CLINICAL STUDY PROTOCOL

Study Title:	A Proof-of-Concept, Open-Label Study Evaluating the Safety and Tolerability of Cilofexor in Subjects with Primary Sclerosing Cholangitis (PSC) and Compensated Cirrhosis
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	131031
Clinical Trials.gov Identifier:	NCT04060147
Indication:	Primary Sclerosing Cholangitis (PSC) and Compensated Cirrhosis
Protocol ID:	GS-US-428-5443
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List
Protocol Version/Date:	Original: 06 May 2019 Amendment 1: 17 July 2019 Amendment 2: 22 November 2019 Amendment 3: 15 January 2021

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
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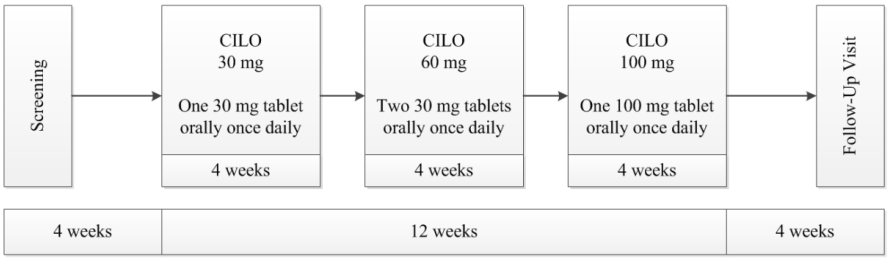
Study Title:	A Proof-of-Concept Open-Label Study Evaluating the Safety and Tolerability of Cilofexor in Subjects with Primary Sclerosing Cholangitis (PSC) and Compensated Cirrhosis
IND Number:	131031
Clinical Trials.gov Identifier:	NCT04060147
Study Centers Planned:	Approximately 10 centers in the United States
Objectives:	The primary objective of this study is as follows: • To assess the safety and tolerability of escalating doses of cilofexor (CILO, previously known as GS-9674) in subjects with primary sclerosing cholangitis (PSC) and compensated cirrhosis CCI [redacted]

Study Design:

This is a proof-of-concept, open-label study evaluating the safety and tolerability of CILO in subjects with PSC and compensated cirrhosis.

Eligible subjects will be enrolled to receive treatment with escalating doses of CILO over a 12-week period. The study will consist of a 4-week Screening period, 12 weeks of treatment (divided into three 4-week dosing stages at 30 mg, 60 mg, and 100 mg orally once daily [QD]), and a follow-up visit 4 weeks after the Week 12 visit.

The overall study design is shown in the figure below:



Number of Subjects Planned: Approximately 20 subjects

Target Population: Males and nonpregnant, nonlactating females equal to or greater than 18 years of age with PSC and compensated cirrhosis

Duration of Treatment: 12 weeks scheduled treatment; up to 16 weeks if subject requires dose re-challenge after study drug dose interruption

Diagnosis and Main Eligibility Criteria:

Key Inclusion Criteria

1) Diagnosis of PSC based on cholangiogram (magnetic resonance cholangiopancreatography [MRCP], endoscopic retrograde cholangiopancreatography [ERCP], or percutaneous transhepatic cholangiogram [PTC]) or liver biopsy
2) Subjects have evidence of cirrhosis based on at least one of the three following criteria
    a) Historical liver biopsy that reveals Ludwig stage F4 fibrosis (or equivalent)

b) Abdominal imaging with features consistent with cirrhosis in the opinion of the investigator (eg, small nodular liver, splenomegaly, evidence of portosystemic collaterals, diffuse surface irregularity). Magnetic resonance imaging (MRI), computed tomography (CT), and/or ultrasound are acceptable modalities to make this determination.

c) Any one of the following completed at the Screening visit:

i) FibroScan ≥ 14.4 kPA

ii) ELF ≥ 11.3

iii) FibroTest ≥ 0.75

3) Subject has the following laboratory parameters at the Screening visit, as determined by the central laboratory:

a) Estimated glomerular filtration rate (eGFR) > 60 mL/min, as calculated by the Cockcroft-Gault equation

b) ALT ≤ 5 × upper limit of the normal (ULN)

c) Total bilirubin ≤ 2 mg/dL, unless the subject is known to have Gilbert's syndrome or hemolytic anemia

d) INR ≤ 1.4, unless due to therapeutic anticoagulation

e) Platelet count ≥ 75,000/μL. Patients with evidence of high-risk esophageal or gastric varices in the opinion of the investigator are excluded

f) Negative anti-mitochondrial antibody

4) For subjects on ursodeoxycholic acid (UDCA), the dose of UDCA must have been stable in the opinion of the investigator for at least 6 months before screening. For subjects not on UDCA, no UDCA use for at least 6 months prior to screening.

Key Exclusion Criteria

1) Current or prior history of any of the following

a) Decompensated liver disease, including ascites, hepatic encephalopathy (HE), or variceal hemorrhage

b) Liver transplantation

c) Cholangiocarcinoma or hepatocellular carcinoma (HCC). If a dominant structure has been identified, cholangiocarcinoma must be adequately excluded in the opinion of the investigator prior to Day 1

2) Model for end-stage liver disease (MELD) score > 12 at screening, unless due to an alternate etiology such as therapeutic anticoagulation
3) Child-Pugh (CP) score > 6 at screening, unless due to an alternative etiology such as Gilbert's syndrome or therapeutic anticoagulation
4) Presence of moderate to severe itch in the opinion of the investigator at screening and baseline/Day 1
5) Ascending cholangitis within 30 days of screening
6) Presence of a percutaneous drain or biliary stent
7) Other causes of liver disease including IgG4-related sclerosing cholangitis, PSC-autoimmune hepatitis overlap syndrome, secondary sclerosing cholangitis, and viral, metabolic, alcoholic, and other autoimmune conditions. Subjects with hepatic steatosis may be included if there is no evidence of nonalcoholic steatohepatitis (NASH) in the opinion of the investigator.
8) Current moderate to severely active inflammatory bowel disease (IBD) (including ulcerative colitis, Crohn's disease, and indeterminate colitis). See Section 6.8.6.

   Note: Subjects with IBD who currently have an external ostomy bag and/or proctocolectomy are not subject to this exclusion criterion and need not undergo IBD Symptom Severity Assessment.
9) Current or prior history of any of the following:
   a) Malignancy within 5 years of screening with the following exceptions:
      i) Adequately treated carcinoma in situ of the cervix
      ii) Adequately treated basal or squamous cell cancer or other localized nonmelanoma skin cancer.

      Subjects under evaluation for possible malignancy are not eligible.
   b) Unstable cardiovascular disease as defined by any of the following:
      i) Unstable angina, myocardial infarction, coronary artery bypass graft surgery or coronary angioplasty within 6 months prior to screening
      ii) Transient ischemic attack or cerebrovascular accident within 6 months prior to screening

iii) Symptomatic obstructive valvular heart disease or hypertrophic cardiomyopathy

iv) Symptomatic congestive heart failure

v) Uncontrolled or recurrent ventricular tachycardia or other arrhythmia requiring an automatic implantable cardioverter defibrillator (AICD). Stable, controlled atrial fibrillation is allowed.

vi) Hypercoagulable condition or venous or arterial thromboembolic disease

vii) Intestinal resection or malabsorptive condition that may limit the absorption of CILO. Prior cholecystectomy and appendectomy are permitted.

10) HIV infection (HIV antibody [Ab] and HIV ribonucleic acid [HIV RNA] positive)

11) Hepatitis B virus (HBV) infection (hepatitis B surface antigen [HBsAg] positive)

12) Hepatitis C virus (HCV) infection (HCV Ab and HCV RNA positive). Subjects cured of HCV infection ≥ 2 years prior to screening are eligible.

13) Habitual alcohol consumption greater than 21 oz/week for males or 14 oz/week for females (1 oz/30 mL of alcohol is present in one 12 oz/360 mL beer, one 4 oz/120 mL glass of wine, and a 1 oz/30 mL measure of 40% proof alcohol)

14) Use of antibiotics (eg, vancomycin, metronidazole, minocycline, etc.) for the treatment of PSC within 60 days of screening. Antibiotic prophylaxis for ascending cholangitis is permitted if stable in the opinion of the investigator for at least 6 months prior to screening

15) Use of any prohibited concomitant medications (CMs) as described in the protocol (refer to Section 5.5)

16) Positive urine screen for amphetamines, cocaine or opiates (ie, heroin, morphine) at screening. Subjects on stable methadone or buprenorphine maintenance treatment for at least 6 months prior to screening may be included. Subjects with a positive urine drug screen due to prescription opioid-based mediation are eligible if the prescription and diagnosis are reviewed and approved by the investigator

Study Procedures/ Frequency:

- After signing the informed consent form, subjects will complete a Screening visit which will include the following assessments: complete medical history, review of inclusion and exclusion criteria, IBD symptom severity assessment (as appropriate, see Section 6.8.6), complete physical examination (PE) including assessment for ascites and HE, vital signs, height, weight, standard 12-lead ECG, laboratory assessments (including blood for biomarkers); serum pregnancy test (for females of childbearing potential), urine drug screen, liver stiffness measurement by FibroScan, calculation of CP and MELD scores, and review of adverse events (AE) related to Screening procedures and CMs.
- After the Screening period, in-clinic study visits will occur at Baseline/Day 1 and at Weeks 1, 4, 8, and 12. At minimum, vital signs, symptom-driven physical examination (PE) including assessment for ascites and HE, safety laboratory tests, calculation of CP and MELD scores, pruritus assessment (VAS and 5D-Itch), review for active IBD, for subjects with history of IBD (as appropriate, see Section 6.8.6), and review of AEs and CMs will be performed at every in-clinic visit.
- Eligible subjects will be enrolled in the study with initial starting dose of CILO of 30 mg daily. Prior to initial dosing, required Baseline/Day 1 assessments will be performed and will include symptom-driven PE, vital signs, laboratory assessments including biomarker assessments (eg, ELF, FibroTest), pregnancy tests (for females of child-bearing potential), blood collection and stool collection (if available), calculation of CP and MELD scores, IBD symptom severity assessment and review for active IBD, for subjects with history of IBD (as appropriate, see Section 6.8.6), pruritus assessment (5D-Itch score and VAS), standard 12 lead ECG, and review of AEs and CMs.

CCI [redacted]

During the treatment phase of the study, subjects will undergo the following procedures and laboratory assessments:

- Pruritus assessments: Pruritus VAS and 5D-Itch at Baseline/Day 1 and at all subsequent in-clinic study visits

- For subjects with history of IBD (as appropriate, see Section 6.8.6):

  IBD symptom severity assessment at Weeks 4, 8, and 12

  Any evidence of active IBD seen on routinely performed colonoscopy will be captured at all in-clinic visits

- [redacted]

- Symptom-directed PE, assessments for ascites and HE, vital signs, and body weight at Baseline/Day 1 and at all subsequent in-clinic study visits
- CP and MELD score calculations at Baseline/Day 1 and at all subsequent in-clinic study visits
- Blood chemistry, eGFR, hematology, and coagulation panel at Baseline/Day 1 and at all subsequent in-clinic study visits
- Lipid profile at Baseline/Day 1 and Weeks 4, 8, and 12
- C-Peptide, Insulin, and hemoglobin A_{1c} (HbA_{1c}) at Baseline/Day 1 and Week 12
- Urine pregnancy testing (females of childbearing potential only) at Baseline/Day 1 and Weeks 4, 8, 12
- Biomarker Testing at Baseline/Day 1 and Weeks 1, 4, 8, and 12 including but not limited to the following biomarkers:

  [redacted]

	• Stool collection (biomarker) at Baseline/Day 1 and Week 12 (if available) • Standard 12-lead ECG at Baseline/Day 1 • Liver stiffness measurement by FibroScan at Week 12 • At the posttreatment follow-up visit, subjects will have a symptom-driven PE including assessments for ascites, HE, calculation of CP and MELD score, IBD symptom severity assessment and review for active IBD, for subjects with history of IBD (as appropriate, see Section 6.8.6), vital signs, weight, laboratory assessments including blood collection for biomarker assessments, urine pregnancy tests (for females of childbearing potential), CCI [redacted] and review of AEs and CMs.
Test Product, Dose, and Mode of Administration:	CILO 30 mg (1 × 30 mg tablet), CILO 60 mg (2 ×30 mg tablets), or CILO 100 mg (1 ×100 mg tablet) administered orally once daily.
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	Safety will be assessed during the study through the reporting of AEs, and by clinical laboratory tests and vital sign assessments at various time points during the study. Concomitant medication usage will also be assessed throughout the study.
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]

Statistical Methods:

Efficacy Analysis:

The biological activity of the study drug will be evaluated using biochemistry endpoints and biomarker variables. CCI [redacted]

Safety Analysis:

All safety data collected will be listed and summarized, as appropriate, by overall.

Sample Size:

Due to the exploratory nature of this study, no formal power calculations were used to determine sample size.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
β-hCG	beta human chorionic gonadotropin
Ab	antibody
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AhR	aryl hydrocarbon receptor
AICD	automatic implantable cardioverter defibrillator
ALDH	aldehyde dehydrogenase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
BAP	biomarker analysis plan
BCRP	breast cancer resistance protein
BMI	body mass index
BUN	blood urea nitrogen
BW	body weight
C4	7-alpha-hydroxy-4-cholesten-3-one
CAR	constitutive androstane receptor
CFR	code of federal regulations
CILO	cilofexor
C_{last}	last observed quantifiable plasma/serum concentration of the drug
CLDQ	Chronic Liver Disease Questionnaire
CM	concomitant medication
C_{max}	maximum observed plasma/serum concentration of drug
CP	Child-Pugh
CPK	creatine phosphokinase
CRF	case report form
CRO	contract (or clinical) research organization
CRP	C-reactive protein
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP2C8	cytochrome P4502C8
CYP2C9	cytochrome P4502C9

CYP3A	cytochrome P4503A
DDI	drug-drug interaction
DILI	drug induced liver injury
DMC	data monitoring committee
EC	ethics committee
EC_{50}	concentration of drug that gives half-maximum response
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis
EQ-5D	EuroQol five dimensions
ERCP	endoscopic retrograde cholangiopancreatography
ESA	erythropoiesis-stimulating agent
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FGF19	fibroblast growth factor 19
FSH	follicle-stimulating hormone
FXR	Farnesoid X Receptor
GCP	Good Clinical Practice
GCSF	granulocyte colony stimulating factor
GGT	gamma glutamyltransferase
GLPS	Global Patient Safety
GSI	Gilead Sciences, Inc.
GWAS	genome-wide association studies
Hb	hemoglobin
HbA_{1c}	hemoglobin A_{1c}
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDPE	high-density polyethylene
HDL-C	high-density lipoprotein cholesterol
HE	hepatic encephalopathy
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLGT	high-level group term
HLT	high-level term

hsCRP	high sensitivity C-reactive protein
IB	investigator's brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IND	Investigational New Drug (Application)
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LLT	lower-level term
LPLV	last patient last visit
MATE	multidrug and toxin extruder
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NASH	nonalcoholic steatohepatitis
NOAEL	no observed adverse event level
NOEL	no observed effect level
NTCP	sodium-taurocholate cotransporter protein
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
OLE	open-label extension
OST	organic solute transporter
PIII-NP	procollagen type III N-terminal propeptide
PBC	primary biliary cholangitis
PD	pharmacodynamic(s)
PE	physical examination
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PRO	patient–reported outcome
PSC	primary sclerosing cholangitis
PSC-PRO	primary sclerosing cholangitis patient-reported outcome

PT	preferred term
PTC	percutaneous transhepatic cholangiogram
PTT	partial prothrombin time
PXR	pregnane X receptor
Q1	first quartile
Q3	third quartile
QD	once daily
QoL	quality of life
RBC	red blood cell count
RNA	ribonucleic acid
RXR	Retinoid X Receptor
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
TEAEs	treatment emergent adverse events
TGR5	bile acid receptor
TIMP	tissue inhibitors of metalloproteinases
TPO	thrombopoietin
UDCA	ursodeoxycholic acid
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of the normal
US	United States
USPI	United States prescribing information
VAS	visual analog scale
VLDL-C	very low-density lipoprotein cholesterol
WBC	white blood cell count

1. INTRODUCTION

1.1. Background

Primary sclerosing cholangitis (PSC) is a chronic progressive liver disease of unknown etiology characterized by persistent inflammation of the bile ducts leading to fibrosis, cholestasis, and biliary cirrhosis {Chapman 2010, Hirschfield 2013}. The overall incidence of PSC is 0.77 per 100,000 person-years, with a median age at diagnosis of 41 years and 2-to-1 male to female predominance {Molodecky 2011}. PSC is associated with inflammatory bowel disease (IBD), typically ulcerative colitis, in up to 90% of patients. Conversely, PSC develops in approximately 8% of all patients with IBD {Saich 2008}. There are likely fewer than 50,000 persons with PSC in the United States (US), making it a rare disease. In Japan there are an estimated 1,211 patients with PSC. PSC affects less than 1.6 in 10,000 people in the European Union (EU), equivalent to a total of fewer than 82,000 people {Boonstra 2012, Isayama 2018}.

