CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-9674 in Subjects with Primary Biliary Cholangitis Without Cirrhosis
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	131032
EudraCT Number:	2016-002443-42
Clinical Trials.gov Identifier:	NCT02943447
Indication:	Primary Biliary Cholangitis (PBC)
Protocol ID:	GS-US-427-4024
Gilead Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD Email: PPD
Protocol Version/Date:	Original: 29 June 2016 Amendment 1: 30 September 2016 Amendment 2: 21 December 2016 Amendment 3: 09 February 2017

CONFIDENTIALITY STATEMENT

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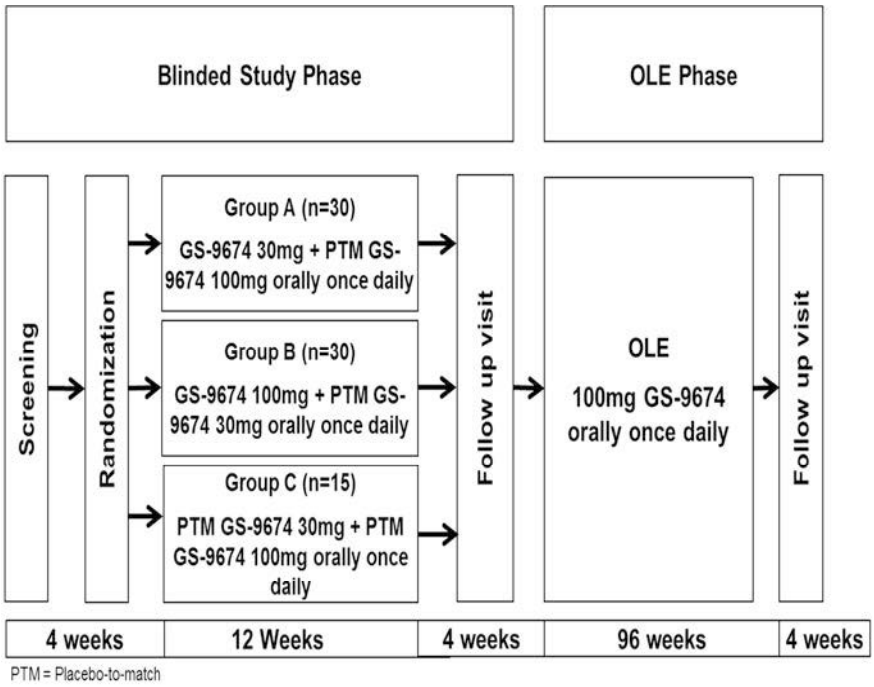
PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404, USA

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-9674 in Subjects with Primary Biliary Cholangitis Without Cirrhosis
IND Number:	131032
EudraCT Number:	2016-002443-42
Clinical Trials.gov Identifier:	NCT02943447
Study Centers Planned:	Approximately 40 centers in North America and Europe
Objectives:	The primary objective of this study is to evaluate the safety and tolerability of GS-9674 in subjects with primary biliary cholangitis (PBC) The exploratory objectives of this study are listed in Section 2.
Study Design:	This is a Phase 2 randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, and efficacy of GS-9674 in subjects with PBC 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 4 week screening period, 12 weeks of blinded treatment, and a Blinded Study Phase follow-up visit 4 weeks after completion of blinded treatment. Subjects completing the Blinded Study Phase without permanently discontinuing study drug will be eligible to participate in the OLE Phase of the study. OLE Phase: Includes a 96 week OLE and an OLE Phase follow-up visit 4 weeks after completion of open label treatment. Participation in the Blinded Study Phase can last up to 20 weeks and the OLE Phase can last up to 100 weeks, thus total study duration can be up to 120 weeks.

Subjects meeting the study's entry criteria will be randomly assigned in a 2:2:1 ratio to 1 of 3 treatment groups during the Blinded Study Phase as shown in the figure below:



Randomization will be stratified by the presence or absence of ursodeoxycholic acid (UDCA) use.

Number of Subjects Planned:	Approximately 75 subjects
Target Population:	Males and non-pregnant females between 18-70 years of age with PBC without cirrhosis
Duration of Treatment:	Total study duration of up to 120 weeks with up to 20 weeks for the Blinded Study Phase and up to 100 weeks for the OLE Phase.
Diagnosis and Main Eligibility Criteria:	Key inclusion and exclusion criteria are as follows:

Inclusion Criteria

- Meets all of the following conditions;
  a) Definite or probable PBC as defined by at least 2 of the 3 following criteria:
     i. Serum alkaline phosphatase (ALP) > the upper limit of normal (ULN)
     ii. Presence of anti-mitochondrial antibodies (AMA) in serum (≥ 1:40 on immunofluorescence)

iii. Liver histological findings consistent with PBC including nonsuppurative, destructive cholangitis affecting mainly the interlobular bile and septal bile ducts;

b) Serum ALP >1.67 x ULN and/or total bilirubin >ULN but ≤ 2x ULN;

c) UDCA use at a stable dose for at least 12 months prior to screening through the end of treatment or intolerant of UDCA with no UDCA use for at least 12 months before screening through the end of treatment;

- Screening FibroSURE/FibroTest® < 0.75, unless a historical liver biopsy within 12 months of screening does not reveal cirrhosis. In subjects with Gilbert's syndrome or hemolysis, FibroSURE/FibroTest® will be calculated using direct bilirubin instead of total bilirubin.

Exclusion Criteria

- ALT > 5x ULN;
- Total bilirubin > 2x ULN;
- INR >1.2 unless on anticoagulant therapy;
- Other causes of liver disease including viral, metabolic, alcoholic, and other autoimmune conditions. Subjects with hepatic steatosis may be included if there is no evidence of nonalcoholic steatohepatitis (NASH) in the opinion of the investigator or on liver biopsy;
- Use of fibrates or obeticholic acid within 3 months prior to screening through the end of treatment;
- Cirrhosis of the liver as defined by any of the following:
  a) Historical liver biopsy demonstrating cirrhosis (e.g. Ludwig stage 4 or Ishak stage ≥5)
  b) History of decompensated liver disease, including ascites, hepatic encephalopathy or variceal bleeding
  c) Liver stiffness >16.9 kPa by FibroScan®.

Please refer to section 4.2 and 4.3 of the protocol for detailed inclusion and exclusion criteria.

Study Procedures/ Frequency:

Blinded Study Phase

After signing the informed consent form, subjects will complete a screening visit which will include the following assessments: complete medical history, complete physical examination (PE), vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature), cirrhosis assessments, laboratory assessments (blood chemistry, hematology, coagulation panel, and biomarkers), serum pregnancy test (for females of childbearing potential), urine drug test, review of adverse events (AEs) related to screening procedures, and concomitant medications (CMs).

After the screening period, visits will occur at Baseline/Day 1, Weeks 1, 2, 4, 8, and 12. At minimum, vital signs, symptom-driven physical examination (PE), safety laboratory tests (blood chemistry, hematology, and coagulation panel), review of adverse events and concomitant medications will be done at every visit.

PPD

Eligible subjects will be randomized to one of three treatment groups of the Blinded Study Phase. Prior to initial dosing, required 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), urine, blood, and stool collection for biomarker assessments, pruritus assessments and Quality of Life (QoL) questionnaires, standard 12-lead ECG, FibroScan® (if available), review of AEs and CMs.

PPD

While on study, subjects will undergo the following procedures and laboratory assessments:

- Symptom-directed physical examination and vital signs, at Baseline/Day 1 and at Week 1, 2, 4, 8 and 12
- Height at Baseline/Day 1 and weight at all visits
- FibroScan® (if available) at Baseline/Day 1 and Week 12
- 12-lead ECGs at Baseline/Day 1 and Week 12
- C-peptide, insulin and hemoglobin A1c (HbA1c) at Baseline/Day 1 and Week 12

- PK and PD sampling at Baseline/Day 1 (PD only) and at Weeks 1, 2, 4, 8 and 12
- Blood for Biomarker assessments at Baseline/Day 1 and at Weeks 1, 4, and 12
- Urine Biomarker collection at Baseline/Day 1 and at Weeks 1, 4, and 12
- Urine pregnancy testing (females of childbearing potential only) at Baseline/Day 1 and Weeks 1, 4, 8 and 12
- Stool collection at Baseline/Day 1 and Week 12
- Hematology, blood chemistry, coagulation panel (PT, PTT, INR) and fasting lipid profile at Baseline/Day 1 and Weeks 1, 2, 4, 8, and 12
- QoL Questionnaires: PBC-40 and SF-36 at Baseline/Day 1 and Week 12
- Pruritus Assessments: Pruritus visual analog scale (VAS) and 5D-Itch at Baseline/Day 1 and Weeks 1, 2, 4, 8, and 12

At the Blinded Study Phase follow-up visit, subjects will have a symptom-driven PE, vital signs, laboratory assessments, urine pregnancy tests (for females of childbearing potential), urine, stool and blood collection for biomarker assessments, QoL and pruritus questionnaires (PBC-40, SF-36, Pruritus VAS and 5D-Itch), weight, review of AEs, and review of CMs and serum will be drawn for hematology, blood chemistry, and a coagulation panel.

Subjects will be unblinded to their Blinded Study Phase treatment assignment after the primary analysis has been completed, approximately 6 weeks after all subjects have completed the Blinded Study Phase.

