing date as an unscheduled visit.

5.1.1.2 Screening Visit 2

The following Screening Visit 2 laboratory assessments will be conducted approximately 4 weeks after Screening Visit 1 to satisfy Exclusion Criterion #11.

- Record AEs.
- Record prior and concomitant medications.
- Obtain clinical laboratory samples for the following:
  - Chemistry: AP, ALT, AST and total bilirubin

A repeat measurement is permissible if any one of the laboratory values from Screening Visit 2 is > 40% higher compared to Screening Visit 1 values. The repeat assessments should be collected at an unscheduled visit a minimum of 1 week after Screening Visit 2.

5.1.2. Day 1 Procedures

Participants will report to this visit fasted for 8 hours with only water allowed.

The following procedures will be performed at the Day 1 visit:

- Assess for AEs from Screening period.
- Assess for concomitant medications.
- Reassess inclusion/exclusion criteria.
- Measure body weight.

- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Conduct a complete physical examination.
- Obtain 12-lead ECG (after participant has been supine for at least 5 minutes).
- Obtain 8 hour fasted clinical laboratory samples for the following:
    - Pre-dose PK blood sample
    - Chemistry
    - Hematology
    - PT/INR
    - Lipids
    - ELF panel
    - C4 and serum bile acids
    - Fibrinogen
    - hs-CRP
    - Pyruvate dehydrogenase kinase 4 (PDK4)
    - PRO-C3
    - PRO-C5
    - Cystatin-C
    - Back-up plasma and serum samples
- Obtain urine samples for the following:
    - Pre-dose pregnancy test
    - Urinalysis
- Perform 5-D Pruritus Scale.
- Perform the PSC PRO.
- Perform Mayo Partial IBD Score.
- Collect Pruritis NRS daily diary from Screening
- Randomize participant (including entry of stratification criteria for UDCA use (Yes/No) and by averaged Screening total bilirubin value (≤ ULN vs > ULN but ≤ 2 × ULN)
- Dispense initial study drug bottle(s) and diary for recording of date/time of study drug dosing.
- Schedule participant for Week 2 visit.

CCI [redacted]

Week 2 Procedures

Participants will report to this visit fasted for 8 hours with only water allowed.

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

- Assess for AEs.
- Assess for concomitant medications.
- Measure body weight.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Conduct a complete physical examination.
- Obtain 8 hour fasted clinical laboratory samples for the following:
  - PK blood sample
  - Chemistry
  - Hematology
  - Cystatin-C
  - Back-up serum and plasma samples
- Perform 5-D Pruritus Scale.
- Perform the PSC PRO.
- Perform Mayo Partial IBD Score.
- Dispense diary.
- Collect empty study drug bottles and diary and conduct reconciliation.
- Schedule participant for Week 4 visit.

5.1.3. Week 4 Procedures

Participants will report to this visit fasted for 8 hours with only water allowed.

The following procedures will be performed at the Week 4 visit:

- Assess for AEs.
- Assess for concomitant medications.
- Measure body weight.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Conduct complete physical examination.
- Obtain 8 hour fasted clinical laboratory samples for the following:
    - PK blood sample
    - Chemistry
    - Hematology
    - PT/INR
    - ELF panel
    - C4 and serum bile acids
    - Fibrinogen
    - hs-CRP
    - PDK4
    - PRO-C3
    - PRO-C5
    - Cystatin-C
    - Back-up serum and plasma samples
- Perform 5-D Pruritus Scale.
- Perform the PSC PRO.
- Perform Mayo Partial IBD Score.
- Dispense Week 4 Pruritis NRS daily diary. Participant will collect data for the 7 days **following** their Week 4 visit.
- Dispense new study drug bottle and diary.
- Collect empty study drug bottle(s) and diary and conduct reconciliation.
- Schedule participant for Week 8 visit.

5.1.4. Week 8 Procedures

Participants will report to this visit fasted for 8 hours with only water allowed.

The following procedures will be performed at the Week 8 visit:

- Assess for AEs.
- Assess for concomitant medications.
- Measure body weight.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Conduct a complete physical examination.
- Obtain 8 hour fasted clinical laboratory samples for the following:
    - PK blood sample
    - Chemistry
    - Hematology
    - Cystatin-C
    - Back-up serum and plasma samples
- Perform 5-D Pruritus Scale.
- Perform the PSC PRO.
- Perform Mayo Partial IBD Score.
- Collect Pruritis NRS daily diary from Week 4.
- Dispense new study drug bottle(s) and diary.
- Collect empty study drug bottle(s) and diary and conduct reconciliation.
- Schedule participant for Week 12 visit.

5.1.5. Week 12 Procedures

Participants will report to this visit fasted 8 hours with only water allowed.

The following procedures will be performed at the Week 12 visit:

- Assess for AEs.
- Assess for concomitant medications.
- Measure body weight.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Conduct a complete physical examination.
- Perform FibroScan® assessment.

- Obtain 8 hour fasted clinical laboratory samples for the following:
  - PK blood sample
  - Chemistry
  - Hematology
  - PT/INR
  - Lipids
  - ELF panel
  - C4 and serum bile acids
  - Fibrinogen
  - hs-CRP
  - PDK4
  - PRO-C3
  - PRO-C5
  - Cystatin-C
  - Back-up serum and plasma samples
- Obtain urine samples for the following:
  - Pre-dose pregnancy test
  - Urinalysis
- Perform 5-D Pruritus Scale.
- Perform the PSC PRO.
- Perform Mayo Partial IBD Score.
- Dispense Week 12 Pruritis NRS daily diary. The participant should be instructed to record their daily assessments for the 7 days **following** their Week 12 visit.
- Dispense new study drug bottle(s) and diary.
- Collect empty study drug bottle(s) and diary and conduct reconciliation.
- Schedule participant for Week 18.

CCI [redacted]

CCI [redacted]

5.1.6. Week 18 Procedures

Participants will report to this visit fasted for 8 hours with only water allowed.