The clinical presentation of PSC is variable, and ranges from asymptomatic disease with mild elevations in serum alkaline phosphatase (ALP) and transaminases to more rapidly progressive, symptomatic disease in 15-30% of all patients. In addition to complications related to cirrhosis and portal hypertension, patients with PSC are prone to repeated episodes of bacterial cholangitis, pruritus, and are at high risk for cholangiocarcinoma. Specifically, the lifetime risk of cholangiocarcinoma in patients with PSC is 10-15%, a rate 160-fold that of the general population {Saich 2008}.

There are no approved therapies for PSC. Medical therapy with ursodeoxycholic acid (UDCA) may improve liver biochemistry, but does not have a beneficial impact on clinical outcomes {Triantos 2011}. Immunosuppressive therapy has also been ineffective {Lindor 2015}. Episodes of ascending cholangitis are managed supportively with antibiotics in conjunction with therapeutic drainage if necessary. Liver transplantation is the only therapeutic option currently available to patients with PSC. Outcomes of transplantation are generally favorable (five-year survival ~85%), but the disease recurs posttransplant in up to 25% of patients {Graziadei 1999}.

The etiology of PSC is unknown. As noted above, there is a strong association with IBD and genome-wide association studies (GWAS) indicate moderate genetic associations with PSC. The strongest associations are in the human leukocyte antigen (HLA) complex on chromosome 6p21 with weaker associations at loci known to be associated with IBD, chromosome 3p21, 2q35 and the GPC5/GPC6 region on chromosome 13q31 {Karlsen 2010}. Several hypotheses as to the underlying cause of the disease have been proposed including aberrant homing of T cells to the bile ducts, autoimmunity, bile acid toxicity, and gut bacterial translocation leading to fibrosing cholangitis, and subsequent cholestasis and hepatotoxicity.

1.2. Investigational Medicinal Product Name

1.2.1. General Information

Cilofexor (CILO, previously known as GS-9674) is a potent and selective small molecule agonist of the farnesoid X receptor (FXR) whose activity in intestinal epithelial cells results in the release of fibroblast growth factor 19 (FGF19). FGF19 is an endocrine peptide which drives a signaling cascade to decrease hepatic lipogenesis, gluconeogenesis, triglyceride accumulation, and bile acid synthesis. Please refer to the Investigator's Brochure (IB) for additional information on CILO including:

- In vitro FXR agonism
- Nonclinical pharmacology and toxicology
- Nonclinical pharmacokinetics (PK) and In vitro metabolism

1.2.2. Nonclinical Pharmacology

CILO interacts with the binding domain of FXR/retinoid X receptor (RXR) consistent with agonist activity and induces an agonist response in biochemical and cell-based assays with half-maximal effective concentration (EC_{50}) of 16 and 43 nM, respectively. The biochemical assay value for CILO was comparable to that of other known FXR agonists and the cell-based assay value was more potent than chenodeoxycholic acid (EC_{50} of 1770 nM), an endogenous agonist of FXR. CILO did not activate the structurally similar bile acid receptor (TGR5), did not activate other nuclear hormone receptors, and did not bind to a panel of other off-target receptors and enzymes.

Oral dose-ranging experiments in male cynomolgus monkeys demonstrated maximal increases in plasma FGF19 at a dose of 5 mg/kg. In addition, the oral administration of CILO (30 mg/kg) to monkeys directly activated intestinal FXR, as measured by the expression of FXR-target genes in the ileum (15-fold increase in FGF19 mRNA, and a 2-fold increase in organic solute transporter [OSTα and OSTβ] mRNA). In monkeys, there were no effects on circulating FGF19 levels after IV dosing of CILO (resulting in systemic exposures higher than those observed after oral dosing) suggesting that FGF19 production is a result of intestinal FXR agonism in response to local enteric concentrations of CILO. The low systemic free drug concentrations contributed to the lack of effects following IV administration of CILO. CILO reduced liver fibrosis in a choline-deficient high fat diet/$NaNO_2$ rat model of liver fibrosis.

There were no CILO-related effects on the central nervous or respiratory systems in mice or the cardiovascular system in cynomolgus monkeys administered up to 600 mg/kg (mice) or 300 mg/kg (monkey) CILO.

Overall, the results from these pharmacology studies demonstrate that CILO is a potent and selective agonist of intestinal FXR with the potential to benefit patients with PSC by inducing FGF19 production and reducing bile acid levels.

1.2.3. Nonclinical Toxicology

The nonclinical toxicity profile of CILO has been assessed in mice, rats, and cynomolgus monkeys administered CILO orally for up to 26, 13, and 39 weeks, respectively. CILO-related effects were primarily limited to nonadverse findings in the liver for all species that are likely related to the pharmacology of the compound. These findings included mild increases in ALP and/or increased liver weight with or without minimal to slight hepatocellular hypertrophy. Minor, nonadverse clinical pathology findings included decreased red blood cell parameters, increased platelets, shortened activated partial thromboplastin time (APTT), decreased serum bile acids, decreased cholesterol and triglycerides, increased albumin, globulin, and total protein, increased phosphorus and/or increased urea nitrogen. All findings are expected to reverse with cessation of dosing based on the transient nature of the finding, type of finding observed and/or evidence of recovery after a 4-week nondosing period in the 26-week mouse and 39-week monkey studies. The no observed adverse event levels (NOAELs) from the 26- (mice), 13- (rats) and 39-week (monkeys) repeat dose toxicity studies were 60 mg/kg/day in mice, 1500 mg/kg/day in rats, and 300 mg/kg/day in monkeys. These doses were associated with exposure margins 8× (male mice), 14× (female mice), 27× (male rats), 18× (female rats), and 20× (male and female monkeys) higher than the human exposure at the 100 mg once daily (QD) dose.

There were no effects of CILO on fetal development at doses of up to 300 mg/kg/day in mice and 200 mg/kg/day in rabbits. There were effects on male and female fertility (reduced conception/copulation rates and longer precoital intervals) at a dose of 300 mg/kg/day, which was associated with exposure margins 24× (male) and 63× (female) higher than the human exposure at the 100 mg QD dose.

1.2.4. Nonclinical Pharmacokinetics

The oral bioavailability of CILO was low in the nonclinical species. Low pH-dependent solubility and high hepatic extraction have been identified as factors likely contributing to the low bioavailability of CILO. In plasma from humans and nonclinical species, CILO was highly protein bound (≥ 99.64%), consistent with the low volumes of distribution (approximately equal to extracellular water, 0.2 L/kg) observed in nonclinical species. In mice, [^{14}C] CILO-derived radioactivity was distributed to most of the tissues, with the highest maximum concentrations of radioactivity determined in organs of absorption and excretion. No quantifiable radioactivity was detected in brain, suggesting [^{14}C] CILO-derived radioactivity did not cross the blood:brain barrier. The primary metabolic pathways for CILO in pooled cryopreserved human hepatocytes were observed to be oxidative. Cytochrome P450 enzymes (CYP)2C8, CYP3A4, and CYP2C19 were shown to metabolize CILO in vitro; in a clinical drug-drug interaction (DDI) study, CYP2C8 was shown to be the primary enzyme responsible for CILO metabolism. The primary metabolic pathways of CILO in vivo were oxidation and O-dealkylation as observed in mice, rats, and monkeys; glutathione conjugation as observed in mice and rats; and dechlorination as observed in mice. Two prominent, inactive, circulating metabolites of CILO have been identified in humans and nonhuman primates: GS-716070 (dihydrodiol metabolite) and GS-1056756 (azetidine-ring-opened-CILO-carboxylic acid metabolite). Fecal elimination was the predominant route of elimination of [^{14}C] CILO-derived radioactivity in both mice and monkeys.

CILO has the potential to affect hepatic uptake of organic anion transporter protein (OATP) substrates or metabolism of CYP3A4 substrates and to a lesser extent CYP2C8 or CYP2C9 substrates in vitro, however, in a clinical DDI study it was not a clinically relevant inhibitor of CYP3A4 and/or OATP substrates. In vitro, CILO was a substrate for efflux transporters P-glycoprotein and breast cancer resistance protein (BCRP), as well as the uptake transporters OATP1B1, OATP1B3, OATP2B1, and sodium-taurocholate cotransporter protein (NTCP); however, in a clinical DDI study, only OATP1B1 and OATP1B3 played a major role in the disposition of CILO. CILO and GS-716070 did not activate nuclear hormone receptors associated with the potential for induction of human drug-metabolizing enzymes and transporters (eg, PXR, CAR, AhR) in cell-based reporter assays. Thus, the liability of CILO and GS-716070 to cause DDIs through proteins regulated by these nuclear receptors is low.

GS-1056756 has shown low potential to inhibit CYP enzymes and uridine diphosphate glucuronosyltransferase (UGT) in vitro. GS-1056756 did not inhibit P-glycoprotein (P-gp), BCRP, OCT2, MATE1, MATE2K, and showed low probability to be clinically relevant inhibitor of OAT1, OAT3, OCT1, OATP1B1, OATP1B3 or OATP2B1. No clinical DDI liability of GS-1056756 on enzymes and transporters was predicted from in vitro characterizations.

GS-1056756 has been identified in nonclinical assays as a substrate of OATP1B1/1B3/2B1. In vitro, GS-1056756 is formed by oxidative metabolism by CYP3A4 and CYP2C8 with additional conversion to enantiomers by dehydrogenases (eg, ALDH), and is subsequently metabolized by CYP3A and CYP2C8 and UGTs. Together with available clinical data described in Section 1.2.5, the potential clinical DDI liability of GS-1056756 is low.

1.2.5. Clinical Trials of CILO

As of 17 October 2019, 6 Phase 1 clinical studies are complete, 2 Phase 1 studies are ongoing (GS-US-454-5280 and GS-US-402-374), 1 Phase 2 study in subjects with nonalcoholic steatohepatitis (NASH) is complete (GS-US-402-1852) 1 Phase 2 study in subjects with Primary Biliary Cholangitis (PBC) (GS-US-427-4024) is complete, and 3 Phase 2 studies in subjects with NASH (GS-US-384-3914, GS-US-454-4378), and PSC (GS-US-428-4025) are ongoing. These Phase 1 and 2 studies are described in the IB. A brief summary of relevant results that are not included in the IB from study GS-US-402-3885 and preliminary results from ongoing study GS-US-428-4025 are presented below. Clinical PK data for the newly identified major circulating CILO metabolite GS-1056756 (the R-enantiomer of M13) is described in Sections 3 and 1.2.8.7. Briefly, GS-1056756 exhibits a plasma half-life of approximately 175 h. Preliminary steady-state plasma concentrations of GS-1056756 in PSC patients administered 100 mg CILO are as expected based on the single dose PK data for GS-1056756 from the ADME study (GS-US-402-4287). Additionally, plasma exposures of GS-1056756 are minimally altered in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function (see Section 1.2.6). These data, taken together with the adequate safety margins from nonclinical safety studies and the nonclinical understanding of the metabolic formation (CYP3A and CYP2C8) and clearance (CYP3A, CYP2C8, and UGTs) mechanisms of GS-1056756 support the concomitant medication (CM) restrictions in Section 5.5.

1.2.6. A Phase 1, Open-Label, Parallel-Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics and Pharmacodynamics of Cilofexor in Subjects with Normal and Impaired Hepatic Function (Study GS-US-402-3885)

Study GS-US-402-3885 is a Phase 1, open-label, parallel-group, single dose study evaluating the safety, tolerability, PK, and pharmacodynamics (PD) of CILO in subjects with normal hepatic function and mild, moderate, or severe hepatic impairment. Up to 60 subjects were planned for enrollment in 1 of 3 hepatic impairment cohorts: Cohort 1 (mild hepatic impairment, Child-Pugh [CP] A), Cohort 2 (moderate hepatic impairment, CP B), and Cohort 3 (severe hepatic impairment, CP C). Within each cohort, each subject with impaired hepatic function (N 10 per cohort) was matched for age (± 10 years), sex, race, and body mass index (BMI: ± 15%) with a control subject with normal hepatic function (N 10 per cohort). Data from healthy subjects were used in >1 cohort if a subject was an appropriate match for a subject with hepatic function in >1 cohort. All subjects in Cohorts 1 and 2 received a single oral dose of CILO 30 mg in the fed state on Day 1 with PD collected on Day -1 and Day 1. All subjects in Cohort 3 received a single oral dose of CILO 10 mg in the fed state on Day 1 with PD collected on Day 1 and Day 1.

1.2.6.1. Subject Disposition

As of 21 August 2019, a total of 57 subjects were enrolled and 56 subjects had received a single dose of study drug. One subject prematurely discontinued study treatment due to quality issues at the site that justified a suspension in dosing at the site. No subjects prematurely discontinued due to an adverse event (AE), withdrew consent, or were lost to follow up.

1.2.6.2. Safety Results

No deaths, serious AEs (SAEs) related to study treatment or study procedures, AEs leading to discontinuation from the study, or pregnancies were reported during the study. Of the 56 subjects in the Safety Analysis Set, 8 subjects (14.3%) each experienced 1 AE (5 Grade 1 [8.9%], 1 Grade 2 [1.8%], and 2 Grade 3 [3.6%]). Of these, 1 AE (1.8%) was assessed by the investigator as related to study drug (Grade 1 headache). A total of 2 subjects (3.6%) experienced SAEs during the study. None of the AEs were experienced by more than 1 subject.

A total of 43 of 56 subjects (76.8%) experienced a graded laboratory abnormality during the study. Grade 3 laboratory abnormalities were experienced by 7 subjects (12.5%) and a Grade 4 laboratory abnormality was experienced by 1 subject (1.8%). The Grade 3 and 4 laboratory abnormalities were consistent with the underlying hepatic impairment or with abnormalities present at baseline. None of the subjects with normal hepatic function in any cohort experienced a laboratory abnormality ≥ Grade 3. There were no clinically significant trends in vital sign measurements. There were no clinically significant electrocardiogram (ECG) assessments.

1.2.6.3. PK and PD Results

In subjects with mild, moderate, or severe hepatic impairment, CILO AUC_{inf} increased 76%, 146%, and 525%, respectively, compared with matched subjects with normal hepatic function. Similarly, GS-716070 AUC_{inf} increased 64%, 94%, and 197% in subjects with mild, moderate, or severe hepatic impairment, respectively, compared with matched subjects with normal hepatic function. Also, GS-1056756 AUC_{inf} increased 28%, 16%, and 71% in subjects with mild, moderate, or severe hepatic impairment, respectively, compared with matched subjects with normal hepatic function.

CCI [redacted]

Serum concentrations of the bile acid intermediate 7-alpha-hydroxy-4-cholesten-3-one (C4) and plasma concentrations of FGF19 were evaluated in subjects with hepatic impairment and in subjects with normal hepatic function under fed conditions to determine the effect of hepatic insufficiency on response to CILO. Response to CILO was similar in the mild and moderate hepatic impairment groups as compared with matched subjects with normal hepatic function. However, subjects with severe hepatic impairment showed a reduced response to CILO, as indicated by smaller changes in FGF19 and C4 levels compared with subjects with normal hepatic function. These findings are likely related to the elevated FGF19 and reduced C4 levels observed in subjects with severe hepatic impairment at baseline.

The clinical relevance of the altered exposures and PD responses with increasing hepatic impairment seen in this study will be evaluated across all studies to determine if dose adjustment is warranted in patients with hepatic impairment.

1.2.7. A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Cilofexor in Subjects with Primary Sclerosing Cholangitis without Cirrhosis (Study GS-US-428-4025)

Study GS-US-428-4025 is a Phase 2, multicenter, randomized, double-blind study evaluating the safety, tolerability, and efficacy of CILO in subjects with PSC without cirrhosis. Subjects with PSC and a serum ALP concentration greater than 1.67-times the upper limit of normal (ULN) were randomized in a 2:2:1 ratio to one of 3 treatment groups:

- CILO 100 mg orally once daily (N = 22)
- CILO 30 mg orally once daily (N = 20)
- Placebo orally once daily (N = 10)

Randomization was stratified by the presence or absence of UDCA use, which was stable for at least 12 months prior to screening.

Subjects who completed the 12-week blinded study phase without permanently discontinuing study drug were eligible to participate in an open-label extension (OLE) phase of the study to receive CILO 100 mg once daily for 96 weeks after a 4-week washout period. During the OLE phase, dose reduction to 30 mg once daily was permitted if required due to AEs. The randomized phase of Study GS-US-428-4025 has completed, but the OLE phase continues.

