CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Cilofexor in Non-Cirrhotic Subjects With Primary Sclerosing Cholangitis
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	131031
EudraCT Number:	2019-000204-14
Clinical Trials.gov Identifier:	NCT03890120
Indication:	Primary Sclerosing Cholangitis
Protocol ID:	GS-US-428-4194
Contact Information:	The medical monitor's name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 04 January 2019 Amendment 1: 25 March 2019 Amendment 1.1: 15 April 2019 (Japan Only) Amendment 2: 23 October 2019 Amendment 3: 07 April 2020 Amendment 4: 30 June 2021 Amendment 5: 16 March 2022

This study will be conducted under United States Food and Drug Administration investigational new drug (IND) regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, the United Kingdom, and Switzerland are not included under the IND and are considered non-IND sites.

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS

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Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Cilofexor in Non-Cirrhotic Subjects With Primary Sclerosing Cholangitis
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	131031 2019-000204-14 NCT03890120
Study Centers Planned:	Approximately 200 centers globally
Objectives:	The primary objective of this study is as follows: • To evaluate whether cilofexor (CILO, previously known as GS-9674) reduces the risk of fibrosis progression among noncirrhotic participants with primary sclerosing cholangitis (PSC) at Blinded Study Phase Week 96 The secondary objectives of this study are as follows: • To assess the safety and tolerability of CILO • To evaluate changes in serum concentrations of alkaline phosphatase (ALP), alanine aminotransferase (ALT), and bile acids at Blinded Study Phase Week 96 • To evaluate whether CILO increases the proportion of participants with $\geq$ 25% relative reduction in serum ALP concentration from baseline (biochemical response) and no worsening of fibrosis according to the Ludwig classification (histologic response) at Blinded Study Phase Week 96 • To evaluate fibrosis stage improvement at Blinded Study Phase Week 96

- To evaluate changes in noninvasive markers of fibrosis, including liver stiffness by FibroScan® and enhanced liver fibrosis test (ELF™ test) score at Blinded Study Phase Week 96
- To evaluate change in PSC Symptoms – Module 1 based on the disease-specific PSC patient-reported outcome (PSC-PRO) at Blinded Study Phase Week 96

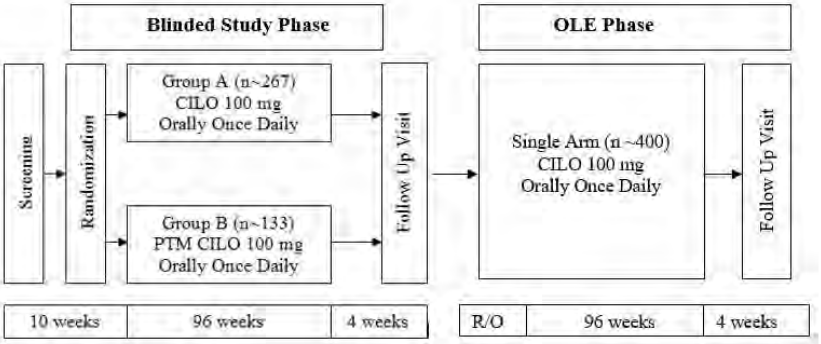
Study Design:

This is a Phase 3, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of CILO in participants with PSC without cirrhosis. The study will consist of 2 phases: a Blinded Study Phase and an Open-Label Extension (OLE) Phase.

Blinded Study Phase: Includes a 10-week screening period, 96 weeks of treatment, and a Blinded Study Phase follow-up visit 4 weeks after completion of Blinded Study Phase Week 96 or early termination (ET). Participants will be randomized 2:1 to receive CILO 100 mg orally once daily or placebo for 96 weeks. Participants who do not permanently discontinue study drug, complete the Blinded Study Phase Week 96 with an evaluable biopsy (noncirrhotic F0-F3) as determined by the central reader and Blinded Study Phase follow-up visit will be eligible to enter into the OLE Phase.

Open-Label Extension Phase: Includes 96 weeks of open-label treatment and an OLE Phase follow-up visit 4 weeks after completion of OLE Phase Week 96 visit or ET visit.

The overall study design is shown in the figure below.



CILO = cilofexor; OLE = open-label extension; PTM = placebo to match; R/O = rollover.

Note:

1) Participants are required to return for a Blinded Study Phase follow-up visit 4 weeks after the Blinded Study Phase Week 96 visit or Blinded Study Phase ET visit.
2) For participants who have consented to and are eligible for the OLE Phase, Gilead recommends completion of the OLE Phase baseline/Day 1 visit within 30 days of completion of the Blinded Study Phase follow-up visit. However, there may be circumstances where the OLE Phase baseline/Day 1 visit will occur more than 30 days after completion of the Blinded Study Phase follow-up visit. Under such circumstances, approval of the Gilead medical monitor will be required and participants will be required to complete select safety assessments prior to the OLE Phase baseline/Day 1 visit.
3) If the Blinded Study Phase follow-up visit and the OLE Phase baseline/Day 1 visit occur on the same day, study assessment procedures should be performed according to the OLE Phase baseline/Day 1 visit.
4) Participants who have consented to and are eligible for the OLE Phase will begin open-label treatment with CILO 100 mg orally once daily.
5) For both the Blinded Study Phase and the OLE Phase, at the discretion of the principal investigator (PI), study drug dosing may be temporarily interrupted, for example, due to an adverse event (AE). During the period of study drug dosing interruption or reduction, for both the Blinded Study Phase and the OLE Phase, participants should continue with study visits per the Study Procedures Table (Appendix 2). Dosage and administration of the study drug and reference product are described in Section 5.3.

Number of Participants Planned:	Approximately 400 participants
Target Population:	Males and non-pregnant, non-lactating females, between 18-75 years of age with PSC without cirrhosis
Duration of Treatment:	Participants will be treated for up to 96 weeks during the Blinded Study Phase. Participants who are enrolled in the OLE Phase will be treated for up to 96 weeks during the OLE Phase. Total treatment duration including both the Blinded Study Phase and the OLE Phase will be up to 192 weeks.

Individual participant participation in the Blinded Study Phase can last up to approximately 110 weeks (consisting of a 10-week screening period, a 96-week Blinded Study Phase treatment period, and a 4-week Blinded Study Phase follow-up period).

For participants who have consented to and are eligible for the OLE Phase, participation in the OLE Phase can last up to approximately 104 weeks (consisting of an approximately 4-week roll-over period, a 96-week open-label treatment period, and a 4-week OLE Phase follow-up period).

Diagnosis and Main Eligibility Criteria:

Key Inclusion Criteria

1) Diagnosis of large duct PSC based on cholangiogram (magnetic resonance cholangiopancreatography [MRCP], endoscopic retrograde cholangiopancreatography [ERCP], or percutaneous transhepatic cholangiogram [PTC])
2) Liver biopsy at screening that is deemed acceptable for interpretation and demonstrates stage F0 - F3 fibrosis (according to the Ludwig classification) in the opinion of the central reader
    a) A historical liver biopsy within 6 months of the screening visit may be accepted as the screening biopsy if the sample is deemed acceptable for interpretation by the central reader.
3) Participant has the following laboratory parameters at the screening visit, as determined by the central laboratory:
    a) Platelet count $\geq$ 150,000/mm^3
    b) Estimated glomerular filtration rate (eGFR) $\geq$ 30 milliliter/minute (mL/min), as calculated by the Cockcroft-Gault equation
    c) ALT $\leq$ 8 $\times$ upper limit of normal (ULN)
    d) Total bilirubin $<$ 2 mg/dL, unless the participant is known to have Gilbert's syndrome or hemolytic anemia
    e) International normalized ratio (INR) $\leq$ 1.4, unless due to therapeutic anticoagulation
    f) Negative anti-mitochondrial antibody
4) For participants 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 participants 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) Cirrhosis as defined by any of the following:
      i. Liver biopsy demonstrating stage F4 fibrosis according to the Ludwig classification (or equivalent)
      ii. Decompensated liver disease, including ascites, hepatic encephalopathy (HE), or variceal hemorrhage
      iii. Liver stiffness > 20.0 kPa by FibroScan
   b) Liver transplantation
   c) Cholangiocarcinoma or hepatocellular carcinoma (HCC). If a dominant stricture has been identified, cholangiocarcinoma must be adequately excluded in the opinion of the investigator prior to Day 1.
   d) Ascending cholangitis within 30 days of screening
2) Presence of a percutaneous drain or biliary stent
3) Other causes of liver disease including immunoglobulin G4 (IgG4)-related sclerosing cholangitis, autoimmune hepatitis/PSC overlap syndrome, secondary sclerosing cholangitis, small duct PSC (histologic evidence of PSC with normal bile ducts on cholangiography), and viral, metabolic, alcoholic, and other autoimmune conditions. Participants with hepatic steatosis may be included if there is no evidence of nonalcoholic steatohepatitis (NASH) on liver biopsy in the opinion of the central reader
4) 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 non-melanoma skin cancer.

   Participants 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.

5) Child-Pugh (CP) score > 6 at screening, unless due to an alternative etiology such as Gilbert's syndrome or therapeutic anticoagulation

6) Model for End-stage Liver Disease (MELD) score > 12 at screening, unless due to an alternate etiology such as therapeutic anticoagulation

7) HIV infection (HIV antibody [Ab] and HIV RNA positive)

8) HBV infection (hepatitis B surface antigen [HBsAg] positive)

9) HCV infection (HCV Ab and HCV RNA positive). Participants cured of HCV infection ≥ 2 years prior to screening are eligible.

10) Current moderate to severe inflammatory bowel disease (IBD) (including ulcerative colitis, Crohn's disease and indeterminate colitis) defined as a screening visit Partial Mayo score of > 4 and/or a score in the screening visit Rectal Bleeding domain > 1, unless bleeding is due to perianal disease. See section 6.9.6.

    Note: Participants with IBD who currently have an external ostomy bag are not subject to this exclusion criterion and need not undergo Partial Mayo evaluation at screening.

11) 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)

12) 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.

13) Use of any prohibited concomitant medications as described in Section 5.5

Study Procedures/ Frequency:

Blinded Study Phase

After signing the informed consent form, participants will complete a screening visit which will include the following assessments: review of inclusion and exclusion criteria; complete medical history; calculation of Partial Mayo score for participants with IBD (as appropriate, see Section 6.9.6); complete physical examination (PE) including assessments for ascites and HE, vital signs and body weight, height; standard 12-lead electrocardiogram (ECG); laboratory assessments including blood collection for biomarker assessment; serum pregnancy test (for females of childbearing potential); urine drug screen; liver stiffness measurement by FibroScan (if available); calculation of CP and MELD scores; liver biopsy (if required); and review of AEs related to screening procedures and concomitant medications.

After the screening period, in-clinic study visits will occur at baseline/Day 1 and at Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84 and 96. At minimum, vital signs, symptom-driven PE, safety laboratory tests, pregnancy tests, calculation of Partial Mayo score for participants with history of IBD (as appropriate, see Section 6.9.6), and review of AEs and concomitant medications will be performed at every visit.

A Blinded Study Phase telephone follow-up visit will also occur at Week 16 to collect information regarding AEs and concomitant medications and review study drug compliance.

CCI [redacted]

Eligible participants will be randomized to 1 of 2 treatment groups. Prior to initial dosing, required Blinded Study Phase baseline/Day 1 assessments will be performed and will include symptom-driven PE, vital signs, laboratory assessments, pregnancy tests (for females of child-bearing potential), blood collection and stool collection (if available) for biomarker assessments, calculation of CP and MELD scores, health resource utilization and QoL questionnaires, pruritus assessments, MRCP (if participant has no contraindications), and review of AEs and concomitant medications. Historical MRCP within 3 months of screening visit or a routinely performed MRCP within screening period may be used.

CCI [redacted] An intensive serial PK and PD sample collection will be completed any time between Week 4 to Week 84 (inclusive) to determine the steady-state PK and PD of CILO and its metabolites (as applicable). CCI [redacted]

During the Blinded Study Phase treatment visit, participants will undergo the following procedures and laboratory assessments:

- Partial Mayo score calculation for participants with a history of IBD (as appropriate, see Section 6.9.6) at baseline/Day 1 and at all subsequent in-clinic study visits
- Pruritus assessments: Pruritus visual analogue scale (VAS) and 5D-Itch at baseline/Day 1 and at all subsequent in-clinic study visits
- Health resource utilization and QoL questionnaires: Short Inflammatory Bowel Disease Questionnaire (for participants with a history of IBD), Chronic Liver Disease Questionnaire, EuroQol (5 dimensions) (EQ-5D), and PSC-PRO at baseline/Day 1, and at Weeks 24, 48, 72, and 96 or ET
- Symptom-driven 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 at Weeks 12, 24, 36, 48, 60, 72, 84 and 96 or ET
- C-peptide, insulin, and hemoglobin A1c (HbA1c) at baseline/Day 1, and at Weeks 12, 24, 48 and 96 or ET
- Pregnancy test (females of childbearing potential only) at baseline/Day 1 and at all subsequent in-clinic visits
- Blood for biomarker assessments at baseline/Day 1, and at Weeks 4, 12, 24, 48, 72, and 96 or ET
- Single PK and PD sampling at Weeks 4, 12, 36, 60, and 84
- Stool collection (biomarker) at baseline/Day 1, and at Weeks 48 and 96 (if available)
- Liver stiffness measurement by FibroScan (if available) at Weeks 24, 48, 72, and 96 or ET
- MRCP at baseline/Day 1, and at Weeks 48 and 96 (if participant has no contraindications). Historical MRCP within 3 months of screening or routinely performed MRCP within screening period may be used.
- Liver biopsy at Week 96

Please refer to Appendix 2 for further details.

At the Blinded Study Phase follow-up visit, participants will have a symptom-driven PE including assessments for ascites and HE, calculation of Partial Mayo score for participants with a history of IBD (as appropriate), vital signs, weight, laboratory assessments including blood collection for biomarker assessments, urine pregnancy tests (for females of childbearing potential), blood collection for biomarker assessments, health resource utilization and QoL questionnaires, pruritus assessments, and review of AEs and concomitant medications.

Interim Analysis:

There will be 1 planned interim futility analysis based on the primary endpoint after the first 160 randomized and dosed participants have completed Week 96 or ET assessments in the Blinded Study Phase. A predictive power (PP) approach will be used for futility assessment. The Data Monitoring Committee (DMC) may recommend early termination of the study due to futility if the criterion of PP $\leq$ 10% is met.

OLE Phase

Participants who do not permanently discontinue study drug, complete the Blinded Study Phase Week 96 with an evaluable biopsy (noncirrhotic F0-F3) as determined by the central reader and Blinded Study Phase follow-up visit will be eligible to enter into the OLE Phase of the study for 96 weeks.

For participants who have consented to and are eligible for the OLE Phase, Gilead recommends completion of the OLE Phase baseline/Day 1 visit within 30 days of completion of the Blinded Study Phase follow-up visit. However, there may be circumstances where the OLE Phase baseline/Day 1 visit will occur more than 30 days after completion of the Blinded Study Phase follow-up visit. Under such circumstances, approval of the Gilead medical monitor will be required, and participants will be required to complete select safety assessments prior to the OLE Phase baseline/Day 1 visit.

Participants will begin open-label treatment with CILO (100 mg orally once daily).

In the OLE Phase, participants will have in-clinic study assessments at OLE Phase baseline/Day 1, OLE Phase Week 4, OLE Phase Week 24, OLE Phase Week 48, OLE Phase Week 72, and OLE Phase Week 96 or ET.

During the OLE Phase, in addition to review of study drug compliance; and review of AEs and concomitant medications, participants will undergo the following procedures and laboratory assessments:

- Partial Mayo score calculation for participants with a history of IBD (as appropriate, see Section 6.9.6) at OLE Phase baseline/Day 1 and at all subsequent in-clinic study visits
- Pruritus assessments: Pruritus VAS and 5D-Itch at OLE Phase baseline/Day 1 and at all subsequent in-clinic study visits
- Health resource utilization and QoL questionnaires: Short Inflammatory Bowel Disease Questionnaire (for participants with a history of IBD), Chronic Liver Disease Questionnaire, EQ-5D, and PSC-PRO at OLE Phase baseline/Day 1, and at OLE Phase Weeks 24, 48, 72, and 96 or ET and OLE Phase follow-up visit
- Symptom-driven PE, assessments for ascites and HE, vital signs, and body weight at OLE Phase baseline/Day 1 and at all subsequent in-clinic study visits

	• CP and MELD score calculations at OLE Phase baseline/Day 1 and OLE Phase Weeks 4, 24, 48, 72, and 96 or ET • Blood chemistry, eGFR, hematology, and coagulation panel at OLE Phase baseline/Day 1 and at all subsequent in-clinic study visits • Lipid profile at OLE Phase baseline/Day 1, and at OLE Phase Weeks 24, 48, 72, and 96 or ET, and the OLE Phase follow-up visit • Pregnancy test (females of childbearing potential only) at baseline/Day 1 and at all subsequent in-clinic visits • Blood for biomarker assessments at OLE Phase baseline/Day 1, and at OLE Phase Weeks 48, 96 or ET, and OLE Phase follow-up visit • Single PK sampling at OLE Phase baseline/Day 1 and at all subsequent in-clinic study visits • Liver stiffness measurement by FibroScan (if available) at OLE Phase baseline/Day 1, and at OLE Phase Weeks 24, 48, 72, and 96 or ET OLE Phase telephone follow-up visits will occur at OLE Phase Weeks 8 and 12 to collect information regarding AEs and concomitant medications and review study drug compliance. Participants will return for an OLE Phase follow-up visit 4 weeks after the OLE Phase Week 96 visit or ET visit. Please refer to Appendix 2 for further details.
Test Product, Dose, and Mode of Administration:	**Blinded Study Phase and OLE Phase:** CILO 100 mg tablet administered orally once daily
Reference Therapy, Dose, and Mode of Administration:	**Blinded Study Phase:** • Treatment Group A: 1 CILO 100 mg tablet administered orally once daily • Treatment Group B: 1 placebo-to-match (PTM) CILO 100 mg tablet administered orally once daily **OLE Phase:** CILO 100-mg tablet administered orally once daily.

Criteria for Evaluation:

Safety: Safety will be assessed 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.

An independent, external DMC that consists of 2 hepatologists and a PhD statistician will convene after 50 participants have completed the Week 4 visit and approximately every 6 months during the Blinded Study Phase and the OLE Phase to monitor the study for safety.

Efficacy:

- The primary endpoint is the proportion of participants with progression of liver fibrosis, as defined by a ≥ 1-stage increase in fibrosis according to the Ludwig classification at Blinded Study Phase Week 96

The secondary endpoints of this study are as follows:

- Changes from baseline in serum concentrations of ALP, ALT, and bile acids at Blinded Study Phase Week 96
- The proportion of participants with ≥ 25% relative reduction in serum ALP concentration from baseline (biochemical response) and no worsening of fibrosis according to the Ludwig classification (histologic response) at Blinded Study Phase Week 96
- The proportion of participants with fibrosis improvement (according to the Ludwig classification) at Blinded Study Phase Week 96
- Changes from baseline in noninvasive markers of fibrosis, including liver stiffness by FibroScan and ELF test score at Blinded Study Phase Week 96
- Change from baseline in PSC Symptoms – Module 1 based on the disease-specific PSC-PRO at Blinded Study Phase Week 96

Pharmacokinetics: Plasma concentrations of CILO and its metabolites (as applicable) will be determined for PK analyses as appropriate.