The following procedures will be performed at the Week 18 visit:

- Assess for AEs.
- Assess for concomitant medications.
- Measure body weight.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Conduct a complete physical examination.
- Obtain 8 hour fasted clinical laboratory samples for the following:
  - PK blood sample
  - Chemistry
  - Hematology
  - Cystatin-C
  - Back-up serum and plasma samples
- Perform 5-D Pruritus Scale.
- Perform the PSC PRO.
- Perform Mayo Partial IBD Score.
- Collect Pruritis NRS daily diary from Week 12.
- Dispense Week 18 Pruritis NRS diary. Participants should be instructed to record their daily assessments for the 7 days **prior** to their Week 24 visit.
- Dispense diary.
- Collect empty study drug bottle(s) and diary and conduct reconciliation.
- Schedule participant for Week 24 visit.

5.1.7. Week 24 Procedures

Participants will report to this visit fasted 8 hours with only water allowed.

The following procedures will be performed at the Week 24 or Early Treatment Withdrawal (ET) visit (if applicable):

- Assess for AEs.
- Assess for concomitant medications.

- Measure body weight.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Conduct a complete physical examination.
- Obtain 12-lead ECG (after participant has been supine for at least 5 minutes).
- Perform MRCP.
- Perform MRI with contrast.
- Perform FibroScan® assessment.
- Obtain 8 hour fasted clinical laboratory samples for the following:
    - PK blood sample
    - Chemistry
    - Hematology
    - PT/INR
    - Lipids
    - Serum pregnancy test as indicated
    - ELF panel
    - C4 and serum bile acids
    - Fibrinogen
    - hs-CRP
    - PDK4
    - PRO-C3
    - PRO-C5
    - Cystatin-C
    - Back-up serum and plasma samples
- Obtain urine samples for urinalysis.
- Perform 5-D Pruritus Scale.
- Perform the PSC PRO.
- Perform Mayo Partial IBD Score.
- Collect Pruritis NRS daily diary from Week 24.
- Collect empty study drug bottle(s) and diary and conduct reconciliation.
- CCI [redacted]

5.1.8. Week 28 (EOS) Procedures

Participants will report to this visit fasted 8 hours with only water allowed.

The following procedures will be performed at the Week 28 or End of Study (EOS) visit:

- Assess for AEs.
- Assess for concomitant medications.
- Measure body weight.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Conduct a full physical examination.
- Obtain 12-lead ECG (after participant has been supine for at least 5 minutes).
- Obtain 8 hour fasted clinical laboratory samples for the following:
    - Chemistry
    - Hematology
    - PT/INR
    - Lipids
    - ELF panel
    - C4 and serum bile acids
    - Fibrinogen
    - hs-CRP
    - PDK4
    - PRO-C3
    - PRO-C5
    - Cystatin-C
    - Back-up serum and plasma biomarkers
- Obtain urine samples for urinalysis.
- Perform 5-D Pruritus Scale.
- Perform the PSC PRO.
- Perform Mayo Partial IBD Score.

5.1.9. Unscheduled (UNS) Visits

Unscheduled visits may be conducted at the Investigator's discretion and/or when repeat of laboratory assessments or procedures are needed. The following information may also be collected at the Investigator's discretion and as indicated by the reason for the unscheduled visit:

- TEAEs.

- Concomitant medications and procedures.
- Vital signs and body weight.
- Blood samples biochemistry and hematology (either partial or complete panels).
- PK blood samples if visit is safety related.
- A symptom-directed complete physical examination.
- 12-lead ECG (in participants with symptoms suggestive for cardiac origin).
- Compliance to study drug.
- Dispense new study drug as needed.
- Additional assessments may be performed, as determined by the Investigator.

5.2. CONCOMITANT AND PROHIBITED MEDICATIONS

5.2.1. Concomitant Medications

Any medication taken within 4 weeks prior to Screening and during the study period, as well as the indication, will be recorded in the source documents and the electronic Case Report Form (eCRFs). Any AEs related to the administration of these medications or procedures must also be documented on the appropriate section in the eCRF.

Participants should refrain from the use of any new prescription medications or products or change in the dose or frequency of existing therapies within 4 weeks prior to Day 1 until EOS. The Sponsor's Medical Monitor should be informed of any changes or addition of medications during this time period.

5.2.2. Prohibited Medications

The following medications are prohibited from 4 weeks prior to Day 1 and through the end of treatment:

- Investigational agents, other than seladelpar, or investigational devices for any indication
- Agents with significant risk of hepatotoxicity
    - Concomitant medication can be screened at http://livertox.nih.gov
    - Patients on stable doses of a medication that may be hepatoxic for a minimum of 12 weeks can be considered for enrollment as long as there has been no evidence of hepatoxicity
- Agents which can ***significantly*** increase or decrease AP
    - Patients on stable doses of a medication that may impact AP for a minimum of 12 weeks can be considered for enrollment

  - Medications which may impact AP should not be started at any time-point during the Screening or study period.

- Agents used for the treatment of any condition listed in the exclusionary enrollment criteria (see Section 4.2)
- Off-label use or experimental therapies for PSC (such as obeticholic acid, fibrates, oral vancomycin) within 12 weeks of Screening through the EOS visit
- Any herbal medications for liver health or known to be hepatotoxic, other than standard vitamin supplements

In addition:

- Participants taking medications for IBD must have been on a stable regimen of these medications for at least 12 weeks prior to Day 1 and should maintain, if possible, a stable regimen and dosing during the study period.
- Participants taking UDCA are eligible but must have been on stable doses of ≤ 20 mg/kg/day for at least 26 weeks prior to their Screening. A minimum of 12 weeks off treatment prior to Screening is required if UDCA has been recently discontinued. Participants should not initiate new UDCA therapy at any timepoint during the study period.

5.3. 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 participants' participation in this trial. Participants will be allowed to receive required procedures to treat new or existing medical conditions.

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

5.4. DIET AND ACTIVITY CONTROL

Participants 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).

5.5. CLINICAL EVALUATIONS

5.5.1. Medical History and Physical Examinations (PEs)

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

Complete PEs will be performed as outlined in Table 5-1. Complete physical examinations will include a full review of the following systems: general, skin, eyes, nose/sinuses, ears, mouth/throat, neck, breasts CCI [redacted] and respiratory, cardiac, gastrointestinal,

peripheral vascular, genitourinary CCI [redacted] musculoskeletal, neurologic, mental health, endocrine and hematologic. Complete PEs 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.