1.2.7.1. Subject Disposition and Demographics

A total of 52 subjects were randomized and treated across 24 sites in North America and Europe (16 sites in the US, 3 sites in Canada, 4 sites in the United Kingdom, and 1 site in Austria). A total of 47 subjects (90.4%) completed study drug in the double-blind phase, which was completed on 29 January 2018. The clinical efficacy data presented herein reflect available information from both the randomized and OLE phases of the study (22 Aug 2019 data cut). Of the 5 subjects who did not complete study drug treatment during the double-blind phase, 3 subjects (14%) discontinued CILO 100 mg due to AEs: pruritus (n 1), acute kidney injury (n 1), and elevated ALP (n 1); one subject (5%) discontinued CILO 30 mg following a decision to withdraw consent; and one subject (10%) in the placebo arm discontinued due to elevated liver biochemistry.

The demographics and baseline characteristics of the study population according to treatment group are listed in Table 1-1. Across all treatment groups, 58% of subjects were male, with a median (first quartile [Q1], third quartile [Q3]) age of 43 years (35, 52). In total, 60% of subjects had intra- and extrahepatic bile duct involvement on magnetic resonance cholangiopancreatography (MRCP), 60% had concomitant IBD, and 46% were prescribed UDCA at baseline. The median (Q1, Q3) serum ALP and bilirubin at baseline were 348 U/L (288, 439) and 0.7 mg/dL (0.5, 1.0), respectively. In general, no clinically relevant differences in baseline demographic, laboratory, and imaging parameters were noted across the 3 treatment groups.

Table 1-1. GS-US-428-4025: Demographics and Baseline Characteristics (Safety Analysis Set)

		CILO 100 mg (N = 22)	CILO 30 mg (N = 20)	Placebo (N = 10)	Total (N = 52)
Demographics	Age (yr)	43 (36, 47)	46 (35, 57)	39 (33, 52)	43 (35, 52)
	Male, n (%)	11 (50%)	14 (70%)	5 (50%)	30 (58%)
	White, n (%)	17 (77%)	15 (75%)	7 (70%)	39 (75%)
	Diabetes, n (%)	6 (27%)	2 (10%)	1 (10%)	9 (17%)
	Weight (kg)	73.5 (67.5, 89.1)	79.8 (68.4, 95.9)	82.2 (63.0, 83.3)	77.9 (67.4, 88.6)
	BMI (kg/m^2)	25.8 (23.2, 30.3)	25.9 (22.8, 29.9)	25.8 (23.9, 29.6)	25.8 (23.2, 29.9)
	IBD, n (%)	13 (59%)	11 (55%)	7 (70%)	31 (60%)
	UDCA, n (%)	10 (46%)	9 (45%)	5 (50%)	24 (46%)
Liver Biochemistry	ALP (U/L)	350 (312, 387)	344 (271, 460)	380 (265, 547)	348 (288, 439)
	GGT (U/L)	305 (192, 542)	564 (255, 910)	377 (224, 622)	423 (203, 628)
	Total bilirubin (mg/dL)	0.6 (0.5, 1.1)	0.8 (0.6, 1.0)	0.6 (0.5, 0.9)	0.7 (0.5, 1.0)
	ALT (U/L)	110 (83, 156)	119 (60, 197)	77 (59, 123)	109 (63, 156)
	AST (U/L)	67 (52, 98)	75 (44, 104)	59 (47, 76)	64 (47, 99)
	Albumin (g/dL)	4.4 (4.2, 4.5)	4.5 (4.2, 4.7)	4.6 (4.2, 4.7)	4.4 (4.2, 4.7)
Fibrosis and Inflammation	ELF	9.26 (8.73, 9.66)	9.77 (9.26, 10.31)	9.09 (8.87, 9.60)	9.38 (8.91, 9.88)
	FibroTest®	0.29 (0.27, 0.44)	0.47 (0.39, 0.57)	0.34 (0.23, 0.51)	0.40 (0.28, 0.51)
	C-reactive Protein (µg/mL)	0.27 (0.15, 0.51)	0.26 (0.10, 0.73)	0.19 (0.12, 0.46)	0.25 (0.13, 0.57)
Markers of Bile Acid Homeostasis	FGF19 (pg/mL)	102 (66, 171)	118 (61, 174)	115 (107, 156)	112 (66, 168)
	C4 (ng/mL)	10.4 (5.1, 23.5)	18.7 (9.8, 30.0)	18.9 (9.3, 27.1)	13.2 (7.3, 27.1)
	Total bile acids (µmol/L)	19.6 (10.3, 33.1)	15.3 (9.4, 32.2)	13.7 (6.4, 17.0)	16.9 (9.6, 30.7)
	Primary bile acids (ng/ml)	3182.3 (2329.3, 7535.0)	2646.1 (1548.7, 7036.5)	1759.5 (1359.4, 2380.9)	2806.4 (1584.3, 5502.5)

		CILO 100 mg (N = 22)	CILO 30 mg (N = 20)	Placebo (N = 10)	Total (N = 52)
Imaging	Intra- and extra-hepatic duct involvement on MRCP	11 (50.0%)	14 (70.0%)	6 (60.0%)	31 (60%)
	Liver stiffness by FibroScan® (kPa)	7.3 (6.2, 10.6)	10.1 (6.9, 12.5)	9.8 (7.9, 10.1)	9.4 (6.8, 10.6)
Metabolism	Glucose (mg/dL)	87 (81, 98)	87 (82, 94)	84 (79, 90)	87 (82, 96)
	Cholesterol (mg/dL)	209 (178, 256)	240 (200, 274)	219 (188, 258)	218 (184, 263)
	LDL-C (mg/dL)	111 (87, 132)	139 (102, 166)	123 (94, 153)	122 (94, 153)
	HDL-C (mg/dL)	82 (64, 97)	75 (64, 86)	75 (58, 87)	77 (63, 91)
	Triglycerides (mg/dL)	80 (58, 93)	99 (80, 120)	105 (83, 123)	90 (69, 118)

ALP alkaline phosphatase; ALT alanine aminotransferase; AST aspartate aminotransferase; BMI body mass index; ELF enhanced liver fibrosis; FGF19 fibroblast growth factor 19; GGT gamma glutamyl transferase; HDL C high density lipoprotein cholesterol; IBD inflammatory bowel disease; LDL C low density lipoprotein cholesterol; MRCP magnetic resonance cholangiopancreatography; UDCA ursodeoxycholic acid.
All data are median (Q1, Q3) or n (%).

1.2.8. GS-US-428-4025: Preliminary Efficacy Results

1.2.8.1. Treatment with CILO Results in a Substantial Improvement in Serum ALP in Subjects with PSC

At the completion of Week 12 of the double-blind phase of GS-US-428-4025 (noncirrhotic study), significant and dose-dependent reductions in serum ALP concentration versus baseline were observed in subjects that received CILO compared with those that received placebo (Table 1-2). Specifically, the median (Q1, Q3) absolute difference from baseline to Week 12 in serum ALP was 73 U/L (106, 14) in the CILO 100 mg group (p 0.026 vs placebo), 21 U/L (60, 40) in the CILO 30 mg group (p 0.37 vs placebo), and +8 U/L (40, 118) in the placebo group (Figure 1-1).

Treatment with CILO led to improvements in most efficacy endpoints assessed in subjects with PSC during both the blinded and OLE phases of the study. Outcomes were independent of UDCA use. Dose-dependent decreases from baseline in serum ALP were observed with CILO treatment in the blinded phase; differences between the CILO 100 mg and placebo groups in percentage change in serum ALP were statistically significant (p 0.0294). Decreases in serum ALP continued in the combined CILO group in the OLE phase. Although few subjects with baseline ALP > ULN or ALP ≥ 1.67 × ULN normalized ALP or reduced ALP to < 1.67 × ULN and ≥ 15% in either phase of the study, half of CILO 100 mg group subjects (10 of 20, 50.0%) in the blinded phase and more than a third of combined CILO group subjects (11 of 32, 34.4%) in the OLE phase had a reduction in ALP of at least 20%. No differences between treatment groups

in median decreases in total bilirubin were observed. Among subjects with baseline total bilirubin > ULN, most normalized total bilirubin at blinded Week 12 (4 of 4 subjects [100.0%] in the CILO 100 mg group, 2 of 3 subjects [66.7%] in the CILO 30 mg group, and 1 of 1 subject [100.0%] in the placebo group).

Dose-dependent decreases in markers of liver injury and function were observed with CILO. Differences between the CILO 100 mg and placebo groups for alanine aminotransferase (ALT) (p 0.0089), aspartate aminotransferase (AST) (p 0.0186), and gamma glutamyltransferase (GGT) (p < 0.0001), and between the CILO 30 mg and placebo groups for GGT (p 0.0027) were statistically significant. The decreases in ALT, AST, and GGT continued in the combined CILO group in the OLE phase. Although there were no improvements in liver fibrosis based on enhanced liver fibrosis (ELF™) score, a trend toward a significant decrease in median value for tissue inhibitor of metalloproteinase 1 (TIMP-1) was observed at Week 12 in the CILO 100 mg group compared with placebo (p 0.0626). No decrease in ELF score was observed in the combined CILO group from OLE baseline to OLE Week 96. A small decrease from baseline FibroSURE/FibroTest® score was observed in the CILO 100 mg group at blinded Week 12. Little change was observed in FibroSURE/FibroTest score in the combined CILO group from OLE baseline to OLE Week 96. Little improvement from baseline in liver fibrosis stage based on FibroScan® was observed across treatment groups in the blinded phase. In the OLE phase, no improvement from OLE baseline in liver fibrosis stage based on magnetic resonance elastography was observed in the combined CILO group. No clinically relevant changes from baseline in body weight were observed across treatment groups in the blinded phase. A small increase from OLE baseline in body weight was observed at OLE Week 96 in the combined CILO group. Small improvements from baseline in inflammation based on C-reactive protein (CRP) were observed in the CILO groups at blinded Week 12. Minimal changes in CRP were observed from OLE baseline to OLE Week 96.

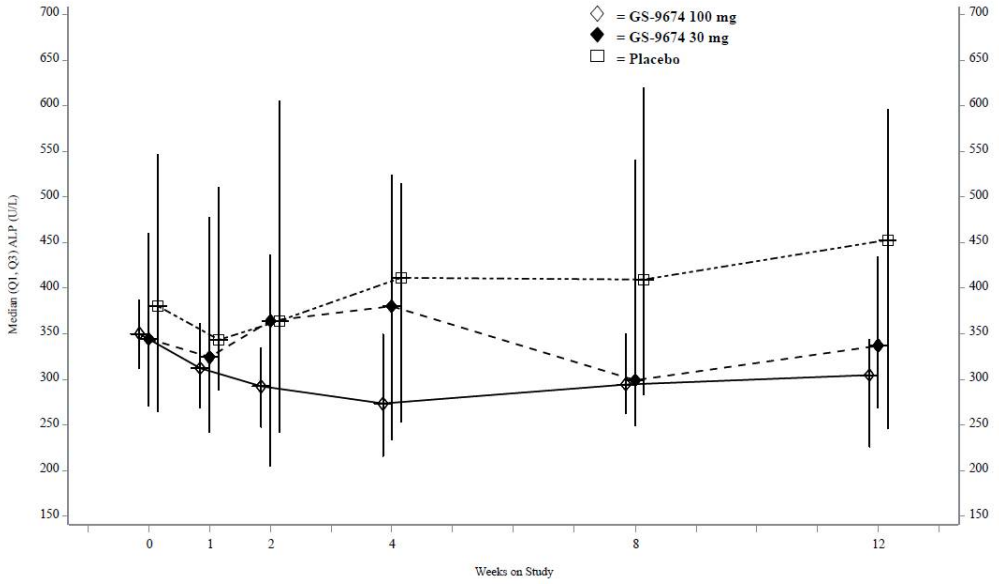
During the blinded phase, fasting FGF19 decreased from baseline in the CILO 100 mg group and increased in the CILO 30 mg group, with increases from OLE baseline at OLE Week 96 in the combined CILO group. Fasting C4 decreased from baseline in both CILO groups in the blinded phase and in the combined CILO group in the OLE phase; decreases in the blinded phase were larger in the CILO 30 mg group than the CILO 100 mg group and significantly different from changes in the placebo group (p 0.0242 for the difference between the CILO 30 mg and placebo groups in percentage change from baseline in fasting C4 at blinded Week 12). Fasting total bile acids decreased from baseline in the CILO 100 mg group, with little change in the CILO 30 mg group during the blinded phase; the decreases continued in the combined CILO group during the OLE phase.

No pattern of changes from baseline at Week 12 was observed across lipid parameters. Dose-dependent decreases from baseline in total cholesterol and high-density lipoprotein cholesterol (HDL-C) were observed at Week 12, with a statistically significant difference between the CILO 100 mg and placebo groups in percentage change in HDL-C (p 0.0403). Increases from baseline were observed at Week 12 in the CILO 100 mg group in fasting triglycerides, fasting low-density lipoprotein cholesterol (LDL-C), fasting very low-density lipoprotein cholesterol (VLDL-C), and fasting non-HDL-C, with small decreases or no change in

the CILO 30 mg group. In the OLE phase, decreases from OLE baseline in total cholesterol, fasting triglycerides, HDL-C, fasting LDL-C, fasting VLDL-C, and non-HDL-C were observed in the combined CILO group at OLE Week 96.

Pooled cohort risk score increased from baseline in the CILO 100 mg group and showed little change in the CILO 30 mg and placebo groups at blinded Week 12. Pooled cohort risk score increased from OLE baseline at OLE Week 96 in the combined CILO group. Mayo risk score decreased from baseline in the CILO 100 mg group and showed little change in the CILO 30 mg and placebo groups at blinded Week 12. Mayo risk score decreased from OLE baseline at OLE Week 96 in the combined CILO group.

Figure 1-1. **GS-US-428-4025: Median (Q1, Q3) Serum ALP Concentration (U/L) by Visit in Double-Blind Phase (Evaluable Subjects, Full Analysis Set)**



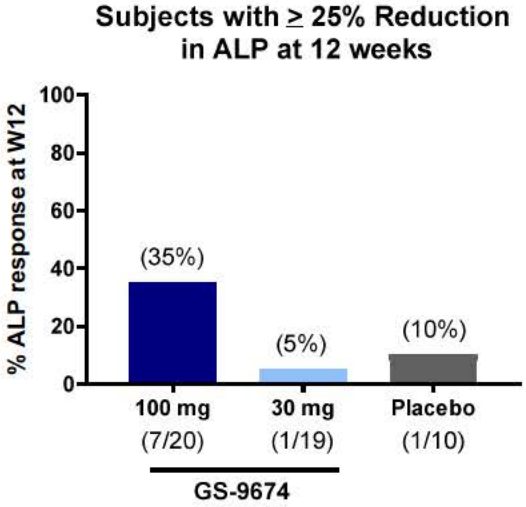
GS-9674 100 mg (n=):	22	22	20	21	20	20
GS-9674 30 mg (n=):	20	19	19	19	19	19
Placebo (n=):	10	10	10	10	10	10

BD = Blinded
Baseline value was determined by averaging all values between screening and Baseline/Day 1.

Similarly, relative reductions from baseline in serum ALP were greatest in subjects that received CILO. Specifically, the median (Q1, Q3) relative difference from baseline to Week 12 in serum ALP was 20.5% (30.2, 3.5) in the CILO 100 mg group (p 0.029 vs placebo), 6.1% (17.6, 16.8) in the CILO 30 mg group (p 0.32 vs placebo), and +3.4% (7.2, 18.6) in the placebo group. The relative improvements in serum ALP concentration from baseline to Week 12 in the CILO 100 mg group were similar between UDCA-treated (n 8) and untreated (n 12) subjects (median, 18.6% vs 20.5%; p 0.85).

At Week 12, more subjects had a clinically relevant serum ALP response, defined as a ≥ 25% relative reduction from baseline, in the CILO 100 mg group (35%, 7 of 20 subjects with evaluable data; p 0.21 vs placebo) compared with the CILO 30 mg group (5.3%, 1 of 19 subjects; p 1.00 vs placebo) and the placebo group (10%, 1 of 10 subjects) (Figure 1-2).

Figure 1-2. GS-US-428-4025: ALP Response at Week 12 of the Randomized Phase (Evaluable Subjects, Full Analysis Set)



These changes in serum ALP concentration with CILO, particularly at the 100 mg dose, represent a significant improvement over placebo on a clinically relevant endpoint reflective of the severity of cholestasis in subjects with PSC.

1.2.8.2. Treatment with CILO Results in Significant Improvement in Liver Biochemistry and Biomarkers in Subjects with PSC

In addition to improvements in serum ALP, treatment with CILO was associated with dose-dependent reductions in other liver biochemistry tests (eg, GGT, AST, ALT), PD markers of FXR agonism (eg, C4, bile acids), and serum fibrosis markers (eg, TIMP-1) compared with placebo at the completion of Week 12 of the double-blind phase (2).

In summary, these data indicate that treatment with CILO is associated with reductions in markers of cholestasis, hepatic inflammation, and potentially fibrosis, in subjects with PSC.