Statistical Methods:

Efficacy Analysis:

Primary Analysis

A stratified Mantel-Haenszel test will be used to compare the difference in the proportion of participants who have progression of liver fibrosis at Blinded Study Phase Week 96 between the CILO group and placebo group at a 1-sided significance level of 0.025, adjusting for baseline UDCA use and fibrosis stage (Ludwig fibrosis score, F3 versus F0, F1, and F2) on screening liver biopsy. Participants with missing data on liver fibrosis will be analyzed as treatment failures. The point estimate and 95% CI for the difference in proportions will be calculated. A 2-dimensional tipping point sensitivity analysis will be conducted to comprehensively explore the space of plausible missing data assumptions for the primary endpoint.

Secondary Analyses

The secondary efficacy endpoints will be tested sequentially in the following order at the same 1-sided significance level of 0.025 after the primary efficacy objective has been achieved. An analysis of covariance (ANCOVA) model will be used for continuous and ordinal endpoints, adjusting for baseline value of the dependent variable, baseline UDCA use, and fibrosis stage (F3 versus F0, F1, and F2) on screening liver biopsy. A stratified Mantel-Haenszel test will be used for binary secondary endpoints, adjusting for baseline UDCA use and fibrosis stage (F3 versus F0, F1, and F2) on screening liver biopsy. If a 1-sided P value ≤ 0.025 is achieved for the corresponding endpoint, the next endpoint will be evaluated; otherwise, testing of the remaining endpoints will cease.

1) Change from baseline in serum ALP at Blinded Study Phase Week 96
2) Change from baseline in serum ALT at Blinded Study Phase Week 96
3) Change from baseline in serum bile acids at Blinded Study Phase Week 96
4) The proportion of participants with $\geq 25\%$ relative reduction in serum ALP concentration from baseline (biochemical response) and no worsening of fibrosis according to the Ludwig classification (histologic response) at Blinded Study Phase Week 96
5) The proportion of participants with fibrosis improvement (according to the Ludwig classification) at Blinded Study Phase Week 96

6) Change from baseline in PSC Symptoms – Module 1 on the disease-specific PSC-PRO at Blinded Study Phase Week 96
7) Change from baseline in ELF test score at Blinded Study Phase Week 96
8) Change from baseline in liver stiffness by FibroScan at Blinded Study Phase Week 96

Safety Analysis:

Safety will be assessed during the study through the reporting of AEs, clinical laboratory tests, and vital sign assessments at various time points during the study.

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

Sample Size:

A sample size of 267 participants in the CILO group and 133 participants in the placebo group has 81% power to detect an absolute difference of 15% in the percentage of participants who meet the primary endpoint at Blinded Study Phase Week 96. Power was calculated using the Pearson's Chi-square test at a 2-sided significance level of 0.05. This calculation assumes that 25% of participants will discontinue the study prematurely (considered as treatment failures), and that among participants with non-missing response data at Week 96, 20% in the CILO group and 40% in the placebo group will meet the primary endpoint.

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

β-hCG	beta-human chorionic gonadotropin
Ab	antibody
ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
AhR	aryl hydrocarbon receptor
AICD	automatic implantable cardioverter defibrillator
ALDH	aldehyde dehydrogenase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{tau}	area under the concentration versus time curve over the dosing interval
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
CAP	controlled attenuation parameter
CAR	constitutive androstane receptor
CI	confidence interval
CILO	cilofexor
C_{last}	last observed quantifiable concentration of the drug
CLDQ	Chronic Liver Disease Questionnaire
C_{max}	maximum observed concentration of drug
COVID-19	coronavirus disease 2019
CP	Child-Pugh
CPK	creatine phosphokinase
CPT	Child-Pugh-Turcotte (score)
CRF	case report form
CRO	contract/clinical research organization
CRP	C-reactive protein
CSR	clinical study report
C_{tau}	observed drug concentration at the end of the dosing interval

CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 enzyme
DDI	drug-drug interaction
DILI	drug induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
eGFR	estimated glomerular filtration rate
ELF Test	enhanced liver fibrosis test
EQ-5D	EuroQol (5 dimensions)
ERCP	endoscopic retrograde cholangiopancreatography
ESA	erythropoiesis-stimulating agent
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FSH	follicle-stimulating hormone
FXR	farnesoid X receptor
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyltransferase
GLPS	Global Patient Safety
GWAS	genome-wide association studies
Hb	hemoglobin
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
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
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
IgG4	immunoglobulin G4
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
IRT	interactive response technology
LC/MS	liquid chromatography-mass spectrometry
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LLT	lower-level term
MATE	multidrug and toxin extrusion transporter
MCV	mean corpuscular volume
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-PDFF	magnetic resonance imaging-proton density fat fraction
mRNA	messenger ribonucleic acid
NASH	nonalcoholic steatohepatitis
$NaNO_2$	sodium nitrite
NOAEL	no observed adverse effect level
NTCP	sodium-taurocholate cotransporter protein
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OLE	open-label extension
OST	organic solute transporter
PBC	primary biliary cholangitis
PD	pharmacodynamic(s)
PE	physical examinations
P-gp	P-glycoprotein

PI	principal investigator
PIIIP-NP	procollagen III amino terminal peptide
PK	pharmacokinetic(s)
PP	predictive power
PRO	patient-reported outcome
PSC	primary sclerosing cholangitis
PSC-PRO	primary sclerosing cholangitis-patient-reported outcome
PT	preferred term
PTC	percutaneous transhepatic cholangiogram
PTM	placebo-to-match
PTT	partial thromboplastin time
PXR	pregnane X receptor
Q1	first quartile
Q3	third quartile
QoL	quality of life
RBC	red blood cell
RNA	ribonucleic acid
RXR	retinoid X receptor
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
SD	standard deviation
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SIM	simtuzumab
SOC	system organ class
SOP	standard operating procedure
SSR	special situations report
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
TEAEs	treatment-emergent adverse events
TGR5	bile acid receptor
TIMP	tissue inhibitor of metalloproteinases
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
TPO	thrombopoietin
UDCA	ursodeoxycholic acid
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of the normal

US, USA	United States, United States of America
VAS	visual analogue scale
VLDL-C	very low-density lipoprotein cholesterol
WBC	white blood cell

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}. Primary sclerosing cholangitis 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 1211 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 effective approved therapies for PSC that have been proven to improve histologic or clinical outcomes. 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 (5-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. Cilofexor

1.2.1. General Information

Cilofexor (CILO, previously known as GS-9674) is a potent agonist of the farnesoid X receptor (FXR) whose activity in intestinal epithelial cells results in the release of fibroblast growth factor 19 (FGF19). The 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 and In Vitro Metabolism

1.2.2. Nonclinical Pharmacology

CILO is a potent and selective small molecule agonist of FXR. 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 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 intravenous (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/sodium nitrite ($NaNO_2$) 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 (RBC) 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 effect levels (NOAELs) from the 26- (mice), 13- (rat) and 39-week (monkey) repeat dose toxicity studies were 60 mg/kg/day in mice, 1500 mg/kg/day in rat and 300 mg/kg/day in monkeys. These doses were associated with exposure margins 9× (male mice), 15× (female mice), 30× (male rats), 21× (female rats), and 23× (male and female monkeys) higher than the human exposure at the 100 mg once daily 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 26× (male) and 66× (female) higher than the human exposure at the 100 mg once daily dose.

1.2.4. Nonclinical Pharmacokinetics

The oral bioavailability of CILO was low in the nonclinical species. Low pH-dependent solubility, efflux transporters, and 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 ($\geq$ 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 (CYP) enzymes CYP2C8, CYP3A4, and CYP2C19 were shown to metabolize CILO in vitro. 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/intestinal uptake of organic anion transporter

protein (OATP) substrates or metabolism of CYP2C8, CYP2C9, or CYP3A4 substrates in vitro, however, when dosed clinically, only a slight increase that would not warrant dose modification was observed for CYP3A/OATP substrate atorvastatin. CILO did not alter the pharmacokinetics (PK) of OATP substrate pravastatin, OATP/breast cancer resistance protein (BCRP) substrate rosuvastatin, or CYP3A4 substrate midazolam. CILO was a substrate for efflux transporters P-glycoprotein (P-gp) and BCRP, as well as the uptake transporters OATP1B1, OATP1B3, OATP2B1, and sodium-taurocholate cotransporter protein (NTCP). However, clinical drug interaction data indicates that intestinal P-gp and OATP2B1 do not play a significant role in CILO disposition, whereas OATP1B1/1B3 play the primary role. Inhibitors or genetic polymorphisms affecting the activity of these transporters may affect CILO intestinal absorption and hepatic uptake. CILO and its 2 prominent metabolites did not activate nuclear hormone receptors associated with the potential for induction of human drug-metabolizing enzymes and transporters (eg, pregnane X receptor [PXR], constitutive androstane receptor [CAR], aryl hydrocarbon receptor [AhR]) in cell-based reporter assays. Thus, the liability of CILO and its metabolites to cause drug-drug interactions (DDIs) through proteins regulated by these nuclear receptors is low. The metabolite GS-716070 had little or no inhibitory effect on the activities of CYP or uridine diphosphate glucuronosyltransferase (UGT) enzymes in vitro. GS-716070 was found to inhibit human OATP1B1, OATP1B3, and OATP2B1, though less potently than CILO, and showed little or no inhibition of P-gp, BCRP, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, multidrug and toxin extrusion transport (MATE)1, and MATE2-K. GS-1056756 has shown low potential to inhibit CYP enzymes and UGT in vitro. GS-1056756 did not inhibit 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-716070 or GS-1056756 on enzymes and transporters was predicted from in vitro characterizations due to high protein binding values similar to CILO. GS-1056756 has been identified in nonclinical assays as a substrate of OATP1B1/1B3. In vitro, GS-1056756 is formed by oxidative metabolism by CYP3A4 and CYP2C8 with additional conversion to enantiomers by dehydrogenases (eg, aldehyde dehydrogenase [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 Studies of CILO

As of 08 September 2021, 7 Phase 1 and 6 Phase 2 clinical studies have been completed, and 4 Phase 1 or 3 studies are ongoing. Two Phase 1 studies in healthy participants are ongoing (GS-US-454-5280 and GS-US-402-4374), 3 Phase 2 studies in participants with nonalcoholic steatohepatitis (NASH) are complete (GS-US-384-3914, GS-US-402-1852, and GS-US-454-4378), 1 Phase 2 study in participants with primary biliary cholangitis (PBC) (GS-US-427-4024) is complete, 1 Phase 2 study in participants with PSC (GS-US-428-4025) is complete, 1 Phase 1b study in participants with PSC and compensated cirrhosis (GS-US-428-5443) is ongoing, and 1 Phase 3 study in participants with PSC without cirrhosis is ongoing. These Phase 1, 2, and 3 studies are described in the IB. Brief summaries of relevant results from Study GS-US-402-3885 and from 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 1.2.6.3 and 1.2.8.6. Briefly, GS-1056756 exhibits a plasma

half-life of approximately 175 hours. Preliminary steady-state plasma concentrations of GS-1056756 in PSC participants administered 100 mg CILO are as expected based on the single-dose PK data for GS-1056756 from the absorption, distribution, metabolism, and elimination (ADME) study (GS-US-402-4287). Additionally, plasma exposures of GS-1056756 are minimally altered in participants with mild or moderate hepatic impairment compared with participants 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 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 CILO in Participants 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 participants with normal hepatic function and mild, moderate, or severe hepatic impairment. Up to 60 participants 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 participant 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 participant with normal hepatic function (N = 10 per cohort). Data from healthy participants were used in > 1 cohort if a participant was an appropriate match for a participant with hepatic function in > 1 cohort. All participants 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 participants 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. Participant Disposition

As of 21 August 2019, a total of 57 participants were enrolled and 56 participants received a single dose of study drug. One participant prematurely discontinued study treatment due to quality issues at the site that justified a suspension in dosing at the site. No participants 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 adverse events (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 participants in the Safety Analysis Set, 8 participants (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 participants (3.6%) experienced SAEs during the study. None of the AEs were experienced by more than 1 participant.

A total of 43 of 56 participants (76.8%) experienced a graded laboratory abnormality during the study. Grade 3 laboratory abnormalities were experienced by 7 participants (12.5%) and a Grade 4 laboratory abnormality was experienced by 1 participant (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 participants 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 participants with mild, moderate, or severe hepatic impairment, CILO AUC_{inf} increased 76%, 146%, and 525%, respectively, compared with matched participants with normal hepatic function. Similarly, GS-716070 AUC_{inf} increased 64%, 94%, and 197% in participants with mild, moderate, or severe hepatic impairment, respectively, compared with matched participants with normal hepatic function. Also, GS-1056756 AUC_{inf} increased 28%, 16%, and 71% in participants with mild, moderate, or severe hepatic impairment, respectively, compared with matched participants with normal hepatic function.

CCI [redacted] nbound fractions of CILO and GS-716070 increased as hepatic impairment increased with minimal impact on the unbound fraction of GS-1056756.

Serum concentrations of the bile acid intermediate 7-alpha-hydroxy-4-cholesten-3-one (C4) and plasma concentrations of FGF19 were evaluated in participants with hepatic impairment and in participants with normal hepatic function under fed conditions to determine the effect of hepatic insufficiency on response to CILO. Blood samples were collected on Day −1 and Day 1 (postdose) over a 16-hour period beginning at approximately the same time each day. Response to CILO was similar in the mild and moderate hepatic impairment groups as compared with matched participants with normal hepatic function. However, participants with severe hepatic impairment showed a reduced response to CILO, as indicated by smaller changes in FGF19 and C4 levels compared with participants with normal hepatic function. These findings are likely related to the elevated FGF19 and reduced C4 levels observed in participants with severe hepatic impairment prior to dosing with CILO.

The clinical relevance of the altered exposure 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 CILO in Participants 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 is evaluating the safety, tolerability, and efficacy of CILO in participants with PSC without cirrhosis. participants with large duct 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 1 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.

Participants 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 based on tolerability. Study GS-US-428-4025 has completed and the clinical study report (CSR) was finalized in December 2020.

1.2.7.1. Participant Disposition and Demographics

A total of 105 participants were screened and 52 participants 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). All 52 participants who were randomized received at least 1 dose of study drug. A total of 47 participants (90.4%) completed study drug in the double-blind phase. Five participants (9.6%) prematurely discontinued study drug in the blinded phase due to AEs (3 participants [13.6%] in the CILO 100 mg group, 1 participant [5.0%] in the CILO 30 mg group, and 1 participant [10.0%] in the placebo group).

Forty-six of the 47 participants who completed study drug in the blinded phase continued study drug in the OLE phase. One participant discontinued the study after completing the blinded phase, and 1 participant who prematurely discontinued study drug in the blinded phase entered the OLE phase. Of the 47 participants who received study drug in the OLE phase, 32 participants (68.1%) completed study drug and 15 participants (31.9%) prematurely discontinued study drug. Reasons for premature discontinuation of study drug in the OLE phase were AEs (10 participants [21.3%]), participant decision (3 participants [6.4%]), and investigator's discretion (2 participants [4.3%]).

A total of 33 participants (63.5%) completed the study and 19 participants (36.5%) prematurely discontinued from the study. Reasons for premature discontinuation from the study were AE (12 participants [23.1%]), withdrew consent (5 participants [9.6%]), and investigator's discretion (2 participants [3.8%]).

The demographics and baseline characteristics of the study population according to treatment group are listed in Table 1-1. At blinded phase baseline, 24 participants (46.2%) used UDCA and 32 participants (61.5%) had a history of IBD. Median (first quartile [Q1], third quartile [Q3]) ALP and total bilirubin were 348 (288, 439) U/L and 0.7 (0.5, 1.0) mg/dL, respectively. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were ≥ ULN in most participants (48 participants [92.3%] and 49 participants [94.2%] for ALT and AST, respectively). Median (Q1, Q3) enhanced liver fibrosis (ELF™) score was 9.38 (8.91, 9.88) and median (Q1, Q3) FibroTest® score was 0.40 (0.28, 0.51) and median (Q1, Q3) liver stiffness by FibroScan® was 9.4 (6.8, 10.6) kPa. Median (Q1, Q3) CRP and fasting total bile acids were 0.246 (0.133, 0.566) mg/dL and 16.9 (9.6, 30.7) µmol/L, respectively.

At OLE phase baseline, median (Q1, Q3) ALP and total bilirubin were 368 (277, 468) U/L and 0.8 (0.5, 0.9) mg/dL, respectively. ALT and AST were ≥ ULN in most participants (45 participants [95.7%] for each parameter). Median (Q1, Q3) ELF score was 9.50 (8.92, 9.95) and median (Q1, Q3) FibroTest score was 0.42 (0.28, 0.55). Median (Q1, Q3) CRP and fasting total bile acids were 0.280 (0.127, 0.536) mg/dL and 14.3 (7.2, 30.2) µmol/L, respectively.

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 (years)	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 (%)	14 (64%)	11 (55%)	7 (70%)	31 (62%)
	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 (ug/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)

		CILO 100 mg (N = 22)	CILO 30 mg (N = 20)	Placebo (N = 10)	Total (N = 52)
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)
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-glutamyltransferase; 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 (%).

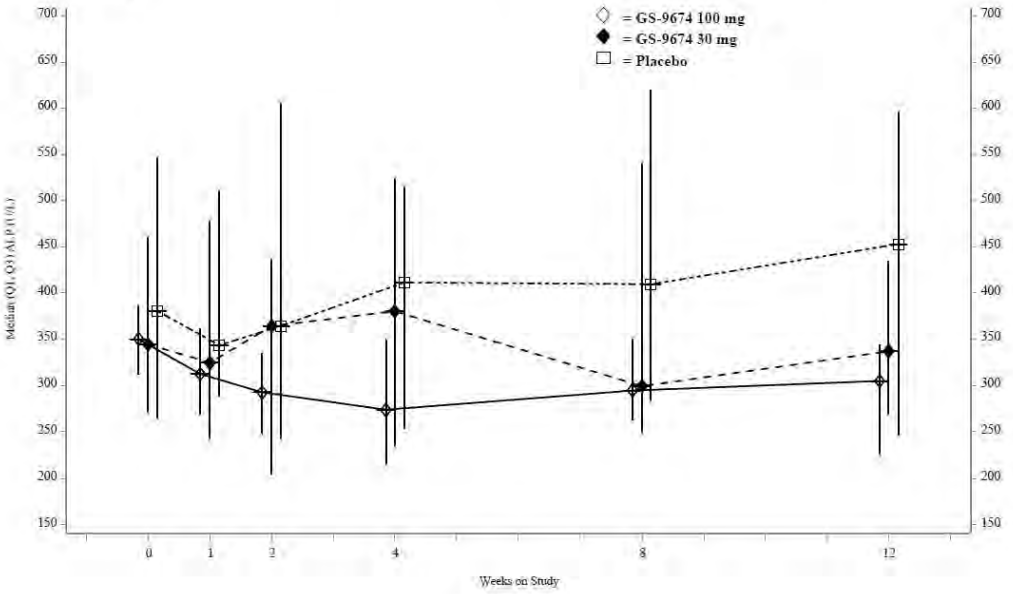
1.2.8. GS-US-428-4025: Efficacy Results

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

At the completion of Week 12 of the double-blind phase of GS-US-428-4025, significant and dose-dependent reductions in serum ALP concentration versus baseline were observed in participants who received CILO compared with those who 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).