5.5.2. Height and Weight

Height measurement will be performed at Screening only; weight will be taken at each study visit per the Schedule of Study Procedures (Table 5-1).

5.5.3. Vital Signs

Vital signs (including temperature, respiratory rate, and seated blood pressure and pulse) will be obtained at Screening and at all study visits as outlined in the Schedule of Study Procedures (Table 5-1).

Seated blood pressure and pulse will be measured after the participant has been seated for at least 5 minutes.

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

5.5.4. Electrocardiograms

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 5-1).

5.5.5. Clinical Laboratory Assessments

Blood samples for laboratory testing from Day 1 and onward will be collected at study visits after at least an 8-hour overnight fast and prior to dosing. If the participant forgets to fast, the site 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.

Laboratory tests will be collected be taken at each study visit per the Schedule of Assessments (Table 5-1) and will include the following parameters:

Biochemistry:

Albumin, ALT, Amylase, AP, AST, Bicarbonate, blood urea nitrogen (BUN)/Urea, Chloride, CK, Bilirubin (total, direct, indirect), Creatinine, Cystatin-C, eGFR, Free Fatty Acid, GGT, Glucose, HDL-C, LDH, LDL-C, Lipase, non-HDL-C, p-ANCA, Potassium, Total Protein, Sodium, Total Cholesterol, Triglycerides, Uric Acid

Hematology:

Erythrocyte Count (RBC), Hemoglobin, Hematocrit, Leukocyte Count (white blood cell count [WBC]), WBC Differential (absolute and percentage), Platelets, PT, INR

CCI [redacted]

Back-Up Blood Sample:

Three additional blood samples (2 plasma and 1 serum) 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 participants of childbearing potential only at Screening and Week 24. Urine pregnancy test will be conducted on Day 1 prior to randomization and first dose of study drug and at the Week 12 visit. This can be tested at additional visits as recommended by the PI and/or local regulations .

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

Urine Drug Screen: At Screening only. Cannabinoids are not included in this drug screen.

5.5.6. Pharmacokinetic Sample Collection and Processing

Blood samples for PK analysis of seladelpar levels will be collected before dosing at all study visits as outlined in the Schedule of Study Procedures (Table 5-1).

CCI [redacted] Samples will be collected at pre-dose and 0.5, 1, 2, 4, 8, 12 and 24 hours after dosing. Additional blood and urine will be collected at specified time-points to assess additional PD and PK parameters. Participants will remain in clinic through the 8-hour timepoint and return to clinic for the 12- and 24-hour sample collection. The window for PK sample collection for the pre-dose is within 15 minutes of dosing, ± 5 minutes for the 0.5-hour through the 8-hour samples, and ± 30 minutes for the 12- and 24-hour samples.

Urine will also be collected over the 24-hour period to assess the renal clearance of seladelpar and the primary metabolites.

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

5.5.7. Colonoscopy

Current guidelines recommend that patients with PSC without IBD should undergo surveillance colonoscopy every 5 years. However, patients with PSC and IBD are recommended to undergo surveillance colonoscopy every 1–2 years from the time of diagnosis of PSC due to the high risk of colonic dysplasia in ulcerative colitis patients with PSC (Chapman 2010). Therefore, participants with concomitant IBD in this study should have a colonoscopy with no evidence of dysplasia within 12 to 18 months of consent (as defined by local guidelines). Participants who have had a colonoscopy within the 12 to 18 months of consent will not be required to have a new colonoscopy if the report is available for review. Participants without a colonoscopy report available will be required to have a colonoscopy performed during Screening. The colonoscopy results will be reviewed, interpreted and reported locally at the study site.

5.5.8. Magnetic Resonance Cholangiopancreatography (MRCP)

MRCP is a noninvasive technique for evaluating the intrahepatic and extrahepatic bile ducts and the pancreatic duct. The imaging protocol will vary depending on the specific magnetic resonance magnet being used, including its field strength (e.g., 1.5 versus 3T) and the manufacturer, as well as institutional experience and preferences. However, all acquisition protocols obtain heavily T2 weighted images as thick slabs and the images are reformatted in planes to optimize depiction of the extrahepatic ducts. Volume rendered images may be used to depict the intra- and extrahepatic bile ducts.

MRCP imaging will be performed with gadolinium contrast at Screening and Week 24 in all participants with fasting. The results will be read centrally for assessment of enrollment criteria and any clinically significant findings. Any clinical findings on any MRCP will be reported to the sites and the Sponsor's Medical Monitor by the central radiologist. Details of the MRCP procedures, data upload and report delivery will be summarized in a separate imaging manual.

5.5.9. Magnetic Resonance Imaging (MRI) with Contrast

Contrast-enhanced MRI is the most sensitive technique available for assessing cholangiocarcinoma. International guidelines recommend surveillance for cholangiocarcinoma in patients with PSC every 6-12 months, although practices vary from using serum measures and clinical assessments to imaging to a combination of the two. Since participants will undergo MRCP to assess their biliary systems in this study, contrast-enhanced MRI can be performed in the same session in the MRI scanner to assess for cholangiocarcinoma appearing as a liver mass rather than a biliary stricture. However, MRI with contrast must be performed sequentially after MRCP imaging. These MRIs will include a comprehensive dynamic MRI protocol. They will also include delayed phase imaging after administration of the gadoxetate disodium contrast agent, which maximizes detection of focal masses. Contrast-enhanced MRI will be performed in fasted participants at Screening and Week 24 (EOT)/Early Treatment Withdrawal (ET).

5.5.10. Liver Transient Elastography (TE) by FibroScan®

Liver TE exam will be used to evaluate liver fibrosis through a noninvasive imaging technique. FibroScan® is the most commonly used liver TE method which uses a modified ultrasound probe to measure the velocity of a shear wave. Cross-sectional elastogram images will be created

depicting the stiffness generated from the wave propagation information. FibroScan® is considered to be a reliable, highly accurate, and precise method for assessing liver stiffness as a marker of liver fibrosis. FibroScan® has demonstrated to independently assess liver stiffness and link fibrosis stage with high diagnostic accuracy for severe fibrosis and cirrhosis in patients with PSC (Corpechot 2014).