During the Blinded Study Phase early termination (ET) visit, subjects who prematurely discontinue participation will complete Week 12 assessments and will also complete the Blinded Study follow-up visit 4 weeks after their last dose if possible.

Open-Label Extension (OLE) Phase

Subjects who do not permanently discontinue study drug and complete the Blinded Study Phase follow-up visit will be eligible to enter into the OLE Phase of the study for 96 weeks. Subjects will begin open-label treatment with GS-9674 (100 mg po once daily). The dose of GS-9674 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 (MM), if required. In the OLE Phase, subjects will have in-clinic study assessments at OLE

	Baseline/Day 1, OLE Week 1, OLE Week 2, OLE Week 4, OLE Week 8, OLE Week 12, and every 12 weeks thereafter for symptom-driven PE, vital signs, laboratory assessments, urine pregnancy tests (for females of childbearing potential at OLE Baseline/Day 1 and every 4 weeks thereafter), urine, stool and blood collection for biomarker assessments (at OLE Baseline/Day 1, Weeks 4, 12 and every 12 weeks thereafter), QoL (PBC-40, SF-36 at OLE Baseline/Day 1, Weeks 4, 12 and every 12 weeks thereafter) and pruritus questionnaires (Pruritus VAS and 5D-Itch), weight, review of AEs and review of CMs. Subjects in the OLE Phase will complete the treatment Week 96 visit and then return for their final visit, the OLE follow-up visit 4 weeks following the last dose of study drug. Subjects who prematurely discontinue participation in the OLE Phase will complete the Week 96 assessments and will also complete the follow-up visit 4 weeks after their last dose if possible. At the OLE follow-up visit, subjects will have a symptom-driven PE, measurement of vital signs, review of AEs, CMs, pruritus and assessment and serum will be drawn for hematology, blood chemistry, lipids, and a coagulation panel. A urine pregnancy test will be performed for females of childbearing potential only.
Test Product:	GS-9674 30 mg tablet administered orally once daily with food. GS-9674 100 mg tablet administered orally once daily with food.
Reference Product:	Placebo-to-match (PTM) GS-9674 30 mg tablet administered orally once daily with food. Placebo-to-match (PTM) GS-9674 100 mg tablet administered orally once daily with food.
Dose and Mode of Administration:	• **Treatment Group A:** GS-9674 30 mg (1 x 30 mg tablet) + PTM GS-9674 100 mg (1 x PTM 100 mg tablet) administered orally once daily with food. • **Treatment Group B:** GS-9674 100 mg (1 x 100 mg tablet) + PTM GS-9674 30 mg (1 x PTM 30 mg tablet) administered orally once daily with food. • **Treatment Group C:** PTM GS-9674 30 mg (1 x PTM 30 mg tablet) + PTM GS-9674 100 mg (1 x PTM 100 mg tablet) administered orally once daily with food.

Criteria for Evaluation:	
Safety:	The primary endpoint is the safety of GS-9674 in subjects with PBC without cirrhosis. Safety will be assessed during the study through the reporting of AEs, and by clinical laboratory tests and vital sign assessments at various time points during the study. Concomitant medication usage will also be assessed throughout the study. An independent, external Data Monitoring Committee (DMC) that consists of two hepatologists and a PhD statistician will convene once 20 subjects have been randomized and every 3 to 4 months thereafter to monitor the study for safety events in the Blinded Study Phase and every 6 months in the OLE Phase . The DMC will meet on an ad hoc basis if there are at least 3 similar Grade ≥ 3 serious, treatment related Common Terminology Criteria for Adverse Events (CTCAE) observed in the study. In the event of two similar treatment related Grade 4 CTCAE events or one treatment related Grade 5 CTCAE, the DMC will review the data and advise the sponsor regarding stopping or continuing the study.
Efficacy:	Efficacy will be assessed through a number of exploratory endpoints. These exploratory endpoints are described in Section 8.1.3.
Pharmacokinetic and Pharmacodynamic:	Plasma concentrations of GS-9674, GS-716070 (metabolite of GS-9674), and other metabolites as appropriate, will be determined for PK analyses as applicable. Plasma or serum concentrations of FGF19, C4, and bile acids will be determined as applicable for PD analyses.
Statistical Methods:	
Safety Analysis:	All safety data collected will be listed and summarized, as appropriate, by treatment group.
Efficacy Analysis:	The biological and histological activity of study drugs will be evaluated using histologic endpoints and biomarker variables. Because efficacy endpoints will be evaluated for exploratory purposes, formal statistical comparisons will not be made for these endpoints. Ninety-five percent confidence intervals (95% CI) will be provided if applicable.
Exploratory Analysis:	PPD

Sample Size:	Due to the exploratory nature of this study, no formal power calculations were used to determine sample size. The number of subjects was chosen based on clinical experience with other similar proof of concept studies.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AMA	anti-mitochondrial antibodies
Apo B	apolipoprotein B
aPTT	activated partial thromboplastine time
AST	aspartate aminotransferase
ATV	atorvastatin
ATP	Adenosine triphosphate
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
β-hCG	beta human chorionic gonadotropin
BAP	Biomarker Analysis Plan
BCRP	breast cancer resistance protein
BUN	blood urea nitrogen
BW	body weight
C4	7-alpha-hydroxy-4-cholesten-3-one
CFR	code of federal regulations
C_{last}	last observed quantifiable plasma/serum concentration of the drug
C_{max}	maximum observed plasma/serum concentration of drug
CMs	concomitant medications
CNS	central nervous system
CRO	contract (or clinical) research organization
CTCAE	Common Terminology Criteria for Adverse Events
CSR	clinical study report
DAB	metabolite of dabigatran etexilate
DDI	drug-drug interaction
DE	dabigatran etexilate
CYP3A	cytochrome P4503A
CV	Cardiovascular
CsA	cyclosporin
DDI	drug-drug interaction
DILI	drug induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid

DSPH	Drug Safety and Public Health
EC50	Concentration of drug that gives half-maximum response
ECG	Electrocardiogram
ET	early terminated
eCRF	electronic case report form
EDC	electronic data capture
e.g.	Example
ELF™ Test	enhanced liver fibrosis test
EU	European Union
FAS	Full analysis set
FDA	(United States) Food and Drug Administration
FSH	Follicle-stimulating hormone
FGF	Fibroblast growth factor
FXR	Farnesoid X Receptor
GCP	good clinical practice
GCSF	granulocyte colony stimulating factor
GFZ	gemfibrozil
GGT	gamma glutamyl transferase
GSI	Gilead Sciences, Inc.
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
Hct	Hematocrit
HDPE	High-density polyethylene
HCV	Hepatitis c virus
Hg	Hemoglobin
HIV	Human immunodeficiency virus
HLT	high-level term
HLGT	high-level group term
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HOMA-IR	homeostatic assessment of insulin resistance
IB	investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
INR	international normalized ratio
IRB	institutional review board

IUD	intrauterine device
IWRS	interactive web response system
kg	Kilogram
LDH	lactate dehydrogenase
LLT	lower-level term
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
mg	Milligram
min	Minute
mL	Milliliter
MDZ	midazolam
mm	Millimeter
mm Hg	millimeters of mercury
MM	Medical Monitor
MRE	Magnetic Resonance Elastography
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NTCP	sodium-taurocholate cotransporting polypeptide
NMR	nuclear magnetic resonance spectroscopy
NOAEL	no observed adverse event level
OATP	Organic anion-transporting polypeptide
OLE	Open Label Extension
PRA	pravastatin
PBC	Primary Biliary Cholangitis
PBMCs	peripheral blood mononuclear cell(s)
PD	Pharmacodynamic
PK	Pharmacokinetic
P-gp	P-glycoprotein
PO	taken by mouth
PSC	Primary Sclerosing Cholangitis
PT	preferred term
PT	prothrombin time
PTT	Partial prothrombin time
QoL	Quality of Life
RBC	red blood cell count
RIF	rifampin
RNA	ribonucleic acid
RXR	Retinoid X receptor
SADR	serious adverse drug reaction
SAE	serious adverse event

SAP	statistical analysis plan
SF-36	Short Form (36) Health Survey
SD	standard deviation
SOC	System Organ Class
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Time required for the terminal elimination half-life of the drug
TEAEs	Treatment emergent adverse events
TGR5	bile acid receptor
TPO	thrombopoietin
TR-FRET	Time-resolved fluorescence resonance energy transfer
T_{last}	last measured concentration
T_{max}	time (observed time point) of C_{max}
UDCA	ursodeoxycholic acid
UGT	uridine dophosphate glucuronosyltransferase
ULN	upper limit of the normal range
US	United States
USPI	United States product insert
Vss	Volume of distribution at steady state
VAS	visual analog scale
VORI	voriconazole
WBC	white blood cell count

1. INTRODUCTION

1.1. Background

Primary Biliary Cholangitis (PBC) is a disorder of unknown etiology characterized by lymphocytic cholangitis and intralobular bile duct destruction that result in the impairment of bile flow (cholestasis). According to a recent systematic review {Boonstra 2012}, the incidence rate for PBC has ranged from 0.33 to 5.8 per 100,000 inhabitants/year and the prevalence has ranged from 1.91 to 40.2 per 100,000 inhabitants. PBC disproportionately affects women as over 90% of patients diagnosed with PBC are female and are generally between the fifth and seventh decades of life. Several studies {Boonstra 2014, Hamlyn 1983, Metcalf 1997} with available data for several consecutive years have demonstrated an increasing prevalence of PBC over time.