Similarly, relative reductions from baseline in serum ALP were greatest in participants 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) participants (median, −18.6% vs −20.5%; P = 0.85).

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

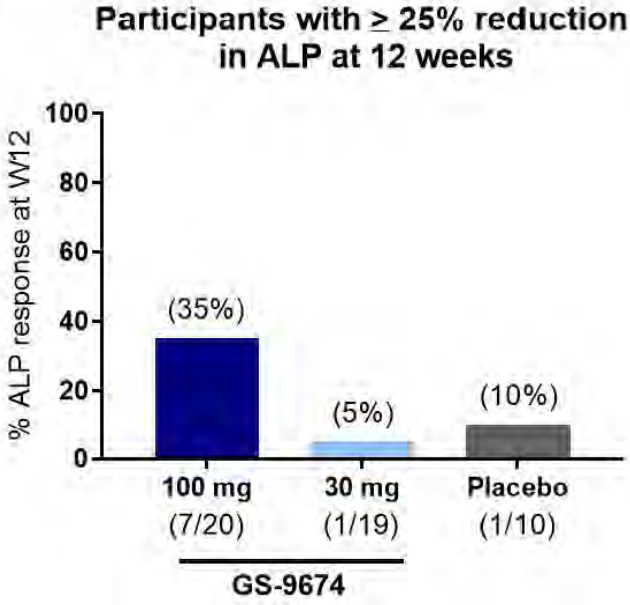


GS-9674 100 mg (n=):	22	22	20	21	20	20
GS-9674 30 mg (n=):	20	19	19	19	19	19
Placebo (n=):	10	10	10	10	10	10

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

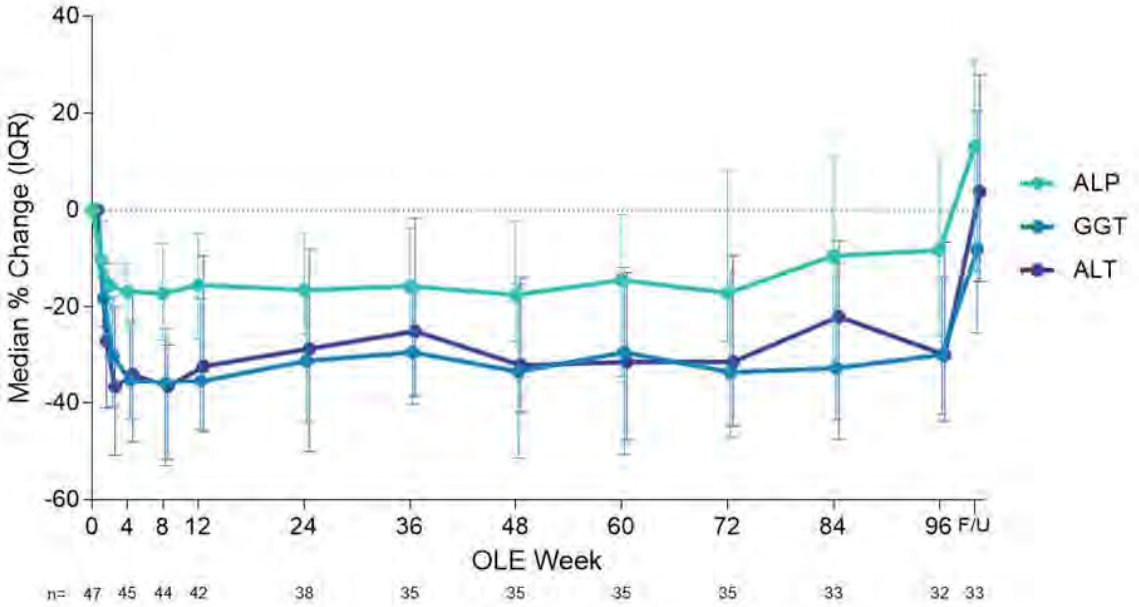
At Week 12, more participants had a clinically relevant serum ALP response, defined as a ≥ 25% relative reduction from baseline, in the CILO 100 mg group (35%, 7 of 20 participants with evaluable data; $P = 0.21$ vs placebo) compared with the CILO 30 mg group (5.3%, 1 of 19 participants; $P = 1.00$ vs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

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



Decreases in serum ALP continued during the OLE phase of the study. At Week 96 of the OLE phase, the median (Q1, Q3) reduction in serum ALP concentration was −8.3% (−25.9, 11.0; $P = 0.066$ vs OLE baseline). Upon discontinuation of CILO after 96 weeks of open-label treatment, serum ALP returned to baseline values (Figure 1-3). Among 42 participants with ALP > 1.67-times ULN at the beginning of the OLE phase, 37 participants competed Week 12, and 12 of these participants (32%) had a ≥ 25% relative reduction in serum ALP 12 weeks after initiating treatment with CILO 100 mg during the OLE phase.

Figure 1-3. **GS-US-428-4025: Relative Changes in Liver Biochemistry Parameters During the OLE Phase (Evaluable Participants, Full Analysis Set)**



All $P < 0.05$ versus baseline except for ALP at Weeks 84 ($P = 0.133$) and 96 ($P = 0.66$); ALT at Week 84 ($P = 0.0509$); and all markers at follow-up.
Follow-up = 4-week posttreatment follow-up (Week 100)
ALT available in 44 and 34 participants at Weeks 4 and 48, respectively.

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 participants with PSC.

Table 1-2. GS-US-428-4025: Overall Summary of Biochemical and Biomarker Responses From Baseline to Week 12 (Evaluable Participants, 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)	19.4 (-12.3, 32.1)	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; C4 = 7-alpha-hydroxy-4-cholesten-3-one; CILO = Cilofexor; CRP = C-reactive protein; ELF = enhanced liver fibrosis; GGT = gamma-glutamyltransferase; PIII-NP = procollagen III amino terminal peptide; TIMP = tissue inhibitor of metalloproteinases; 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 liquid chromatography-mass spectrometry (LC/MS).

1.2.8.2. Treatment With CILO Results in Significant Improvement in Liver Biochemistry and Biomarkers in Participants With PSC

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

Data from the OLE phase with CILO 100 mg daily support these findings. At Week 96 of the OLE phase, the median (Q1, Q3) reductions from OLE baseline in serum liver biochemistry tests were −29.8% (−42.3, −13.9; $P < 0.001$) for GGT, −29.8% (−43.7, −6.6; $P = 0.002$) for ALT, and −16.7% (−35.3, 1.0; $P = 0.010$) for AST (Figure 1-3). At Week 96, CILO treatment was also associated with a significant median (Q1, Q3) reduction in serum C4 (−29.8% [−64.3, −8.5]; $P = 0.001$). In participants with detectable serum bile acids at baseline (n = 40), bile acids decreased −23.9% (−44.4, −0.6; $P = 0.006$) at Week 48 (n = 28) and −25.7% (−35.9, 53.7; $P = 0.912$) at Week 96 (n = 26). No improvements in markers of fibrosis such as ELF score or FibroTest score were observed at Week 96 of the OLE phase; however, the absence of an untreated control group precludes definitive conclusions.

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

1.2.8.3. 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 participants in each treatment group experienced at least 1 AE: CILO 100 mg, 18 of 22 participants (81.8%); CILO 30 mg, 14 of 20 participants (70.0%); and placebo, 10 of 10 participants (100.0%). Most AEs were Grade 1 or 2 in severity. Four participants discontinued study treatment in the double-blind phase due to AEs: 3 participants (13.6%) in the CILO 100 mg group (due to acute kidney injury, pruritus, and increased ALP, respectively), 1 participant (5.0%) in the CILO 30 mg group (due to pyrexia, pruritus, and rash pruritus), and 1 participant (10.0%) in the placebo group (due to increased AST, ALT, and ALP). No deaths were reported during the study.

During the OLE phase, at least 1 AE was reported in most participants in the combined CILO group (43 of 47 participants, 91.5%); the majority of reported AEs were Grade 1 or 2 in severity (Table 1-4). Grade 3 or higher AEs were reported in 12 participants (25.5%) including 1 participant (2.1%) with a Grade 4 AE (sepsis). Adverse events considered related to study drug were reported in 13 participants (27.7%); study drug-related Grade 3 AEs were reported in 4 participants (8.5%). Serious AEs were reported in 10 participants (21.3%); none were considered related to study drug. Adverse events leading to premature discontinuation of study drug were reported in 10 participants (21.3%). No deaths were reported in the OLE phase.

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%)	14(70.0%)	32 (76.2%)	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%)	6 (30.0%)	11 (26.2%)	2 (20.0%)
Treatment-related AE with grade of 3 or higher	1 (4.5%)	1 (5.0%)	2 (4.8%)	1 (10.0%)
Treatment-related AE with Highest grade of 3	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%)	1 (5.0%)	4 (9.5%)	1 (10.0%)
Death during the study	0	0	0	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; OLE = open-label extension; TE = treatment-emergent; TEAE = treatment-emergent adverse event
Adverse events were coded according to MedDRA Version 23. Severity grades were defined by the CTCAE Version 4.03. TEAEs of the blinded phase began on or after the study drug start date of the blinded phase up to 30 days after permanent discontinuation of study drug in blinded phase (and before the first dose date in OLE phase), or led to premature study drug discontinuation.
Death includes any death that occurred during the study phase.

Table 1-4. GS-US-428-4025: Overall Summary of Treatment-Emergent Adverse Events, OLE Phase (OLE Analysis Set)

	OL CILO Previously in			OL CILO Total (N = 47)
	CILO 100 mg (N = 19)	CILO 30 mg (N = 18)	Placebo (N = 10)	
AE	17 (89.5%)	17 (94.4%)	9 (90.0%)	43 (91.5%)
AE with grade of 3 or higher	5 (26.3%)	6 (33.3%)	1 (10.0%)	12 (25.5%)
AE with highest grade of 3	4 (21.1%)	6 (33.3%)	1 (10.0%)	11 (23.4%)
AE with highest grade of 4	1 (5.3%)	0	0	1 (2.1%)
Treatment-related AE	7 (36.8%)	5 (27.8%)	1 (10.0%)	13 (27.7%)
Treatment-related AE with grade of 3 or higher	1 (5.3%)	3 (16.7%)	0	4 (8.5%)
Treatment-related AE with Highest Grade of 3	1 (5.3%)	3 (16.7%)	0	4 (8.5%)
SAE	4 (21.1%)	4 (22.2%)	2 (20.0%)	10 (21.3%)
Treatment-related SAE	0	0	0	0
AE leading to premature discontinuation of study drug	3 (15.8%)	5 (27.8%)	2 (20.0%)	10 (21.3%)
Death during the study	0	0	0	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; OL = open label; OLE = open-label extension; TE = treatment-emergent; TEAE = treatment-emergent adverse event
Adverse events were coded according to MedDRA Version 23. Severity grades were defined by the CTCAE Version 4.03.
TEAEs of the OLE phase began on or after the study drug start date of the OLE phase up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Death includes any death that occurred during the study phase.

1.2.8.4. Adverse Events

Table 1-5 presents the treatment-emergent AEs (TEAEs) reported for ≥ 2 participants 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 1-6 presents the TEAEs reported for ≥ 10% of participants during the OLE phase. The most common AEs in the combined CILO treatment group during the OLE phase were pruritus, nasopharyngitis, headache upper abdominal pain, and fatigue. Most AEs were Grade 1 or 2 in severity and deemed not to be treatment-related by the investigator.

Table 1-5. GS-US-428-4025: Treatment-Emergent Adverse Events by Preferred Term Reported in More than 10% of Participants in the Pooled Cilofexor or Placebo Group – Blinded Phase (Safety Analysis Set)

Preferred Term	GS-9674 100 mg (N = 22)	GS-9674 30 mg (N = 20)	GS-9674 Pooled (N = 42)	Placebo (N = 10)
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	4 (18.2%)	2 (10.0%)	6 (14.3%)	1 (10.0%)
Fatigue	3 (13.6%)	3 (15.0%)	6 (14.3%)	2 (20.0%)
Headache	1 (4.5%)	4 (20.0%)	5 (11.9%)	2 (20.0%)
Alanine aminotransferase increased	0	0	0	2 (20.0%)
Aspartate aminotransferase increased	0	0	0	2 (20.0%)
Nausea	0	1 (5.0%)	1 (2.4%)	3 (30.0%)

AE = adverse event; OLE = open-label extension; PT = preferred term; TEAE = treatment-emergent adverse event
Adverse events were coded according to MedDRA Version 23.
TEAEs of the blinded phase began on or after the study drug start date of the blinded phase up to 30 days after permanent discontinuation of study drug in blinded phase (and before the first dose date in OLE phase), or led to premature study drug discontinuation.
Multiple AEs were counted only once per participant for each PT.
PTs were presented by decreasing frequency in the GS-9674 100 mg group.

Table 1-6. GS-US-428-4025: Treatment-Emergent Adverse Events Reported for at Least 10% of Participants in the Combined CILO Group by Preferred Term (PT), OLE Phase (OLE Analysis Set)

	OL CILO Previously in			
Preferred Term	CILO 100 mg (N = 19)	CILO 30 mg (N = 18)	Placebo (N = 10)	OL CILO Total (N = 47)
Pruritus	7 (36.8%)	9 (50.0%)	4 (40.0%)	20 (42.6%)
Nasopharyngitis	7 (36.8%)	5 (27.8%)	2 (20.0%)	14 (29.8%)
Headache	1 (5.3%)	5 (27.8%)	1 (10.0%)	7 (14.9%)
Abdominal pain upper	1 (5.3%)	2 (11.1%)	3 (30.0%)	6 (12.8%)
Fatigue	2 (10.5%)	2 (11.1%)	2 (20.0%)	6 (12.8%)
Arthralgia	2 (10.5%)	3 (16.7%)	0	5 (10.6%)
Influenza	1 (5.3%)	3 (16.7%)	1 (10.0%)	5 (10.6%)
Nausea	1 (5.3%)	3 (16.7%)	1 (10.0%)	5 (10.6%)

AE = adverse event; OL = open label; OLE = open-label extension; PT = preferred term; TEAE = treatment-emergent adverse event
Adverse events were coded according to MedDRA Version 23.
TEAEs of the OLE phase began on or after the study drug start date of the OLE phase up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Multiple AEs were counted only once per participant for each PT.
PTs were presented by descending order of the total frequencies.

Table 1-7 presents Grade 3 TEAEs reported during the double-blind phase. No Grade 4 AEs were reported. Overall, Grade 3 AEs were uncommon. A total of 3 Grade 3 AEs were reported in > 1 participant: pruritus (2 participants each in the CILO 100 mg and CILO 30 mg groups and 1 participant in the placebo group); increased blood ALP (1 participant each in the CILO 100 mg and placebo groups); and muscle spasms (1 participant each in the CILO 100 mg and CILO 30 mg groups).

Table 1-7. 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 participants 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

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; OLE = open-label extension; PT = preferred term; TEAE = treatment-emergent adverse event
Adverse events were coded according to MedDRA Version 23. Severity grades were defined by the CTCAE Version 4.03.
TEAEs of the blinded phase began on or after the study drug start date of the blinded phase up to 30 days after permanent discontinuation of study drug in blinded 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 participant for each PT.
PTs were presented by decreasing frequency in the GS-9674 100 mg group.

Table 1-8 presents Grade 3 or higher TEAEs reported during the OLE phase. The only Grade 3 or higher TEAEs reported in more than 1 participant in the combined CILO group were pruritus (4 participants [8.5%]) and bile duct obstruction (2 participants [4.3%]). A Grade 4 TEAE of sepsis was reported in 1 participant (2.1%). No Grade 5 TEAE were reported in the OLE phase.

Table 1-8. GS-US-428-4025: Grade 3 or Higher Treatment-Emergent Adverse Events by Preferred Term – OLE Phase (OLE Analysis Set)

	OL GS-9674 – Previously in			
Preferred Term	**CILO 100 mg (N = 19)**	**CILO 30 mg (N = 18)**	**Placebo (N = 10)**	**OL CILO Total (N = 47)**
Number (%) of participants with any TEAE of Grade 3 or higher	5 (26.3%)	6 (33.3%)	1 (10.0%)	12 (25.5%)
Pruritus	1 (5.3%)	3 (16.7%)	0	4 (8.5%)
Bile duct obstruction	0	1 (5.6%)	1 (10.0%)	2 (4.3%)
Abdominal pain	1 (5.3%)	0	0	1 (2.1%)
Abdominal pain upper	0	0	1 (10.0%)	1 (2.1%)
Anorectal discomfort	0	1 (5.6%)	0	1 (2.1%)
Cholangitis sclerosing	1 (5.3%)	0	0	1 (2.1%)
Gamma-glutamyltransferase increased	0	1 (5.6%)	0	1 (2.1%)
Hyperbilirubinaemia	0	0	1 (10.0%)	1 (2.1%)
Influenza	1 (5.3%)	0	0	1 (2.1%)
Meniscus injury	0	1 (5.6%)	0	1 (2.1%)
Myalgia	0	1 (5.6%)	0	1 (2.1%)
Organising pneumonia	1 (5.3%)	0	0	1 (2.1%)
Paraesthesia	0	1 (5.6%)	0	1 (2.1%)
Prostatitis	0	1 (5.6%)	0	1 (2.1%)
Sepsis	1 (5.3%)	0	0	1 (2.1%)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; OL = open label; OLE = open-label extension; PT = preferred term; TEAE = treatment-emergent adverse event
AEs were coded according to MedDRA Version 23. Severity grades were defined by the CTCAE Version 4.03.
TEAEs of the OLE phase began on or after the study drug start date of the OLE phase up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Multiple AEs were counted only once per participant for each PT.
PTs were presented by descending order of the total frequencies.

1.2.8.5. Serious Adverse Events

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

In the OLE phase, SAEs were reported in 10 participants (21.3%) in the combined CILO group; none were considered related to study drug. The only SAE reported in more than 1 participant in the OLE phase was bile duct obstruction in 2 participants (4.3%). One participant previously in the blinded phase CILO 30 mg group had a Grade 3 SAE of bile duct obstruction and another participant previously in the blinded phase placebo group had a Grade 3 SAE of bile duct obstruction. Both SAEs resolved.