Participants will undergo liver TE exams by FibroScan® at Screening, Week 12 and Week 24 (EOT)/ET visits. Clinical sites will determine the logistics of scheduling the liver TE exam and complete within the study visit window. Participants will be instructed to fast for 4 or more hours (if possible) prior to the scheduled liver elastography examination but will be allowed to take necessary medications and small quantities of water. Details of the FibroScan® procedures, data upload and report delivery will be summarized in a separate imaging manual.

5.5.11. PSC PRO

The PSC PRO (Appendix C) is a 42-item instrument that contains two modules (Symptoms and Impact of Symptoms) which was recently developed and undergone external validation (Younossi 2018). PSC PRO is self-administered and developed according to FDA guidelines. Reliability and validity have been established using clinical data from patient cohorts and clinical trials as well as comparative evaluations to multiple other commonly used instruments. The PSC PRO has been evaluated in a broad range of PSC patients, including patients with and without IBD, as well as both cirrhotics and non-cirrhotics.

The PSC PRO is to be administered at all study visits as outlined in the Schedule of Study Procedures (Table 5-1).

5.5.12. 5-D Pruritus Scale

The 5-D Pruritus Scale (Appendix D) is a modified version of the Total Neuropathy Scale (Elman 2010). It is a brief multidimensional questionnaire used to measure the chronic itch. The instrument claims to serve as a monitoring instrument for the long-term course of pruritus. This instrument has been evaluated in numerous cohorts of participants with either primary or secondary pruritus, though none had PBC or PSC. The 5-D Pruritus Scale has five questions that assess degree, duration, direction, disability, and distribution of pruritic symptoms.

The 5-D Pruritus Scale is to be administered at all study visits as outlined in the Schedule of Study Procedures (Table 5-1).

5.5.13. Pruritus Numeric Rating Scale (NRS)

An 11-point NRS scale for pruritus will be completed by participants at the following timepoints:

- Dispense at Screening and instruct the participants to record daily for approximately 7 days prior to Day 1
- Dispense at Week 4 and instruct the participants to record daily for 7 days after the visit
- Dispense at Week 12 and instruct the participants to record daily for 7 days after the visit

- Dispense at Week 18 and instruct the participants to record daily for 7 days prior to the Week 24 visit

Participants will use the scale (Appendix E) to rate severity ranging from 0 "none" to 10 "worst possible." The participants will initiate collecting the daily diary at the beginning of the study week and complete the final assessment at the specified study visit in clinic.

5.5.14. Mayo Partial IBD Score

The Mayo Partial IBD Score (Appendix B) is a non-invasive 9-point partial Mayo score used as an outcome measure for clinical trials assessing therapy for ulcerative colitis (Lewis 2008). The partial score evaluates changes in stool frequency, rectal bleeding, and physician assessment of disease severity, with defined changes in the score correlating with clinical responses to treatment. The Mayo Partial IBD Score will be assessed by study site personnel as outlined in the Schedule of Study Procedures (Table 5-1).

5.5.15. Imaging Procedures and Laboratory Assessments Results Reporting

All results from imaging procedures will be unblinded and reported to sites throughout the duration of the study.

Screening AP and GGT values will be collected and reported to the sites in order to determine participant eligibility, as outlined in Section 4. Sites will be provided with absolute values from all Screening visits and the relative change of AP, ALT, AST and total bilirubin values between Screening Visit 1 and all other Screening visits. AP and GGT laboratory values will be blinded to the sites and participants from the Day 1 visit and all subsequent study visits.

If AP or GGT levels exceed the predefined safety thresholds, sites will be notified and provided with the values in order to manage participant safety. All other biochemical laboratory assessments will be collected and reported unblinded to sites for all study visits.

6. CLINICAL SUPPLIES

6.1. INVESTIGATIONAL PRODUCT

Seladelpar, as well as matched placebo, will be supplied in a blinded fashion as 5 mg, 10 mg, and 25 mg capsules. The study drug (seladelpar or placebo) will be administered orally, once daily for 24 weeks. The study drug should be taken in the fasted state, approximately 2 hours before or after a meal. The participant will take one capsule every day, approximately at the same time each day. Study drug will be dispensed at Day 1 and Week 4, 8 and 12 visits and will be reconciled at all visits.

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.

6.3. STUDY DRUG STORAGE

All supplies of study drug must be stored as defined in the Pharmacy Manual.

6.4. RANDOMIZATION AND STRATIFICATION

This will be a double blind, placebo-controlled study with participants stratified based on UDCA use and average total bilirubin values during Screening. Randomization will be managed through an IWRS. Once all laboratory and imaging are available and the participant has been confirmed to meet all the inclusion and none of the exclusion criteria, the participant will be invited to Day 1 visit. Randomization will occur at Day 1 visit via the IWRS system and dosing of placebo, 5 mg, 10 mg, or 25 mg seladelpar will be initiated.

6.5. DOSE REDUCTION AND TEMPORARY INTERRUPTION OF STUDY MEDICATION

Participants who meet specific safety monitoring criteria in Section 7.4 are eligible for the dose down-titration. Participants who are initially assigned to 25 mg will be down-titrated to 10 mg, participants initially assigned to 10 mg will be down-titrated to 5 mg, and participants initially assigned to 5 mg will be down-titrated to placebo. Participants initially assigned to placebo will remain on placebo. Participants who experience a significant AE that, in the investigator's judgement, warrants a dose reduction are also eligible for a similar dose titration. Dose down-titration must be approved by the Sponsor's Medical Monitor or their designee and will be performed in a blinded manner. Participants may only be down-titrated a single time during the study period. Participants who have a temporary interruption from study drug due to an AE may

resume their originally assigned dose if the AE of interest has resolved and was determined to be unrelated to study drug. Study drug may be held temporarily for appropriate medical procedures, illness, travel restrictions or other activities that may hinder the participant's ability to dose per protocol (PP). The temporary interruption should not exceed 7 days, and the Sponsor's Medical Monitor should be advised of any interruption as soon as possible.