The pathophysiology of PBC is complex and is likely related to interplay between genetic and environmental factors. Genetics play an important role as evidence by first degree relatives of patients with PBC having an increased risk of developing the disease with daughters of women with PBC having the highest risk {Gershwin 2005}. Studies including genome wide association have implicated HLA alleles, as well as immune pathways involving antigen presentation, T-cell differentiation and natural-killer T-cells in the pathogenesis of PBC {Carbone 2014}. Biliary epithelial cells are targeted in PBC and may amplify the immune response by acting as antigen presenting cells {Selmi 2009}. The autoimmune destruction of biliary epithelial cells leads to cholestasis and resulting liver injury.

Cholestasis results in increased hepatic and serum bile acids and eventually to liver toxicity, fibrosis, and cirrhosis {Woolbright 2012}. Increasing concentrations of bile acids including via bile duct ligation or direct administration to cultured hepatocytes are frequently used models for hepatotoxicity. While the exact mechanism of bile acid induced hepatotoxicity remains to be elucidated, bile acids have been shown to increase apoptosis, hepatic inflammation, and necrosis. Reduction of toxic bile acids with UDCA {Hirschfield 2015} or by agonism of the farnesoid X receptor (FXR) {Hirschfield 2015} has been shown to be protective both in models of cholestatic liver disease as well as in patients with PBC.

1.2. GS-9674

1.2.1. General Information

GS-9674 is a potent agonist of Farnesoid X Receptor (FXR) whose activity in intestinal epithelial cells results in the release of fibroblast growth factor 19 (FGF19). FGF19 is an endocrine peptide which drives a signaling cascade to decrease lipogenesis, gluconeogenesis, hepatic triglyceride accumulation, and bile acid synthesis.

Please refer to the Investigator's Brochure (IB) for additional information on GS-9674 including:

- In Vitro FXR agonism
- Nonclinical Pharmacokinetics and In Vitro Metabolism
- Nonclinical Pharmacology and Toxicology

1.2.2. Nonclinical Toxicology

The nonclinical toxicity profile of GS-9674 has been assessed in mice and cynomolgus monkeys administered GS-9674 orally up to 26 and 39 weeks, respectively. GS-9674-related effects were primarily limited to non-adverse findings in the liver for both species that are likely related to the pharmacology of the compound. Mild increases in alkaline phosphatase (ALP) activity and liver weights were observed in the 4 week and chronic (26 or 39 week) studies. In the 4-week studies and 26-week mouse study, these findings were associated with hepatocellular hypertrophy (both species) and minimal oval cell hyperplasia (monkeys). In the chronic monkey study, there were no correlating histological changes in the liver after 39 weeks of dosing. The above findings were observed at ≥ 100 mg/kg/day after 4 weeks of dosing and at all doses (≥ 20mg/kg/day) after 26 weeks of dosing in mice. In monkeys, the above findings were observed at doses of 300 mg/kg/day after both 4 and 39 weeks of dosing. The decreases in cholesterol (≥ 60 mg/kg/day) and triglycerides (≥ 100 mg/kg/day) as well as increased albumin (≥ 60 mg/kg/day) observed in mice after 4 and/or 26 weeks of dosing as well as the decrease in serum bile acids (300 mg/kg/day) in monkeys 39 weeks of dosing are also likely to be related to the pharmacology of GS-9674. Other minimal to mild, non-adverse findings observed after 26 or 39 weeks of dosing in mice or monkeys, respectively, that were considered GS-9674-related included decreased red blood cell parameters (mouse; ≥ 20 mg/kg/day), increased platelets (mouse; 600/300 mg/kg/day), shortened activated partial thromboplastin time (monkey; 300 mg/kg/day), and increased phosphorus (mouse; 600/300 mg/kg/day). All findings showed evidence of reversibility after a 4-week recovery period. The no-observed-adverse effect levels (NOAEL) in mice after 26 weeks of dosing and in monkeys after 39 weeks of dosing were 60 and 300 mg/kg/day, respectively.

Preliminary PK data from Cohort 5 (administration of GS-9674 100 mg with food) in the ongoing Phase 1 study of GS-9674 (GS-US-402-1851: included in IB) indicate adequate safety margins based on GS-9674 exposures at the nonclinical NOAEL doses in mouse and cynomolgus monkey (Table 1-1).

Table 1-1. Exposure Margins for GS-9674 Based on Observed GS-9674 Exposure After Administration of 100 mg GS-9674 Under Fed Conditions in Cohort 5 Compared to Exposures Observed at NOAEL Doses in Mouse and Cynomolgus Monkey

Species	NOAEL		Exposure Margin[a]
	Dose mg/kg/day	AUC_{tau} µg*hr/mL	
Mouse	60	Male: 66 Female: 110	Male: 13 Female: 22
Cynomolgus Monkey	300	163	32

a Calculated using observed human AUC_{inf} of 5.02 µg*hr/mL at 100 mg QD dose administered fed from cohort 5 in Study GS-US-402-1851.

1.2.3. Nonclinical Pharmacology

GS-9674 is a potent and selective agonist of FXR. This conclusion is supported by the following data: 1) modeling demonstrated an interaction of GS-9674 with the binding domain of FXR consistent with agonist activity, 2) GS-9674 induced an agonist response in a time-resolved fluorescence resonance energy transfer (TR-FRET) biochemical assay with an EC_{50} of 16 nM, which was comparable to that of other known FXR agonists, and 3) GS-9674 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.

The cellular potency of GS-9674 to activate FXR-mediated transcription was characterized using a firefly luciferase reporter gene engineered under the control of a FXR/Retinoid X receptor (RXR) response element (PC-402-2012). GS-9674 caused complete FXR activation with an EC_{50} value of 43 nM, which was more potent than chenodeoxycholic acid (EC_{50} of 1770 nM).

Oral dose-ranging experiments in male cynomolgus monkeys demonstrated maximal increases in plasma FGF19 at a dose of 5 mg/kg (PC-402-2016). In addition, the oral administration of GS-9674 (30 mg/kg) to cynomolgus 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) (PC-402-2005).

The effects of GS-9674 on FGF19 levels were compared in cynomolgus monkeys following both oral and intravenous (IV) administration (PC-402-2016). Despite greater exposures following IV administration, only the oral administration of GS-9674 increased circulating FGF19 levels. These data suggest that intestinal FXR agonism by GS-9674 causes FGF19 production, whereas low systemic free drug concentrations limit effects following IV administration of GS-9674.

GS-9674 was evaluated in a choline-deficient high fat diet /$NaNO_2$ rat model of liver fibrosis (PC-402-2015). This in vivo model utilized “2 hits” to mimic the metabolic and oxidative stress components of NASH disease in humans {Murakami 2013, Nakamoto 2009}. Treatment with

GS-9674 dose-dependently reduced both biochemical and histological measures of liver fibrosis in this model.

Safety pharmacology studies have been conducted to examine the potential effects of GS-9674 on the cardiovascular (CV), respiratory, and central nervous system (CNS) systems. There were no GS-9674-related effects on the CNS or respiratory system in mice administered up to 600 mg/kg. In addition, there was no significant human ether-a-go-go-related gene inhibition at concentrations up to 100 μM or GS-9674-related effects on the CV system in monkeys administered up to 300 mg/kg.

Overall, the results from these pharmacology studies demonstrate that GS-9674 is a potent and selective agonist of intestinal FXR with the potential to benefit PBC patients by inducing FGF19 production.

1.2.4. Nonclinical Pharmacokinetics

GS-9674 has shown low oral bioavailability in nonclinical species (approximately 10% and 20% when dosed as partially crystalline zwitterion or tromethamine salt, respectively). Low, pH-dependent solubility and efflux transport have been identified as factors likely limiting GS-9674 absorption.

The low systemic clearance (CL) of GS-9674 in rats, dogs and monkeys was considerably lower than the predicted hepatic clearance based on in vitro studies with hepatocytes. This discrepancy is most likely a result of protein-restricted clearance in vivo due to the very high plasma protein binding (> 99.6%) across species. The volume of distribution (V_{ss}) of GS-9674 was consistent with extracellular fluid (ranging from 0.16-0.21 L/kg) in rats, dogs, and monkeys.

After oral dosing to albino and pigmented mice, [^{14}C] GS-9674-derived radioactivity was distributed to most of the tissues, with the highest maximum concentrations of radioactivity determined in organs of absorption and excretion. Generally similar distribution patterns and tissue concentrations of [^{14}C]GS-9674-derived radioactivity were observed in albino and pigmented mice with no observed binding to melanin. In both strains, no quantifiable radioactivity was detected in brain, suggesting [^{14}C] GS-9674-derived radioactivity did not cross the blood-brain barrier. Fecal elimination was a predominant route of elimination of [^{14}C] GS-9674-derived radioactivity in both mice (85.7% and 5.45% recovered in feces and urine, respectively) and monkeys (78.2% and 69.7% recovered in feces in intact and bile duct cannulated animals) likely representing drug not absorbed from the gastrointestinal tract. Approximately 6% of the administered radioactivity was excreted in bile and urine in monkeys. Radiolabeled material was primarily excreted within the first 48 hours.