1.2.8.6. PK Results

The average steady-state GS-1056756 plasma concentration in participants 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 h*ng/mL, C_{max} was 35.5 ng/mL, and $t_{1/2}$ was approximately 175 hours.

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. The 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 patients with PSC, 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 participants 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. Specifically, a ≥ 25% relative reduction in serum ALP from baseline to Week 12 was observed in 35% of participants (7 of 20) in the CILO 100 mg group and 5.3% of participants (1 of 20) in the CILO 30 mg group compared with 10% of participants (1 of 10) in the placebo group. 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 participants, those treated with CILO 100 mg had greater reductions in other markers of cholestasis (eg, serum GGT, bile acids, and C4), hepatic inflammation (eg, ALT and AST), and fibrosis (eg, TIMP-1). Improvements in liver biochemistry and pharmacodynamic markers of FXR activation were also observed during open-label therapy with CILO 100 mg daily for up to 96 weeks. Based on these Phase 2 data, CILO is hypothesized to be beneficial in participants with PSC.

Inclusion criteria for this study were developed in order to identify participants with large duct PSC without cirrhosis. These participants are at an increased risk of PSC-related sequelae including progression to cirrhosis and its complications including hepatic decompensation, the need for liver transplantation, and death. Participants with clinical and histologic evidence of cirrhosis will be excluded from this study due to the uncertain PK and PD properties of CILO in the setting of PSC-related cirrhosis. Targeting interventions in the currently proposed study population will provide evidence for the safety and efficacy of CILO in participants at risk for progressive hepatic fibrosis and the development of cirrhosis. The 96-week OLE phase of the study will provide additional data regarding the long-term safety and efficacy of CILO in this patient population.

1.4. Rationale for Dose Selection of CILO

The dose of CILO 100 mg administered orally once a day was selected for the Phase 3 study. The rationale for this dose was based on the safety, efficacy and PK data from the dose-ranging, Phase 2 PSC study (GS-US-428-4025) and supported by data from the Phase 2 NASH study (GS-US-402-1852) and Phase 1 studies. In addition, CILO exhibits less dose proportional increases in exposure above 100 mg, which may provide only marginal incremental benefits in efficacy with a higher potential risk of pruritus at doses higher than 100 mg.

In the Phase 2 PSC study, the magnitude of improvements in serum ALP, other liver biochemistry tests (ALT, AST, GGT), TIMP-1, serum bile acids, and CRP after 12 weeks of treatment with CILO were greater with the 100 mg dose compared to the 30 mg dose. CILO 100 mg resulted in significant relative reductions from baseline to Week 12 in serum ALP (−21%), GGT (−30%), ALT (−49%), and AST (−42%) relative to placebo, whereas 30 mg CILO resulted in lesser reductions in ALP (−6%) and GGT (−16%). In the NASH Phase 2 study, reductions in liver fat by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) were greater with 100 mg than 30 mg of CILO administered over 24 weeks.

From a safety perspective, the tolerability of CILO 100 mg and 30 mg were similar in PSC participants in the Phase 2 study. Specifically, the incidence of treatment-related AEs, including Grade 2 or 3 pruritus, SAEs, and Grade 3-4 laboratory abnormalities were similar between the groups.

Data from Phase 1 studies indicate that CILO exposure following administration in the fasted state falls within the range of exposures observed when CILO is administered with food (light meal vs high-fat meal). Thus, the observed efficacy and safety in the Phase 2 PSC study in which CILO was dosed with food without regard to meal type, support administration of CILO without regard to food.

In summary, the combined safety, efficacy, and PK data for CILO support evaluation of CILO 100 mg once daily (QD) in participants with PSC in the proposed Phase 3 study.

1.5. Risk/Benefit Assessment for the Study

This study will provide information on the safety and efficacy of CILO for the treatment of patients with PSC who do not have cirrhosis, for whom no therapies exist that have been demonstrated to improve histologic or clinical outcomes. The results from this study may inform whether nonsteroidal FXR agonists such as CILO can improve biochemical parameters of cholestasis and reduce progression of liver fibrosis in patients with PSC.

The potential benefits of CILO for the treatment of PSC in the proposed study population 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. Participants with PSC randomized to the placebo control group in the study may benefit from frequent medical monitoring and close assessment of their PSC and associated pathologies during the duration of placebo treatment.

CILO is a new chemical entity, and as such, its long-term safety profile has yet to be established. 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 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 participants (31%, 13 of 42 participants treated with 100 mg or 30 mg) compared with those administered placebo (60%, 6 of 10 participants). Grade 2 or 3 pruritus was also lower with CILO 100 mg (14%, 3 of 22 participants) and 30 mg (20%, 4 of 20 participants) compared with placebo (40%, 4 of 10 participants). Only 1 participant treated with CILO 100 mg discontinued treatment due to pruritus during the blinded phase of the study. In the OLE phase of this study, Grade 2-3 pruritus has been reported in 13 of 47 PSC participants (28%) treated with CILO 100 mg and 5 participants (10.6%) have discontinued treatment prematurely due to pruritus. To mitigate the risk of treatment discontinuation due to pruritus, a pruritus management plan has been included in this Phase 3 study protocol (see Section 7.5, Toxicity Management: Pruritus Management). This plan includes temporary 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 participants. Specifically, Grade 3 or 4 ALT elevation was observed in 3.9% of participants (6 of 154) treated with CILO and 2.6% of participants (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 participants, respectively. In the majority of these cases, an alternative etiology was identified including natural fluctuations in underlying disease activity and biliary obstruction in a participant with PSC that resolved following endoscopic intervention. To mitigate the potential risk of liver injury in the planned Phase 3 study, participants will be monitored closely; defined rules for close observation and drug cessation due to elevated liver tests have been specified in the protocol; and all potential cases of drug hepatotoxicity will be adjudicated by an independent Drug-Induced Liver Injury (DILI) Adjudication Committee (see Section 7.5, Toxicity Management: Observation for Drug-Induced Liver Injury). Moreover, study drug will be discontinued in participants with clinical or histologic evidence of progression to cirrhosis.

Additional risks to study participants 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. Moreover, liver biopsy is an invasive procedure that may be associated with pain, bleeding, and rarely death. Strategies to mitigate these risks include close monitoring of lab values as well as AEs. Parameters for discontinuation of the study drugs due to AEs and non–hepatic laboratory abnormalities are also defined and will be closely followed.

As PSC is a serious, life-threatening condition with large unmet medical need, the potential benefits of treatment with CILO 100 mg, as described above, outweigh the known risks. The available data in PSC participants treated, as well as the favorable safety profile seen across ongoing and completed studies, provide strong support for the evaluation of CILO in this Phase 3 study of participants with PSC.

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 as follows:

- To evaluate whether CILO reduces the risk of fibrosis progression among noncirrhotic participants with PSC at Blinded Study Phase Week 96

The **secondary objectives** of this study are as follows:

- To assess the safety and tolerability of CILO
- To evaluate changes in serum concentrations of ALP, ALT, and bile acids at Blinded Study Phase Week 96
- To evaluate whether CILO increases the proportion of participants with ≥ 25% relative reduction in serum ALP concentration from baseline (biochemical response) and no worsening of fibrosis according to the Ludwig classification (histologic response) at Blinded Study Phase Week 96
- To evaluate fibrosis stage improvement at Blinded Study Phase Week 96
- To evaluate changes in noninvasive markers of fibrosis, including liver stiffness by FibroScan and enhanced liver fibrosis test (ELF test) score at Blinded Study Phase Week 96
- To evaluate change in PSC Symptoms – Module 1 based on the disease-specific PSC patient-reported outcome (PSC-PRO) at Blinded Study Phase Week 96

The **exploratory objectives** of this study are as follows:

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- CCI [redacted]

3. STUDY DESIGN

3.1. Study Design Overview

This is a Phase 3, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of CILO in participants with PSC without cirrhosis. The study will consist of 2 phases: a Blinded Study Phase and an Open-label Extension (OLE) Phase.

Blinded Study Phase: Includes a 10-week screening period, 96 weeks of treatment, and a Blinded Study Phase follow-up visit 4 weeks after completion of Blinded Study Phase Week 96 or early termination (ET). Participants meeting the study's entry criteria will be randomly assigned in a 2:1 ratio to receive CILO 100 mg orally once daily or placebo. Randomization will be stratified by the presence or absence of UDCA use and presence or absence of bridging fibrosis (Ludwig fibrosis score, F3 versus F0, F1, and F2) on the screening liver biopsy. Study drug will be administered for a total of 96 weeks from the baseline/Day 1 visit.

Participants who do not permanently discontinue study drug, complete the Blinded Study Phase Week 96 with an evaluable biopsy (noncirrhotic F0-F3) as determined by the central reader and Blinded Study Phase follow-up visit will be eligible to enter into the OLE Phase.

Interim Analysis:

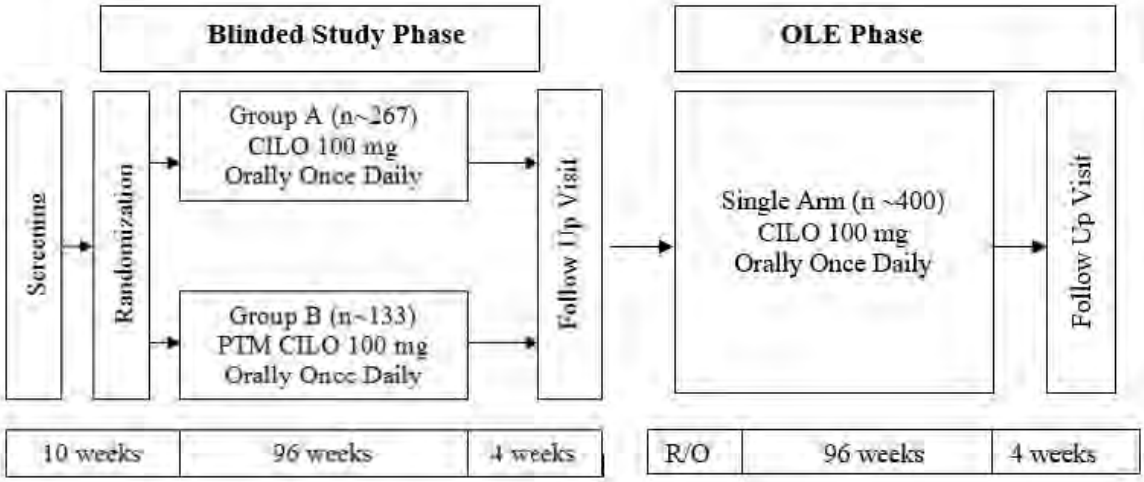
There will be 1 planned interim futility analysis based on the primary endpoint after the first 160 randomized and dosed participants have completed Week 96 or ET assessments in the Blinded Study Phase. A predictive power (PP) approach will be used for futility assessment. The DMC may recommend early termination of the study due to futility if the criterion of PP $\leq$ 10% is met.

If the DMC recommends early termination of the study, a restricted group of senior management at Gilead will be unblinded to evaluate the study data. Unblinding of specific Gilead personnel will be documented per the appropriate standard operating procedures (SOPs).

Open-label Extension Phase: Includes 96 weeks of open-label treatment and an OLE Phase follow-up visit 4 weeks after completion of the OLE Phase Week 96 visit or ET visit.

The overall study design is presented graphically in Figure 3-1.

Figure 3-1. Overall Study Design



CILO = cilofexor; OLE = open-label extension; PTM = placebo to match; R/O = rollover.

Note:

1) Participants are required to return for a Blinded Study Phase follow-up visit 4 weeks after the Blinded Study Phase Week 96 visit or ET visit.

2) For participants who have consented to and are eligible for the OLE Phase, Gilead recommends completion of the OLE Phase baseline/Day 1 visit within 30 days of completion of the Blinded Study Phase follow-up visit. However, there may be circumstances where the OLE Phase baseline/Day 1 visit will occur more than 30 days after completion of the Blinded Study Phase follow-up visit. Under such circumstances, approval of the Gilead medical monitor will be required and participants will be required to complete select safety assessments prior to the OLE Phase baseline/Day 1 visit.

3) If the Blinded Study Phase follow-up visit and the OLE Phase baseline/Day 1 visit occur on the same day, study assessment procedures should be performed according to the OLE Phase baseline/Day 1 visit.

4) Participants who have consented to and are eligible for the OLE Phase will begin open-label treatment with CILO 100 mg orally once daily.

5) For both the Blinded Study Phase and the OLE Phase, at the discretion of the PI, study drug dosing may be temporarily interrupted, for example, due to an AE. During the period of study drug dosing interruption or reduction, for both the Blinded Study Phase and the OLE Phase, participants should continue with study visits per the Study Procedures Table (Appendix 2). Dosage and administration of the study drug and reference product are described in Section 5.3.

3.2. Study Treatments

Blinded Study Phase:

- Treatment Group A: 1 CILO 100 mg tablet administered orally once daily
- Treatment Group B: 1 placebo-to-match (PTM) CILO 100 mg tablet administered orally once daily

OLE Phase: CILO 100-mg tablet administered orally once daily.

3.3. Duration of Treatment

Participants will be treated for up to 96 weeks during the Blinded Study Phase. Participants who are enrolled in the OLE Phase will be treated for up to 96 weeks during the OLE Phase. Total treatment duration including both the Blinded Study Phase and the OLE Phase will be up to 192 weeks.

Individual participant participation in the Blinded Study Phase can last up to approximately 110 weeks (consisting of a 10-week screening period, a 96-week Blinded Study Phase treatment period, and a 4-week Blinded Study Phase follow-up period).

For participants who have consented to and are eligible for the OLE Phase, participation in the OLE Phase can last up to approximately 104 weeks (consisting of an approximately 4-week roll-over period, a 96-week open-label treatment period, and a 4-week OLE Phase follow-up period).

3.4. Adjudication Committees

3.4.1. Hepatic Events Adjudication Committee

An objective of this study is to evaluate whether CILO treatment will prevent progression to cirrhosis and associated complications. A composite of clinical events that constitute this clinical efficacy endpoint have been identified and include:

1) Progression to cirrhosis as defined by a liver biopsy showing F4 fibrosis according to the Ludwig classification in the opinion of the central reader or clinical evidence (eg, based on the presence of newly diagnosed esophageal varices, changes in biomarkers [including, but not limited to, low serum albumin, high serum bilirubin, a low platelet count, prolonged INR, or elevated liver stiffness], imaging parameters [eg, nodular liver, portosystemic collateral veins, or splenomegaly], or development of other clinical signs or symptoms of cirrhosis).

2) AEs of hepatic decompensation including:

   a) Clinically apparent ascites

   b) Hepatic encephalopathy (HE) of Grade 2 or above (according to the West Haven Criteria defined in Appendix 5) requiring treatment

   c) Portal hypertension-related upper gastrointestinal bleeding (including AEs of bleeding from esophageal varices, gastric varices, and portal hypertensive gastropathy) identified by endoscopy and requiring hospitalization

3) Liver transplantation or qualification for liver transplantation, defined as MELD score ≥ 15 on at least 2 consecutive occasions at least 4 weeks apart

4) All-cause mortality

Each of the clinical AEs (except histologic progression to cirrhosis, all-cause mortality, and liver transplantation) will require confirmation by a Hepatic Events Adjudication Committee. All deaths will be reviewed by this committee to determine if they are liver related. The committee will also review all cases of cholangiocarcinoma, HCC, ascending cholangitis, and dominant strictures as events of special interest.

The adjudication of these AEs will be performed in a blinded fashion for the purposes of data analysis. The Hepatic Events Adjudication Committee's specific activities will be defined by a charter that will define the Hepatic Events Adjudication Committee's membership, conduct, and meeting schedule as well as provide detailed definitions for each AE. The Data Monitoring Committee (DMC, Section 8.10) and Hepatic Events Adjudication Committee members will be independent of each other. Adjudication of the AEs will be applicable in the Blinded Study Phase and the OLE Phase.

Once the clinical AE has been confirmed by the Hepatic Events Adjudication Committee, or a participant has histologic progression to cirrhosis, undergoes liver transplantation, or develops cholangiocarcinoma or HCC; the participant must discontinue study drug, but should continue with study visits per the Study Procedures Table (Appendix 2). Events of special interest such as ascending cholangitis and dominant strictures that are confirmed by the Hepatic Events Adjudication Committee may continue study drug and continue study visits per the Study Procedures Table (Appendix 2).

3.4.2. Drug-Induced Liver Injury (DILI) Adjudication Committee

Due to the challenge of recognizing and diagnosing DILI in participants with preexisting hepatic dysfunction, a DILI Adjudication Committee will review potential cases of DILI (refer to Section 7.5.1). DILI AEs will be adjudicated as the AEs are identified. Participants will be categorized as those for whom DILI or worsening of hepatic function attributable to study drug could be excluded (eg, a clear and alternative explanation exists); those for whom DILI or worsening of hepatic function attributable to study drug could not be excluded (eg, no clear and alternative explanation exists); and those with insufficient data to make a determination.

3.5. Biomarker Testing

3.5.1. Biomarker Samples to Address the Study Objectives

Biological specimens will be collected from all participants who have provided consent to participate in this study and may be used to evaluate the association of systemic and/or tissue 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, tissue, 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 (eg, FGF19, C4, and bile acids) may also be determined. Biomarkers that may be useful in predicting the occurrence of pruritus, such as serum autotaxin, lysophosphatidic acid, and bile acids may also be assessed. Stool samples (if available) will be collected for bile acids, and potentially microbiome analyses, and stool calprotectin may be analyzed to assess intestinal inflammation. Analysis of RNA levels in tissue may be used to evaluate changes in disease-related biomarkers and biomarkers of FXR activity.

Samples will be destroyed no later than 15 years after the end of the study. CCI [redacted]

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4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

This study will enroll approximately 400 participants, between 18-75 years old with noncirrhotic PSC.

4.1.1. Participant Replacement

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

4.2. Inclusion Criteria

Participants 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 between 18-75 years of age; inclusive based on the date of the screening visit
3) Diagnosis of large duct PSC based on cholangiogram (MRCP, endoscopic retrograde cholangiopancreatography [ERCP], or percutaneous transhepatic cholangiogram [PTC])
4) Liver biopsy at screening deemed acceptable for interpretation and demonstrates stage F0 - F3 fibrosis (according to the Ludwig classification) in the opinion of the central reader
    a) A historical liver biopsy within 6 months of the screening visit may be accepted as the screening biopsy if the sample is deemed acceptable for interpretation by the central reader
5) Participant has the following laboratory parameters at the screening visit, as determined by the central laboratory:
    a) Platelet count $\geq 150{,}000/mm^3$
    b) Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min, as calculated by the Cockcroft-Gault equation
    c) ALT $\leq 8 \times$ ULN
    d) Total bilirubin < 2 mg/dL, unless the participant is known to have Gilbert's syndrome or hemolytic anemia
    e) INR ≤ 1.4, unless due to therapeutic anticoagulation
    f) Negative antimitochondrial antibody

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

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

10) Participants 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

Participants 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) Cirrhosis as defined by any of the following:

      i) Liver biopsy demonstrating stage F4 fibrosis according to the Ludwig classification (or equivalent)

      ii) Decompensated liver disease, including ascites, HE, or variceal hemorrhage

      iii) Liver stiffness > 20.0 kPa by FibroScan

   b) Liver transplantation

   c) Cholangiocarcinoma or HCC. If a dominant stricture has been identified, cholangiocarcinoma must be adequately excluded in the opinion of the PI prior to Day 1.

   d) Ascending cholangitis within 30 days of screening

2) Presence of a percutaneous drain or biliary stent

3) Other causes of liver disease including immunoglobulin G4 (IgG4)-related sclerosing cholangitis; autoimmune hepatitis/PSC overlap syndrome; secondary sclerosing cholangitis; small duct PSC (histologic evidence of PSC with normal bile ducts on cholangiography); and viral, metabolic, alcoholic, and other autoimmune conditions. Participants with hepatic steatosis may be included if there is no evidence of NASH on liver biopsy in the opinion of the central reader.