6.6. REMOVAL OF STUDY BLIND

In the event of a medical emergency, where knowledge of the participant's treatment assignment is necessary per the medical judgment, the investigator or the Sponsor can break the blind. Randomization blind will be managed through an IWRS. The unblinding must be clearly justified and explained by a comment in the source documentation, along with the date on which the code was broken and the identity of the person authorizing the unblinding. The date and time when the PI removed the study blind for an individual participant will be documented by the IWRS, and an automated notification will be sent to the Sponsor. The contract research organization's pharmacovigilance team may also be required to break the blind for regulatory reporting purposes.

7. ADVERSE EVENTS

7.1. DEFINITION OF ADVERSE EVENTS

An AE is any medical occurrence in a participant 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 or reactions to concomitant medications.

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

7.2. 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 participant'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 participant 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.

7.3. ASSESSMENT OF ADVERS EVENTS

7.3.1. Severity

The severity of an AE will be graded from 1 to 5 according to NCI CTCAE criteria (version 5.0, 27 November 2017) (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

7.3.2. Outcome

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

One of the four outcomes listed below must be recorded:

- **Resolved** – The participant has fully recovered from the event with no residual effects observable or returned to baseline status.
- **Resolved with sequelae** – The participant has recovered from the event with some residual side effects observable.
- **Ongoing** – Effects of the event are still present, regardless of whether the effect is changing or stable and persistent.
- **Fatal outcome** (for serious adverse events only)

7.3.3. Relationship to Study Drug

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

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

7.3.4. Action Taken with Study Medication

The action taken with the study drug due to an AE can be categorized as one of the following:

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

7.3.5. Recording, Reporting, and Follow-Up of Adverse Events

7.3.5.1. Non-Serious Adverse Events

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

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

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

Abnormal laboratory findings will be determined by review of all laboratory data collected on the participants. At each visit, the Investigator is responsible for assuring that the participant 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.

7.3.5.2. Serious Adverse Events

The Sponsor or designee is responsible for regulatory submissions and reporting to the investigators of SAEs including suspected unexpected serious adverse reactions (SUSARs) per the International Council for Harmonisation (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 (safety vendor) using the SAE Report Form. Planned hospitalizations or procedures will not be considered as SAEs.

The criteria for seriousness will be indicated on the SAE Report Form as defined in Section 7.3.1.

The outcome for the event will be listed on the SAE Report Form as defined in Section 7.3.2.

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

SAEs must be collected and reported by the Investigator for the whole period from the signing of ICF until the last study visit. 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:

- Participant'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.

7.4. SAFETY MONITORING

Enrolled participants with the following lab abnormalities should be monitored closely and the dose may be decreased, or the study drug may be interrupted and/or discontinued if criteria are met. The Sponsor's Medical Monitor should be contacted as soon as possible if any of these events are observed.

Table 7.4.1-1: DILI Criteria for Participants with Normal Baseline ALT and AST

	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 < ULN	ALT or AST > 8 × ULN	--	**Stop study drug permanently**
	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*	

*** Clinical symptoms: appearance of fatigue, nausea, right upper quadrant pan or tenderness, fever, rash, jaundice and/or eosinophilia (> 5%).**

Table 7.4.1-2: DILI Criteria for Participants with Abnormal Baseline ALT and AST

	ALT or AST during Study Treatment Duration	Other Concurrent Parameters Required during Study Treatment Duration	Study Action
ABNORMAL BASELINE ALT and AST			
ALT and AST > ULN	ALT or AST > 2 × baseline measurement (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* **AND** concomitant total bilirubin (> 2 × BLM)	
ALT and AST < 2 × ULN	ALT or AST > 5 × BLM	--	**Interrupt study drug**
ALT and AST ≥ 2 × ULN but < 5 × ULN	ALT or AST > 3 × BLM		
ALT and AST ≥ 5 × ULN	ALT or AST > 2 × BLM		

*** Clinical symptoms: appearance of fatigue, nausea, right upper quadrant pan or tenderness, fever, rash, jaundice and/or eosinophilia (> 5%).**

- **Interrupt study drug:** Repeat AST, ALT, total bilirubin, and PT/INR within 3 days and closely observe the participant (see Appendix F). 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 participant (see Appendix F).
- If close observation of a participant is not possible, **stop study drug permanently.**

7.4.1. Muscle Injury Safety Monitoring

The following algorithm should be followed to assess potential drug-induced muscle injury.

Table 7.4.2-1: Muscle Injury Safety Criteria for Study Drug Interruption or Stopping Rules

Creatine Kinase (CK) during Study Treatment	Grade 3 CTCAE Myalgia or Myopathy	Repeat CK Test Results	Study Action
CK > 2.5 × ULN	Not observed	CK level is ≤ 2.5 × ULN	• **Study drug may be reinitiated** at this time at the current dose level.
CK > 2.5 × ULN	Not observed	CK level is > 2.5 × ULN	• Study drug should remain held and CK testing should be performed weekly until CK ≤ 2.5 × ULN. **Study drug may then be reinitiated** at this time at a decreased dose level as outlined in Section 6.5 of the study protocol.
CK > 2.5 × ULN	Observed	CK level is > 2.5 × ULN	• Study drug should remain held and CK testing should be performed weekly until CK ≤ 2.5 × ULN. **Study drug may then be reinitiated** at this time at a decreased dose level as outlined in Section 6.5 of the study protocol. • If symptoms reappear after re-challenge and there is no clinical explanation, then the **study drug should be permanently discontinued**. • The participant should continue to be routinely monitored until complete resolution of symptoms or study completion, whichever comes first.

7.4.2. Renal Safety Monitoring

The following algorithm should be followed to assess potential drug-induced renal injury.

Table 7.4.3-1: Renal Safety Criteria for Study Drug Interruption or Stopping Rules

Serum Creatinine (sCr) during Study Treatment	Repeat sCr Test Results	Alternative Etiology Identified?	Study Action
sCr > 1.5 × ULN but ≤ 2.0 × ULN	sCr < 1.5 × ULN	N/A	• **Continue study drug.**
	sCr > 1.5 × ULN	Yes	• **Interrupt study drug.** • Participant should be monitored weekly until event resolution. • **Study drug may be reinitiated** after sCr returns to baseline levels at the current dose level.
	sCr > 1.5 × ULN	No	• **Stop study drug permanently.** • Participant should be monitored weekly until event stabilization or resolution.
sCr > 2.0 × ULN	sCr > 2.0 × ULN	N/A	• **Stop study drug permanently.** • Participant should be monitored weekly until event stabilization or resolution.