GS-9674 undergoes oxidative metabolism in human hepatocytes. Comparison of metabolism in hepatocytes from mice, rats, dogs, monkeys, and humans did not identify any metabolites unique to humans, supporting the selection of mice and monkeys for the assessment of the toxicology of GS-9674. Of the recombinant human CYP isozymes tested, CYP2C8, CYP3A4, and CYP2C19 were shown to metabolize GS-9674. Potent inhibitors of these CYPs therefore may affect metabolism of GS-9674. GS-9674 had little inhibitory effect on the activities of CYP1A2,

CYP2B6, CYP2C19 or CYP2D6 (IC_{50} > 25 μM). For CYP2C8, CYP2C9, and CYP3A, IC_{50} values of 2.4 to 13.6 μM were obtained but GS-9674 was not a mechanism-based inhibitor of these enzymes. GS-9674 showed moderate inhibition of human UGT1A1, sodium-taurocholate cotransporting polypeptide (NTCP), and bile salt export pump (IC_{50} 2.8-7.7 μM). GS-9674 inhibited human OATP1B1, OATP1B3, and OATP2B1 with IC_{50} values of 0.68, 0.41, and 0.21 μM, respectively. GS-9674 therefore has the potential to affect hepatic/intestinal uptake of OATP substrates or metabolism of CYP2C8, CYP2C9, or CYP3A4 substrates when its concentrations are sufficiently high. However, low solubility, high protein binding (> 99.98%) and low systemic levels reduce the potential for GS-9674 to cause drug-drug interactions via inhibition of metabolic enzymes and transporters.

GS-9674 was a substrate for efflux transporters P-glycoprotein and breast cancer resistance protein, as well as the uptake transporters OATP1B1, 1B3, and 2B1, and NTCP. Inhibitors or genetic polymorphisms affecting the activity of these transporters may affect GS-9674 intestinal absorption and hepatic uptake. This was illustrated in an in vivo study in monkeys where pretreatment with cyclosporin A, a known inhibitor of efflux transporters, increased the bioavailability of GS-9674 approximately 5-fold.

GS-9674 is highly selective for FXR over other nuclear hormone receptors in cell-based reporter assays, including those associated with potential for induction of human drug metabolizing enzymes and transporters (eg, pregnane X receptor, constitutive androstane receptor). Thus the liability of GS-9674 to cause drug-drug interactions through proteins regulated by these nuclear receptors is low.

1.2.5. Clinical Trials of GS-9674

As of 23 Sept 2016, 4 Phase 1 clinical studies are ongoing (GS-US-402-1851, GS-US-402-3885, GS-US-402-2102, and GS-US-402-2101), and 4 Phase 2 studies in subjects with NAFLD, NASH, PBC, and PSC are ongoing or planned (GS-US-384-3914, GS-US-402-1852, GS-US-427-4024, and GS-US-428-4025, respectively). These Phase 1 and 2 studies are described in the IB.

A brief summary of preliminary results, not included in the IB from ongoing study GS-US-402-2102 is presented below.

1.2.5.1. GS-US-402-2102

Study GS-US-402-2102 is an ongoing Phase 1, open-label, multicenter, multiple-cohort study designed to evaluate transporter and CYP-mediated drug-drug interactions (DDIs) between GS-9674 100 mg and various probe drugs in healthy subjects. A total of approximately 180 subjects are planned to be enrolled.

Preliminary PK results from the following cohorts are presented below and in Table 1-2 and Table 1-3:

- Cohort 1: Impact of OATP/MRP2/P-gp inhibition (single dose cyclosporine 600 mg: CsA) or OATP1B1/1B3 inhibition (single dose rifampin 600 mg: RIF) on single dose administration of GS-9674 100 mg with food (N=24). Single doses of CsA or RIF significantly increased GS-9674 exposure (6.5- and 8.0-fold respectively), with more modest increases in GS-716070 exposure (3.3- and 4.9-fold respectively).These data indicate the GS-9674 is a sensitive substrate of hepatic OATP with intestinal P-gp playing a minimal to no role in GS-9674 absorption as seen by a smaller increase in GS-9674 by CsA compared to single dose RIF. Based on these data coadministration of GS-9674 with potent inhibitors of OATP is not recommended and moderate inhibitors of OATP should be used with caution whereas GS-9674 may be coadministered with P-gp inhibitors.

- Cohort 2: Impact of CYP3A inhibition (multiple dose voriconazole 200 mg BID 4 days: VORI) and CYP2C8 inhibition (multiple dose gemfibrozil 600 mg BID 4 days: GFZ) on single dose administration of GS-9674 100 mg with food (N=18). Coadministration of GS-9674 with VORI did not result in clinically meaningful changes in GS-9674 or GS-716070 exposures indicating that CYP3A plays a minimal role in the disposition of GS-9674 and GS-716070. As such, GS-9674 may be coadministered with CYP3A inhibitors. Coadministration of GS-9674 with GFZ increased GS-9674 exposure 75% with reduction of GS-716070 exposure by 55% indicating that biotransformation of GS-9674 to GS-716070 is predominantly mediated by CYP2C8. Based on the less than 2-fold increase in GS-9674 exposure, GS-9674 may be coadministered with inhibitors of CYP2C8.

- Cohort 3: Impact of CYP3A/2C8/OATP/P-gp induction (multiple dose rifampin 600 mg QD 7 days in the evening: RIF) on single dose AM administration of GS-9674 100 mg with food(N=18). Plasma exposure of GS-9674 and GS-716070 were substantially reduced after multiple dose administration of RIF indicating that GS-9674 and GS-716070 are sensitive to induction of OATP and CYP2C8. As such coadministration of GS-9674 with potent or moderate inducers of OATP or CYP2C8 is not recommended.

- Cohort 5: Impact of single dose administration of GS-9674 100 mg with food on CYP3A activity (single dose midazolam: MDZ) or OATP/CYP3A activity (single dose atorvastatin: ATV) (N=24). GS-9674 did not alter MDZ exposure (90%CIs of the %GMR for AUC and Cmax were contained within the predetermined lack of effect bounds of 70-143%) indicating that GS-9674 is not an inhibitor of CYP3A. As such GS-9674 may be coadministered with CYP3A substrates. GS-9674 modestly increased ATV exposure (39%). Similar increases in ATV exposure do not necessitate a priori dose modification as per the LIPITOR® United States product insert (USPI). As such, ATV may be coadministered with GS-9674.

- Cohort 6: Impact of single dose administration of GS-9674 100 mg with food on P-gp (single dose dabigatran etexilate 75 mg: DE), OATP (single dose pravastatin 40 mg: PRA) or OATP/BCRP (single dose rosuvastatin 10 mg: ROS) (N=24). GS-9674 did not alter DE (free or total dabigatran: DAB metabolite of DE), PRA, or ROS exposures (90%CIs of the %GMR for AUC and C_{max} were contained within the predetermined lack of effect bounds of 70-143%) indicating the GS-9674 is not an inhibitor of P-gp, OATP, or BCRP. As such GS-9674 may be coadministered with P-gp, OATP, or BCRP substrates.

Table 1-2. Preliminary Pharmacokinetic Results from Study GS-US-402-2102 Evaluating the Effect of DDIs on Administration of 100 mg GS-9674 with Food (Cohorts 1-3)

		%GMR (90%CI) Test/Reference				
		Cohort 1 (N=24)		Cohort 2 (N=18)		Cohort 3 (N=18)
Analyte	PK Parameter	CsA	RIF[a]	VORI	GFZ	RIF[b]
GS-9674	AUC_{inf}	655 (577, 743)	796 (719, 880)	95.9 (81.0, 114)	175 (149, 206)	32.8 (27.9, 38.4)
	C_{max}	512 (448, 584)	547 (497, 603)	76.8 (60.2, 97.9)	139 (115, 168)	35.5 (29.1, 43.3)
GS-716070	AUC_{inf}	331 (297, 369)	493 (442, 551)	129 (109, 154)	44.5 (38.7, 51.1)	12.6 (10.5, 15.0)
	C_{max}	211 (191, 232)	301 (274, 331)	99.2 (81.1, 121)	31.2 (26.1, 37.4)	17.0 (13.7, 21.2)

Data are presented to 3 significant digits
a Single Dose
b Multiple Dose

Table 1-3. Preliminary Pharmacokinetic Results from Study GS-US-402-2102 Evaluating the Effect of GS-9674 100 mg with Food on CYP3A, OATP/CYP3A, P-gp, OATP, or OATP/BCRP (Cohorts 5-6)

Cohort	Enzyme/ Transporter	Analyte	PK Parameter	Test	Reference	% GMR (90%CI) Test/Reference
5 (N=24)	CYP3A	MDZ	AUC_{inf}	37.3 (27.5)	63.9 (29.1)	102 (95.8, 108)
			C_{max}	7.79 (27.6)	7.92 (35.6)	100 (94.8, 106)
	OATP/ CYP3A	ATV	AUC_{inf}	15.5 (33.5)	10.8 (39.0)	139 (124, 156)
			C_{max}	1.06 (35.6)	0.98 (35.9)	107 (94.6, 120)
6 (N=24)	P-gp	Total DAB	AUC_{inf}	624 (32.0)	535 (34.3)	118 (109, 128)
			C_{max}	84.4 (40.0)	68.0 (37.8)	125 (112, 139)
		Free DAB	AUC_{inf}	543 (32.0)	477 (37.3)	116 (108, 124)
			C_{max}	75.0 (39.6)	60.8 (42.5)	125 (114, 138)
	OATP	PRA	AUC_{inf}	109 (55.6)	99.6 (66.7)	115 (104, 126)
			C_{max}	41.7 (58.8)	42.4 (66.5)	104 (91.5, 117)
	OATP/ BCRP	ROS	AUC_{inf}	38.3 (40.3)	34.9 (39.5)	111 (101, 121)
			C_{max}	3.06 (40.4)	2.86 (43.4)	108 (98.3, 119)