4) 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.

      Participants 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.

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

6) MELD score > 12 at screening, unless due to an alternate etiology such as therapeutic anticoagulation

7) HIV infection (HIV antibody [Ab] and HIV RNA positive)

8) HBV infection (hepatitis B surface antigen [HBsAg] positive)

9) HCV infection (HCV Ab and HCV RNA positive). Participants cured of HCV infection ≥ 2 years prior to screening are eligible.

10) Current moderate to severe IBD (including ulcerative colitis, Crohn's disease, and indeterminate colitis) defined as a screening visit Partial Mayo score of > 4, and/or a score in the screening visit rectal bleeding domain > 1, unless bleeding is due to perianal disease. See Section 6.9.6.

    Note: Participants with IBD who currently have an external ostomy bag are not subject to this exclusion criterion and need not undergo Partial Mayo evaluation at screening.

11) 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)

12) Use of antibiotics (eg, vancomycin, metronidazole, and 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.

13) Use of any prohibited concomitant medications as described in Section 5.5

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

15) Concurrent participation in another therapeutic clinical study

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

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

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

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

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Code Access

5.1.1. Randomization

Blinded Study Phase:

An interactive response technology (IRT) will be used for centralized randomization and treatment assignment. Randomization will be stratified by the presence or absence of UDCA use and presence or absence of bridging fibrosis (Ludwig fibrosis score, F3 versus F0, F1, F2) based on screening liver biopsy.

Investigative site personnel will obtain the participant's identification number and study drug assignment from the IRT. Participants and all personnel directly involved in the conduct of the study will be blinded to treatment assignment.

Study drug will be dispensed by the study pharmacist, or designee in a blinded fashion to the participants.

OLE Phase:

An IRT will be used for study drug dispensation during the OLE Phase. Participants, investigative site personnel, and all personnel directly involved in the conduct of the study will not be blinded to the open-label treatment assignment.

5.1.2. Blinding

During the Blinded Study Phase, participants and all personnel directly involved in the conduct of the study will be blinded to treatment assignment. Specified personnel may be unblinded based on their study role. Study drug will be dispensed by the study pharmacist, or designee, in a blinded fashion to the participants. After all participants have completed Blinded Study Phase Week 96 or ET, the treatment assignments will be unblinded to the sponsor only. Investigators and participants will remain blinded to the Blinded Study Phase treatment assignment until approximately 6 weeks after all participants have completed the OLE Phase follow-up visit. The PK File Administrator, or designee in Bioanalytical Operations and/or Clinical Data Management, who facilitates the data transfer of PK files between Gilead and vendors, will remain unblinded. Individuals in Clinical Packaging & Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in the IRT system for purposes of study drug inventory management will remain unblinded. Individuals in Global Patient Safety (GLPS) responsible for safety signal detection, investigational new drug (IND) safety reporting and/or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) may be unblinded to individual case data and/or group level summaries. Regulatory Quality and Compliance personnel in Research and Development may also be unblinded for purposes of supporting Quality Assurance activities and/or Regulatory Agency inspections. Biostatisticians and programmers employed by contract research organizations (CROs) may be unblinded to verify treatment assignment and for DMC data review as needed.

If the DMC recommends early termination of the study, a restricted group of senior management at Gilead will be unblinded to evaluate the study data. Unblinding of specific Gilead personnel will be documented per the appropriate SOPs.

5.1.3. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the participant, the investigator may obtain treatment assignment directly from the IRT system for that participant. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine participant emergency medical care. The rationale for unblinding must be clearly explained in source documentation along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical study and therefore, if a participant's treatment assignment is disclosed to the investigator, the participant will have study treatment discontinued. All participants will be followed until study completion unless consent to do so is specifically withdrawn by the participant.

5.2. Description and Handling of CILO and PTM CILO

5.2.1. Formulation

CILO is supplied as 100 mg and 30 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 polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, yellow iron oxide, and black iron oxide. CILO 100 mg tablets are capsule-shaped, film-coated green tablets debossed with "100" on one side and "GSI" on the other side. CILO 30 mg tablets are round, film-coated green tablets debossed with "30" on one side and "GSI" on the other side.

Placebo-to-match (PTM) CILO 100 mg and 30 mg tablets are identical in size, shape, color, debossing and appearance to their corresponding strengths of active CILO tablets. PTM CILO tablets contain the following ingredients: lactose monohydrate; microcrystalline cellulose; croscarmellose sodium; magnesium stearate; and film-coating material comprised of polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, yellow iron oxide, and black iron oxide.

5.2.2. Packaging and Labeling

CILO tablets and PTM CILO tablets are packaged in white, high-density polyethylene 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 drugs 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), EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

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Until dispensed to the participants, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, study drugs 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 drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling CILO tablets and PTM CILO tablets.

5.3. Dosage and Administration of CILO/PTM CILO

CILO and PTM CILO tablets will be provided by Gilead. During the treatment phase of the study, each participant will be supplied with bottles of CILO 100 mg or PTM CILO 100 mg. Dosing for each treatment group in the treatment phase will be as follows:

- **Treatment Group A**: 1 CILO 100-mg tablet administered orally once daily
- **Treatment Group B**: 1 PTM CILO 100-mg tablet administered orally once daily

Participants who require dosage reduction of CILO due to pruritus or AE will be supplied with bottles of CILO 30 mg or PTM CILO 30 mg.

During the OLE Phase of the study, participants will be provided with bottles of 100-mg CILO only, unless reassigned to the 30-mg dose due to tolerability. The dose of CILO may be reduced from 100 mg to 30 mg (or subsequently increased back to 100 mg) at the PI's discretion with the approval of the medical monitor, as required.

For both the Blinded Study Phase and OLE Phase, at the discretion of the PI, study drug dosing may be temporarily interrupted, for example, due to an AE. During the period of study drug dosing interruption, participants should continue with study visits per the Study Procedures Table (Appendix 2). Study drug dosing may be reinitiated at the discretion of the PI. Dose interruption/reduction for the management of pruritus (see Section 7.5.3) or for other AEs (see Section 7.5.4) is permitted.

The study drug dose should be taken at approximately the same time each day.

A dose will be considered missed if the participant cannot take the dose within 12 hours of their regular dosing time. If a participant misses a dose, the participant 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 drugs 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® US prescribing information. Participants taking atorvastatin with CILO should be monitored as per label recommendations.

There are no substantial safety data regarding the concomitant administration of the COVID-19 vaccines and CILO. Participants are allowed to receive the COVID-19 vaccine, and study visits should continue as planned if vaccination occurs while the participant is on the study. Investigators should follow local guidelines for concomitant administration of the COVID-19 vaccines with the study drug.

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 [G-CSF]; thrombopoietin [TPO] mimetics)
- Investigational agents or devices for any indication. Participants enrolled in the current protocol may participate concurrently in a HepQuant™ sponsored investigational device study at participating US sites only (Investigational Device Exemption # G170034/S007), once approved by the applicable IRB/IEC.
- 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 drugs may result in PK interactions resulting in increases or decreases in exposure of study drugs or concomitant medications. 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[c], 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[e], Colestipol[e], Colestilan
Other[e]	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 and 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
e Not approved in Japan

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, and transplantation) are not listed under this prohibited medication section and are disallowed in the study. For participants 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 participants not on UDCA at screening, UDCA should not be administered during the treatment period.

5.6. Accountability for CILO/PTM CILO

The investigator is responsible for ensuring adequate accountability of all used and unused study drugs. This includes acknowledgement of receipt of each shipment of study drugs (quantity and condition). All used and unused study drugs dispensed to participants 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 drugs kits
- Record the date, participant number, and the study drugs kit number dispensed
- Record the date, quantity of used and unused study drugs 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 participant 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 CRO.

6.1. Blinded Study Phase Participant 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 participants are eligible to participate in the study prior to randomization and throughout the study.

Documentation of the personally signed and dated informed consent of each participant 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 participant's identification number and study drug assignment from the IRT.

6.2. Blinded Study Phase Pretreatment Assessments - Screening Visit

Participants will be screened within 10 weeks before randomization to determine eligibility for participation in the study. The screening period may be extended under special circumstances with the explicit approval of the medical monitor.

Participants who fail to meet eligibility criteria may be rescreened once if there is a reasonable expectation that the participant will meet eligibility after repeat screening. Retesting of participant'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 IRT
- Obtain medical history
- Review and record whether the participant meets inclusion and exclusion criteria

- Calculate Partial Mayo score for participants with IBD (as appropriate, see Section 6.9.6)
- Complete physical examination (PE) 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 participants of childbearing 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 (if available)
- CP and MELD scores
- Perform liver biopsy and provide liver tissue for central reading (if required)
  - A historical liver biopsy within 6 months of the screening visit may be accepted as the screening biopsy if the sample is deemed acceptable for interpretation by the central reader.
- Record any SAEs and all AEs related to protocol-required procedures occurring after signing of the ICF.
- Record all concomitant medications that the participant has taken within 28 days prior to screening

Participants meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 10 weeks after screening for randomization into the study.

From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any AEs related to protocol-required procedures on the AEs eCRF. 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 case report form (CRF)/eCRF. See Section 7: Adverse Events and Toxicity Management, for additional details.

6.3. Blinded Study Phase Baseline/Day 1 Randomization and Assessments

Participants returning to the clinic for randomization at 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, participants will be randomized to study drug assignment and receive their Participant Identification Number via the IRT prior to their first dose of study drug. Randomization will be stratified by the presence or absence of UDCA use and presence or absence of bridging fibrosis (F3 versus F0, F1, F2 according to the Ludwig classification) on screening liver biopsy.

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

- Health resource utilization and QoL Questionnaires (Short Inflammatory Bowel Disease Questionnaire [SIBDQ] [for participants with a history of IBD], Chronic Liver Disease Questionnaire [CLDQ], EuroQol [5 dimensions] [EQ-5D], and PSC-PRO)

  Note: It is recommended that QoL questionnaires be completed prior to any study procedures being performed and prior to the participant seeing a health care provider. Refer to the Site Operations Manual for guidance on QoL questionnaire administration.

- Pruritus assessments (Pruritus visual analogue scale [VAS] and 5D-Itch)

- Calculate Partial Mayo score for participants with a history of IBD (as appropriate, see Section 6.9.6)

- Symptom-driven PE including ascites and HE assessments

- Record vital signs and body weight

- Obtain blood samples for:
  - Chemistry
  - eGFR
  - Hematology
  - Coagulation panel
  - Lipid profile
  - C-peptide, insulin, and hemoglobin A1c (HbA1c)
  - Biomarkers
  - CCI [redacted]
- Perform MRCP (+ 14 day visit window) and forward images to the central reader (if participant has no contraindications as stated in Section 6.9.11). Historical MRCP within 3 months of screening visit or a routinely performed MRCP within screening period may be used.
- CP and MELD scores
- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- Collect stool sample (if available)
- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs related to protocol-required procedures occurring since the screening visit
- Dispense study drug, and provide participant with instruction on appropriate dosing and administration

Once all visit procedures have been completed, participants will take their baseline/Day 1 dose of study drug while at the investigative site.

6.4. Blinded Study Phase Treatment Assessments

6.4.1. Blinded Study Phase Weeks 4, 8, 12, 24, and 36 (± 3 days)

Participants 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.

Participants 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:

- Health resource utilization and QoL Questionnaires (SIBDQ [for participants with a history of IBD], CLDQ, EQ-5D, and PSC-PRO) at Week 24

  Note: It is recommended that QoL questionnaires be completed prior to any study procedures being performed and prior to the participant seeing a health care provider. Refer to the Site Operations Manual for guidance on QoL questionnaire administration.

- Pruritus assessments (Pruritus VAS and 5D-Itch)
- Calculate Partial Mayo score for participants with a history of IBD (as appropriate, see Section 6.9.6)
- Symptom-driven PE including ascites and HE assessments
- Record vital signs and body weight
- Obtain blood samples for:
  - Chemistry
  - eGFR
  - Hematology
  - Coagulation panel
  - Lipid profile at Weeks 12, 24, and 36
  - C-peptide, insulin, and HbA1c at Weeks 12 and 24
  - Biomarkers at Weeks 4, 12, and 24
  - Single PK and PD sampling at Weeks 4, 12, and 36
  - CCI [redacted]

- Obtain urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- For participants with history of IBD, any evidence of active IBD seen on routinely performed colonoscopy will be captured
- Perform FibroScan (if available) at Week 24
- CP and MELD scores
- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit
- Dispense the study drug as directed by IRT
  - Review study drug compliance and drug administration instructions with participant
  - Reconcile study drug administration using pill counts

6.4.2. Blinded Study Phase Week 48 (± 14 days)

Participants 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 Week 48 visits to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

Participants 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 this visit:

- Health resource utilization and QoL Questionnaires (SIBDQ [for participants with a history of IBD], CLDQ, EQ-5D, and PSC-PRO)

  Note: It is recommended that QoL questionnaires be completed prior to any study procedures being performed and prior to the participant seeing a health care provider. Refer to the Site Operations Manual for guidance on QoL questionnaire administration.
- Pruritus assessments (Pruritus VAS and 5D-Itch)
- Calculate Partial Mayo score for participants with a history of IBD (as appropriate, see Section 6.9.6)
- Symptom-driven PE including ascites and HE assessments
- Record vital signs and body weight

- Obtain blood samples for:
  - Chemistry
  - eGFR
  - Hematology
  - Coagulation panel
  - Lipid profile
  - C-peptide, insulin, and HbA1c
  - Biomarkers
  - CCI [redacted]
  - CCI [redacted]
- Obtain urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- Collect stool sample (if available)
- For participants with history of IBD, any evidence of active IBD seen on routinely performed colonoscopy will be captured
- Perform FibroScan (if available)
- Perform MRCP and forward images to the central reader (if participant has no contraindications as stated in Section 6.9.11)
- CP and MELD scores
- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit
- Dispense the study drug as directed by IRT
  - Review study drug compliance and drug administration instructions with participant
  - Reconcile study drug administration using pill counts

6.4.3. Blinded Study Phase Weeks 60, 72, and 84 (± 3 days)

Participants 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.

Participants should 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:

- Health resource utilization and QoL Questionnaires (SIBDQ [for participants with a history of IBD], CLDQ, EQ-5D, and PSC-PRO) at Week 72

  Note: It is recommended that QoL questionnaires be completed prior to any study procedures being performed and prior to the participant seeing a health care provider. Refer to the Site Operations Manual for guidance on QoL questionnaire administration.

- Pruritus assessments (Pruritus VAS and 5D-Itch)
- Calculate Partial Mayo score for participants with a history of IBD (as appropriate, see Section 6.9.6)
- Symptom-driven PE including ascites and HE assessments
- Record vital signs and body weight
- Obtain blood samples for:
  - Chemistry
  - eGFR
  - Hematology
  - Coagulation panel
  - Lipid profile
  - Biomarkers at Week 72
  - Single PK and PD sampling at Weeks 60 and 84
  - CCI [redacted]

- Obtain urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- For participants with history of IBD, any evidence of active IBD seen on routinely performed colonoscopy will be captured
- Perform FibroScan (if available) at Week 72
- CP and MELD scores
- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit
- Dispense the study drug as directed by IRT
  - Review study drug compliance and drug administration instructions with participant
  - Reconcile study drug administration using pill counts

6.4.4. Blinded Study Phase Telephone Follow-up Visit: Week 16 (± 3 days)

A telephone follow-up visit will be completed at Week 16. The following assessments are to be completed and documented during this visit:

- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit
- Review study drug compliance with participant
- At the discretion of the investigator, an unscheduled visit may be completed if the participant reports abnormal or concerning symptoms.

6.4.5. Blinded Study Phase Week 96 (± 14 days)

Participants 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.

Participants should 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 this visit:

- Health resource utilization and QoL Questionnaires (SIBDQ [for participants with a history of IBD], CLDQ, EQ-5D, and PSC-PRO)

  Note: It is recommended that QoL questionnaires be completed prior to any study procedures being performed and prior to the participant seeing a health care provider. Refer to the Site Operations Manual for guidance on QoL questionnaire administration.

- Pruritus assessments (Pruritus VAS and 5D-Itch)
- Calculate Partial Mayo score for participants with a history of IBD (as appropriate, see Section 6.9.6)
- Symptom-driven PE including ascites and HE assessments
- Record vital signs and body weight
- Obtain blood samples for:
  - Chemistry
  - eGFR
  - Hematology
  - Coagulation panel
  - Lipid profile
  - C-peptide, insulin, and HbA1c
  - Biomarkers
  - CCI [redacted]
- Obtain urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- Collect stool sample (if available)
- For participants with history of IBD, any evidence of active IBD seen on routinely performed colonoscopy will be captured
- Perform FibroScan (if available)

- Perform MRCP and forward images to the central reader (if participant has no contraindications as stated in Section 6.9.11)
- CP and MELD scores
- Perform liver biopsy and provide liver tissue for central reading
- Review study drug compliance
  - Reconcile study drug administration using pill counts
  - All study drugs should be returned at this visit
- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

Once all visit procedures have been completed, participants will self-administer their last dose of study drug while at the investigative site.

6.4.6. Blinded Study Phase Early Termination (ET) Visit

Participants prematurely discontinuing from the study should complete an ET visit within 30 days of the last dose.

If a participant discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related procedures per the Study Procedures Table (see Appendix 2). If a participant 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.