Table 1-2. GS-US-428-4025: Overall Summary of Biochemical and Biomarker Responses from Baseline to Week 12 (Evaluable Subjects, Full Analysis Set)*

	CILO 100 mg (N = 22)	CILO 30 mg (N = 20)	Placebo (N = 10)	P-values	
				100 mg vs. Placebo	30 mg vs Placebo
ALP	-20.5 (-30.2, -3.5)	-6.1 (-17.6, 16.8)	3.4 (-7.2, 18.6)	**0.029**	0.32
UDCA use	-18.6 (-35.2, -3.5)	-7.8 (-14.3, -1.6)	1.3 (-7.2, 18.6)	0.12	0.27
No UDCA use	-20.5 (-27.9, 0.5)	0.0 (-19.2, 21.0)	5.6 (-5.8, 14.7)	0.23	1.00
≥ 25% ALP reduction, % (n/N)	35% (7/20)	5.3% (1/19)	10% (1/10)	0.21†	1.00†
Absolute ALP change, U/L	-73 (-106, -14)	-21 (-60, 40)	8 (-40, 118)	**0.026**	0.37
GGT	-30.3 (-47.8, -21.8)	-16.3 (-29.7, -7.2)	1.1 (-6.1, 15.0)	**< 0.001**	**0.003**
ALT	-49.4 (-60.7, -22.5)	-26.2 (-36.8, 1.7)	-12.9 (-22.9, -12.1)	**0.009**	0.24
AST	-42.3 (-51.1, -10.9)	-22.5 (-34.7, 20.4)	-10.8 (-24.6, 10.5)	**0.019**	0.32
Total bilirubin	0.0 (-22.1, 29.2)	14.3 (-11.1, 34.5)	-11.0 (-27.3, 25.0)	0.58	0.35
Fasting C4	-23.2 (-71.2, 25.7)	-30.5 (-50.5, 5.6)	10.0 (-14.3, 29.7)	0.21	**0.024**
Total bile acids	-38.6 (-55.6, 19.5)	0.0 (-41.5, 57.1)	5.5 (-12.4, 44.6)	0.17	0.67
Primary bile acids#	-45.1 (-65.8, 18.3)	-5.3 (-53.1, 78.3)	4.3 (-35.3, 32.4)	0.15	0.92
ELF	-0.4 (-2.9, 3.0)	0.1 (-1.9, 4.7)	1.2 (-1.9, 2.8)	1.00	0.55
TIMP-1	-8.2 (-13.2, 3.5)	3.8 (-12.7, 17.7)	0.3 (-5.2, 15.5)	0.063	0.73
Hyaluronic acid	-4.3 (-20.6, 17.7)	10.0 (-17.7, 56.5)	9.9 (-2.2, 14.3)	0.69	0.59
PIII-NP	2.2 (-6.0, 18.2)	-5.4 (-12.8, 22.2)	-6.2 (-30.8, 15.5)	0.23	0.30
CRP	-12.2 (-65.7, 40.5)	-28.7 (-43.8, 14.8)	8.5 (-23.1, 30.5)	0.56	0.085

ALP alkaline phosphatase; ALT alanine aminotransferase; AST aspartate aminotransferase; CRP C reactive protein; ELF enhanced liver fibrosis; GGT gamma glutamyltransferase; PIII NP procollagen type III N terminal propeptide; TIMP 1 tissue inhibitors of metalloproteinase 1; UDCA ursodeoxycholic acid

* Unless indicated, all data are median relative (%) changes from baseline and p values were from Wilcoxon rank sum test.

† P value by Fisher exact test.

Primary bile acid species measured by LC/MS.

PIII NP procollagen III amino terminal peptide

1.2.8.3. Preliminary Results from the OLE Phase

As of 22 August 2019, 47 subjects had completed the 12-week randomized phase and entered the OLE phase after a 4-week washout period to receive CILO 100 mg once daily. At Week 12 of the OLE phase, the median relative change in serum ALP from the OLE baseline was 14.6% in the group previously treated with placebo, 15.5% in the CILO 30 mg group, and 16.2% in the CILO 100 mg group. Among 42 subjects with ALP > 1.67-times ULN at the beginning of the OLE phase, 37 subjects completed Week 12 and 12 of these subjects (32%) had a ≥ 25% relative reduction in serum ALP 12 weeks after initiating treatment with CILO 100 mg during the OLE phase. The median relative change in serum GGT from the OLE baseline at Week 12 was 35.3% in the CILO 100 mg group, 38.8% in the CILO 30 mg group, and 34.2% in the placebo group. Overall, Grade 2 or 3 pruritus (including pruritus generalized) has been reported in 12 subjects (26%), and 4 subjects (9%) have discontinued treatment prematurely due to pruritus. Rash (including rash macular and papular) occurred in 4 subjects (9%), none of which were Grade 3 or higher, or led to study drug discontinuation. This ALP response in subjects previously treated with placebo and CILO 30 mg during the blinded phase provides additional evidence to support the therapeutic efficacy of CILO 100 mg.

1.2.8.4. Preliminary Safety Results

Treatment with CILO 100 or 30 mg was generally well tolerated in Study GS-US-428-4025. Table 1-3 presents an overall summary of AEs during the 12-week double-blind phase. A majority of subjects in each treatment group experienced at least 1 AE: CILO 100 mg, 18 of 22 subjects (81.8%); CILO 30 mg, 13 of 20 subjects (65.0%); and placebo, 10 of 10 subjects (100.0%). Most AEs were Grade 1 or 2 in severity. Four subjects discontinued study treatment in the double-blind phase due to AEs: 3 subjects (13.6%) in the CILO 100 mg group (due to acute kidney injury, pruritus, and increased ALP, respectively) and 1 subject (10.0%) in the placebo group (due to increased AST, ALT, and ALP). No deaths were reported during the study.

Table 1-3. GS-US-428-4025: Overall Summary of Treatment-Emergent Adverse Events, Double-Blind Phase (Safety Analysis Set)

	CILO 100 mg (N = 22)	CILO 30 mg (N = 20)	CILO Pooled (N = 42)	Placebo (N = 10)
AE	18 (81.8%)	13 (65.0%)	31 (73.8%)	10 (100.0%)
AE with grade of 3 or higher	5 (22.7%)	3 (15.0%)	8 (19.0%)	2 (20.0%)
AE with highest grade of 3	5 (22.7%)	3 (15.0%)	8 (19.0%)	2 (20.0%)
Treatment-related AE	5 (22.7%)	5 (25.0%)	10 (23.8%)	2 (20.0%)
Treatment-related AE with grade of 3 or higher	1 (4.5%)	1 (5.0%)	2 (4.8%)	1 (10.0%)
SAE	3 (13.6%)	0	3 (7.1%)	0
Treatment-related SAE	0	0	0	0
AE Leading to Premature Discontinuation of Study Drug	3 (13.6%)	0	3 (7.1%)	1 (10.0%)
Death during the Study	0	0	0	0

Adverse events were coded according to MedDRA Version 20.1. Severity grades were defined by the CTCAE Version 4.03.
Treatment emergent events of the Double Blind Phase began on or after the study drug start date of the Double Blind Phase up to 30 days after permanent discontinuation of study drug in the Double Blind Phase (and before the first dose date in the OLE Phase), or led to premature study drug discontinuation.
Death includes any death that occurred during the study.

1.2.8.5. Adverse Events

Table 1-4 presents the treatment-emergent AEs reported for ≥ 2 subjects in any treatment group during the double-blind phase. The most common AEs in each treatment group during the double-blind phase were pruritus, nasopharyngitis, upper abdominal pain, and fatigue (CILO 100 mg); pruritus, nasopharyngitis, and headache (CILO 30 mg); and pruritus and nausea (placebo). Most AEs were Grade 1 or 2 in severity and deemed not to be treatment-related by the investigator.

Table 1-4. GS-US-428-4025: Treatment-Emergent Adverse Events Reported for at Least 2 Subjects in Any Treatment Group by Preferred Term, Double-Blind Phase (Safety Analysis Set)

Preferred Term	CILO 100 mg (N = 22)	CILO 30 mg (N = 20)	CILO Pooled (N = 42)	Placebo (N = 10)
Number (%) of Subjects with Any AE	18 (81.8%)	13 (65.0%)	31 (73.8%)	10 (100.0%)
Pruritus	8 (36.4%)	5 (25.0%)	13 (31.0%)	6 (60.0%)
Nasopharyngitis	5 (22.7%)	5 (25.0%)	10 (23.8%)	2 (20.0%)
Abdominal pain upper	3 (13.6%)	2 (10.0%)	5 (11.9%)	1 (10.0%)
Fatigue	3 (13.6%)	2 (10.0%)	5 (11.9%)	2 (20.0%)
Abdominal discomfort	2 (9.1%)	0	2 (4.8%)	1 (10.0%)
Abdominal distension	2 (9.1%)	0	2 (4.8%)	1 (10.0%)
Blood alkaline phosphatase increased	2 (9.1%)	0	2 (4.8%)	1 (10.0%)
Constipation	2 (9.1%)	0	2 (4.8%)	0
Diarrhoea	2 (9.1%)	1 (5.0%)	3 (7.1%)	0
Dizziness	2 (9.1%)	1 (5.0%)	3 (7.1%)	0
Electrocardiogram abnormal	2 (9.1%)	0	2 (4.8%)	0
Upper respiratory tract infection	2 (9.1%)	0	2 (4.8%)	1 (10.0%)
Viral infection	2 (9.1%)	0	2 (4.8%)	0
Alanine aminotransferase increased	1 (4.5%)	0	1 (2.4%)	2 (20.0%)
Back pain	1 (4.5%)	2 (10.0%)	3 (7.1%)	0
Headache	1 (4.5%)	4 (20.0%)	5 (11.9%)	2 (20.0%)
Muscle spasms	1 (4.5%)	2 (10.0%)	3 (7.1%)	0
Pyrexia	1 (4.5%)	2 (10.0%)	3 (7.1%)	0
Aspartate aminotransferase increased	0	0	0	2 (20.0%)
Nausea	0	1 (5.0%)	1 (2.4%)	3 (30.0%)

Adverse events (AEs) were coded according to MedDRA Version 20.1.
Treatment emergent events of the Double Blind Phase began on or after the study drug start date of the Double Blind Phase up to 30 days after permanent discontinuation of study drug in the Double Blind Phase (and before the first dose date in the OLE Phase), or led to premature study drug discontinuation.
Multiple AEs were counted only once per subject for each preferred term (PT).
PTs were presented by decreasing frequency in the CILO 100 mg group.

Table 1-5 presents Grade 3 treatment-emergent AEs. No Grade 4 AEs were reported. Overall, Grade 3 AEs were uncommon. A total of 3 Grade 3 AEs were reported in > 1 subject: pruritus (2 subjects each in the CILO 100 mg and CILO 30 mg groups and 1 subject in the placebo group); increased blood ALP (1 subject each in the CILO 100 mg and placebo groups); and muscle spasms (1 subject each in the CILO 100 mg and CILO 30 mg groups).

Table 1-5. GS-US-428-4025: Grade 3 Treatment-Emergent Adverse Events by Preferred Term, Double-Blind Phase (Safety Analysis Set)

Preferred Term	CILO 100 mg (N = 22)	CILO 30 mg (N = 20)	CILO Pooled (N = 42)	Placebo (N = 10)
Number (%) of Subjects with Any AE of Grade 3 or Higher	5 (22.7%)	3 (15.0%)	8 (19.0%)	2 (20.0%)
Pruritus	2 (9.1%)	2 (10.0%)	4 (9.5%)	1 (10.0%)
Acute kidney injury	1 (4.5%)	0	1 (2.4%)	0
Anal abscess	1 (4.5%)	0	1 (2.4%)	0
Asthenia	1 (4.5%)	0	1 (2.4%)	0
Blood alkaline phosphatase increased	1 (4.5%)	0	1 (2.4%)	1 (10.0%)
Dehydration	1 (4.5%)	0	1 (2.4%)	0
Diarrhoea	1 (4.5%)	0	1 (2.4%)	0
Fatigue	1 (4.5%)	0	1 (2.4%)	0
Muscle spasms	1 (4.5%)	1 (5.0%)	2 (4.8%)	0
Rib fracture	1 (4.5%)	0	1 (2.4%)	0
Alanine aminotransferase increased	0	0	0	1 (10.0%)
Aspartate aminotransferase increased	0	0	0	1 (10.0%)
Gamma-glutamyltransferase increased	0	1 (5.0%)	1 (2.4%)	0

Adverse events (AEs) were coded according to MedDRA Version 20.1. Severity grades were defined by the CTCAE Version 4.03.
Treatment emergent events of the Double Blind Phase began on or after the study drug start date of the Double Blind Phase up to 30 days after permanent discontinuation of study drug in the Double Blind Phase (and before the first dose date in the OLE Phase), or led to premature study drug discontinuation.
Multiple AEs were counted only once per subject for each preferred term (PT).
PTs were presented by decreasing frequency in the CILO 100 mg group.

1.2.8.6. Serious Adverse Events

Serious AEs were reported in 3 subjects during the double-blind phase, all in the CILO 100 mg group. No SAEs were reported in subjects in the CILO 30 mg group or placebo group. The SAEs were Grade 3 rib fracture (1 subject), Grade 3 acute kidney injury (1 subject), and Grade 3 diarrhea and dehydration (1 subject). None of these events were considered related to study drug; the event of Grade 3 acute kidney injury resulted in premature discontinuation of study drug.

1.2.8.7. Preliminary PK Results

The average steady-state GS-1056756 plasma concentration in subjects with PSC administered 100 mg CILO was consistent with predicted exposure based on PK data in Study GS-US-402-4287 (ADME Study), in which AUC_{inf} was 8220 hr*ng/mL, C_{max} was 35.5 ng/mL, and $t_{1/2}$ was approximately 175 hr.

1.3. Rationale for This Study

PSC is a chronic disease of unknown etiology characterized by inflammation and fibrosis of the intrahepatic and/or extrahepatic bile ducts that result in the impairment of bile flow (cholestasis). Accumulation of excess bile acids causes hepatocellular cytotoxicity that leads to progressive injury characterized by biliary strictures, liver fibrosis, and eventually cirrhosis. CILO is a potent and selective, small molecule agonist of the nuclear hormone receptor FXR. FXR is the master regulator of bile acid homeostasis and modulates the transcription of genes controlling the synthesis, conjugation, transport, and absorption of bile acids {Inagaki 2005, Mudaliar 2013, Pellicciari 2002}. This homeostatic balance is disturbed in patients with PSC in whom bile acids are markedly elevated compared with unaffected individuals. By agonizing FXR in the intestine and stimulating the release of FGF19 and suppression of CYP7A1-mediated bile acid synthesis, CILO is expected to reduce hepatic bile acid accumulation in PSC patients, and thereby decrease hepatocellular and cholangiocyte cell death, inflammation, and progressive fibrosis characteristic of this condition. Indeed, data from animal models of liver fibrosis have demonstrated that oral administration of CILO increased FGF19 synthesis, reduced hepatic CYP7A1 expression and bile acid levels, and led to improvements in markers of hepatic inflammation and fibrosis. Moreover, in a rodent model of advanced fibrosis, CILO administration resulted in a reduction in elevated portal pressure, which accounts for the majority of complications in patients with cirrhosis due to PSC.

Finally, in a Phase 2 study (GS-US-428-4025) of 52 subjects with noncirrhotic PSC and elevated serum ALP (> 1.67× ULN) at baseline, treatment with CILO for 12 weeks led to dose-dependent improvements in serum ALP compared with placebo treatment. The decrease in serum ALP was evident by 4 weeks of CILO treatment, which supports the design of the current study to evaluate each dose for 4 weeks before escalating to a higher dose. This endpoint is clinically relevant and has been associated with a reduced risk of liver-related complications in prior studies. Consistent with improvement in serum ALP, compared with placebo-treated subjects, those treated with CILO 100 mg had greater reductions in other markers of cholestasis (eg, serum GGT, bile acids, C4), hepatic inflammation (eg, ALT, AST), and fibrosis (eg, TIMP-1). Based on these Phase 2

data, CILO is hypothesized to be beneficial in subjects with PSC however to date, these observations have been limited to subjects with noncirrhotic disease.

PSC is a progressive disorder with frequent progression to cirrhosis which confers an increased risk of complications including ascites, variceal hemorrhage, hepatic encephalopathy, malignancy, as well as decreased survival {Tischendorf 2008}. As no available therapies have been shown to improve clinical outcomes in patients with cirrhosis due to PSC, aside from liver transplantation, there is a large unmet medical need in this patient population.

In an effort to expand our understanding of the safety, tolerability, and efficacy of CILO to cirrhotic patients with PSC, inclusion criteria for this study were developed in order to identify subjects with PSC and cirrhosis. Only subjects who meet clinical, histologic, or noninvasive criteria consistent with cirrhosis and have preserved liver function will be included. In this open-label study design, the aim will be to evaluate safety, efficacy, CCI [redacted] properties of CILO in the setting of PSC-related cirrhosis.

1.4. Rationale for Dose Selection of CILO

In this study we aim to evaluate the safety and tolerability of escalating daily doses of CILO from 30 to 100 mg once daily in a PSC population with compensated cirrhosis.