Data are presented as mean (%CV) to three significant

1.3. Rationale for this Study

PBC is an autoimmune disorder characterized by lymphocytic cholangitis and intralobular bile duct destruction that result in the impairment of bile flow (cholestasis). Accumulation of excess bile acids causes hepatocellular cytotoxicity that may lead to progressive liver fibrosis, including cirrhosis in some patients. In pre-clinical and clinical studies, FXR agonism has been shown to reduce bile acid levels via FGF19-mediated suppression of cholesterol-7-hydroxylase (CYP7A1), the rate-limiting enzyme in bile acid biosynthesis {Inagaki 2005, Mudaliar 2013, Pellicciari 2002}. In addition, in a murine model of fibrosis caused by administration of a methionine choline deficient diet and sodium nitrite injections, GS-9674 has demonstrated an anti-fibrotic effect. Clinical data with obeticholic acid, a semi-synthetic analog of the primary bile acid chenodeoxycholic acid (CDCA) which activates FXR, has also demonstrated improvements in liver biochemistry in subjects with PBC supporting the potential of FXR agonists in this condition {Hirschfield 2015}. Thus, GS-9674 is postulated to be beneficial in subjects with PBC.

This study will evaluate the safety, tolerability, and efficacy of 30 mg and 100 mg GS-9674 administered with food for 12 weeks in subjects with PBC. The doses were selected based on short-term safety, PD and PK results from Study GS-US-402-1851 in healthy subjects.

Across the range of GS-9674 doses evaluated (10 to 300 mg QD), doses $\geq$ 30 mg provide comparable intestinal FXR agonism assessed by increases in plasma FGF19 exposure. Food, by

slowing oral absorption of GS-9674, results in prolonged elevation of plasma FGF19 concentrations. Exposure-response relationships show that changes in C4 exposure are negatively correlated with changes in FGF19 exposure as well as GS-9674 exposure. Based on these results, GS-9674 doses of 30 and 100 mg with food are selected for further study as they are expected to 1) provide enteral FXR agonism, reductions in bile acid pools, and liver biochemical improvements in subjects with PBC; and 2) inform regarding the impact of increasing systemic GS-9674 exposure on safety and efficacy.

In the Phase 1 study, GS-US-402-1851, GS-9674 was tested at doses up to 300 mg once daily for up to 14 days and was well-tolerated. Taken together, these data support the evaluation of GS-9674 30 and 100 mg in subjects with PBC.

Inclusion criteria for this study were developed to identify subjects with PBC who have persistently abnormal liver biochemistry despite treatment with UDCA and subjects intolerant of UDCA. Compared with individuals with normal liver biochemistry, these subjects are at an increased risk of PBC-related complications including the need for liver transplantation and death {Carbone 2016, Corpechot 2008, Lammers 2015}. Subjects with clinical and histologic evidence of cirrhosis will be excluded from this study due to the uncertain PK and PD properties of GS-9674 to the setting of subjects with cirrhosis. Targeting interventions in the proposed study population will provide evidence for the safety and efficacy of GS-9674 in subjects at risk for progressive hepatic fibrosis and cirrhosis.

1.4. Risk/Benefit Assessment for the Study

This study will provide information on the safety and efficacy of GS-9674 for the treatment of patients with PBC. Alternate therapies for the treatment of PBC include UDCA and obeticholic acid. The potential benefits of GS-9674 for the treatment of PBC in the current study population include hypothesized improvements in hepatic injury due to reduced bile acid synthesis attributable to FXR agonism. Improvements in liver biochemistry, hepatic fibrogenesis, and potentially quality of life, would be expected to ensue based on these effects. Subjects with PBC randomized to the placebo control arm in the study may benefit from frequent medical monitoring and close assessment of their PBC and associated pathologies during the duration of placebo treatment. Moreover, all subjects, including those treated with placebo during the randomized phase, have the opportunity to receive GS-9674 treatment during a long-term open-label extension phase.

In the Phase 1 study, 94 subjects have received GS-9674 in single or multiple doses (14 days) up to 300 mg. All treatment emergent adverse events (TEAEs) were mild to moderate (Grade 1 or 2), and overall, the rate of any adverse events (AEs) was similar between subjects treated with GS-9674 or placebo. The predominant toxicities were anemia, back pain, diarrhea, and headache. Grade 2 or 3 elevations in serum ALT were seen in five (5%) GS-9674 treated subjects and one (4%) placebo treated subject. Grade 2 or 3 ALT elevations that occurred on-treatment were observed in 2/23 (9%) BID treated subjects, but none of the 71 subjects who received once daily (QD) GS-9674 dosing. In these cases, elevations in serum bilirubin or prolongation of INR were not observed, serum ALT levels normalized upon treatment cessation, and no evidence of drug hypersensitivity syndrome (e.g., fever, rash, eosinophilia) was noted. In nonclinical studies,

effects on the liver have been limited to non-adverse mild increases in alkaline phosphatase 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) in the nonclinical studies to suggest direct cellular damage. In order to mitigate the potential risk of hepatotoxicity with GS-9674, QD dosing of GS-9674 has been chosen for this study. Moreover, close monitoring of liver biochemistry values will be performed and parameters for discontinuation of the study drugs due to liver test abnormalities have been defined (see Section 7.5, Toxicity Management: Observation for Drug-Induced Liver Injury) and will be closely followed.

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

Overall, the nonclinical and limited preliminary clinical data show a positive benefit/risk ratio in support of the study in subjects with PBC.

1.5. Compliance

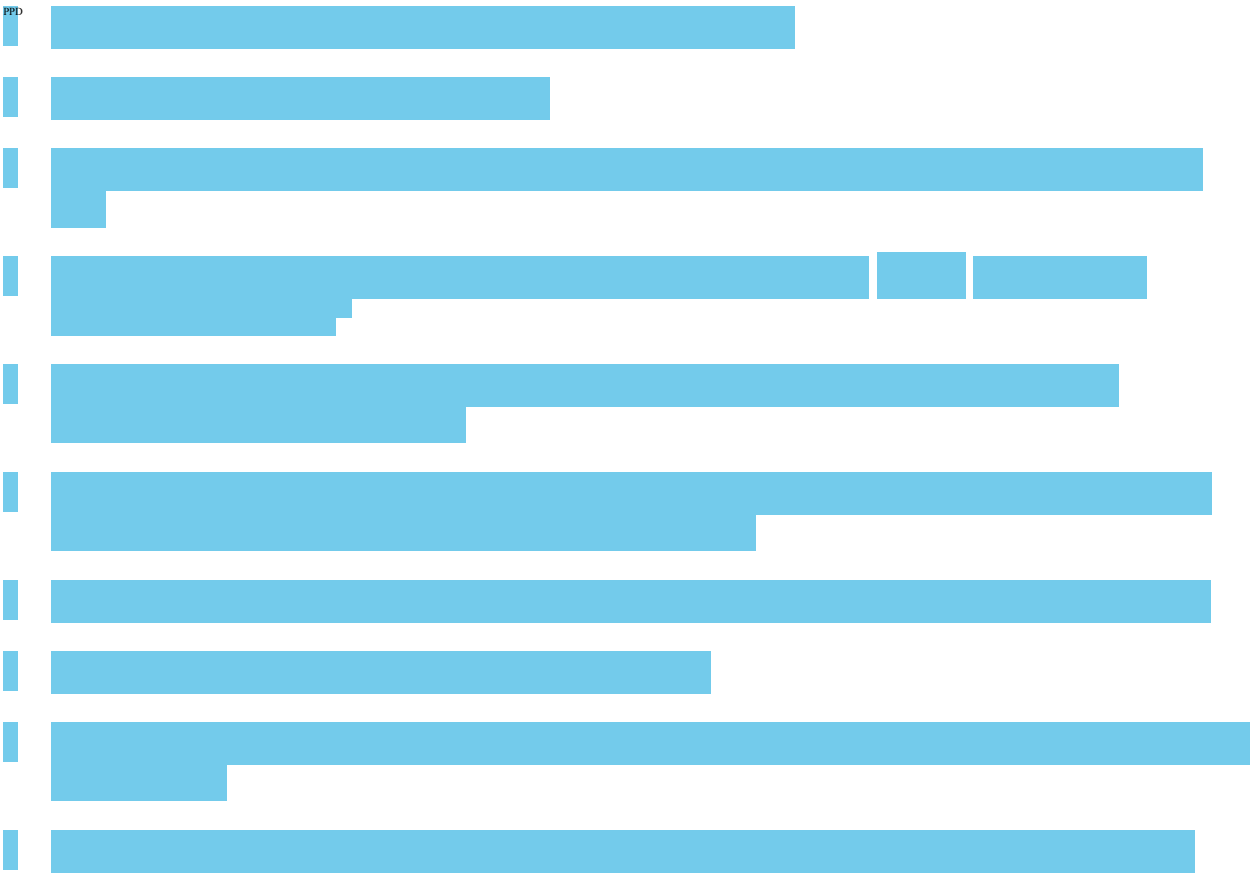
The study will be conducted in accordance with Good Clinical Practice (GCP), and all applicable rules and regulations.