Participants 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:

- Health resource utilization and QoL Questionnaires (SIBDQ [for participants with a history of IBD], CLDQ, EQ-5D, and PSC-PRO)

  Note: It is recommended that QoL questionnaires be completed prior to any study procedures being performed and prior to the participant seeing a health care provider. Refer to the Site Operations Manual for guidance on QoL questionnaire administration.
- Pruritus assessments (Pruritus VAS and 5D-Itch)

- Calculate Partial Mayo score for participants with a history of IBD (as appropriate, see Section 6.9.6)
- Symptom-driven PE including ascites and HE assessments
- Record vital signs and body weight
- Obtain blood samples for:
  - Chemistry
  - eGFR
  - Hematology
  - Coagulation panel
  - Lipid profile
  - C-peptide, insulin, and HbA1c
  - Biomarkers
  - Single PK and PD sampling
  - CCI [redacted]
- Obtain urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- For participants with history of IBD, any evidence of active IBD seen on routinely performed colonoscopy will be captured
- Perform FibroScan (if available)
- Perform MRCP and forward images to the central reader (if participant has no contraindications as stated in Section 6.9.11)
- CP and MELD scores
- At the discretion of the investigator, perform liver biopsy and provide liver tissue for central reading

- Review study drug compliance
  - Reconcile study drug administration using pill counts
  - All study drugs should be returned at this visit
- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

6.4.7. Blinded Study Phase Follow-up Visit (± 5 days)

Participants will return for a Blinded Study Phase follow-up visit 4 weeks after the Week 96 visit or ET visit.

Note: If the Blinded Study Phase follow-up visit and the OLE Phase baseline/Day 1 visit occur on the same day, study assessment procedures should be performed according to the OLE Phase baseline/Day 1 visit.

Participants 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 visit 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:

- Health resource utilization and QoL Questionnaires (SIBDQ [for participants with a history of IBD], CLDQ, EQ-5D, and PSC-PRO)

  Note: It is recommended that QoL questionnaires be completed prior to any study procedures being performed and prior to the participant seeing a health care provider. Refer to the Site Operations Manual for guidance on QoL questionnaire administration.
- Pruritus assessments (Pruritus VAS and 5D-Itch)
- Calculate Partial Mayo score for participants with a history of IBD (as appropriate, see Section 6.9.6)
- Symptom-driven PE including ascites and HE assessments
- For participants with history of IBD, any evidence of active IBD seen on routinely performed colonoscopy will be captured
- Record vital signs and body weight

- Obtain blood samples for:
  - Chemistry
  - eGFR
  - Hematology
  - Coagulation panel
  - Lipid profile
  - Biomarkers
- Obtain urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

6.5. OLE Phase Treatment Assessments

6.5.1. OLE Phase Baseline/Day 1 Assessments

Participants who do not permanently discontinue study drug, complete the Blinded Study Phase Week 96 with an evaluable (noncirrhotic F0-F3) as determined by the central reader and Blinded Study Phase follow-up visit will be eligible to enter into the OLE Phase.

For participants who have consented to and are eligible for the OLE Phase, Gilead recommends completion of the OLE Phase baseline/Day 1 visit within 30 days of completion of the Blinded Study Phase follow-up visit. However, there may be circumstances where the OLE Phase baseline/Day 1 visit will occur more than 30 days after completion of the Blinded Study Phase follow-up visit. Under such circumstances, approval of the Gilead medical monitor will be required and participants will be required to complete select safety assessments prior to the OLE Phase baseline/Day 1 visit.

Participants returning to the clinic for the OLE Phase baseline/Day 1 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 ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

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

- Obtain written informed consent before initiation of any OLE Phase baseline/Day 1 procedures. Reconsent at the OLE Phase baseline/Day 1 visit is not necessary if the participant has previously provided written informed consent to participate in the OLE Phase and there has been no update to the ICF since the participant previously provided written informed consent
- Health resource utilization and QoL Questionnaires (SIBDQ [for participants with a history of IBD], CLDQ, EQ-5D, and PSC-PRO)

  Note: It is recommended that QoL questionnaires be completed prior to any study procedures being performed and prior to the participant seeing a health care provider. Refer to the Site Operations Manual for guidance on QoL questionnaire administration.
- Pruritus assessments (Pruritus VAS and 5D-Itch)
- Calculate Partial Mayo score for participants with a history of IBD (as appropriate, see Section 6.9.6)
- For participants with history of IBD, any evidence of active IBD seen on routinely performed colonoscopy will be captured
- Symptom-driven PE including ascites and HE assessments
- CP and MELD scores
- Record vital signs and body weight
- Perform FibroScan (if available)
- Obtain blood samples for:
  - Chemistry
  - eGFR
  - Hematology
  - Coagulation panel
  - Lipid profile
  - Biomarkers
  - Single PK sampling

- Collect urine samples for:
  - — Urine pregnancy test for females of childbearing potential only
- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs related to protocol-required procedures occurring since the screening visit
- Dispense study drug, and provide participant with instructions on appropriate dosing and administration

Participants who have consented to and are eligible for the OLE Phase will begin open-label treatment with CILO 100 mg orally once daily.

Once all visit procedures have been completed, participants will take their OLE Phase baseline/Day 1 dose of study drug while at the investigative site.

6.5.2. OLE Phase Weeks 4, 24, 48, and 72 (± 5 days) and OLE Phase Week 96 (± 14 days)

Participants 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.

Participants should 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 visits:

- Health resource utilization and QoL Questionnaires (SIBDQ [for participants with a history of IBD], CLDQ, EQ-5D, and PSC-PRO) at OLE Phase Weeks 24, 48, 72, and 96

  Note: It is recommended that QoL questionnaires be completed prior to any study procedures being performed and prior to the participant seeing a health care provider. Refer to the Site Operations Manual for guidance on QoL questionnaire administration.
- Pruritus assessments (Pruritus VAS and 5D-Itch)
- Calculate Partial Mayo score for participants with a history of IBD (as appropriate, see Section 6.9.6)
- Symptom-driven PE including ascites and HE assessments
- Record vital signs and body weight

- Obtain blood samples for:
  - Chemistry
  - eGFR
  - Hematology
  - Coagulation panel
  - Lipid profile at OLE Phase Weeks 24, 48, 72, and 96
  - Biomarkers at OLE Phase Weeks 48 and 96
  - Single PK sampling
- Obtain urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- Perform FibroScan (if available) at OLE Phase Weeks 24, 48, 72, and 96
- 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 concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit
- Dispense the study drug as directed by IRT at OLE Phase Weeks 4, 24, 48, and 72
  - Review study drug compliance and drug administration instructions with participant
  - Reconcile study drug administration using pill counts

6.5.3. OLE Phase Telephone Follow-up Visit: Weeks 8 and 12 (± 5 days)

A telephone follow-up visit will be completed at Weeks 8 and 12. The following assessments are to be completed and documented during these visits:

- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit
- Review study drug compliance with participant
- At the discretion of the investigator, an unscheduled visit may be completed if the participant reports abnormal or concerning symptoms.

6.5.4. OLE Phase ET Visit

Participants prematurely discontinuing from the OLE Phase of the study should complete an ET visit within 30 days of the last dose.

If a participant discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related procedures per the Study Procedures Table (see Appendix 2). If a participant 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.

Participants 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:

- Health resource utilization and QoL Questionnaires (SIBDQ [for participants with a history of IBD], CLDQ, EQ-5D, and PSC-PRO)

  Note: It is recommended that QoL questionnaires be completed prior to any study procedures being performed and prior to the participant seeing a health care provider. Refer to the Site Operations Manual for guidance on QoL questionnaire administration.

- Pruritus assessments (Pruritus VAS and 5D-Itch)
- Calculate Partial Mayo score for participants with a history of IBD (as appropriate, see Section 6.9.6)
- Symptom-driven PE including ascites and HE assessments

- Record vital signs and body weight
- Obtain blood samples for:
  - Chemistry
  - eGFR
  - Hematology
  - Coagulation panel
  - Lipid profile
  - Biomarkers
  - Single PK sampling
- Obtain urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- Perform FibroScan (if available)
- CP and MELD scores
- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

6.5.5. OLE Phase Follow-up Visit (±7 days)

Participants will return for an OLE Phase follow-up visit 4 weeks after the OLE Phase Week 96 visit or ET visit.

Participants 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 visit 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:

- Health resource utilization and QoL Questionnaires (SIBDQ [for participants with a history of IBD], CLDQ, EQ-5D, and PSC-PRO)

  Note: It is recommended that QoL questionnaires be completed prior to any study procedures being performed and prior to the participant seeing a health care provider. Refer to the Site Operations Manual for guidance on QoL questionnaire administration.

- Pruritus assessments (Pruritus VAS and 5D-Itch)
- Calculate Partial Mayo score for participants with a history of IBD (as appropriate, see Section 6.9.6)
- Symptom-driven PE including ascites and HE assessments
- Record vital signs and body weight
- Obtain blood samples for:
  - Chemistry
  - eGFR
  - Hematology
  - Coagulation panel
  - Lipid profile
  - Biomarkers
- Obtain urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

6.5.6. Unscheduled Visits

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

Participants 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.

Participants 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.

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

- Calculate Partial Mayo score for participants with IBD (as appropriate, see Section 6.9.6)
- Symptom-driven PE including ascites and HE assessments
- Record vital signs and body weight
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - eGFR
- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit
- Urine pregnancy test for females of childbearing potential only

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.

6.6. Assessments for Premature Discontinuation From Study

If a participant discontinues study drug dosing (for example, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related procedures per the Study Procedures Table (see Appendix 2). If a participant 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 participant or investigator, the participant may be withdrawn from the study.

Participants prematurely discontinuing from the study, either during the Blinded Study Phase or during the OLE Phase (for example, as a result of an AE) should have an ET visit completed followed by a follow-up visit 4 weeks after the last dose of the study drug. The study assessments to be performed at the Blinded Study Phase or OLE Phase ET visit are the same as those performed at the Blinded Study Phase or OLE Phase Week 96 visit (see Section 6.4.5 and Section 6.5.2). The study assessments to be performed at the follow-up visits are listed in Section 6.4.7 and 6.5.5, respectively.

6.7. Criteria for Discontinuation of Study Treatment

Study drug must 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 participant may resume study drug 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 participant's best interest
- Any participant without a history of IBD who develops new onset IBD while participating in the study, or any participant with a history of IBD who experiences a > 2-point increase in the Partial Mayo score from baseline while in the study consistent with worsening of IBD in the opinion of the investigator
- Any participant who experiences a clinical AE that is positively adjudicated by the Hepatic Events Adjudication Committee (see Section 3.4.1), histologically confirmed progression to cirrhosis, or liver transplantation
- CP score ≥ 7 on 2 consecutive occasions at least 2 weeks apart unless due to an alternate etiology (eg, therapeutic anticoagulation), refer to Section 7.5.
- Participant requests to discontinue for any reason
- Participant noncompliance
- Significant protocol deviation that impacts participant safety
- Pregnancy during the study; refer to Appendix 4
- Discontinuation of the study at the request of Gilead, a regulatory agency or an IRB/IEC

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6.9. Procedures and Specifications

6.9.1. 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, and GGT

eGFR:

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

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

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

S_{cr} = serum creatinine (mg/dL)

BW = body weight (kg)

Actual body weight will be used for the eGFR.

Hematology:

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

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, HbA1c, lipid profile, HIV-1 (reflex to HIV-1 RNA), HBV (HBsAg) and HCV (reflex to HCV RNA) serology, eGFR as calculated by 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 7.5.1).

Biomarker Tests

Inflammation - High-sensitivity CRP

Liver fibrosis - ELF Test and FibroSURE/FibroTest

Bile acid homeostasis - FGF19, C4, and bile acids

Pharmacokinetic (PK) and Pharmacodynamic (PD) Assessments

Single PK and PD Sampling

Single PK and PD plasma samples will be collected and archived for 1) PK analysis of CILO (and its metabolites as applicable); 2) to measure the concentration of PD biomarkers. Single PD sampling is not applicable for the OLE Phase.

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6.9.2. 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 participants during screening.

6.9.3. Physical Examination

A complete PE 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, and nails; musculoskeletal and neurological, and assessments for ascites and HE.

The focus of a symptom-driven PE should include assessments for ascites and HE, and will be determined by the investigator based on participant complaint. For example, if a participant 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.

6.9.4. 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:

- Participant 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 millimeters of mercury (mm Hg) mark on the manometer or to the nearest whole number on an automatic device.

6.9.5. 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 hepatic clinical AEs requiring adjudication. Assessment of ascites and HE will be determined by the site at all visits, except the follow-up and the telephone follow-up visit, 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** Participant is lethargic, may have moderate confusion Participant 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 participants on dialysis, did the participants 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.

6.9.6. Partial Mayo Score

The Partial Mayo score is a survey for the assessment of IBD that considers stool frequency, rectal bleeding, and physician assessment of IBD severity. Participants with a history of IBD (includes ulcerative colitis, Crohn's disease, and indeterminate colitis) will receive a diary with instructions to document stool frequency and rectal bleeding. Any participant who experiences worsening IBD symptoms should be instructed to contact the site. Partial Mayo Score does not need to be evaluated in participants who currently use an external ostomy bag even if they have history of IBD. Partial Mayo Score should be evaluated in any participant whose external ostomy is reversed while on the study.

6.9.7. Amsterdam-Oxford Model

The Amsterdam-Oxford model for PSC considers age at PSC diagnosis, PSC subtype along with lab values for serum albumin, ALP, AST, bilirubin, and platelets {de Vries 2017}. The resultant Amsterdam-Oxford score, which will be calculated by Gilead based on central laboratory values and medical history, may be utilized to estimate transplant-free survival in patients with PSC.

6.9.8. Health Resource Utilization, Quality of Life (QoL) Questionnaires, and Pruritus Assessments

It is recommended that these questionnaires be completed prior to the clinical and laboratory assessments. The participant should read the questionnaires by himself/herself and record the answers by himself/herself.

6.9.8.1. Health Resource Utilization Questionnaire

This questionnaire is designed to capture health resource utilization since the last study visit. Specifically, visits to health care professionals (outpatient and emergency department visits), in-patient hospitalizations, and imaging procedures will be recorded.

6.9.8.2. Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

This disease-specific questionnaire for participants with a history of IBD comprises 10 questions divided into 4 health subscales: bowel symptoms, systemic symptoms, including sleep disorders and fatigue, emotional function such as depression, and social function; meaning the ability to participate in social activities and to work.

6.9.8.3. Chronic Liver Disease Questionnaire (CLDQ)

The CLDQ assesses health-related QoL in participants with liver disease based on 29 items in the following domains: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry.

6.9.8.4. Primary Sclerosing Cholangitis-Patient-Reported Outcome (PSC-PRO) Measure

The PSC-PRO addresses the severity of common everyday symptoms of PSC (eg, pruritus, fatigue, and right upper quadrant abdominal discomfort); and their functional impact (eg, on physical function, activities of daily living, and work productivity, etc).

6.9.8.5. EuroQol 5 Dimensions (EQ-5D) Questionnaire

The EQ-5D questionnaire is a standard measure of health status developed by the EuroQol group to provide a simple, generic measure of health for clinical and economical appraisal {The EuroQol Group 1990}. The EQ-5D is not disease specific and has been validated in numerous health states. The tool consists of the EQ-5D descriptive system and the EQ VAS. The descriptive part comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each of these 5 dimensions has 5 levels (no problem, slight problems, moderate problems, severe problems, and unable to). Results for each of the 5 dimensions are combined into a 5-digit number to describe the participant's health state. The VAS records the participant's health on a 0-100 mm VAS scale, with 0 indicating "the worst health you can imagine" and 100 indicating "the best health you can imagine".

6.9.8.6. Pruritus Visual Analogue Scale (VAS) Measure

The Pruritus VAS is a tool that uses a numeric scale for measuring the intensity of pruritus.

6.9.8.7. 5D-Itch Questionnaire

The 5D-Itch questionnaire is a validated survey for the assessment of the severity of pruritus in patients with chronic pruritus due to dermatological and nondermatological disorders.

6.9.9. Electrocardiogram (ECG)

Standard 12-lead ECG assessments will be performed during the Blinded Study Phase (see Appendix 2). The investigator will review the ECGs for any clinically significant abnormalities to ensure participant 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.

6.9.10. FibroScan

Liver stiffness will be assessed by FibroScan if available. It is recommended that each participant's FibroScan assessments be done with the same type of probe at each study visit. Where available, the median Controlled Attenuation Parameter (CAP) and the interquartile range of CAP values will be recorded from FibroScan examinations.

Please refer to the Site Operations Manual for instructions on FibroScan measurements.

6.9.11. Magnetic Resonance Cholangiopancreatography (MRCP)

Imaging of the biliary and pancreatic ducts will be performed by MRCP at Blinded Study Phase baseline/Day 1, Weeks 48, and 96 or ET. Historical MRCP images within 3 months of screening visit or a routinely performed MRCP within a screening period may be used. MRCP images should be read locally for any clinically significant abnormalities to ensure participant safety. MRCP images will also be sent and read by a central reader. MRCP central reader results will not be disclosed to the investigator or participant. It is recommended that each participant's MRCP assessment is performed using the same procedure for each study visit. If the participant has any contraindications to magnetic resonance imaging (eg, claustrophobia or metal implants), the MRCP is not required.

Please refer to the MRCP imaging guidelines manual for additional instructions.

6.9.12. Liver Biopsy

Liver biopsies will be performed at screening and at the Blinded Study Phase Week 96 or Blinded Study Phase ET visits. All possible attempts should be made to acquire a liver biopsy specimen of at least 2.0 cm in length to ensure accurate staging of fibrosis and other histological lesions. A second pass may be considered, if necessary, to obtain an adequate specimen. If possible, biopsies should be performed under ultrasound guidance; 16 gauge needles are preferred. Follow-up biopsies should be performed in the same hepatic lobe as the screening biopsy to minimize sampling variability. A historical biopsy within 6 months of the screening visit may be accepted as the screening biopsy.

Liver biopsies will be sent to a central laboratory for review by a central reader. The central reader will review all screening biopsies for eligibility, which will include an assessment of the adequacy of the specimen, and confirmation of F0 - F3 fibrosis. The liver biopsy sample must be deemed adequate for evaluation by the central reader for inclusion. If the liver biopsy is deemed unacceptable by the central reader, it may be repeated. Histology results from local readers will be collected, if available.

If a liver biopsy is performed per standard of care outside of protocol-required assessments (eg, to confirm clinical suspicion of progression to cirrhosis), all possible attempts should be made to submit the biopsy specimen to the central reader for evaluation. If progression to cirrhosis is confirmed by the central reader, the participant will be discontinued from the study treatment.

Please refer to the Site Operations Manual for additional information.

6.10. End of Study

If a participant is enrolled in the OLE Phase, end of study is defined as the completion of the OLE Phase follow-up visit. If a participant is not enrolled in the OLE Phase, end of study is defined as the completion of the Blinded Study Phase follow-up visit.

The end of this study will be the last participant's last visit.

6.10.1. Sample Storage

Residual biological samples from all visits will be frozen and stored. These stored samples may be used by Gilead or our research partners to help answer questions about the study drug, PSC and its associated conditions, or clinical laboratory testing to provide additional safety data. No human genetic testing will be performed without express consent of the study participants. CCI [redacted] If participants provide additional specific consent, residual PK samples may be destroyed no later than 15 years after the end of the study or per country requirements.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a study drug that 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 study drug, whether or not the AE is considered related to the study drug. AEs may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, or 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 (Section 7.6.1).
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history.