A dose of CILO 100 mg daily provided greater therapeutic benefit than a dose of CILO 30 mg in a Phase 2 study in subjects with PSC without cirrhosis (Study GS-US-428-4025). Subjects with compensated cirrhosis are expected to have approximately 1.8-fold higher CILO plasma exposure compared to those without cirrhosis (GS-US-402-3885; Section 1.2.6). CILO is a hepatic OATP substrate, and the higher CILO plasma exposure observed in subjects with compensated cirrhosis is attributable to decreases in hepatic uptake by OATP, and not expected to alter the hepatic exposure of CILO. Thus, a similar dose of CILO 100 mg is expected to be needed for efficacy in subjects with PSC and compensated cirrhosis. Adequate exposure margins (5- to 11-fold relative to preclinical NOAEL exposures) are expected after 100 mg CILO administration in subjects with PSC and compensated cirrhosis.

The current study is designed to assess the safety of increasing daily doses of CILO from 30 to 100 mg daily in subjects with PSC and compensated cirrhosis. The starting dose, CILO 30 mg once daily, was well tolerated following 12 weeks of treatment in subjects with compensated cirrhosis due to NASH (GS-US-384-3914) and conferred improvements in liver biochemistry (eg, GGT) and markers of cholestasis (eg, C4) in patients with noncirrhotic PSC (GS-US-428-4025). After 4 weeks of dosing with CILO 30 mg, the dose will escalate to 60 mg and then to 100 mg over 4-week intervals, to evaluate the safety, tolerability and improvements in ALP and other liver biochemistry tests at each dose level in subjects with PSC and compensated cirrhosis.

Dosing of CILO in this study will be without regard to food based on PK, PD, safety and efficacy data from Phase 1 studies in healthy subjects and subjects with hepatic impairment (GS-US-402-1851, GS-US-454-4315, and GS-US-402-3885) and Phase 2 studies in subjects with NASH with or without cirrhosis (GS-US-402-1852 and GS-US-384-3914).

1.5. Risk/Benefit Assessment for the Study

This study will provide information on the safety and potential efficacy of CILO for the treatment of patients with PSC who also have compensated cirrhosis. The results from this study may inform the potential of nonsteroidal FXR agonists such as CILO to be tolerated in patients with hepatic impairment, and their future potential to improve biochemical parameters of cholestasis and/or regression of liver fibrosis in patients with PSC and cirrhosis.

The potential benefits of CILO for the treatment of PSC with cirrhosis include improvements in hepatic injury due to reduced bile acid synthesis attributable to FXR agonism. Based on these effects, improvements in liver biochemistry, hepatic fibrogenesis, and potentially health-related quality of life (QoL) would be expected to ensue.

Cilofexor is a new chemical entity, and as such, its long-term safety profile has yet to be established in this patient population. However, available data from the Phase 1 and 2 studies indicate that CILO is safe and generally well tolerated. The primary risk of CILO treatment across different diseases studied, especially in subjects with more advanced fibrosis at baseline, is the potential for pruritus, a symptom commonly associated with cholestatic liver diseases - particularly PSC and PBC - and a known complication of FXR agonist therapy. During the 12-week double-blind period of the Phase 2 PSC study (GS-US-428-4025), the overall incidence of treatment-emergent pruritus was lower in CILO-treated PSC subjects (31%, 13 of 42 subjects treated with 100 mg or 30 mg) compared with those administered placebo (60%, 6 of 10 subjects). Grade 2 or 3 pruritus was also lower with CILO 100 mg (14%, 3 of 22 subjects) and 30 mg (20%, 4 of 20 subjects) compared with placebo (40%, 4 of 10 subjects). Only one subject treated with CILO 100 mg discontinued treatment due to pruritus. In the ongoing OLE phase of this study, Grade 2-3 pruritus has thus far been reported in 8 of 46 PSC subjects (17%) treated with CILO 100 mg and 3 subjects (7%) have discontinued treatment prematurely due to pruritus.

In this study, we will further evaluate the frequency of pruritus in a population of subjects with PSC and cirrhosis taking CILO. The study is designed to dose escalate every 4 weeks based on investigator assessment of tolerability of CILO (particularly with respect to pruritus), with additional quantitative measures of pruritus (eg, the 5D-Itch and visual analog scale [VAS] questionnaires) performed every 4 weeks. For subjects who develop significant pruritus, a formal pruritus management plan has been included in this study which includes, temporary study drug dose interruption of CILO dosing, dose reduction, and supportive management with antihistamines and bile acid sequestrants.

Another potential risk of CILO treatment is drug-related hepatotoxicity. In nonclinical studies, effects on the liver have been limited to nonadverse mild increases in ALP and liver weights and minimal hepatocellular hypertrophy that are likely a pharmacological response to FXR agonism. There were no elevations in liver transaminases or changes in liver pathology (degeneration/necrosis) to suggest direct cellular damage. During the randomized phases of the Phase 2 NASH (GS-US-402-1852) and PSC studies (GS-US-428-4025), similar rates of treatment-emergent elevations in liver biochemistry tests were observed in CILO versus placebo-treated subjects. Specifically, Grade 3 or 4 ALT elevation was observed in 3.9% of subjects (6 of 154) treated with CILO and 2.6% of subjects (1 of 38) treated with placebo in these studies. Grade 3 or 4 AST elevations occurred in 4.5% (7 of 154) and 5.3% (2 of 38) of subjects, respectively. In the majority of these cases, an alternative etiology was identified including natural fluctuations in underlying disease activity and biliary obstruction in a subject with PSC that resolved following endoscopic intervention. To mitigate the potential risk of liver injury in this study, subjects will be monitored closely and defined rules for close observation and drug cessation due to elevated liver tests have been specified in the protocol (see Section 7.5. Toxicity Management: Observation for Drug-Induced Liver Injury).

Additional risks to study subjects include those attributable to study participation in general, including risks associated with frequent clinic visits and laboratory blood draws, and the associated pain and discomfort of phlebotomy. Strategies to mitigate these risks include close monitoring of lab values as well as AEs. Parameters for discontinuation of the study drug due to AEs and nonhepatic laboratory abnormalities are also defined and will be closely followed.

As PSC is a serious, life-threatening condition with no available therapies, the potential benefits of treatment with CILO, as described above, outweigh the known risks. The available data in noncirrhotic PSC subjects treated for 12 weeks, as well as the favorable safety profile seen across ongoing and completed studies provide strong support for furthering the evaluation of CILO in subjects with PSC and compensated cirrhosis as an additional step in its evaluation as a potential therapy for this patient population.

1.6. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To assess the safety and tolerability of escalating doses of CILO in subjects with PSC and compensated cirrhosis

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3. STUDY DESIGN

3.1. Study Design

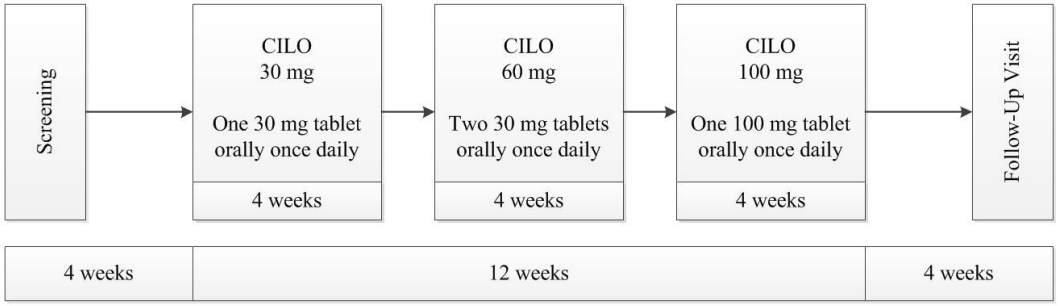
This is a proof of concept, open-label study evaluating the safety and tolerability of CILO in subjects with PSC and compensated cirrhosis.

Eligible subjects will be enrolled and receive treatment with escalating doses of CILO over 12 weeks. Subjects will dose escalate at Week 4 (from 30 mg to 60 mg once daily) and Week 8 (from 60 mg to 100 mg once daily) if in the opinion of the principal investigator (PI) study drug is being tolerated.

Individual subject participation in the study can last up to 20 weeks, which includes a 4-week screening period, a 12-week treatment period (divided into three 4-week dosing stages at 30 mg QD, 60 mg QD, and 100 mg QD), and a follow-up visit 4 weeks after the Week 12 visit.

Study drug dosing may be interrupted for up to 4 consecutive weeks at the discretion of the PI if a subject experiences an AE (eg, intolerable pruritus) thought to be related to the study drug. During the period of study drug dose interruption, subjects are not required to attend in-clinic visits per the Study Procedures Table (Appendix 2) but will be monitored via weekly telephone follow-up visits (refer to Section 7.5.5). If a study drug dose interruption requires reinitiation of a dosing stage, participation in the study could be extended from up to 20 weeks to up to 28 weeks to complete 4 consecutive weeks of dosing at each dose stage.

The overall study design is shown in the figure below:



3.2. Study Treatments

Individual subjects will receive escalating doses of CILO 30 mg (1 × 30 mg tablet), 60 mg (2 × 30 mg tablets), then 100 mg (1 × 100 mg tablet), administered orally once daily. If tolerated, subjects will dose escalate after 4 weeks on each dose.

3.3. Duration of Treatment

Subject will be treated with study drug for 12 weeks; up to 16 weeks if subject requires dose re-challenge after study drug dose interruption.

3.4. Biomarker Testing

3.4.1. Biomarker Samples to Address the Study Objectives:

Biological specimens will be collected from all subjects who have provided consent to participate in this study and may be used to evaluate the association of systemic based biomarkers with study drug response, including efficacy and/or AEs and to better understand the biological pathways, biology of PSC or related diseases such as PBC and/or the validation of a companion diagnostic for PSC. The specific analyses will include, but will not be limited to, the biomarkers and assays listed below. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to specify prospectively all tests that may be performed on the specimens provided. As such, the testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon new state of art knowledge.

Biomarker testing may include biomarkers in blood and stool, that monitor hepatic fibrosis (collagen synthesis and degradation such as ProC3 and ProC5), cell apoptosis and necrosis (CK18 M30 and M65), and other biochemicals, biological macromolecules, and naturally occurring metabolites that may indicate disease progression or response to therapy. In addition, biomarkers of FXR activity CCI [redacted] may also be determined. Biomarkers that may be useful in predicting the occurrence of pruritus, such as serum autotaxin, CCI [redacted] may also be assessed. Stool samples (if available) will be collected for CCI [redacted], and potentially microbiome analyses, and stool calprotectin may be analyzed to assess intestinal inflammation.

CCI [redacted] The specimen storage period will be in accordance with the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)-approved Informed Consent Form (ICF) and applicable laws (eg, health requirements).

CCI [redacted]

CCI

CCI

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

This study will target approximately 20 subjects for enrollment who are equal to or greater than 18 years of age with PSC and compensated cirrhosis.

4.1.1. Subject Replacement

Subjects who discontinue prior to the end of the study will not be replaced.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1) Willing and able to give informed consent prior to any study-specific procedures being performed

2) Males and nonpregnant, nonlactating females equal to or greater than 18 years of age; inclusive based on date of the Screening visit

3) Diagnosis of PSC based on cholangiogram (MRCP, endoscopic retrograde cholangiopancreatography [ERCP], or percutaneous transhepatic cholangiogram [PTC]) or liver biopsy

4) Subjects have evidence of cirrhosis based on at least one of the three following criteria

    a) Historical liver biopsy that reveals Ludwig stage F4 fibrosis (or equivalent)

    b) Abdominal imaging with features consistent with cirrhosis in the opinion of the investigator (eg, small nodular liver, splenomegaly, evidence of portosystemic collaterals, diffuse surface irregularity). magnetic resonance imaging (MRI), computed tomography (CT), and/or ultrasound are acceptable modalities to make this determination.

    c) Any one of the following completed at Screening visit:

        i) FibroScan $\geq$ 14.4 kPA

        ii) ELF $\geq$ 11.3

        iii) FibroTest $\geq$ 0.75

5) Subject has the following laboratory parameters at the Screening visit, as determined by the central laboratory:

   a) Estimated glomerular filtration rate (eGFR) > 60 mL/min, as calculated by the Cockcroft-Gault equation

   b) ALT ≤ 5 × ULN

   c) Total bilirubin ≤ 2 mg/dL, unless the subject is known to have Gilbert's syndrome or hemolytic anemia

   d) INR ≤ 1.4, unless due to therapeutic anticoagulation

   e) Platelet count ≥ 75,000/μL. Patients with evidence of high-risk esophageal or gastric varices in the opinion of the investigator are excluded

   f) Negative anti-mitochondrial antibody

6) For subjects on UDCA, the dose of UDCA must have been stable in the opinion of the investigator for at least 6 months before screening. For subjects not on UDCA, no UDCA use for at least 6 months prior to screening.

7) For subjects being administered biologic treatments (eg, anti-tumor necrosis factor or anti-integrin monoclonal antibodies), immunosuppressants, or systemic corticosteroids, the dose must have been stable in the opinion of the investigator for at least 3 months prior to screening and anticipated to remain stable throughout the study.

8) Females of childbearing potential (as defined in Appendix 4) must have a negative serum pregnancy test at the Screening visit and a negative urine pregnancy test on the Baseline/Day 1 visit prior to the first dose of study drug.

9) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use specified method(s) of contraception as described in Appendix 4.

10) Subjects must be able to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) Current or prior history of any of the following

   a) Decompensated liver disease, including ascites, hepatic encephalopathy (HE), or variceal hemorrhage

b) Liver transplantation

c) Cholangiocarcinoma or hepatocellular carcinoma (HCC). If a dominant structure has been identified, cholangiocarcinoma must be adequately excluded in the opinion of the investigator prior to Day 1

2) Model for end-stage liver disease (MELD) score > 12 at screening, unless due to an alternate etiology such as therapeutic anticoagulation

3) CP score > 6 at screening, unless due to an alternative etiology such as Gilbert's syndrome or therapeutic anticoagulation

4) Presence of moderate to severe itch in the opinion of the investigator at screening and Baseline/Day 1

5) Ascending cholangitis within 30 days of screening

6) Presence of a percutaneous drain or biliary stent

7) Other causes of liver disease including IgG4-related sclerosing cholangitis, PSC-autoimmune hepatitis overlap syndrome, secondary sclerosing cholangitis, and viral, metabolic, alcoholic, and other autoimmune conditions. Subjects with hepatic steatosis may be included if there is no evidence of NASH in the opinion of the investigator.

8) Current moderate to severely active IBD (including ulcerative colitis, Crohn's disease, and indeterminate colitis). See Section 6.8.6.

   Note: Subjects with IBD who currently have an external ostomy bag and/or proctocolectomy are not subject to this exclusion criterion and need not undergo IBD Symptom Severity Assessment.

9) Current or prior history of any of the following:

   a) Malignancy within 5 years of screening with the following exceptions:

      i) Adequately treated carcinoma in situ of the cervix

      ii) Adequately treated basal or squamous cell cancer or other localized nonmelanoma skin cancer.

   Subjects under evaluation for possible malignancy are not eligible.

   b) Unstable cardiovascular disease as defined by any of the following:

      i) Unstable angina, myocardial infarction, coronary artery bypass graft surgery or coronary angioplasty within 6 months prior to screening

      ii) Transient ischemic attack or cerebrovascular accident within 6 months prior to screening

iii) Symptomatic obstructive valvular heart disease or hypertrophic cardiomyopathy

iv) Symptomatic congestive heart failure

v) Uncontrolled or recurrent ventricular tachycardia or other arrhythmia requiring an automatic implantable cardioverter defibrillator (AICD). Stable, controlled atrial fibrillation is allowed.

c) Hypercoagulable condition or venous or arterial thromboembolic disease

d) Intestinal resection or malabsorptive condition that may limit the absorption of CILO. Prior cholecystectomy and appendectomy are permitted.

10) HIV infection (HIV antibody [Ab] and HIV ribonucleic acid [HIV RNA] positive)

11) Hepatitis B virus (HBV) infection (hepatitis B surface antigen [HBsAg] positive)

12) Hepatitis C virus (HCV) infection (HCV Ab and HCV RNA positive). Subjects cured of HCV infection ≥ 2 years prior to screening are eligible.

13) Habitual alcohol consumption greater than 21 oz/week for males or 14 oz/week for females (1 oz/30 mL of alcohol is present in one 12 oz/360 mL beer, one 4 oz/120 mL glass of wine, and a 1 oz/30 mL measure of 40% proof alcohol)

14) Use of antibiotics (eg, vancomycin, metronidazole, minocycline, etc.) for the treatment of PSC within 60 days of screening. Antibiotic prophylaxis for ascending cholangitis is permitted if stable in the opinion of the investigator for at least 6 months prior to screening.

15) Use of any prohibited CMs as described in the protocol (refer to Section 5.5).