2. OBJECTIVES

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

- To evaluate the safety and tolerability of GS-9674 in subjects with PBC

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



3. STUDY DESIGN

3.1. Study Design

This is a Phase 2 randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, and efficacy of GS-9674 in subjects with PBC without cirrhosis.

The study will consist of 2 phases, a Blinded Study Phase and an OLE Phase.

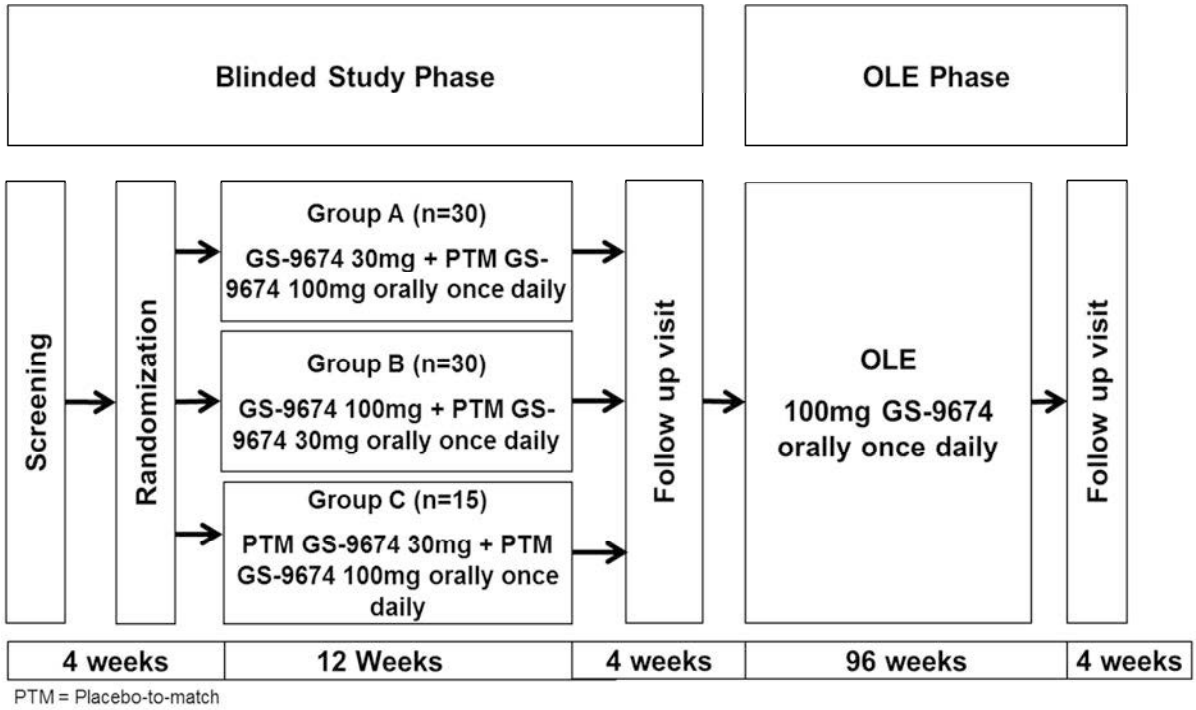
Blinded Study Phase: Includes a 4 week screening period, 12 weeks of blinded treatment, and a Blinded Study Phase follow-up visit 4 weeks after completion of blinded treatment.

Subjects completing the Blinded Study Phase without permanently discontinuing study drug will be eligible to participate in the OLE Phase of the study.

OLE Phase: Includes a 96 week OLE and an OLE Phase follow-up visit 4 weeks after completion of open label treatment.

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

Figure 3-1. Overall Study Design



3.2. Treatment Plan and Regimen

Subjects meeting the study's entry criteria will be randomly assigned in a 2:2:1 ratio to 1 of 3 different treatment groups during the Blinded Study Phase as shown in Figure 3-1. Randomization will be stratified by the presence or absence of UDCA use.

Study drug(s) will be administered for a total of 12 weeks from the Baseline/Day 1 visit during the Blinded Study Phase and 96 weeks during the OLE Phase. During the OLE Phase subjects will begin open label treatment with GS-9674 (100 mg po daily). The dose of GS-9674 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 MM, as required.

Subjects will be unblinded to their Blinded Study Phase treatment assignment after the primary analysis has been completed, approximately 6 weeks after all subjects have completed the Blinded Study Phase.

Dosage and administration of the study drug(s) and reference product are described in Section 5.3.

3.3. Biomarker Testing

3.3.1. Biomarker Samples to Address the Study Objectives:

PPD

3.3.2. Biomarker Samples for Optional Future Research

PPD

3.3.3. Biomarker Samples for Optional Genomic Research

PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

This study will enroll approximately 75 adults, between 18-70 years old with non-cirrhotic PBC.

4.2. Inclusion Criteria

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

1) Males and females between 18-70 years of age; inclusive based on the date of the screening visit;

2) Willing and able to give informed consent prior to any study specific procedures being performed;

3) Meets all of the following conditions:

   a) Definite or probable PBC as defined by at least 2 of the 3 following criteria:

      i. Serum alkaline phosphatase (ALP) > the upper limit of normal (ULN)

      ii. Presence of anti-mitochondrial antibodies (AMA) in serum (≥1:40 on immunofluorescence)

      iii. Liver histological findings consistent with PBC including nonsuppurative, destructive cholangitis affecting mainly the interlobular bile and septal bile ducts;

   b) Serum ALP >1.67 x ULN and/or total bilirubin >ULN but ≤2x ULN;

   c) UDCA use at a stable dose for at least 12 months prior to screening through the end of treatment or intolerant of UDCA with no UDCA use for at least 12 months before screening through the end of treatment;

4) Screening FibroSURE/FibroTest® <0.75, unless a historical liver biopsy within 12 months of screening does not reveal cirrhosis. In subjects with Gilbert's syndrome or hemolysis, FibroSURE/FibroTest® will be calculated using direct bilirubin instead of total bilirubin.

5) Platelet count ≥ 150,000/mm^3;

6) Albumin ≥ 3.3 g/dL;

7) Serum creatinine ≤ ULN;

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(s);

9) All female subjects of childbearing potential who engage in heterosexual intercourse must agree to use a highly effective method of contraception from the screening visit throughout the study period and for 30 days following the last dose of study drug (see definition in Appendix 4);

10) Male subjects with female partners of childbearing potential must use condoms during treatment and for 90 days after the last dose of study drug(s);

11) Male subjects must agree to avoid sperm donation from Baseline/Day 1 visit throughout the study period and for 90 days after the last dose of study drug(s);

12) Female subjects must refrain from egg donation and in-vitro fertilization during treatment and until at least 30 days after the last dose of study drug(s);

13) Willing and able to comply with scheduled visits, drug administration plan, laboratory tests, liver biopsies, other study procedures, and study restrictions;

14) Must be able to read and complete QoL questionnaires independently.

4.3. Exclusion Criteria

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

1) Pregnant or lactating females; lactating females must agree to discontinue nursing before the study drug (s) is administered;

2) ALT > 5x ULN;

3) Total bilirubin > 2x ULN;

4) INR > 1.2 unless on anticoagulant therapy;

5) Other causes of liver disease including viral, metabolic, alcoholic, and other autoimmune conditions. Subjects with hepatic steatosis may be included if there is no evidence of nonalcoholic steatohepatitis (NASH) in the opinion of the investigator or on liver biopsy;

6) Cirrhosis of the liver as defined by any of the following:

   a) Historical liver biopsy demonstrating cirrhosis (e.g. Ludwig stage 4 or Ishak stage ≥5)

   b) History of decompensated liver disease, including ascites, hepatic encephalopathy or variceal bleeding

c) Liver stiffness >16.9 kPa by FibroScan®;

7) History of intestinal resection or malabsorptive condition that may limit the absorption of GS-9674. Prior cholecystectomy and appendectomy are permitted;

8) History of liver transplantation;

9) History of hepatocellular carcinoma or cholangiocarcinoma;

10) Chronic hepatitis B (HBsAg positive);

11) Chronic hepatitis C (HCV antibody and RNA positive);

12) HIV Ab positive;

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

14) Positive urine screen for amphetamines, cocaine or opiates (i.e. heroin, morphine) at screening. Subjects on stable methadone or buprenorphine maintenance treatment for at least 6 months prior to screening may be included in the study. Subjects 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;

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

a) Unstable angina within 6 months prior to screening

b) Myocardial infarction, coronary artery bypass graft surgery or coronary angioplasty within 6 months prior to screening

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

d) Obstructive valvular heart disease or hypertrophic cardiomyopathy

e) Congestive heart failure;

16) Known hypercoagulable condition or history of venous or arterial thromboembolic disease;

17) Use of immunosuppressive drugs including systemic corticosteroids (intra-articular, topical, nasal, or inhaled steroids are allowed), methotrexate, tacrolimus, sirolimus, cyclosporine, azathioprine, and mycophenolate mofetil within 30 days of screening through the end of treatment;

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

19) Use of fibrates or obeticholic acid within 3 months prior to screening through the end of treatment;

20) History of a malignancy within 5 years of screening with the following exceptions:

    a) Adequately treated carcinoma in situ of the cervix

    b) Adequately treated basal or squamous cell cancer or other localized non-melanoma skin cancer;

21) Any laboratory abnormality or condition that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results;

22) Participation in another investigational study of a drug or device within 1 month prior or within 5 half-lives of the prior investigational agent (whichever is longer) prior to screening;

23) Concurrent participation in another therapeutic clinical study;

24) Known hypersensitivity to GS-9674, the metabolites, or formulation excipient;

25) Presence of any condition that could, in the opinion of the investigator, compromise the subject's ability to participate in the study, including a history of substance abuse or psychiatric conditions;

26) Unavailable for follow-up assessment or concern for subject's compliance with the protocol procedures.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

An Interactive Web Response System (IWRS) will be used for centralized randomization and treatment assignment. Randomization will be stratified by the presence or absence of UDCA use.