7.4.3. Pancreatic Safety Monitoring

- If serum lipase > 3 × ULN with clinical symptoms of acute pancreatitis, interrupt study drug and repeat the test within 3 days.
- If test is confirmed, perform abdominal imaging to exclude an alternative cause for the event.
- Study drug may be reinitiated at the same or lower dose if there is no evidence of acute pancreatitis or an alternative etiology for the pancreatitis is identified.
- Study drug permanently discontinued if related to study drug and participant closely monitored the participant until the event resolves.

7.5. PRECAUTIONS

7.5.1. Pregnancy

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

As a precaution, female participants 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 dose. A female participant is considered to be of childbearing potential unless she is post-hysterectomy or post-menopausal (defined as 2 years since their last menstrual period for women ≥ 55 years of age). Male participants who are sexually active with female partners of reproductive potential must use barrier contraception and their female partners must use a second effective birth control method during the study and for at least 90 days after the last dose. Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

A second effective birth control method may include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomized partner

Pregnancy 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.

8. STUDY WITHDRAWAL OF INDIVIDUAL PARTICIPANTS

Participants will be informed that they are free to withdraw from the study at any time and for any reason. The PI may remove a participant from the study if it is not in the best interest of the participant to continue the study. The participant should be informed of new approved and available treatment to make an informed decision regarding continuation in the study. The availability of a new standard of care does not automatically terminate a participant from study participation.

Participants may be also be discontinued for the following reasons:

- Enrolled into the study in violation of this protocol
- Required the use of a prohibited concomitant medication. Participant may continue in the study if an acceptable alternative acceptable medication can be prescribed
- Withdrawal of informed consent
- At the discretion of the investigator for medical reasons
- Female participants who become pregnant
- At the discretion of the investigator or Sponsor for noncompliance
- Significant protocol deviation
- Administrative decision by the investigator or Sponsor or designee
- Lost to follow-up
- The following CTCAE stopping criteria are achieved:
    - Evidence of hepatic decompensation, including variceal bleeding, hepatic encephalopathy and ascites,
    - CTCAE Grade 3 or higher, possible or probably related to study drug, or
    - CTCAE Grade 4 or higher, regardless of attribution to study drug

Notification of discontinuation will be made immediately to the Sponsor's Medical Monitor. In case of premature discontinuation of study participation, efforts will be made to perform all final Week 24 (EOT) and Week 28 (EOS) visits and required assessments. The date the participant is withdrawn from the study and the reason for discontinuation will be recorded on the participant's eCRF. All withdrawn participants will be followed until resolution of any AEs or until any unresolved AEs are judged by the PI to have stabilized.

9. STUDY STOPPING CRITERIA

The entire study may be paused, and clinical data may be reviewed by the DSMC for safety if:

- Three participants develop the same Grade 3 CTCAE related to study drug,
- Two participants develop any Grade 4 CTCAE related to study drug, or
- One participant develops a Grade 5 CTCAE

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
- Difficulties in the recruitment of patients
- Cancellation of seladelpar drug development

10. DATA MANAGEMENT AND STATISTICAL CONSIDERATIONS

10.1. DATA MANAGEMENT

A data validation manual (DVM) 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 DVM 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.

10.2. STATISTICAL ANALYSIS

10.2.1. Sample Size

A sample size of 25 participants randomized per treatment group was chosen in order to gather sufficient proof-of-concept treatment response and safety data on seladelpar in this population. The sample size yields 20 completing participants per treatment group, assuming 20% dropout rate, from randomization to Week 24. A sample size of 20 in each group will have at least 90% power to detect a difference in means of 25% in change of AP from baseline assuming that the common standard deviation is 20% using a two-sample t-test with a 0.0166 two-sided significance level, where the significance level of 0.0166 is the multiplicity-adjusted level using Bonferroni approach. Assumptions underlying the means are based on studies evaluating UDCA as a first line therapy and in studies where secondary or combination therapies with UDCA have been utilized.

10.2.2. Interim Analysis (IA)

An IA will be conducted when approximately 10 participants/cohort have completed the Week 12 visit. At the IA, the evidence regarding the safety and efficacy of seladelpar in the PSC indication will be assessed, in order to evaluate the appropriateness of continuing the study and dose selection for the OLE study.

A separate Statistical Analysis Plan (SAP) for the IA will be generated, describing the conduct of the IA in detail.

10.2.3. Analysis Sets

The analysis sets are detailed below. Details of any others will be described in the SAP.

10.2.3.1. Randomized Set

All randomized participants will be included in the Randomized Set. In analyses using this set, participants will be grouped according to randomized treatment.

10.2.3.2. Safety Set

All randomized participants who receive at least one dose of study drug will be included in the Safety Set. In analyses using this set, participants will be grouped according to actual treatment received.

All safety analyses will be performed using the Safety Set.

10.2.3.3. Full Analysis Set (FAS)

All randomized participants who receive at least one dose of study drug and have at least one valid, non-missing post dose AP assessment will be included in the FAS. This will be the set for the primary analyses of efficacy and PD endpoints. In FAS analyses, participants will be grouped according to randomized treatment, i.e. participants will be analyzed by the intention-to-treat approach.

10.2.3.4. Per Protocol (PP)

The PP Set will constitute a subset of the FAS. It will include participants who have at least one valid, non-missing post dose AP measurement. In addition, FAS participants who deviate from the conduct of the study or have an AE deemed by the Medical Monitor to be impactful on the primary endpoint will be excluded from the PP Set. In associated analyses, participants will be grouped according to actual treatment received, if it differs from the randomized treatment.

The PP Set may be used to perform sensitivity analysis on efficacy endpoints.