16) Positive urine screen for amphetamines, cocaine or opiates (ie, heroin, morphine) at screening. Subjects on stable methadone or buprenorphine maintenance treatment for at least 6 months prior to screening may be included. Subjects with a positive urine drug screen due to prescription opioid-based mediation are eligible if the prescription and diagnosis are reviewed and approved by the investigator

17) Participation in another investigational study of a drug or device within 28 days prior to or within 5 half-lives of the prior investigational agent (whichever is longer) prior to screening.

18) Concurrent participation in another therapeutic clinical study

19) Known hypersensitivity to CILO, its metabolites, or formulation excipient

20) Presence of any concomitant medical condition that could, in the opinion of the investigator, compromise the subject's ability to participate in the study

21) Psychiatric hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 2 years

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Treatment Codes Access

An interactive web response system (IWRS) will be used for treatment assignment. Investigative site personnel will obtain the subject's identification number and study drug assignment from the IWRS**.** Study drug will be dispensed by the study pharmacist, or designee.

5.2. Description and Handling of CILO

5.2.1. Formulation

CILO is supplied as 30 mg and 100 mg strength (as free form equivalent) tablets. The tablets contain cilofexor tromethamine and inactive ingredients mannitol, microcrystalline cellulose, crospovidone, magnesium stearate and film-coating material comprised of polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, yellow iron oxide and black iron oxide. CILO tablets, 30 mg, are round, film-coated green tablets debossed with "30" on one side and "GSI" on the other side. CILO tablets, 100 mg, are capsule-shaped, film-coated green tablets debossed with "100" on one side and "GSI" on the other side.

5.2.2. Packaging and Labeling

CILO tablets, 30 mg and 100 mg, are packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed, aluminum-faced liner.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US Food and Drug Administration (FDA), and/or other local regulations.

5.2.3. Storage and Handling

Study drug CILO tablets should be stored below 30 °C (86 °F). Storage conditions are specified on the label.

Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize study drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling CILO tablets.

5.3. Dosage and Administration of CILO

CILO tablets will be provided by Gilead Sciences, Inc. During the treatment phase of the study, each subject will be supplied with open-label bottles of CILO tablets.

Enrolled subjects will start with 1 bottle containing 30 CILO tablets and will be instructed to take one (30 mg tablet) orally once daily for 4 weeks. Upon dose escalating, subjects will be provided with 2 bottles of CILO, each containing 30 tablets, and will be instructed to take two (30 mg) tablets orally once daily for 4 weeks. Upon final dose escalation, subjects will be provided with 1 bottle of CILO containing thirty 100 mg tablets and will be instructed to take one (100 mg) tablet orally once daily for 4 weeks.

The study drug should be taken at approximately the same time each day. A dose will be considered missed if the subject cannot take the dose within 12 hours of their regular dosing time. If a subject misses a dose, the subject should take their next dose at the regular dosing time.

5.4. Prior and Concomitant Medications

Concomitant use of certain medications or herbal/natural supplements with study drug may result in PK and/or PD interactions resulting in increases or decreases in exposure of study drug(s) or these medications.

Concomitant medications taken within 28 days of screening through the follow-up visit need to be recorded in the source documents and electronic case report forms (eCRFs).

CILO increased atorvastatin exposure (39%) which does not necessitate a priori dose modification based on the LIPITOR United States prescribing information (USPI). Subjects taking atorvastatin with CILO should be monitored as per label recommendations.

5.5. Prohibited Medications

The following medications are prohibited from 28 days prior to Baseline/Day 1 up to and including the day of the last dose of study drug:

- Hematologic stimulating agents (eg, erythropoiesis-stimulating agents [ESAs]; granulocyte colony stimulating factor [GCSF]; thrombopoietin [TPO] mimetics)
- Investigational agents or devices for any indication
- Concomitant use of certain medications or herbal/natural supplements (potent inhibitors of OATP or potent or moderate inducers of OATP, CYP2C8, P-gp, or CYP3A) with study drug(s) may result in PK interactions resulting in increases or decreases in exposure of study drug(s) or CMs. Examples of representative medications which are prohibited from 28 days prior to Baseline/Day 1 through the treatment period are listed below in Table 5-1.

Table 5-1. List of Medications Prohibited and to be used with Caution

Drug Class	Agents Disallowed	Use with Caution
Antibiotics		Clarithromycin, Erythromycin
Acid Reducing Agents	H2-Receptor Antagonists[a]	Antacids[b]
Anticonvulsants[c]	Carbamazepine, Phenobarbital, Phenytoin	
Antimycobacterials[c]	Rifabutin, Rifapentine, Rifampin	
Endothelin Receptor Antagonists	Bosentan	
Herbal/Natural Supplements[c]	St. John's Wort, Echinacea. Milk thistle (ie, silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
Bile Acid Sequestrants[d]		Cholestyramine, Colesevelam, Colestipol, Colestilan
Other[c]	Modafinil	

a H2 Receptor Antagonists can be taken up to 3 days prior to study drug dosing.
b Antacids that directly neutralize stomach pH (ie, Tums, Maalox) are permitted but may not be taken within 4 hours (before or after) study drug administration.
c May result in a decrease in the concentrations of study drugs.
d Bile acid sequestrants are permitted but must not be taken within 4 hours (before or after) of study drug administrations.

Use of obeticholic acid or norursodeoxycholic acid is prohibited within 3 months prior to screening through the end of treatment. Medications for disease conditions excluded from the protocol (eg, HIV-1, HBV, or HCV infection, active cancer, transplantation) are not listed under this prohibited medication section and are disallowed in the study. For subjects on UDCA, the dose of UDCA must have been stable in the opinion of the investigator for at least 6 months before screening and anticipated to remain stable throughout the study. For subjects not on UDCA at screening, UDCA should not be administered during the treatment period.

5.6. Accountability for CILO

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to subjects must be returned to the site.

Study drug accountability records will be provided to each study site to:

- Record the date received and quantity of study drug kits
- Record the date, subject number and the study drug kit number dispensed
- Record the date, quantity of used and unused study drug returned, along with the initials of the person recording the information

5.6.1. Study Drugs Return or Disposal

Refer to Section 9.1.8 for instructions regarding study drug return or disposal.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows. Additional information is provided in the Site Operations Manual.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

It is the responsibility of the investigator to ensure that subjects are eligible to participate in the study prior to enrollment and throughout the study.

Documentation of the personally signed and dated informed consent of each subject, using the study-specific ICF, is required before initiating the Screening process.

After written informed consent has been obtained and eligibility to participate established, investigative site personnel will obtain the subject's identification number and study drug assignment from the IWRS.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened to determine eligibility for participation in the study, with screening visit occurring no more than 4 weeks prior to treatment. The Screening period may be extended under special circumstances with the explicit approval of the medical monitor.

Subjects who fail to meet eligibility criteria may be re-screened once if there is a reasonable expectation that the subject will meet eligibility after repeat screening. Retesting of subject's Screening labs may be permitted if there are reasons to believe that the retest values will be within protocol specified parameters.

The following will be performed and documented at screening:

- Obtain written informed consent before initiation of any Screening procedures
- Obtain Screening number from IWRS
- Obtain medical history

- Review and record whether the subject meets inclusion and exclusion criteria
- For subjects with history of IBD (as appropriate, see Section 6.8.6):

  IBD symptom severity assessment
- Complete physical examination including ascites and HE assessments
- Record vital signs, body weight, and height
- Conduct standard 12-lead ECG
- Obtain blood samples for

  Chemistry

  eGFR

  Hematology

  Coagulation Panel

  Biomarkers

  HIV-1, HBV and HCV Serology

  Serum pregnancy test (female subjects of child bearing potential only)

  Serum follicle-stimulating hormone (FSH) (only for women of any age with amenorrhea of ≥ 12 months, see Appendix 4)
- Urine drug screen
- Perform FibroScan
- CP and MELD scores
- Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the consent form.
- Record all CMs that the subject has taken within 28 days prior to screening

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 4 weeks after screening for treatment.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all SAEs, as well as any AEs related to protocol-mandated procedures on the AEs case report form (CRF). All other untoward medical occurrences observed during the Screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF/eCRF. See Section 7: Adverse Events and Toxicity Management, for additional details.

After the Screening Period, in-clinic study visits will occur at Baseline/Day 1 and at Weeks 1, 4, 8, and 12. At minimum, vital signs, symptom-driven physical examination (PE) including ascites and HE, safety laboratory tests, pruritus assessment (VAS and 5-Itch), review for active IBD, for subjects with history of IBD (as appropriate, see Section 6.8.6), and review of AEs and CMs will be performed at every in-clinic visit.

6.3. Baseline/Day 1 Assessments

Subjects returning to the clinic Baseline/Day 1 will be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the Baseline/Day 1 visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

After review of inclusion and exclusion criteria to confirm continued eligibility, subjects will be assigned study drug and receive their Subject Identification Number via the IWRS prior to their first dose of study drugs.

The following will be performed and documented at the Baseline/Day 1 visit prior to dosing:

[redacted]

- For subjects with history of IBD (as appropriate, see Section 6.8.6):

  IBD symptom severity assessment

  any evidence of active IBD seen on routinely performed colonoscopy will be captured

- Symptom-driven physical examination including ascites and HE assessments
- Record vital signs and body weight
- Conduct standard 12-lead ECG

- Obtain blood samples for:

  Chemistry

  eGFR

  Hematology

  Coagulation Panel

  Lipid Profile

  C-peptide, Insulin and Hemoglobin A_{1c} (HbA_{1c})

  Biomarkers

  CCI [redacted]

- CP and MELD scores
- Collect urine samples for:

  Urine pregnancy test for females of child bearing potential only

- Collect stool sample (if available)
- Record all CMs that the subject has taken since the previous visit
- Record any SAEs and all AEs related to protocol-mandated procedures occurring since the Screening visit
- Dispense study drug, and provide subject with instruction on appropriate dosing and administration
- Once all visit procedures have been completed, subjects will take their Baseline/Day 1 dose of study drug while at the investigative site.

6.4. Treatment Assessments

6.4.1. Week 1, Week 4, Week 8, and Week 12 (± 3 days)

Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

Subjects should also be instructed to HOLD their dose of study drug on the day of their visit until all blood sample collections have been completed.

The following treatment procedures/assessments are to be completed and documented at these in-clinic visits:

[redacted]

- For subjects with history of IBD (as appropriate, see Section 6.8.6):

  IBD symptom severity assessment (Week 4, Week 8, and Week 12)

  any evidence of active IBD seen on routinely performed colonoscopy will be captured at all in-clinic visits

- Symptom-driven physical examination including ascites and HE assessments
- Record vital signs and body weight
- Obtain blood samples for:

  Chemistry

  eGFR

  Hematology

  Coagulation Panel

  Lipid Profile (Week 4, Week 8, and Week 12)

  C-peptide, Insulin and HbA_{1c} (Week 12)

Biomarkers (Week 1, Week 4, Week 8, and Week 12)

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The date and time of the previous study drug dose will need to be documented

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- CP and MELD scores
- Obtain urine samples for:

  Urine pregnancy testing for females of childbearing potential only at Week 4, 8, and 12
- Collect stool sample (Week 12) for bile acids by mass spectrometry (if available)
- Perform FibroScan at Week 12
- Record all CMs that the subject has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit
- Dispense the study drug as directed by IWRS (Week 4 and Week 8)
- Review study drug compliance and study drug administration instructions with subject

  Reconcile study drug administration using pill counts

In the case of a PI approved study drug dose interruption, subjects will have weekly telephone follow-up assessments as detailed in Section 6.4.2. During the study drug dose interruption, subjects are otherwise not required to complete in-clinic assessments unless deemed necessary given the rationale for their study drug dose interruption (eg, Close Observation for drug-induced liver injury [DILI], follow up of non-DILI laboratory abnormalities).

6.4.2. Telephone Follow-Up Visit (weekly; during PI approved study drug dose interruption)

A telephone follow-up visit will occur only if a subject is on a PI approved study drug dose interruption.

The telephone follow up will occur once a week and will document the following:

- Record all CMs that the subject has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit
- Record home urine pregnancy test for females of childbearing potential only

  Urine pregnancy test to be taken at home every 2 weeks during PI approved study drug dose interruption.

- At the discretion of the investigator, an unscheduled visit may be completed if the subject reports abnormal or concerning symptoms, or if the subject requires additional follow up of laboratory abnormalities

6.4.3. Early Termination Visit

Subjects prematurely discontinuing from the study should complete an early termination (ET) visit within 30 days of last dose.

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related procedures per the Study Procedures Table (see Appendix 2). If a subject who discontinues study dosing and continues to perform the required study-related procedures decides to prematurely discontinue from the study, an ET visit should be completed within 30 days of last study visit.

Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the ET visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

The following treatment procedures/assessments are to be completed and documented at this visit.

[redacted]

- For subjects with history of IBD (as appropriate, see Section 6.8.6):

  IBD symptom severity assessment

  any evidence of active IBD seen on routinely performed colonoscopy will be captured

- Symptom-driven physical examination including ascites and HE assessments
- Record vital signs body weight
- Obtain blood samples for:

  Chemistry

  eGFR

  Hematology

  Coagulation Panel

  Lipid Profile

  C-peptide, Insulin and HbA_{1c}

  Biomarkers

  CCI [redacted]
- Obtain urine samples for:

  Urine pregnancy test for females of child bearing potential only
- Perform FibroScan
- CP and MELD scores
- Review study drug compliance

  Reconcile study drug administration using pill counts

  All study drugs should be returned at this visit
- Record all CMs that the subject has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

6.4.4. Follow- Up Visit (± 5 Days)

Subjects will return for a follow-up visit 4 weeks after the Week 12 or ET visit.

Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to their visits to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

The following will be performed and documented at this visit.

- Pruritus assessments (Pruritus VAS and 5D-Itch)
- For subjects with history of IBD (as appropriate, see Section 6.8.6):

  IBD symptom severity assessment

  any evidence of active IBD seen on routinely performed colonoscopy will be captured
- Symptom-driven physical examination including ascites and HE assessments
- Record vital signs, body weight
- Obtain blood samples for:

  Chemistry

  eGFR

  Hematology

  Coagulation Panel

  Lipid Profile

  C-peptide, Insulin and HbA_{1c}

  Biomarkers
- CP and MELD scores
- Obtain urine samples for:

  Urine pregnancy testing for females of childbearing potential only
- Record all CMs that the subject has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

6.4.5. Unscheduled Visit

Additional unscheduled assessments may be performed at the discretion of the investigator.

Subjects returning to the clinic for an unscheduled visit will be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

Subjects should also be instructed to HOLD their dose of study drug on the day of an unscheduled visit until all blood samples have been completed. Unscheduled visits may also occur while on a PI approved study drug dose interruption as detailed in Section 6.4.2.

At a minimum, the following will be performed and documented.

- For subjects with history of IBD (as appropriate, see Section 6.8.6):

  IBD symptom severity assessment

  any evidence of active IBD seen on routinely performed colonoscopy will be captured

- Symptom-driven physical examination including ascites and HE assessments
- Record vital signs and body weight
- Obtain blood samples for:

  Chemistry

  Hematology

  eGFR

- Record all CMs that the subject has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

If the Unscheduled visit is performed for the sole purpose of distribution of study drug, the assessments noted above do not need to be performed.

6.5. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE thought to be related to study drug), every attempt should be made to keep the subject in the study and continue to perform the required study-related procedures per the Study Procedures Table (see Appendix 2). If a subject who discontinues study dosing and continues to perform the required study-related procedures decides to prematurely discontinue from the study, an ET visit should be completed within 30 days of last study visit. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.6. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator.
- Unacceptable toxicity (Section 7.5), or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Any subject without a history of IBD who develops new onset IBD while participating in the study, or any subject with a history of IBD who experiences a clinically significant worsening in IBD symptoms (eg, stool frequency, bleeding) or endoscopic evidence of disease worsening in the opinion of the PI.
- CP score ≥ 7 on two consecutive occasions at least two weeks apart unless due to an alternate etiology (eg, therapeutic anticoagulation), refer to Section 7.5
- Any subject who experiences a hepatic decompensation event, including ascites, HE, or portal hypertension-related upper gastrointestinal bleeding (eg, bleeding from esophageal varices, gastric varices, or portal hypertensive gastropathy)
- Subject request to discontinue for any reason
- Subject noncompliance
- Significant protocol deviation that impacts subject safety
- Pregnancy during the study; refer to Appendix 4
- Discontinuation of the study at the request of Gilead, a regulatory agency or an IRB or IEC

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6.8. Procedures and Specifications

6.8.1. Clinical Laboratory Analytes

Chemistry:

Alanine aminotransferase, AST, albumin, ALP, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphorus, potassium, sodium, total and direct bilirubin, total protein, uric acid, GGT

eGFR:

eGFR is estimated by creatinine clearance calculated by the Cockcroft-Gault equation {Cockcroft 1976}.