Investigative site personnel will obtain the subject's identification number and study drug assignment from the IWRS**.** Subjects and all personnel directly involved in the conduct of the study will be blinded to treatment assignment.

Study drug(s) will be dispensed by the study pharmacist, or designee, in a blinded fashion to the subjects.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IWRS system for that subject (refer to the Study Reference Binder for IWRS unblinding instructions). 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 subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the case report form/ electronic case report form (eCRF), 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 trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead Drug Safety and Public Health (DSPH) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of GS-9674 and PTM GS-9674

5.2.1. Formulation

GS-9674 is supplied as 30 mg and 100 mg strength (as free form equivalent) tablets. The tablets contain GS-9674-02 (tromethamine salt) and inactive ingredients microcrystalline cellulose, mannitol, crospovidone, magnesium stearate and film-coating material comprised of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide, red iron oxide and black iron oxide. GS-9674 tablets, 30 mg, are round, plain-faced, film-coated orange tablets and GS-9674 tablets, 100 mg are capsule-shaped, plain-faced, film-coated orange tablets.

Placebo-to-match (PTM) GS-9674 tablets are identical in size, shape, color and appearance to their corresponding strengths of active GS-9674 tablets. PTM GS-9674 tablets contain the following ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and film-coating material comprised of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide, red iron oxide and black iron oxide.

5.2.2. Packaging and Labeling

GS-9674 tablets and PTM GS-9674 tablets are packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed, aluminum-faced liner.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States 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

Study drug GS-9674 and PTM GS-9674 tablets should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label.

Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling GS-9674 tablets and PTM GS-9674 tablets.

5.3. Dosage and Administration of GS-9674/PTM GS-9674

GS-9674 and PTM GS-9674 tablets will be provided by Gilead Sciences. In order to maintain the blind, each subject will be supplied with 2 bottles of tablets during the blinded phase of the trial. One bottle will contain GS-9674 30 mg or PTM GS-9674 30 mg; the second bottle will contain GS-9674 100 mg or PTM GS-9674 100 mg.

Dosing for each treatment group will be as follows:

- **Treatment Group A:** GS-9674 30 mg (1 x 30 mg tablet) + PTM GS-9674 100 mg (1 x PTM 100 mg tablet) administered orally once daily with food
- **Treatment Group B:** GS-9674 100 mg (1 x 100 mg tablet) + PTM GS-9674 30 mg (1 x PTM 30 mg tablet) administered orally once daily with food

- **Treatment Group C:** PTM GS-9674 30 mg (1 x PTM 30 mg tablet) + PTM GS-9674 100 mg (1 x PTM 100 mg tablet) administered orally once daily with food

During the OLE Phase of the study, subjects will be provided with 100 mg bottles of GS-9674 only, unless reassigned to the 30 mg dose due to tolerability. The dose of GS-9674 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 MM, as required.

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

A dose will be considered missed if the subject cannot take the dose within 12 hours of their regular dosing time. If a subject misses a dose, the subject should take their next dose at the regular dosing time.

5.4. Prior and Concomitant Medications

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

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

Subjects with co-morbid diseases requiring medication(s) must be taking the medication(s) without a change in dose within 28 days of Baseline/Day 1.

GS-9674 increased atorvastatin exposure (39%) which does not necessitate a priori dose modification based on the LIPITOR USPI. Subjects taking atorvastatin with GS-9674 should be monitored as per label recommendations.

5.5. Prohibited Medications

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

- Vitamin E

- Hematologic stimulating agents (e.g. erythropoiesis-stimulating agents (ESAs); granulocyte colony stimulating factor (GCSF); thrombopoietin (TPO) mimetics)

- Chronic systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (eg, infliximab). Use for <2 weeks total is allowed

- Investigational agents or devices for any indication

- Concomitant use of certain medications or herbal/natural supplements (potent inhibitors of OATP or potent or moderate inducers of OATP, CYP2C8, P-gp, or CYP3A) with study drug(s) may result in PK interactions resulting in increases or decreases in exposure of study drug(s) or 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, Oxcarbazepine, Phenobarbital, Phenytoin	
Antimycobacterials[c]	Rifabutin, Rifapentine, Rifampin	
Endothelin Receptor Antagonists	Bosentan	
Herbal/Natural Supplements[c]	St. John's Wort, Echinaccea. Milk thistle (ie, silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
Bile Acid Sequestrants[d]		Cholestyramine, Colesevelam, Colestipol
Other [c]	Modafinil	

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

Medications for disease conditions **excluded** from the protocol (eg, HIV-1, HBV, or HCV infection, active cancer, transplantation) are not listed under this prohibited medication section and are disallowed in the study.

5.6. Accountability for GS-9674/ PTM GS-9674

The investigator or designee (eg, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug bottles. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition), subject dispensing records, and returned or destroyed study product. All used and unused study drug bottles dispensed to subjects must be returned to the site.

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

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

5.6.1. Investigational Medicinal Product Return or Disposal

Refer to Section 9.1.7 for instructions regarding study drug return or disposal.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject randomized in the study are presented in tabular form in Appendix 2 and described in the text that follows. Additional information is provided in Study Reference Binder.

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

6.1. Subject Randomization and Treatment Assignment

It is the responsibility of the investigator to ensure that subjects 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 subject, using the study-specific ICF, is required before initiating the screening process.

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

6.2. Pretreatment Assessments-Screening Visit

Subjects will be screened within 4 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.

Subjects who fail to meet eligibility criteria may be rescreened. Retesting of subject's screening labs may be permitted if there are reasons to believe that the retest values will be within protocol specified parameters. Reasons may include but will not be limited to sample processing errors during initial sampling and extenuating circumstances such as inter-current infections, lab mishandling and results abnormal from historic.

Screening labs may be repeated once within the screening period, prior to administration of study drug to rule out laboratory error, if any. This will be done at the discretion of the investigator.

The following will be performed and documented at Screening:

- Obtain written informed consent before initiation of any screening procedures
- Review and record whether the subject meets inclusion and exclusion criteria
- Obtain screening number from IWRS
- Obtain medical history

- Complete physical examination
- Record vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature), body weight, and height
- Obtain blood samples for
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Biomarkers
  - HIV-1/2, HBV and HCV Serology
  - Serum pregnancy test (female subjects of child bearing potential only)
  - Serum FSH (only for some female subjects - see Appendix 4)
- Cirrhosis assessment: FibroSURE/FibroTest® and review of historical liver biopsy or FibroScan® if available.
- Urine drug screen for amphetamines, cocaine and opiates (ie, heroin, morphine)
- Record any SAEs and all AEs related to protocol mandated procedures occurring after signing of the consent form.
- Record all concomitant medications (CMs) that the subject has taken within 28 days prior to screening

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

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any AEs related to protocol-mandated procedures on the adverse events case report form (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 eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

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

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

After review of inclusion and exclusion criteria to confirm continued eligibility, subjects will be randomized to study drug assignment and receive their Subject Identification Number via the IWRS prior to their first dose of study drug. Randomization will be stratified by the presence or absence of UDCA use.

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

- QoL Questionnaires (PBC-40 and SF-36,)
- Pruritus assessments (Pruritus VAS and 5D-Itch)

Note: It is recommended that QoL questionnaires be completed prior to any study procedures being performed and prior to the subject seeing a health care provider. Refer to the Study Reference Binder for guidance on QoL questionnaire administration.

- Symptom-driven physical examination
- Record vital signs, weight and height
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Lipid Profile
  - C-peptide, insulin and hemoglobin A1c (HbA1c)
  - Biomarker
  - Single PD Sampling

PPD 

- Conduct standard 12-Lead ECG

- Perform FibroScan®(if available)
- Perform MRE (if available)
- Collect urine samples for:
  - Urine pregnancy test for females of child bearing potential only
  - Biomarkers
- Collect stool sample
- Dispense study drug, and provide subject with instruction on appropriate dosing and administration
- Record all CMs that the subject has taken since the previous visit
- Record any SAEs and all AEs occurring since the Screening visit

Once all visit procedures have been completed, subjects will take their Baseline/Day 1 dose of study drug with food while at the investigative site

Subjects will return to the investigative site at Week 1 (±3 days).

6.4. Treatment Assessments (Blinded Study Phase)

6.4.1. Weeks 1, 2, 4 and 8 (± 3 days)

Subjects 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.

Subjects should also be instructed to HOLD their dose of study drug on the day of their visit until all visit procedures have been completed. The study drug dose should be taken with food after the visit.

The following treatment procedures/assessments are to be completed at the end of Weeks 1, 2, 4, and 8 for all subjects (see Appendix 2).