10.2.3.5. Pharmacokinetic Set

All randomized participants who receive at least one dose of study drug, had a pre-dose (Baseline) blood draw, and provided at least one qualified (above the limit of quantification) post-dose sample will be included in the PK Set. Participants with protocol violations will be assessed by the Medical Monitor for inclusion in this set. In associated analyses, participants will

be grouped according to the actual treatment received, if it differs from that to which the participant was randomized.

10.2.4. Efficacy and Pharmacodynamics Analysis

The primary efficacy endpoint, relative change in AP from Baseline to Week 24, will be analyzed using the ANCOVA model with treatment arm, UDCA stratification group (Yes/No) and total bilirubin stratification group (≤ ULN vs > ULN but ≤ 2 × ULN) as factors. Baseline AP, as a covariate, on the observed cases on the FAS population will also be included in the model. The statistical comparison of each seladelpar treatment arm against the placebo group on the primary endpoint will be made at a two-sided significance level of 0.0166, where the significance level of 0.0166 is the multiplicity-adjusted level using Bonferroni approach.

A sensitivity analysis for the primary efficacy endpoint will be performed using a mixed model for repeated measures (MMRM) approach assuming missing data is missing at random. The model will include treatment arm, study visit (Week 2, 4, 8, 12, 18, 24), UDCA stratification group (Yes/No) and total bilirubin stratification group (≤ULN vs > ULN but ≤ 2 × ULN) as factors. Baseline AP, as a covariate, and the interaction between treatment arms and study visits will also be included in the model. The model will assume an unstructured covariance matrix. The MMRM analysis will be conducted using the observed cases on the FAS population.

The secondary endpoints will be analyzed descriptively. The confidence intervals of differences between each seladelpar treatment arm and the placebo arm will be provided. The ANCOVA and MMRM approaches used for the primary endpoint may also be applied to the secondary endpoints when applicable.

Details of statistical parameters and methods to be applied will be provided in an SAP prior to database lock (unblinding).

10.2.5. Safety and Tolerability Analysis

Safety and tolerability analysis will be conducted on the Safety Set. AEs, including SAEs, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AE summaries will be restricted to TEAEs only, defined as AEs that commence after the time of start of first dose of study drug and up to 30 days after the last dose of study drug. The number and percentage of participants experiencing a TEAE will be summarized for each system organ class (SOC) and preferred term by treatment group. Separate summaries will be provided for TEAEs by severity, causality, and relationship to study drug. AEs will also be listed.

Observed values and changes from Baseline for select clinical laboratories will be summarized at each PP time point for each treatment group. Shift tables may also be presented for select chemistry and hematology parameters. Laboratory values will also be listed, with out of range and clinically significant laboratory values identified.

Descriptive statistics for physical examination results, vital signs and other safety endpoints will also be provided.

Detailed analysis methods for safety and tolerability will be provided in the SAP.

10.3. PHARMACOKINETIC ANALYSIS

The parameters describing the PK will be derived from plasma concentrations and actual sample draw times from the noncompartmental analysis with the software program Phoenix WinNonlin® (Version 6.4 or later).

Plasma concentration data for seladelpar and 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 participant plasma concentration profile versus time
- Mean concentration (± SD) versus time, designated by cohort

PK parameters for seladelpar, M1, M2, and M3 may 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 dose group. 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} and AUC_{last}.

Urine samples will also be collected over the 24-hour period and similar PK analyses will be performed.

All summaries will be prepared with the PK analysis set.

11. ADMINISTRATIVE ASPECTS

11.1. 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 participant safety will occur without the express written approvals of the Sponsor, PI, and EC.

11.2. 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 to initiate the study, prior to the first treatment of the first participant, and at agreed upon times throughout the study, including at the end of the study. Study drug dispensing and clinical drug supply records will be 100% verified at the study sites by the monitor. It is understood that all participant specific information is confidential and no documentation that can link study information to the specific participant 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 sites 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 participants) at any time these are requested by the sponsor or designee. In turn, the monitor will adhere to all requirements for participant 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.

11.2.1. 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 eCRFs against the source documentation.

11.2.2. Case Report Forms

Participants who have signed the ICF will be assigned a participant number and will have study data entered into an eCRF. eCRF completion is important to the medical monitoring of the trial and should be completed promptly after each participant visit.

11.2.3. Protocol Deviations

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

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

11.3. AUDITS AND INSPECTIONS

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

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

11.4. ETHICS

11.4.1. 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 Institutional Review Board (IRB)/Ethics Committee (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.

11.4.2. Ethical Conduct

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.

11.4.3. Informed Consent

This study will be conducted in compliance with 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 participant. Participation in this meeting should be documented in the participant's file. The participant 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 participants screened in the trial and before study related activities are performed on a participant. The process of obtaining written informed consent will be documented in the source documents of the participant. 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 participant. Signed consent forms must remain in the participant's study file and be available for verification by Sponsor or its representative at any time.

11.5. RECORDS

The results from Screening and data collected during the study will be recorded in the participant's eCRF. To maintain confidentiality, the participants will be identified only by numbers. 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.

The 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 the Sponsor's standards/procedures; otherwise, the retention period will default to the retention period of 15 years following completion of the clinical trial.

11.6. QUALITY ASSURANCE

Clinical data will be recorded in eCRF. Data will be verified and confirmed by the investigators. All data that will be used in the safety analyses and adverse events will be source documents verified by the monitors. Additionally, the Sponsor will conduct audit reviews of monitored eCRFs. A final audit of the electronic database against the final eCRF will be done.

11.7. 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.

11.8. DATA SAFETY MONITORING COMMITTEE (DSMC)

A DSMC will be established in order to protect participant welfare, preserve study integrity, and provide recommendations as needed regarding study conduct. The DSMC will be comprised of two external liver disease clinical experts as well as a statistician and a medical team member from the Sponsor. The DSMC will meet at predefined time points and on an as needed basis based on enrollment, treatment milestones, and safety. The DSMC will also review all SAEs, liver-related safety events, elevations in ALT/AST, sCr, CK and lipase that meet safety monitoring criteria. Formal minutes and recommendations will be provided by the DSMC to the Sponsor regarding additional data requests and the continuation of the conduct of the study as outlined in the current protocol. The DSMC will operate under the guidance of an agreed upon charter.