Male: $\text{eGFR (mL/min)} \quad \frac{[140 - \text{age (years)}] \times \text{BW(kg)}}{72 \times S_{cr}}$

Female: $\text{eGFR(mL/min)} \quad \frac{[140 - \text{age (years)}] \times \text{BW(kg)} \times 0.85}{72 \times S_{cr}}$

BW body weight; S_{cr} serum creatinine (mg/dL)

Actual body weight will be used for the eGFR.

Hematology:

Hematocrit, hemoglobin (Hb), platelet count, red blood cell count (RBC), white blood cell count (WBC) with differential (absolute and percentage) including lymphocytes, monocytes, neutrophils, eosinophils, basophils, and reticulocyte count and mean corpuscular volume.

Coagulation Panel:

Prothrombin time, partial thromboplastin time (PTT), and INR.

Pregnancy Tests:

Serum beta human chorionic gonadotropin (β-hCG) or urine β-hCG (if positive, requires immediate confirmation with serum β-hCG), and serum FSH.

Additional Tests:

C-peptide, insulin and HbA_{1c}, Lipid Profile, HIV-1 (reflex to HIV-1 RNA), HBV (HBsAg) and HCV (reflex to HCV RNA) serology, eGFR as calculated by modification of diet in renal disease (MDRD), urine drug screen (for amphetamines, cocaine, opiates), stool collection (if available), genomic sample collection, and creatine phosphokinase (CPK) testing (for Close Observation as needed per Section 7.5.2).

Biomarker tests:

- Inflammation high sensitivity C-reactive protein (hsCRP)

[redacted]

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[redacted]

6.8.2. Medical History

Medical history including details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing, and medication history, including nicotine and alcohol use, will be collected on all subjects during screening.

6.8.3. Physical Examination

A complete physical examination should include source documentation of general appearance, and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes; abdomen; skin, hair, nails; musculoskeletal and neurological, and assessments for ascites & HE.

The focus of a symptom-driven physical examination should include assessments for ascites and HE and will be determined by the investigator based on subject complaint. For example, if a subject complains of a cough a respiratory exam should be performed. If consistent with pneumonia (eg, rales or crackles are identified) then an AE would be documented.

Height and body weight will be collected at specified time points.

6.8.4. Vital Signs

Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate and temperature.

Blood pressure will be measured using the following standardized process:

- Subject should sit for ≥ 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level;
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery;
- Measure and record the blood pressure to the nearest 2 millimeter of mercury (mmHg) mark on the manometer or to the nearest whole number on an automatic device.

6.8.5. Clinical Liver Assessments

The MELD and CP scores will be calculated from the central laboratory values attained at each visit. CP will be calculated by the site at screening to assess eligibility; MELD may also be calculated by the sites at screening to determine eligibility if the central laboratory is unable to perform the calculation. MELD will be monitored by site at each visit for safety. Assessment of ascites and HE will be determined by the site at all visits as in the Table 6-1 and will be entered into the eCRF. Dialysis in the preceding week will also be determined by the site at each visit. HE will also be assessed using the West Haven Criteria (Appendix 5).

Table 6-1. Child-Pugh (CP) Classification of the severity of cirrhosis

	1	2	3
Hepatic Encephalopathy (HE)	**None** No encephalopathy and not on any treatment for hepatic encephalopathy	**Medication-Controlled** Subject is lethargic, may have moderate confusion Subject is receiving medical therapy for HE	**Medication-Refractory** Marked confusion/incoherent, rousable but sleeping or comatose
Ascites	**None** No ascites and not on treatment for ascites	**Mild/Moderate** Cross sectional imaging showing ascites Abdominal distension Medication for ascites	Severe (diuretic-refractory) Visible clinically
Bilirubin (mg/dL)	< 2	2-3	> 3
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
INR	< 1.7	1.7-2.3	> 2.3

CP score is obtained by adding the score for each parameter.

CP class: A 5-6 points
B 7-9 points
C 10-15 points

The MELD score will be calculated by using the following formula:

$10 \times ((0.378 \times \ln(\text{Total Bilirubin (mg/dL)})) + (1.12 \times \ln(\text{INR})) + (0.957 \times \ln(\text{Serum Creatinine (mg/dL)})) + 0.643)$.

Serum creatinine in μmol/L will be converted to mg/dL by multiplying by 0.01131. Total bilirubin in μmol/L will be converted to mg/dL by multiplying by 0.05848. Round total bilirubin to 1 decimal place and serum creatinine to 2 decimal places prior to using values in formula or calculation criteria.

If the serum creatinine is < 1.00 mg/dL, the calculation will use 1.00 as the serum creatinine value. If the serum creatinine is > 4.00 mg/dL or if "For subjects on dialysis, did the subjects have 2 or more dialysis treatments within the prior week?" is answered as "Yes", the calculation will use 4.00 as the serum creatinine value. If the total bilirubin is < 1.0 mg/dL, the calculation will use 1.0 as the total bilirubin value. If the INR is < 1.0, the calculation will use 1.0 as the INR value. If the creatinine is resulted as "Icteric Test Not Performed", the calculation will use serum enzymatic creatinine.

The online calculator https://www.mdcalc.com/meld-score-original-pre-2016-model-end-stage-liver-disease may also be used.

6.8.6. IBD Symptom Severity Assessment

IBD (includes ulcerative colitis, Crohn's disease, and indeterminate colitis) Symptom Severity Assessment is a survey for the assessment of IBD that considers stool frequency, rectal bleeding, and physician assessment of IBD for disease severity assessment. Evaluation of any changes in symptoms related to IBD including stool frequency and bleeding, as detailed in Appendix 6. Any subject who experiences worsening IBD symptoms should be instructed to contact the site. IBD Symptom Severity Assessment does not need to be evaluated in subjects who currently use an external ostomy bag and/or subjects who have undergone proctocolectomy, even if they have history of IBD. IBD Symptom Severity Assessment should be evaluated in any subject whose external ostomy is reversed while on the study.

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and anxiety/depression). Each of these 5 dimensions has 5 levels (no problem, slight problems,

[redacted]

6.8.8. Electrocardiogram

Standard 12-lead ECG assessments will be performed. The investigator will review the ECGs for any clinically significant abnormalities to ensure subject safety. Abnormal ECG findings that are considered clinically significant by the investigator and meet the definition of an AE should be reported and recorded in the AE eCRF page.

[redacted]

6.9. End of Study

End of study is defined as the last patient last visit (LPLV) when the last subject's follow-up visit (4 weeks after completing Week 12 visit) occurs or the ET follow-up visit, whichever occurs later.

[redacted]

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or posttreatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.6.1.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified sub-investigator is responsible for assessing the relationship to study drug therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, or CM).

- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.

- **Yes:** The AE occurred as a result of protocol procedures, (eg, venipuncture)

7.2.2. Assessment of Severity

The severity grading of AEs will be assessed as Grade 1, 2, 3, or 4 according to the Common Terminology Criteria for Adverse Events (CTCAE). Refer to the Site Operations Manual for additional CTCAE information.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the CRF/eCRF: all SAEs and AEs related to protocol-mandated procedures.

<u>Adverse Events</u>

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30-days after last administration of study drug must be reported to the CRF/eCRF database as instructed.

All AEs should be followed up until resolution or until the AE is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol-defined follow-up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required posttreatment follow-up period, must be reported to the CRF/eCRF database and Gilead Global Patient Safety (GLPS) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 30 days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, he/she should promptly document and report the event to Gilead GLPS.

All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead GLPS within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, because the eCRF database cannot be accessed or is not available (including at study start), record the SAE on the paper SAE report form and submit by e-mail or fax within 24 hours of the investigator's knowledge of the event to:

Gilead GLPS:	Fax:	PPD
	E-mail:	PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the CM section of the subject's CRF/eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, which may be in the form of line listings, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

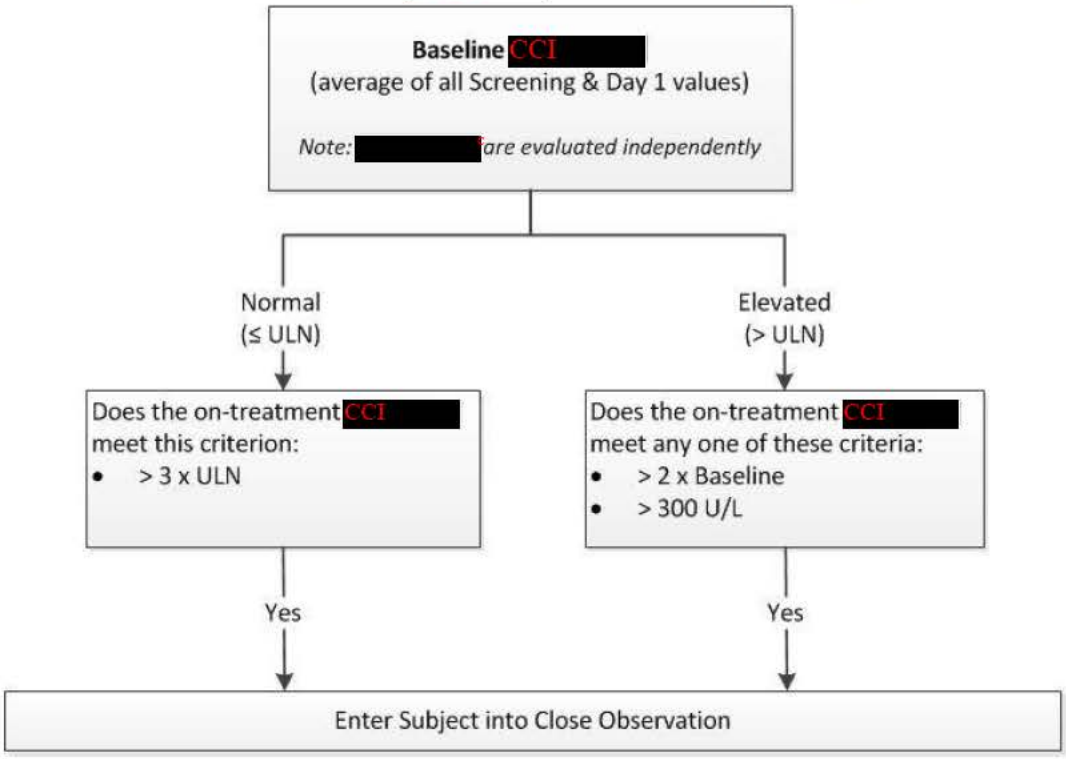
7.5. Toxicity Management

7.5.1. Observation for Drug-Induced Liver Injury

At baseline, some subjects may have liver biochemistry levels above the ULN. Baseline values for liver tests CCI [redacted] will be determined by averaging the values obtained between and including screening and Day 1. Please refer to the Covance Laboratory Manual or individual subject Covance laboratory report for gender and age specific reference ranges.

On-treatment elevations CCI [redacted] should be confirmed with repeat testing within 48-72 hours of results. If the results are confirmed, and if no other cause of the laboratory abnormalities is immediately apparent, notify the medical monitor. Subjects with CCI [redacted] elevations as per Figure 7-1 must be placed into close observation (as described below).

Figure 7-1. On-Treatment [redacted] Monitoring Requiring Close Observation



7.5.2. Close Observation

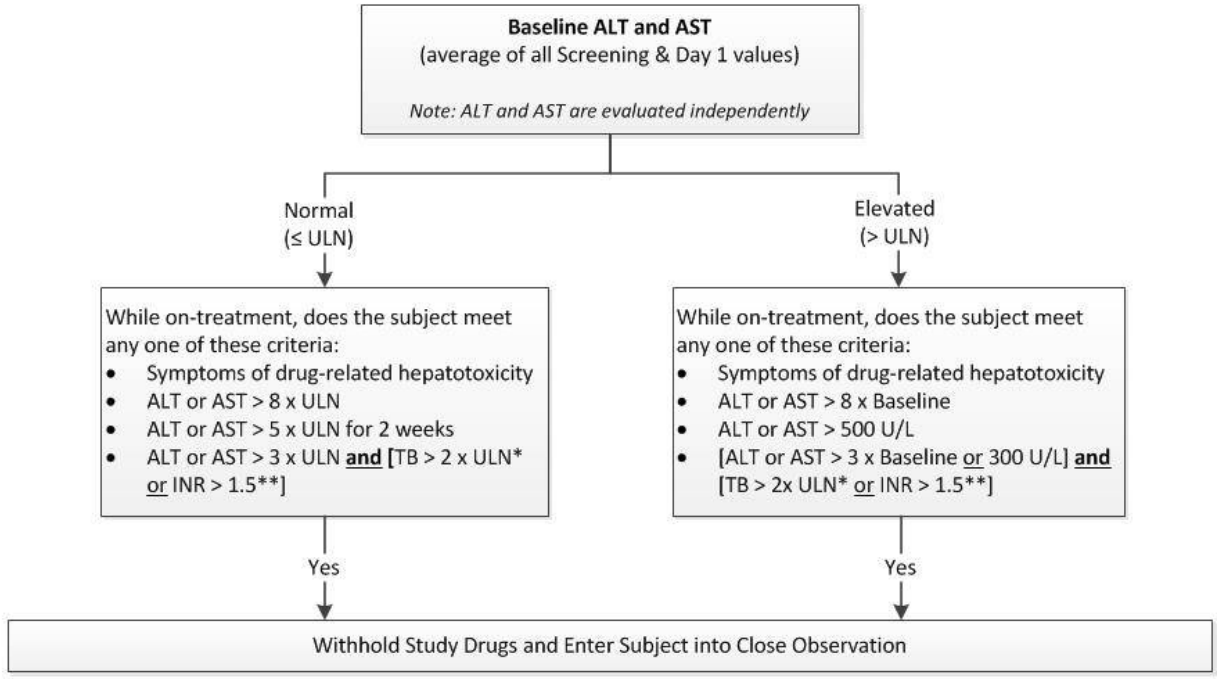
Close observation includes:

- Repeating liver biochemistries ([redacted]) and obtaining a CPK level within 48-72 hours of confirmatory results collected prior to entering close observation.
- Obtaining a more detailed history of symptoms and prior or concurrent disease
- Obtaining a history of CM use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Obtaining a history of exposure to environmental chemical agents
- Ruling out other causes of liver disease as needed (obtain viral hepatitis panel, imaging for evaluation of biliary tract disease, etc. if required in the opinion of the investigator)
- Continue to monitor liver biochemistries at least twice weekly. Frequency can decrease to once a week or less if abnormalities stabilize or study drugs have been discontinued and the subject is asymptomatic.

During a period of close observation for DILI, study drugs can be continued, if desired, at the discretion of both the medical monitor and investigator.

If on-treatment elevations of ALT and/or AST exceed the values shown in Figure 7-2, are confirmed on repeat testing within 48-72 hours of results, and no alternative cause is immediately apparent, the subject must be placed into close observation and study drug must be withheld.

Figure 7-2. On-Treatment Monitoring Requiring Withholding of Study Drugs



* Unless subject has Gilbert's syndrome, in which case a direct bilirubin > 2 x baseline (average of Screening & Day 1 values) will be used instead of total bilirubin.
**If not on therapeutic anticoagulation (e.g. warfarin). If on therapeutic anticoagulation, INR criteria is disregarded.

Abbreviations:
ULN – Upper limit of normal range
TB – Total Bilirubin

If study drugs are withheld, they may be reintroduced with approval from the Gilead medical monitor. In instances where study drug is withheld in the context of DILI, up to a 4-week study drug dose interruption is permitted. Upon resuming study drug, the subject should restart at prior dose as outlined in Section 3.

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the medical monitor. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Other than in the case of the liver enzymes noted above, Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 48-72 hours of results, and preferably within 3 calendar days of receipt of the original test results. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

Any questions regarding toxicity management should be directed to the medical monitor.

7.5.3. Child-Pugh Score

If a subject has an increase in their CP score to ≥ 7, this should be confirmed with repeat testing within 48-72 hours of receipt of results. If confirmed, the medical monitor should be notified, and the subject should be placed into close observation as described above, unless an alternate etiology (eg, therapeutic anticoagulation) is identified. If the CP remains ≥ 7 for at least 2 consecutive weeks, and an alternate etiology has not been identified, study drug must be discontinued.

7.5.4. Pruritus Management

The development or worsening of pruritus during the study is a consideration for patients with PSC. Management of pruritus may include nonpharmacologic interventions (eg, skin moisturization, minimized heat exposure, avoidance of skin irritants, scratch reduction), topical corticosteroids, oral antihistamines, and/or bile acid sequestrants (eg, cholestyramine). Bile acid sequestrants must be taken more than 4 hours before or after the study drug dosing, as described in Table 5-1. Rifampin may not be used for management of pruritus.

7.5.5. Management of Study Drug Dose Interruption Due to AE

If subject experiences an AE (eg, intolerable pruritus) which in the opinion of the investigator may be related to the study drug, the subject may temporarily hold study drug at the investigator's discretion. If study drug dosing is held for longer than 5 days, this is considered a PI approved study drug dose interruption which may not last longer than 4 consecutive weeks. During this period, subjects are not required to attend in-clinic visits per Study Procedures Table (Appendix 2); however, will be monitored via weekly telephone follow-up visits. Female subjects of childbearing potential will be required to perform at home pregnancy tests every 2 weeks during a PI approved study drug dose interruption.