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

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

- Death
- A life-threatening situation (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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 participant 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 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.

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, ECG, x-rays, and 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 Hb).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.1.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator 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 subinvestigator 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, concomitant medication).
- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug.

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 (see Appendix 3). For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 3).

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. Severity 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 SAEs listed above.

7.3. Investigator Reporting 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 drug, the following types of events must be reported on the eCRF: all SAEs and AEs related to protocol-required procedures.

Adverse Events

Following initiation of study drug, collect all AEs regardless of cause or relationship, until 30 days after last administration of study drug and report the AEs on the eCRFs as instructed.

All AEs and clinically significant laboratory abnormalities should be followed until resolution or until the AE is stable, if possible. Gilead 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 occur after the participant first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the protocol-required posttreatment follow-up period, must be reported on the applicable eCRFs and to Gilead GLPS as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF 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 the protocol-defined follow-up period has concluded and the SAE is deemed relevant to the use of study drug, the investigator should promptly document and report the SAE to Gilead GLPS.

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

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel will record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead GLPS within 24 hours of the investigator's knowledge of the SAE. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record and transmit 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 reporting form and submit by email or fax within 24 hours of the investigator's knowledge of the SAE to:

Gilead Global Patient Safety:	Fax:	PPD
	Email:	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 email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant 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 concomitant medication section of the participant's eCRF and the SAE narrative section of the Safety Report Form eCRF

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 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.

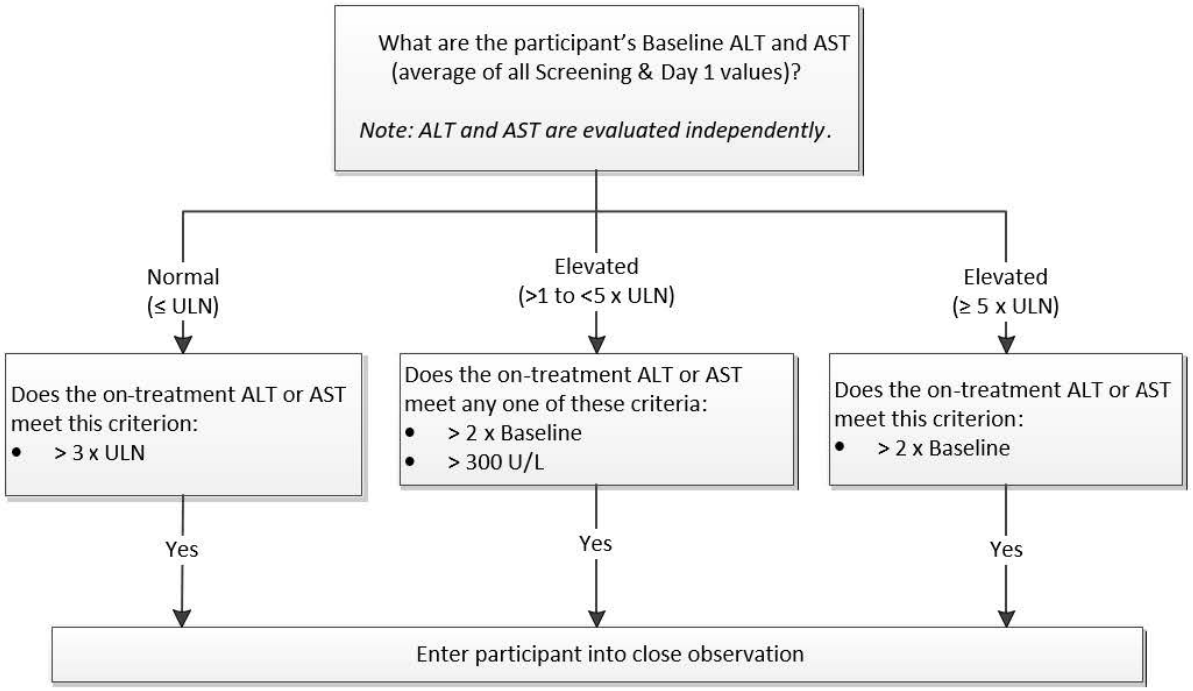
7.5. Toxicity Management

7.5.1. Observation for Drug-Induced Liver Injury (DILI)

At baseline, many PSC participants have liver biochemistry levels above the ULN. Baseline values for liver tests (ALT, AST, ALP, GGT, and total bilirubin) will be determined by averaging the values obtained between and including screening and Day 1. Please refer to the Covance Laboratory Manual or individual participant Covance laboratory report for gender and age specific reference ranges.

If no other cause of the laboratory abnormalities is immediately apparent, on-treatment elevations of ALT and/or AST should be confirmed with repeat testing within 48-72 hours. Participants with ALT or AST elevations as per Figure 7-1 must be placed into close observation (as described below).

Figure 7-1. On-Treatment ALT/AST Monitoring Requiring Close Observation



Abbreviations
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal range.

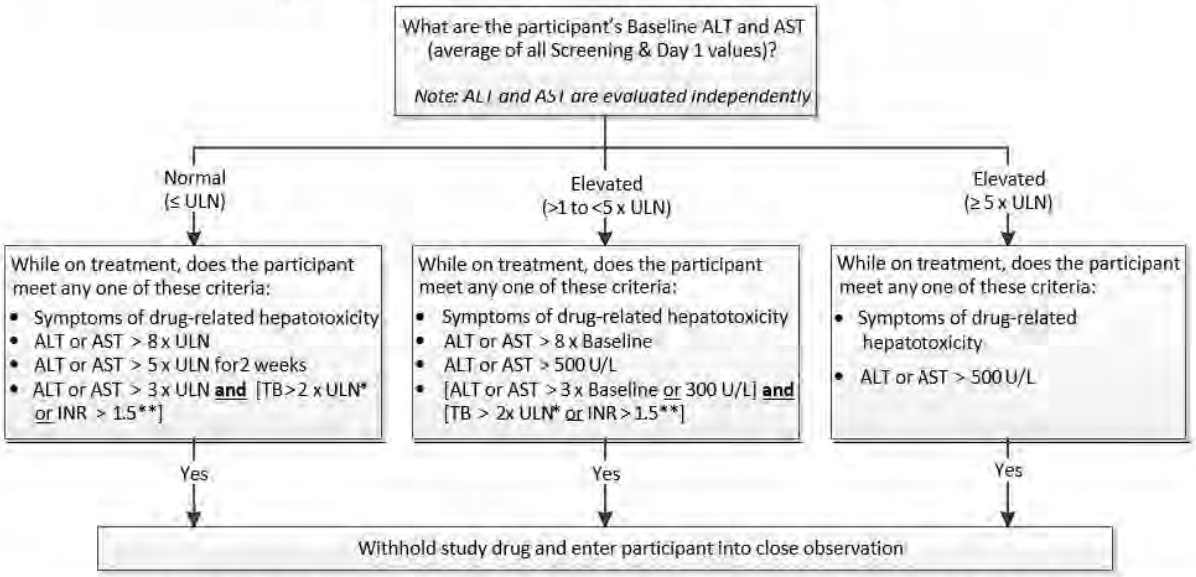
Close observation includes:

- Repeating liver biochemistries (ALT, AST, ALP, GGT, total bilirubin, INR) and obtaining a CPK level within 48-72 hours of results
- Obtaining a more detailed history of symptoms and prior or concurrent disease
- Obtaining a history of concomitant drug 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 drug has been discontinued and the participant is asymptomatic

During close observation, study drug can be continued, if desired, at the discretion of the Gilead medical monitor and the principal 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 participant must be placed into close observation and study drug must be withheld.

Figure 7-2. On-treatment ALT/AST Monitoring Requiring Study Drug Withholding



*Unless participant has Gilbert's syndrome, in which case a direct bilirubin > 2 x baseline (average of Screening and Day 1 values) will be used instead of total bilirubin.

**If not on therapeutic anticoagulation (eg warfarin). If on therapeutic anticoagulation, INR criteria is disregarded.

Abbreviations

ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TB = total bilirubin; ULN = upper limit of normal range.

Participants who develop signs or symptoms of liver toxicity (such as right upper quadrant discomfort, fever, nausea, vomiting, jaundice, rash, or eosinophilia > 5%) which are suspected by the principal investigator to be drug-related; must have study drug withheld and be placed into close observation.

If study drug is withheld, it may be reintroduced with approval from the medical monitor if another etiology of elevated liver tests is identified. Study drug must be discontinued if close monitoring is not possible or if total bilirubin, ALT, or AST elevation recurs following rechallenge with study drug. Participants who discontinue study drug due to suspected hepatotoxicity must be followed until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels, until there is a satisfactory explanation for the changes observed, or for 3 months after drug discontinuation, whichever is longer.

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 participants 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 AEs should be confirmed by repeat testing as soon as practical to do so, and preferably within 3 calendar days of receipt of the original test results.

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

7.5.2. Child-Pugh (CP) Score

If a participant has an increase in their CP score to ≥ 7, this should be confirmed with repeat testing within 72 hours of receipt of results. If confirmed, the medical monitor should be notified and the participant 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 drugs must be discontinued.

7.5.3. 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; bile acid sequestrants (eg, cholestyramine); and/or the opioid receptor agonist; nalfurafine (in Japan). 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.

In participants with intolerable pruritus:

- Interruption of study drug may be considered at the discretion of the investigator.
- Once pruritus returns to baseline levels or resolves upon study drug interruption, re-initiation of study drug will be permitted under a reduced dosing schedule. Specifically, study drug may be resumed starting with a single 30 mg tablet of CILO (or PTM) once daily.
- If the single 30 mg CILO (or PTM) tablet once daily is tolerated for approximately 4 weeks, the dosage of CILO (or PTM) may be increased to two 30 mg CILO (or PTM) tablets daily (60 mg total); and if tolerated for approximately 4 weeks, the dosage of CILO (or PTM) may be increased to a single 100 mg CILO (or PTM) tablet daily.
- In participants who require dose reduction for pruritus on 3 or more occasions, continued management should be discussed with the medical monitor.

7.5.4. Study Drug Interruptions/Reductions for AEs Other Than Pruritis

For both the Blinded Study Phase and OLE Phase, dose interruptions/reductions for other AEs may be considered at the discretion of the investigator, with medical monitor consultation as needed. Drug re-initiation can occur as follows:

- At the discretion of the investigator, re-initiation of study drug can occur under the original dosing schedule.
- At the discretion of the investigator, re-initiation of study drug can also occur under a reduced dosing schedule with a gradual return to the initial dose. Specifically, study drug may be resumed starting with a single 30 mg tablet of CILO (or PTM) once daily, increasing after approximately 4 weeks or the investigators' discretion to two 30 mg CILO (or PTM) tablets daily (60 mg total), and approximately 4 weeks later or at the investigator's discretion, the dosage of CILO (or PTM) may be increased to return to a single 100 mg CILO (or PTM) tablet daily.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports 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, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, participant, 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 study drug by a participant.

Misuse is defined as any intentional and inappropriate use of a study drug 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 study drug given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the participant has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug 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 study drug.

Counterfeit or falsified medicine is defined as any study drug with a false representation of a) its identity, (b) its source, or (c) its history.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study participants that are identified after initiation of study drug and throughout the study, including the posttreatment follow-up period, to Gilead GLPS using the pregnancy report form within 24 hours of becoming aware of the pregnancy using the pregnancy report form. Contact details for transmitting the pregnancy report form are as follows:

Gilead Global Patient Safety
Email: PPD
or
Fax: PPD
PPD

Refer to Section 7.3 and the 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.

All other premature termination of pregnancy (eg, a spontaneous abortion, and 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 the study must be reported to Gilead GLPS.

The participant 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/partner 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

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

7.6.3. Concomitant Medications Reports

7.6.3.1. Gilead Concomitant Medications Special Situations Report

Special situations reports (SSRs) involving a Gilead concomitant medication (not considered study drug) that occur after the first consent to participate in the study (ie, signing of the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead GLPS utilizing the paper special situations report (Section 7.4).

7.6.3.2. Non-Gilead Concomitant Medications Report

Special situations involving non-Gilead concomitant medications do not need to be reported on the special situations report form; however, for special situations that result in AEs because of a non-Gilead concomitant medication, the AE should be reported on the AE eCRF.

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

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

7.6.4. Special Situations Reporting Process

Site personnel will record all SSR data on the applicable eCRFs and from there transmit the SSR information within 24 hours of the investigator's knowledge to Gilead GLPS (or to the designated CRO) from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If for any reason it is not possible to record and transmit the SSR information electronically, record the SSR on the paper special situations reporting form and transmit within 24 hours to:

Gilead Global Patient Safety
Email: PPD
or
Fax: PPD
PPD

If an SSR has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SSR reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to Gilead GLPS.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

Details will be provided in the statistical analysis plan (SAP).

8.1.1. Analysis Objectives

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

- To evaluate whether CILO reduces the risk of fibrosis progression among noncirrhotic participants with PSC at Blinded Study Phase Week 96

The **secondary objectives** of this study are as follows:

- To assess the safety and tolerability of CILO
- To evaluate changes in serum concentrations of ALP, ALT, and bile acids at Blinded Study Phase Week 96
- To evaluate whether CILO increases the proportion of participants with ≥ 25% relative reduction in serum ALP concentration from baseline (biochemical response) and no worsening of fibrosis according to the Ludwig classification (histologic response) at Blinded Study Phase Week 96
- To evaluate fibrosis stage improvement at Blinded Study Phase Week 96
- To evaluate changes in noninvasive markers of fibrosis, including liver stiffness by FibroScan and ELF test score at Blinded Study Phase Week 96
- To evaluate change in PSC Symptoms – Module 1 based on the disease-specific PSC-PRO at Blinded Study Phase Week 96

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8.1.2. Primary Endpoint

The primary endpoint is the proportion of participants with progression of liver fibrosis, as defined by a ≥ 1-stage increase in fibrosis according to the Ludwig classification at Blinded Study Phase Week 96.

8.1.3. Secondary Endpoints

The secondary endpoints of this study are as follows:

- Changes from baseline in serum concentrations of ALP, ALT, and bile acids at Blinded Study Phase Week 96
- The proportion of participants with ≥ 25% relative reduction in serum ALP concentration from baseline (biochemical response) and no worsening of fibrosis according to the Ludwig classification (histologic response) at Blinded Study Phase Week 96
- The proportion of participants with fibrosis improvement (according to the Ludwig classification) at Blinded Study Phase Week 96
- Changes from baseline in noninvasive markers of fibrosis, including liver stiffness by FibroScan and ELF test score, at Blinded Study Phase Week 96
- Change from baseline in PSC Symptoms – Module 1 based on the disease-specific PSC-PRO at Blinded Study Phase Week 96

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8.2. Planned Analysis

8.2.1. Interim DMC Analysis

Before the final analysis, interim analyses will be conducted, and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program.

There will be 1 planned interim futility analysis based on the primary endpoint after the first 160 randomized and dosed participants have completed Week 96 or ET assessments in the Blinded Study Phase. A predictive power (PP) approach will be used for futility assessment. The DMC may recommend early termination of the study due to futility if the criterion of PP $\leq$ 10% is met. Further details about the futility analysis will be included in the DMC charter and an interim analysis communication plan.

The PP is calculated by assuming a noninformative prior Beta(1, 1) for the response rate in each treatment arm and each stratum, updating it to a posterior distribution using observed data at the interim analysis, and then computing the averaged conditional power over the posterior distributions, where the conditional power is the probability of successfully rejecting the null hypothesis at the primary analysis as described in Section 8.5.1, given the data observed at an interim and an assumed response rate in each treatment arm and each stratum.

8.2.2. Primary Analysis

The primary analysis on the primary and secondary endpoints (Section 8.5) will be conducted after all the randomized and dosed participants have completed Week 96 or ET assessments in the Blinded Study Phase, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized for the analysis. This analysis will serve as the final analysis for the primary and secondary endpoints to evaluate the treatment effect of CILO over placebo. The overall type I error rate will be controlled at the 1-sided 0.025 significance level.

8.2.3. Final Analysis

The final analysis will be performed after all participants have completed the OLE Phase follow-up visit, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.3. Analysis Conventions

All individual participant data will be listed as measured. All statistical summaries and analyses will be performed using statistical analysis software (SAS®) (SAS Institute, Cary, North Carolina, USA).

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The primary analysis set for efficacy analyses will be the Full Analysis Set (FAS) which includes all participants who were randomized into the study and received at least 1 dose of study drug.

Participants who receive study drug other than that to which they were randomized will be analyzed according to the treatment group to which they were randomized.

8.3.1.2. Safety

The primary analysis set for safety analyses will include all participants who received at least 1 dose of study drug. Treatment-emergent data will be analyzed and defined as data collected from the first dose of study drug through the date of last dose of study drug plus 30 days. Participants who received study drug other than that to which they were randomized will be analyzed according to the study drug received.

All data collected during treatment will be included in the safety summaries.

8.3.1.3. Pharmacokinetics

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The PK analysis set will include all randomized participants who took at least 1 dose of study drug and for whom concentration data of analytes CILO (and its metabolites as applicable) are available. The PK analysis set will be used for analyses of population PK.

CCI [redacted]

8.3.1.4. Biomarker

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

8.3.2. 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.

Participants with missing data on the primary response variable (ie, missing data on fibrosis stage) at Week 96 will be considered as treatment failures.

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

8.4. 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 treatment group and overall. Demographic summaries will include sex, race/ethnicity, randomization stratification group, age, body weight, height, and body mass index.

Baseline data will include a summary of randomization stratification groups (presence or absence of UDCA use and presence or absence of bridging fibrosis [Ludwig fibrosis score, F3 versus F0, F1, and F2]) and other disease characteristics.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

A stratified Mantel-Haenszel test will be used to compare the difference in the proportion of participants who have progression of liver fibrosis at Blinded Study Phase Week 96 between the CILO group and placebo group at a 1-sided significance level of 0.025, adjusting for baseline UDCA use and fibrosis stage (Ludwig fibrosis score, F3 versus F0, F1, and F2) on screening liver biopsy. Participants with missing data on liver fibrosis will be analyzed as treatment failures. The point estimate and 95% CI for the difference in proportions will be calculated. A 2-dimensional tipping point sensitivity analysis will be conducted to comprehensively explore the space of plausible missing data assumptions for the primary endpoint.

8.5.2. Secondary Analyses

The secondary efficacy endpoints will be tested sequentially in the following order at the same 1-sided significance level of 0.025 after the primary efficacy objective has been achieved. An analysis of covariance (ANCOVA) model will be used for continuous and ordinal endpoints, adjusting for baseline value of the dependent variable, baseline UDCA use, and fibrosis stage (F3 versus F0, F1, and F2) on screening liver biopsy. A stratified Mantel-Haenszel test will be used for binary secondary endpoints, adjusting for baseline UDCA use and fibrosis stage (F3 versus F0, F1, and F2) on screening liver biopsy. If a 1-sided P value ≤ 0.025 is achieved for the corresponding endpoint, the next endpoint will be evaluated; otherwise, testing of the remaining endpoints will cease.