11.9. FINANCING INSURANCE

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

INVESTIGATOR PROTOCOL REVIEW AND SIGNATURE FORM

Protocol Number: CB8025-21845

Protocol Title: A Phase 2, Randomized, Double Blind, Placebo Controlled, Multiple Center Study to Evaluate the Safety, Tolerability, and Efficacy of Seladelpar Administered for 24 Weeks in Adult Patients with Primary Sclerosing Cholangitis (PSC)

I have read the above-mentioned Protocol dated 05 June 2019.

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)

SPONSOR PROTOCOL APPROVAL AND SIGNATURE PAGE

Protocol Number: CB8025-21845

Protocol Title: A Phase 2, Randomized, Double Blind, Placebo Controlled, Multiple Center Study to Evaluate the Safety, Tolerability, and Efficacy of Seladelpar Administered for 24 Weeks in Adult Patients with Primary Sclerosing Cholangitis (PSC)

I have read the above-mentioned Protocol dated 05 June 2019.

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

Date

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APPENDICES

APPENDIX A - NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE)

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

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

The NCI CTCAE may also be accessed here:

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

APPENDIX B - MAYO PARTIAL IBD SCORE

Components of the Partial Mayo Score

Stool Frequency
0 = Normal
1 = 1–2 stools/day more than normal
2 = 3–4 stools/day more than normal
3 = >4 stools/day more than normal
Rectal bleeding [a]
0 = None
1 = Visible blood with stool less than half the time
2 = Visible blood with stool half of the time or more
3 = Passing blood alone
Physician rating of disease activity
0 = Normal
1 = Mild
2 = Moderate
3 = Severe

[a] A score of 3 for bleeding required patients to have at least 50% of bowel motions accompanied by visible blood and at least one bowel motion with blood alone.

APPENDIX C – PATIENT REPORTED OUTCOMES (PRO)

Questions included in the final PSC PRO.

Module 1 – PSC Symptoms

Scores: 0 = "no symptoms" to 10 = "symptoms as bad as you could imagine"; recall period 24 hours.

1. Are you currently experiencing a flare-up of your PSC symptoms (also known as acute cholangitis or an infection in the bile ducts)? Y/N
2. Over the past 24 hours, how bad was the pain in your upper abdomen due to PSC at its worst?
3. Over the past 24 hours, how bad was the discomfort in your upper abdomen due to PSC at its worst?
4. Over the past 24 hours, how bad was your itching at its worst?
5. Over the past 24 hours, how bad was your physical tiredness at its worst?
6. Over the past 24 hours, how bad was the yellowing of your eyes or skin at its worst?
7. Over the past 24 hours, how bad was your difficulty concentrating at its worst?
8. Over the past 24 hours, how bad was your nausea at its worst?
9. Over the past 24 hours, how bad was your mental tiredness at its worst?
10. Over the past 24 hours, how bad was the darkening (brown or tea color) of your urine at its worst?
11. Over the past 24 hours, how bad were your fever (high temperature) symptoms?
12. Over the past 24 hours, how bad were your chills?
13. Over the past 24 hours, how bad were your sweats?

Module 2 - Impacts of Symptoms

Scores: 1 = "Never" to 5 = "Always"; recall period 7 days.

Physical Function

1. Over the past 7 days, how often was it difficult for you to go up or down stairs because of your PSC?
2. Over the past 7 days, how often did you have to rest or take breaks because of your PSC?
3. Over the past 7 days, how often were you limited in what you could do physically because of your PSC?
4. Over the past 7 days, how often was it difficult for you to lift or carry objects because of your PSC?

Activities of Daily Living

5. Over the past 7 days, how often was it difficult for you to complete household chores because of your PSC?
6. Over the past 7 days, how often did you have difficulty falling or staying asleep because of your PSC?
7. Over the past 7 days, how often was it difficult to run errands or get things done outside the home because of
your PSC?

8. Over the past 7 days, how often did you avoid certain foods because of your PSC?

Work Productivity
9. Are you currently employed or self-employed? Y/N (if N then skip the section)
10. Over the past 7 days, how often did PSC interfere with your productivity at work?
11. Over the past 7 days, how often did you limit your hours at work because of your PSC?
12. Over the past 7 days, how often was it an extra effort to do your work because of your PSC?
13. Over the past 7 days, how often was it difficult to concentrate on your work because of your PSC?

Role Function
14. Over the past 7 days, how often did you need to ask for help around your home because of your PSC?
15. Over the past 7 days, how often did you feel like a burden on your family because of your PSC?
16. Over the past 7 days, how often were you limited in the activities you could do with your family because of
your PSC?
17. Over the past 7 days, how often was it difficult to enjoy time with your family because of your PSC?

Emotional Impact
18. Over the past 7 days, how often were you worried about your health because of your PSC?
19. Over the past 7 days, how often were you depressed about your health because of your PSC?
20. Over the past 7 days, how often did you feel emotional stress because of your PSC?
21. Over the past 7 days, how often did you feel scared about the future because of your PSC?

Social/Leisure Impact
22. Over the past 7 days, how often did you limit your social activities because of your PSC?
23. Over the past 7 days, how often did you limit the things you did for enjoyment because of your PSC?
24. Over the past 7 days, how often did you isolate yourself from other people because of your PSC?
25. Over the past 7 days, how often did you have limited energy for sexual activity because of your PSC?
Quality of Life
26. Over the past 7 days, how often was it difficult to work towards your goals in life because of your PSC?
27. Over the past 7 days, how often were you unable to enjoy life because of your PSC?
28. Over the past 7 days, how often did you feel like you missed out on meaningful activities because of your
PSC?
29. Over the past 7 days, how often did you feel discouraged about your quality of life because of your PSC?

APPENDIX D - 5-D PRURITUS SCALE

5-D Pruritus Scale

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

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

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

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

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

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

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

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

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

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

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

APPENDIX E - NUMERIC RATING SCALE FOR ITCH

Itch Scale

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

APPENDIX F - CLOSE OBSERVATION CRITERIA*

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 5-Days
    b. Monitor the participant every 2 to 3 days until the lab abnormality stabilization
    c. After lab abnormality is stabilized, monitor the participant 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

*As recommended by the FDA's Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009