Following the PI approved study drug dose interruption (ie, the AE has resolved or in the case of pruritus, has returned to baseline severity), the subject may initiate a 4-week re-challenge of the most recent dose. In-clinic visits and associated assessments per Appendix 2 will also resume, beginning with a repeat of the initial visit for that dose stage (ie, Day 1 for 30 mg, Week 4 for 60 mg, and Week 8 for 100 mg). If resumption of study drug is tolerated in the opinion of the investigator for 4 consecutive weeks, the study drug dose can be escalated (ie, subject must complete 4 consecutive weeks at 30 mg and 60 mg before escalating to 60 mg and 100 mg, respectively).

If after resumption of study drug the subject experiences another AE thought to be related to study drug (eg pruritus) that necessitates study drug interruption, the study drug should be stopped, and the medical monitor should be notified. Only a single study drug dose interruption period of up to 4 consecutive weeks is permitted.

For study drug dose interruptions due to AEs that are deemed unrelated to study drug in the opinion of the PI, the aforementioned approach should also be followed (ie, only 5-day drug interruption permitted before requirement to repeat 4 week dosing stage).

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose; medication error with an AE; intercepted medication error; or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead investigational product.

Counterfeit or falsified medicine: Any investigational product with a false representation of:

a) Its identity

b) Its source, or

c) Its history

7.6.2. Instructions for Reporting Special Situations

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the post-treatment follow-up period, must be reported to Gilead GLPS. Adverse events and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance (Section 7.3).

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the study drug follow-up period, to Gilead GLPS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Reports should be sent directly to Gilead GLPS at fax number PPD or email PPD

Refer to Section 7.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome after study completion must be reported to Gilead GLPS.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead GLPS using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead GLPS. Gilead GLPS contact information is as follows:
Email: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead GLPS using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead GLPS, fax number PPD or email PPD

Refer to Appendix 4 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

Site personnel must record all other special situations data in the eCRF database and from there transmit the special situations information to Gilead GLPS within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines. All special situations data will be recorded in the eCRF database within the timelines outlined in the eCRF completion guidelines. These reports must consist of situations that involve study drug and/or Gilead CMs, but do not apply to non-Gilead CMs.

If it is not possible to record and submit the special situations information electronically, because the eCRF database cannot be accessed or is not available (including at study start), record the information on the paper special situations report form and submit by e-mail or fax within 24 hours of the investigator's knowledge of the event to Gilead GLPS. Gilead GLPS contact information is as follows:

Email: PPD and Fax: PPD

As soon as it is possible to do so, any special situations reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines. If any special situations have been reported via a paper form because the eCRF database has been locked, no further action is necessary.

Special situation reports involving a Gilead concomitant therapy (not considered study drug), that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up period, must be reported to Gilead GLPS utilizing the paper SSR form.

Special situations involving non-Gilead CMs do not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead CM, the AE should be reported on the AE form.

Any inappropriate use of CMs prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

Details will be provided in the Statistical Analysis Plan (SAP).

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The **primary objective** of this study is as follows:

- To assess the safety and tolerability of escalating doses of CILO in subjects with PSC and compensated cirrhosis

CCI [redacted]

8.1.2. Primary Endpoint

The primary endpoint is the safety and tolerability of CILO in subjects with PSC and cirrhosis. The safety and tolerability of CILO will be evaluated by examining treatment-emergent adverse events (TEAEs), including SAEs, clinical laboratory tests, and vital signs assessments at various time points during the study.

CCI [redacted]

[redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The primary analysis set for efficacy analyses will be the Safety Analysis Set, which includes all subjects who were enrolled into the study and received at least 1 dose of study drug.

8.2.1.2. Safety

The primary analysis set for safety analyses will include all subjects who received at least 1 dose of study drug.

CCI [redacted]

CCI [redacted]

8.2.1.5. Biomarkers

The Biomarker Analysis Set will include data from subjects in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.2.2. Data Handling Conventions

Missing data can have an impact on the interpretation of the study data. In general, values for missing data will not be imputed.

Where appropriate, safety data for subjects that did not complete the study will be included in summary statistics. For example, if a subject received study medication, the subject will be included in a summary of AEs according to the treatment received; otherwise, if the subject is not dosed then they will be excluded from the summary. If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point. If the subject is missing a predose value, then the subject will be excluded from the calculation of summary statistics for the predose value and the change from predose values.

Values for missing safety laboratory data and vital signs will not be imputed; however, a missing baseline result will be replaced with a screening result, if available. If no pretreatment laboratory value is available, the baseline value will be assumed to be normal (ie, no grade [Grade 0]) for the summary of graded laboratory abnormalities.

8.3. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods (n, mean, SD, median, Q1, Q3, minimum, and maximum) by overall. Demographic summaries will include sex, race/ethnicity, and age.

Baseline characteristics summary will include body weight, height, body mass index, and other disease characteristics.

8.4. Efficacy Analysis

The biological activity of CILO will be evaluated using biomarker variables. CCI [redacted] oint estimates and 95% CI will be provided if applicable.

For all continuous endpoints, descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided. For categorical variables, descriptive statistics will be calculated with count and percentage of subjects in each category.

8.5. Safety Analysis

All safety data collected on or after the date that CILO was first dispensed up to the date of last dose of CILO plus 30 days will be summarized by overall. Data for the pretreatment and follow-up periods will be included in data listings.

8.5.1. Extent of Exposure

Data for a subject's extent of exposure to CILO will be generated from the study drug administration eCRF. Exposure data will be summarized by overall.

8.5.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database. Adverse event severity will be graded using the CTCAE Version 5.0.

Events will be summarized on the basis of the date of onset for the event. Treatment-emergent AEs are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug

Summaries (number and percentage of subjects) of TEAEs by SOC and PT will be provided. Treatment-emergent AEs will also be summarized by relationship to study drug and severity. In addition, TEAEs leading to premature discontinuation of study drug and study will be summarized and listed.

All AEs collected during the course of the study will be presented in data listings with a field for treatment-emergent event (yes/no).

8.5.3. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by study visit along with the corresponding change from baseline values.

Graded laboratory abnormalities will be defined using the grading scheme in the CTCAE Version 5.0 (see Appendix 3). Grading of laboratory abnormalities for analysis purposes will be performed by the central laboratory.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time from baseline up to and including the date of last dose of study drug plus 30 days will be summarized by overall. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the subject has been discontinued from treatment for at least 30 days will be included in a data listing.

8.5.4. Other Safety Evaluations

Vital sign measurements and 12-lead ECG data will be summarized by overall and listed by subject.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.8. Biomarker Analysis

Descriptive statistics of biomarker expression and change from baseline will be provided at each sampling time by overall. Point estimates and 95% confidence intervals may be calculated.

CCI [redacted]

[redacted]

8.9. Sample Size

Due to the exploratory nature of this study, no formal power calculations were used to determine sample size.

8.10. Data Monitoring Committee

An internal multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety data. DMC meeting may be held after approximately 10 subjects enrolled have completed 4 weeks of 30 mg treatment. Subsequent meetings will be held on an ad hoc basis.

The DMC's specific activities will be defined by a mutually agreed upon charter, which will define the DMC's membership, conduct, and meeting schedule.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6 (R2) GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and sub-investigators will provide documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any sub-investigator's) participation in the study. The investigator and sub-investigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC/EC. The investigator will not begin any study subject activities until approval from the IRB/IEC/EC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC/EC any modifications made to the protocol or any accompanying material to be provided to the subject after IRB/IEC/EC initial approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB/IEC/EC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by local IRB/IEC/EC requirements. The consent form will inform subjects about genomic testing and/or planned sample retention. CCI [redacted]

CCI [redacted]

9.1.5. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to the sponsor, IRB/IEC/EC or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the study. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, CRF/eCRF, the study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB/IEC/EC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender)
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented subject is not enrolled

- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date, and including causality and severity)
- Concomitant medication (including start and end date, dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.7. Electronic Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is completed in electronic data capture (EDC). The eCRF should be completed in a timely manner to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria and Enrollment eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data

fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points, and as instructed by Gilead), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF will capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the study, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigational Medicinal Product Accountability and Return

Where possible, study drug should be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files. If study drug is destroyed on site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for eventual destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals. For both disposal options listed above, the study monitor must first perform drug accountability during an on-site monitoring visit. However, study drug may be disposed prior to review of the accountability records by the study monitor for the following situations, provided appropriate documentation is available at the site:

- study sites do not have the storage capacity for saving empty drug product containers;
- institutional and/or pharmacy SOP requires the study drug that is classified as hazardous to be destroyed immediately following subject use.

9.1.9. Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRB/IEC/EC, or to regulatory authority or health authority inspectors.

9.1.10. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC/EC in accordance with local requirements and receive documented IRB/IEC/EC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see 9.1.5).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at investigator's meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any

expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered in them. The monitor should have access to any subject records needed to verify the entries on the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authorities (IRBs/IECs/ECs). In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404, USA

STUDY ACKNOWLEDGEMENT

A Proof-of-Concept Open-Label Study Evaluating the Safety and Tolerability of Cilofexor in Subjects with Primary Sclerosing Cholangitis (PSC) and Compensated Cirrhosis

GS-US-428-5443, Amendment 3, 15 January 2021

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

PPD (Printed)
Medical Monitor

PPD

Signature

15 Jan 2021

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

Study Procedures Table – Screening to Follow-Up Visit

Assessments	Screening[a]	Treatment Visits (± 3 days)[b c d]						Follow-Up (± 5 days)
		Baseline/ Day 1	Week 1	Week 4	Week 8	Week 12	ET[e]	
Subject Fasting		X	X	X	X	X	X	X
Written Informed Consent	X							
Medical History	X							
Review Inclusion/Exclusion Criteria	X	X						
Physical Examination[f]	X	X	X	X	X	X	X	X
Assess ascites and HE	X	X	X	X	X	X	X	X
CP and MELD Scores	X	X	X	X	X	X	X	X
Vital Signs[g] and Body Weight	X	X	X	X	X	X	X	X
Height	X							
IBD Symptom Severity Assessment[h]	X	X		X	X	X	X	X
CCI								
CCI								
Review for Active IBD[j]		X	X	X	X	X	X	X
12-lead ECG	X	X						
CCI								
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Dispense Study Drug		X		X	X			

Assessments	Screening[a]	Treatment Visits (± 3 days)[b c d]						Follow-Up (± 5 days)
		Baseline/ Day 1	Week 1	Week 4	Week 8	Week 12	ET[e]	
Review Study Drug Compliance			X	X	X	X	X	
Laboratory Assessments								
Chemistry, eGFR, Hematology, Coagulation Panel	X	X	X	X	X	X	X	X
Lipid Profile		X		X	X	X	X	X
C-Peptide, Insulin and HbA_{1c}		X				X	X	X
HIV-1, HBV and HCV Serology	X							
Urine Drug Screen	X							
Pregnancy Testing[l]	X	X		X	X	X	X	X
Serum FSH[m]	X							
CCI								
Blood for Biomarkers	X	X	X	X	X	X	X	X
CCI								
CCI								
CCI								

AE adverse event; CLDQ Chronic Liver Disease Questionnaire; CP Child Pugh; ECG electrocardiogram; EDC electronic data capture; eGFR estimated glomerular filtration rate; EQ 5D EuroQol five dimensions; ET early termination; FSH follicle stimulating hormone; HBV hepatitis B virus; HbA_{1c} hemoglobin A_{1c}; HCV hepatitis C virus; HE hepatic encephalopathy; HIV 1 human immunodeficiency virus type 1; IBD inflammatory bowel disease; IWRS interactive web response system; MELD model for end stage liver disease; PD pharmacodynamic(s); PE physical examination; PI principal investigator; PK pharmacokinetic(s);

PRO patient reported outcome; PSC primary sclerosing cholangitis; QoL quality of life; SIBDQ short inflammatory bowel disease questionnaire; VAS visual analog scale

a. Subjects will be screened up to 4 weeks prior to treatment. The screening period may be extended under special circumstances with the explicit approval of the medical monitor.
b. At the discretion of the PI, study drug dosing may be temporarily interrupted if subject experiences an AE thought to be related to study drug, including pruritus. In the event this occurs, the PI should notify the medical monitor and the subject should hold study drug until the AE has resolved or pruritus has returned to baseline levels. When resuming study drug, the subject should resume dosing at the prior dose and restart a 4 week challenge on this dose. If subject tolerates study drug for the subsequent 4 weeks, the subject may dose escalate at the discretion of the PI (refer to Section 7.5.5). The same in clinic visits and associated study assessments during regular visits would be performed when re challenging a dose (referenced as postinterruption visit in IWRS and EDC). If reinitiating dose stage of 30 mg study drug, subjects are not required to redo Baseline/Day1 QoLs.
c. Telephone follow up visit will occur only for subjects on PI approved study drug dose interruption. During the period of study drug dose interruption, subjects will be contacted on a weekly basis for up to 4 consecutive weeks (refer to Section 6.4.2).
d. Treatment visits windows are ±3 days unless otherwise stated (see Section 6.4.).
e. Subjects prematurely discontinuing from the study should complete an ET visit within 30 days of last study visit.
f. Symptom directed PE. The focus of a symptom driven physical examination will be determined by the investigator based on subject complaint. A complete PE will be completed at screening.
g. Vital signs include heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature.
h. For subjects with history of IBD. Assessment of Bleeding History and Daily Bowel Movement Count as detailed in Appendix 6.
[redacted]
j. For subjects with history of IBD, any evidence of active IBD seen on routinely performed colonoscopy will be captured.
[redacted]
l. Females of childbearing potential only (see Appendix 4). Serum pregnancy tests at screening and urine pregnancy tests at Day 1, Weeks 4, 8, 12 while on treatment. Urine pregnancy test to be taken at home every 2 weeks during PI approved study drug dose interruption.
m. Women of any age with amenorrhea of ≥ 12 months (see Appendix 4).
[redacted]
p. For Week 12, subjects must be on active treatment for time point PK/PD sampling in order to collect samples at 2 hours and 4 hours postdose.
[redacted]

Appendix 3. Common Terminology Criteria for Adverse Events (CTCAE)

Refer to the Site Operations Manual for additional CTCAE information.

Appendix 4. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle-stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered of fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

CILO has not yet been studied in pregnant women. There were no effects on embryofetal development other than a decrease in fetal body weights in pregnant rabbits administered 1000 mg/kg/day. The decrease in fetal body weights is considered secondary to maternal toxicity rather than a direct effect of CILO. The no observed effect level (NOEL) for embryofetal development is 300 mg/kg/day in mice and 200 mg/kg/day in rabbits. These doses were associated with exposures that are ≥ 38-fold higher than the estimated human exposure at the 100 mg once daily dose. DDI data do not suggest a potential for interaction with hormones used for contraception. Please refer to the latest version of the IB for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must have a negative serum pregnancy test at screening and a negative pregnancy test on the Baseline/Day 1 visit prior to enrollment. Pregnancy tests will be performed at monthly intervals at study visits including the follow-up visit; follow-up telephone assessments will confirm home pregnancy tests are negative as needed. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy tests must be performed to rule out pregnancy. This is true for women of childbearing potential with infrequent or irregular periods.

Female subjects must agree to one of the following from screening until 30 days following the last dose of the study drug CILO.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.

  Intrauterine device (IUD) with a failure rate of <1% per year

  Intrauterine hormone-releasing system (IUS) with a failure rate of <1% per year

  Tubal sterilization

  Essure micro-insert system (provided confirmation of success 3 months after procedure)

  Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Or

- Consistent and correct use of one hormonal method and one barrier method.

  Barrier methods

  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Male condom (with or without spermicide)

  Hormonal methods

  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Implants of levonorgestrel
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the last dose of the study drug CILO.

3) Contraception Requirements for Male Subjects

During the study, male subjects with female partners of childbearing potential should use condoms when engaging in intercourse of reproductive potential.

Male subjects must agree to avoid sperm donation during the study.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.

Appendix 5. West Haven Criteria

http://www.mdcalc.com/hepatic-encephalopathy-grades-stages/

Grade of Hepatic Encephalopathy	Description	Suggested Operative Criteria
Grade I	• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/ behavioral decay with respect to his or her standard on clinical examination or to the caregivers
Grade II	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms
Grade III	• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms
Grade IV	• Coma	Does not respond even to painful stimuli

Adapted from {Vilstrup 2014}

Appendix 6. IBD Symptom Severity Assessment

Bleeding History [1]	❒ 0 no recent bleeding ❒ 1 rare, minimal blood ❒ 2 blood in some stools ❒ 3 blood in most stools, or blood alone in any stool
Daily Bowel Movement Count	❒ 0 no change from a typical day ❒ 1 < 3 more stools than on a typical day ❒ 2 3-5 more stools than on a typical day ❒ 3 > 5 more stools than on a typical day

1 Does not include history of perianal bleeding