1) Change from baseline in serum ALP at Blinded Study Phase Week 96

2) Change from baseline in serum ALT at Blinded Study Phase Week 96

3) Change from baseline in serum bile acids at Blinded Study Phase Week 96

4) The proportion of participants with $\geq 25\%$ relative reduction in serum ALP concentration from baseline (biochemical response) and no worsening of fibrosis according to the Ludwig classification (histologic response) at Blinded Study Phase Week 96

5) The proportion of participants with fibrosis improvement (according to the Ludwig classification) at Blinded Study Phase Week 96

6) Change from baseline in PSC Symptoms – Module 1 on the disease-specific PSC-PRO at Blinded Study Phase Week 96

7) Change from baseline in ELF test score at Blinded Study Phase Week 96

8) Change from baseline in liver stiffness by FibroScan at Blinded Study Phase Week 96

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8.6. Safety Analysis

Safety will be assessed during the study through the reporting of AEs, clinical laboratory tests, and vital sign assessments at various time points during the study.

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

8.6.1. Extent of Exposure

A participant's extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be summarized by treatment group.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the 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.

AEs will be summarized on the basis of the date of onset for the AE. 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 participants) 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).

8.6.3. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the grading scheme in the CTCAE (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 post baseline up to and including the date of last dose of study drug plus 30 days, will be summarized by treatment group. 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 participant has been discontinued from treatment for at least 30 days will be included in a data listing.

8.6.4. Other Safety Evaluations

Vital sign measurements will be summarized by treatment group and listed by participant.

8.7. Pharmacokinetic Analysis

Plasma concentrations of CILO (and its metabolites, as applicable) will be listed and summarized. CCI [redacted]

8.8. Biomarker Analysis

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

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8.9. Sample Size

A sample size of 267 participants in the CILO group and 133 participants in the placebo group has 81% power to detect an absolute difference of 15% in the percentage of participants who meet the primary endpoint at Week 96. Power was calculated using Pearson's Chi-square test at a 2-sided significance level of 0.05. This calculation assumes that 25% of participants will discontinue the study prematurely (considered as treatment failures), and that among participants with nonmissing response data at Blinded Study Phase Week 96, 20% in the CILO group and 40% in the placebo group will meet the primary endpoint.

The primary endpoint rate of 40% for participants in the placebo group with nonmissing response data at Blinded Study Phase Week 96 was estimated based on Week 96 data from noncirrhotic participants in the simtuzumab (SIM) Phase 2 study (GS-US-321-0102).

8.10. Data Monitoring Committee

A multidisciplinary DMC that consists of 2 hepatologists and a PhD statistician will review the progress of the study and perform interim reviews of safety data and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study drug warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. If the DMC recommends early termination of the study, a restricted group of senior management at Gilead will be unblinded to evaluate the study data. Unblinding of specific Gilead personnel will be documented per the appropriate SOPs.

The DMC will convene after 50 participants have completed the Week 4 visit and approximately every 6 months thereafter to monitor the study for safety events. The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

CCI [redacted] If the DMC recommends stopping the study for lack of efficacy, a Gilead Oversight Committee will be unblinded to confirm the DMC recommendation.

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 subinvestigators will provide documentation of their financial interest or arrangements with Gilead, or proprietary interests in the study drug. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator 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 participant completes the protocol-defined activities.

9.1.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) 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 participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC/EC. The investigator will not begin any study participant 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 participant after initial IRB/IEC/EC approval, with the exception of those necessary to reduce immediate risk to study participants.

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 ICF for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the participant or the participant's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC/EC local requirements.

The ICF will inform participants about genomic testing and/or planned sample retention. [redacted]

9.1.5. Confidentiality

The investigator must assure that participants' 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 participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all participants screened and for all participants enrolled in the study. Participant 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 2 categories: (1) investigator's study file; and (2) participant 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, ICF, 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 participant:

- Participant identification (name, date of birth, gender);
- Documentation that participant meets eligibility criteria; ie, history, PE, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented participant 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, and 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. CCI [redacted]

9.1.7. Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the electronic data capture (EDC) system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol Study Procedures Table, unless collected by a nonelectronic data capture vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the CRF Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee 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). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the PI of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the PI will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the PI with a read-only archive copy of the data entered. 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 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:

- CCI [redacted]
- institutional and/or pharmacy SOP requires the study drug that is classified as hazardous to be destroyed immediately following participant 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 the 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 participants, 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 CSR will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. 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. For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 6.10).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical study agreement.

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 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 on them. The monitor should have access to any participant records needed to verify the entries in 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 participants' interests.

10. REFERENCES

Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. J Hepatol 2012;56 (5):1181-8.

Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology 2010;51 (2):660-78.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

de Vries EM, Wang J, Williamson KD, Leeflang MM, Boonstra K, Weersma RK, et al. A novel prognostic model for transplant-free survival in primary sclerosing cholangitis. Gut 2017.

Graziadei IW, Wiesner RH, Marotta PJ, Porayko MK, Hay JE, Charlton MR, et al. Long-term results of patients undergoing liver transplantation for primary sclerosing cholangitis. Hepatology 1999;30 (5):1121-7.

Hirschfield GM, Karlsen TH, Lindor KD, Adams DH. Primary sclerosing cholangitis. Lancet 2013:1587-99.

Inagaki T, Choi M, Moschetta A, Peng L, Cummins CL, McDonald JG, et al. Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. Cell metabolism 2005;2 (4):217-25.

Isayama H, Tazuma S, Kokudo N, Tanaka A, Tsuyuguchi T, Nakazawa T, et al. Clinical Guidelines for Primary Sclerosing Cholangitis 2017. J Gastroenterol 2018;53:1006-34.

Karlsen TH, Franke A, Melum E, Kaser A, Hov JR, Balschun T, et al. Genome-wide association analysis in primary sclerosing cholangitis. Gastroenterology 2010;138 (3):1102-11.

Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the Non-invasive Components of the Mayo Score to Assess Clinical Response in Ulcerative Colitis [Author Manuscript]. Inflammatory bowel diseases 2008;14 (12):1660-6.

Lindor KD, Kowdley KV, Harrison ME, American College of G. ACG Clinical Guideline: Primary Sclerosing Cholangitis. Am J Gastroenterol 2015;110 (5):646-59; quiz 60.

Molodecky NA, Kareemi H, Parab R, Barkema HW, Quan H, Myers RP, et al. Incidence of primary sclerosing cholangitis: a systematic review and meta-analysis. Hepatology 2011;53 (5):1590-9.

Mudaliar S, Henry RR, Sanyal AJ, Morrow L, Marschall HU, Kipnes M, et al. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. Gastroenterology 2013;145 (3):574-82 e1.

Pellicciari R, Fiorucci S, Camaioni E, Clerici C, Costantino G, Maloney PR, et al. 6alpha-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem 2002;45 (17):3569-72.

Saich R, Chapman R. Primary sclerosing cholangitis, autoimmune hepatitis and overlap syndromes in inflammatory bowel disease. World J Gastroenterol 2008;14 (3):331-7.

The EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990;16 (3):199-208.

Triantos CK, Koukias NM, Nikolopoulou VN, Burroughs AK. Meta-analysis: ursodeoxycholic acid for primary sclerosing cholangitis. Aliment Pharmacol Ther 2011;34 (8):901-10.

Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014;60 (2):715-35.

11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404, USA

STUDY ACKNOWLEDGMENT

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Cilofexor in Non-Cirrhotic Subjects With Primary Sclerosing Cholangitis

GS-US-428-4194, Amendment 5, 16 March 2022

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

PPD Medical Monitor	*[See appended electronic signature]* Signature
[See appended electronic signature] 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

Appendix Table 1. Study Procedures Table –Blinded Study Phase: Screening to Week 48

			Treatment Visits (± 3 days)[p]						
Assessments	**Screening[a]**	**Baseline/ Day 1**	**Week 4**	**Week 8**	**Week 12**	**Telephone Follow-up Week 16**	**Week 24**	**Week 36**	**Week 48 (± 14 days)**
Participant Fasting	X[q]	X	X	X	X		X	X	X
Written Informed Consent	X								
Medical History	X								
Review Inclusion/Exclusion Criteria	X	X							
Physical Examination[d]	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[e] and Body Weight	X	X	X	X	X		X	X	X
Height	X								
Partial Mayo Score[b]	X	X	X	X	X		X	X	X
Pruritus VAS and 5D-Itch		X	X	X	X		X	X	X
Health Resource Utilization Questionnaire		X					X		X
Quality of Life Questionnaires[c]		X					X		X
12-lead ECG	X								
Review for Active IBD[n]			X	X	X		X	X	X
FibroScan[i] (if available)	X						X		X
MRCP[j]		X[p]							X
Liver Biopsy[k]	X								
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Dispense Study Drugs		X	X	X	X		X	X	X

Assessments	Screening[a]	Baseline/ Day 1	Treatment Visits (± 3 days)[p]						
			Week 4	Week 8	Week 12	Telephone Follow-up Week 16	Week 24	Week 36	Week 48 (± 14 days)
Review Study Drug Compliance			X	X	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
C-Peptide, Insulin and HbA1c		X			X		X		X
HIV-1, HBV and HCV Serology	X								
Urine Drug Screen	X								
Pregnancy Testing[f]	X	X	X	X	X		X	X	X
Serum FSH[g]	X								
Stool Collection (if available)		X							X
Blood for Biomarkers	X	X	X		X		X		X
Single PK and PD Sampling			X		X			X	
[redacted]									
[redacted]									

Study Procedures Table – Blinded Study Phase: Week 60 to Follow-Up

	Treatment Visits (±3 days)[o]					
Assessments	**Week 60**	**Week 72**	**Week 84**	**Week 96 (± 14 days)**	**ET[n]**	**Follow-Up Visit (± 5 days)[r]**
Participant Fasting	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X
Assess Ascites and HE	X	X	X	X	X	X
CP and MELD Scores	X	X	X	X	X	
Vital Signs[e] and Body Weight	X	X	X	X	X	X
Partial Mayo Score[b]	X	X	X	X	X	X
Pruritus VAS and 5D-Itch	X	X	X	X	X	X
Health Resource Utilization Questionnaire		X		X	X	X
Quality of Life Questionnaires[c]		X		X	X	X
Review for Active IBD[m]	X	X	X	X	X	X
FibroScan[i] (if available)		X		X	X	
MRCP[j]				X	X	
Liver Biopsy[k]				X	X	
Concomitant Medications	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X
Dispense Study Drugs	X	X	X			
Review Study Drug Compliance	X	X	X	X	X	
Laboratory Assessments						
Chemistry, eGFR, Hematology, Coagulation Panel	X	X	X	X	X	X
Lipid Profile	X	X	X	X	X	X
C-Peptide, Insulin, and HbA1c				X	X	
Pregnancy Testing[f]	X	X	X	X	X	X
Stool Collection (if available)				X		

Assessments	Treatment Visits (±3 days)[o]					
	Week 60	Week 72	Week 84	Week 96 (± 14 days)	ET[n]	Follow-Up Visit (± 5 days)[r]
Blood for Biomarkers		X		X	X	X
Single PK and PD Sampling	X		X		X	
CCI						
CCI						

CP = Child-Pugh; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HE = hepatic encephalopathy; IBD = inflammatory bowel disease; MELD = Model for End-stage Liver Disease; MRCP = Magnetic Resonance Cholangiopancreatography; PD = pharmacodynamic(s); PK = pharmacokinetic(s); VAS = visual analogue scale

a Participants will be screened within 10 weeks before randomization. The screening period may be extended under special circumstances with the explicit approval of the medical monitor.
b Partial Mayo score calculation for participants with a history of IBD (as appropriate). See Section 6.9.6 for details.
c Quality of life (QoL) questionnaires to include: Short Inflammatory Bowel Disease Questionnaire (for participants with a history of IBD), Chronic Liver Disease Questionnaire, EuroQol (5 dimensions [EQ-5D]), and primary sclerosing cholangitis-patient-reported outcome. It is recommended that Health Resource Utilization and QoL questionnaires are completed prior to any study procedures being performed and prior to the participant seeing a health care provider.
d Symptom-driven physical examination. The focus of a symptom-driven physical examination will be determined by the investigator based on participant complaint. A complete physical examination will be completed at screening.
e Vital signs include heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature.
f Females of childbearing potential only (see Appendix 4). Serum pregnancy test at screening and urine pregnancy tests at all other visits except telephone follow-up visits.
g Women of any age with amenorrhea of ≥ 12 months (see Appendix 4).
h CCI
i Participant should be in fasted state for FibroScan collection. Refer to the Site Operations Manual for further details.
j If the participant has any contraindications to magnetic resonance imaging, the MRCP is not required. Refer to the MRCP imaging guidelines manual for additional instructions.
k A historical liver biopsy within 6 months of screening may be used if deemed acceptable by the central reader. For ET visit, perform liver biopsy at the discretion of the investigator.
l CCI
m For participants with history of IBD, any evidence of active IBD seen on routinely performed colonoscopy will be captured.
n Participants prematurely discontinuing should complete an ET visit (see Section 6.4.6).
o Treatment visit windows are ± 3 days unless otherwise stated (see Section 6.4).
p MRCP visit window for baseline/Day 1 is + 14 days. Historical MRCP within 3 months of screening visit or a routinely performed MRCP within screening period may be used.
q Fasting for FibroScan per standard of care
r If the Blinded Study Phase follow-up visit and the OLE Phase baseline/Day 1 visit occur on the same day, study assessment procedures should be performed according to the OLE Phase baseline/Day 1

Appendix Table 2. Study Procedures Table – Open-Label Extension Phase: Baseline/Day 1 to Follow-Up

Assessments	Baseline/ Day 1	Treatment Visits (± 5 days)[i]								
		Week 4	Telephone Follow-up Week 8	Telephone Follow-up Week 12	Week 24	Week 48	Week 72	Week 96 (± 14 days)	ET[h]	Follow- Up Visit (± 7 days)
Participant Fasting	X[j]	X			X	X	X	X	X	X
Written Informed Consent	X[k]									
Physical Examination[a]	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	
Vital Signs[b] and Body Weight	X	X			X	X	X	X	X	X
Review for Active IBD[g]	X									
Partial Mayo Score[c] (IBD only)	X	X			X	X	X	X	X	X
Pruritus VAS and 5D-Itch	X	X			X	X	X	X	X	X
Health Resource Utilization Questionnaire[d]	X				X	X	X	X	X	X
Quality of Life Questionnaires[d]	X				X	X	X	X	X	X
FibroScan (if available)[e]	X				X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Dispense Study Drugs	X	X			X	X	X			
Review Study Drug Compliance		X	X	X	X	X	X	X		
Laboratory Assessments										
Chemistry, eGFR, Hematology, Coagulation Panel	X	X			X	X	X	X	X	X

Assessments	Baseline/ Day 1	Treatment Visits (± 5 days)[i]								
		Week 4	Telephone Follow-up Week 8	Telephone Follow-up Week 12	Week 24	Week 48	Week 72	Week 96 (± 14 days)	ET[h]	Follow- Up Visit (± 7 days)
Lipid Profile	X				X	X	X	X	X	X
Pregnancy Testing[f]	X	X			X	X	X	X	X	X
Blood for Biomarkers	X					X		X	X	X
Single PK Sampling	X	X			X	X	X	X	X	

CLDQ = Chronic Liver Disease Questionnaire; CP = Child-Pugh; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol (5 dimensions); ET = early termination; HE = hepatic encephalopathy; IBD = inflammatory bowel disease; MELD = Model for End-stage Liver Disease; PK = pharmacokinetic(s); PSC-PRO = primary sclerosing cholangitis-patient-reported outcome; SIBDQ = Short Inflammatory Bowel Disease Questionnaire; VAS = visual analogue scale

a Symptom-driven physical examination. The focus of a symptom-driven physical examination will be determined by the investigator based on participant complaint. A complete physical examination to be completed at OLE Phase baseline/ Day 1 visit.
b Vital signs include heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature.
c Partial Mayo score calculation for participants with a history of IBD (as appropriate). See Section 6.9.6 for details.
d Quality of life (QoL) questionnaires include: SIBDQ (for participants with a history of IBD), CLDQ, EQ-5D, and PSC-PRO. It is recommended that QoL questionnaires are completed prior to any study procedures being performed and prior to the participant seeing a health care provider.
e Participant should be in fasted state for FibroScan collection. Refer to the Site Operations Manual for further details. FibroScan is not required at OLE Phase baseline/Day 1 if FibroScan was completed within 90 days of the OLE Phase baseline/Day 1 visit.
f Females of childbearing potential only (see Appendix 4). Urine pregnancy test at all visits, except telephone follow-up visits.
g For participants with history of IBD, any evidence of active IBD seen on routinely performed colonoscopy will be captured.
h Participants prematurely discontinuing should complete an OLE Phase ET visit (see Section 6.5.4).
i Treatment visit windows are ± 5 days unless otherwise stated, with the exception of the OLE Phase baseline/Day 1 visit (see Section 6.4).
j Fasting for FibroScan per standard of care.
k Re-consent at OLE Phase baseline/Day 1 visit is not necessary if the participant has previously provided written informed consent to participate in the OLE Phase and there has been no update to the informed consent form since participant previously provided written informed consent.

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 participant assigned female at birth is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the participant is permanently sterile or with medically documented ovarian failure.

Participants assigned female at birth 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, participants assigned female at birth 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 participant assigned female at birth of any age.

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Participants of Childbearing Potential

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. Drug-drug interaction (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 Participants of Childbearing Potential

The inclusion of female participants 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 randomization. Pregnancy tests will be performed at site visits and approximately 30 days after the last study drug dose. In the event of a delayed menstrual period (over 1 month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is applicable also for female participants of childbearing potential with infrequent or irregular periods. Female participants of childbearing potential must also agree to 1 of the following from screening until 30 days after last study drug dose:

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the participant'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 1 hormonal method and 1 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*

*Not approved in Japan

Not all of these methods may be approved in each of the countries where the study is being conducted: please refer to local product information. Additional local regulatory requirements may apply.

Female participants of childbearing potential 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 Participants

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

Participants assigned male at birth must agree to avoid sperm donation until 30 days after the end of the study.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Participants 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. Participants 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. Participants 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 3 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 3 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. Partial Mayo Score

Stool Frequency	❒ 0	Normal number of stools for participant
	❒ 1	1 to 2 stools per day more than normal
	❒ 2	3 to 4 stools more than normal
	❒ 3	≥ 5 stools more than normal
Rectal Bleeding	❒ 0	No blood seen
	❒ 1	Streaks of blood with stool less than half the time
	❒ 2	Obvious blood with stool half or more than half of the time
	❒ 3	Blood alone passes
Physician's Global Assessment	❒ 0	Normal
	❒ 1	Mild disease
	❒ 2	Moderate disease
	❒ 3	Severe disease

Adapted from {Lewis 2008}

GS-US-428-4194-amd-05

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	16-Mar-2022 14:38:20