- Pruritus assessments (Pruritus VAS and 5D-Itch)
- Symptom-driven physical examination
- Record vital signs, and body weight

- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Lipid Profile at Weeks 1, 4 and 8
  - Biomarker at Weeks 1 and 4
  - Single PK and PD sampling
  - PPD [redacted]
- Obtain urine sample for:
  - Urine pregnancy testing (female of childbearing potential only) at Week 1, 4 and 8
  - Biomarkers at Weeks 1 and 4
- Dispense the study drug as directed by IWRS
  - Review study drug compliance and drug administration instructions with subject
  - Reconcile study drug administration using pill counts at Weeks 4 and 8
- Record all CMs that the subject has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

6.4.2. Week 12 (± 3 days)

Subjects 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 Week 12 visits 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 at this visit.

- QoL Questionnaires (PBC-40 and SF-36)
- Pruritus assessments (Pruritus VAS and 5D-Itch)

- Symptom-driven physical examination
- Record vital signs and body weight
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Lipid Profile
  - C-peptide, insulin, and hemoglobin A1c
  - Biomarkers
  - Single PK and PD sampling
- Obtain urine samples:
  - Urine pregnancy testing (female of childbearing potential only)
  - Biomarker assessments
- Collect stool sample
- Conduct standard 12-Lead ECG
- Perform FibroScan® (if available)
- Review study drug compliance
  - Reconcile study drug administration using pill counts
  - All study drugs should be returned at this visit
- Record all CMs that the subject has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

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

If a subject discontinues treatment early for any reason they should complete the 12 week treatment visit assessment/ Early Termination Visit (ET) assessments and then the follow-up visit (4 weeks following the last dose of the study drug) should be completed (see Appendix 2).

6.5. Blinded Study Phase follow-up Visit (±5 days)

Subjects will return for a Blinded Study Phase follow-up visit after completing their 12 weeks of treatment. The ET subjects should also complete the follow-up visit after completing the ET visit.

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

The Blinded Study Phase follow-up visit will be completed 4 week post last dose of study drug.

The following will be performed and documented at this visit (see Appendix 2).

- QoL Questionnaires (PBC-40 and SF-36)
- Pruritus assessments (Pruritus VAS and 5D-Itch)
- Symptom-driven physical examination
- Record vital signs and body weight
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Lipid Profile
  - Biomarkers
- Obtain urine samples for:
  - Urine pregnancy testing (females of childbearing potential only)
  - Biomarkers
- Collect stool sample
- Record all CMs that the subject has taken since the previous visit

- Record any SAEs and all AEs occurring since the previous visit

Subjects will be unblinded to their Blinded Study Phase treatment assignment after the primary analysis has been completed, approximately 6 weeks after all subjects have completed the Blinded Study Phase or early terminated.

Subjects must have their OLE Baseline/Day 1 visit within 30 days of completing the Blinded Study Phase follow-up.

If OLE Baseline/Day 1 and Blinded Study Phase follow-up visit is on the same day subjects should only complete OLE Baseline /Day 1 assessments.

6.6. Open Label Extension (OLE) Phase (± 3 days for Weeks 1–12 and ± 5 days for Weeks 24-96)

Subjects 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 their visits to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

Subjects should also be instructed to HOLD their dose of study drug on the day of the Baseline/Day 1 visit until all visit procedures have been completed. The study drug dose should be taken with food after the visit.

The following treatment procedures/assessments are to be completed at the OLE Baseline/Day 1 Visit, followed by OLE Weeks 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84 and 96 weeks (see Appendix 2).

- QoL Questionnaires (PBC-40 and SF-36) at OLE Baseline/Day 1, Weeks 4, 12 and every 12 weeks thereafter
- Pruritus assessments (Pruritus VAS and 5D-Itch)
- Symptom-driven physical examination
- Record vital signs and body weight
- Perform MRE at weeks 48 and 96 (if available)
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel

- Lipid Profile
- Biomarkers at OLE Baseline/Day 1, Weeks 4, 12 and every 12 weeks thereafter

- Obtain Urine samples for:
  - Urine pregnancy testing (females of childbearing potential only) at OLE Baseline/Day 1 and every 4 weeks thereafter
  - Biomarkers at OLE Baseline/Day 1, Weeks 24, 48, 72 and 96 only
- Collect stool sample at OLE Baseline/Day 1, Week 48 and Week 96 only
- Dispense the study drug as directed by IWRS at OLE Baseline/Day 1, Weeks 4, 8, 12 and every 12 weeks thereafter
  - Review study drug compliance and drug administration instructions with subject
  - Reconcile study drug administration using pill counts
  - Study drug should be returned at 96 week visit
- Record all CMs that the subject has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

6.7. Unscheduled Visits

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

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

Subjects should also be instructed to HOLD their dose of study drug on the day of an unscheduled visit until all visit procedures have been completed. The study drug dose should be taken with food after the visit.

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

- Symptom-driven physical examination

- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Single PK and PD should be collected for any unscheduled visit during Blinded Study Phase (Weeks 1 to 12 visits).
- Record body weight
- Record all CMs that the subject has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

6.8. OLE follow-up Visit (±5 days)

Subjects will return for OLE follow-up visit after completing their OLE Week 96 visit. Subjects should also complete the follow-up visit after completing the ET visit for the OLE Phase.

The OLE follow-up visit will be completed 4 week post last dose of study drug.

The following will be performed and documented at this visit (see Appendix 2).

- Pruritus assessments (Pruritus VAS and 5D-Itch)
- Symptom-driven physical examination
- Record vital signs and body weight
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Lipid Profile
- Urine pregnancy test for female subjects of child bearing potential only
- Record all CMs that the subject has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

6.9. Assessments for Premature Discontinuation from Study

Subjects 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 Early Termination (ET) visit completed followed by a follow-up visit 4 weeks after the last dose of the study medication. The study assessments to be performed at the ET visit are the same as those performed at the Week 12 visit (refer to Section 6.4.2) for ET subjects in the Blinded Study Phase and Week 96 visit for ET subjects in the OLE Phase (refer to Section 6.6). The study assessments to be performed at the follow-up visits are listed in Section 6.5 and 6.8 respectively. The subject will then be withdrawn from the study.

If these visits are not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.10. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator.
- Subject noncompliance
- Sponsor discretion

Study medication must be discontinued in the following instances:

- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Subject request to discontinue for any reason
- Pregnancy
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

6.11. PK and PD Substudy Visits

6.12. Procedures and Specifications

6.12.1. Clinical Laboratory Analytes

Chemistry:

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, alkaline phosphatase (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, gamma-glutamyl transferase (GGT). Also includes C-Peptide, insulin and hemoglobin A1c (HbA1c) for the Baseline/Day1 and Week 12 visits.

Hematology:

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

Coagulation Panel:

Prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR)

Pregnancy Tests:

Serum β-hCG or urine β-hCG (if positive, requires immediate confirmation with Serum β-hCG)

Additional Tests:

Lipid Profile, Creatine Phosphokinase, HIV-1, HBV & HCV Serology, urine drug screen (for amphetamines, cocaine, opiates), and genomic sample collection

Biomarker tests

Including, but not limited to, biomarkers of:

Circulating lipids - ApoB and NMR lipoprofile

Inflammation – hsCRP and TNF-α

Autoimmune disease - AMA and Immunoglobulins (IgM, IgA, IgG)

Bone formation – bone specific ALP and PTH

Liver fibrosis – ELF Test and FibroSURE/FibroTest®

FXR pathway activity - FGF19, C4, bile acids

Urine samples:

PPD

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 GS-9674, GS-716070 (metabolite of GS-9674), and other metabolites as applicable, 2) to measure the concentration of the PD biomarkers FGF19 and C4.

PPD

6.12.2. Medical History

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

6.12.3. Physical Examination

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

The focus of a symptom-driven physical examination will be determined by the investigator based on subject complaint. For eg, if a subject complains of a cough, a lung exam should be performed. If consistent with pneumonia (rales/crackles on exam) then an AE would be documented.

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

6.12.4. Quality of Life (QoL) Measures and Pruritus Assessments

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

6.12.4.1. Short Form-36 (SF-36) Health Survey

The SF-36 Health Survey asks 36 questions to measure functional health and well-being from the subject's point of view and consists of eight health domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health). These health domain scales contribute to the physical health and mental health summary measures).

6.12.4.2. Primary Biliary Cirrhosis-40 (PBC-40) Questionnaire

The PBC-40 is a health-related QoL questionnaire that includes 40 questions regarding PBC-related symptoms including itch, fatigue, cognition, and social and emotional assessments.

6.12.4.3. Pruritus Visual Analog Scale (VAS) Measure

Pruritus VAS is a tool for measuring the intensity of pruritus.

6.12.4.4. 5-D Itch Questionnaire

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

6.12.5. Electrocardiogram

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

6.12.6. FibroScan®

Liver stiffness will be assessed by FibroScan®. It is required that each subject's FibroScan® assessments be done with the same type of probe at each study visit. If FibroScan® is not available at a site the test may be omitted.

Please refer to the Study Reference Binder for instructions on FibroScan® measurements.

6.12.7. Magnetic Resonance Elastography

Liver stiffness will be assessed by MRE. It is recommended that each subject's MRE assessment is performed using the same procedure for each study visit. If MRE is not available at the site, the procedure may be omitted.

Please refer to the Study Reference Binder for instruction on MRE imaging guidelines.

6.13. End of Study

End of study is defined as when the last patient last visit (LPLV) for the OLE follow-up visit occurs 4 weeks after completing OLE treatment or the OLE ET follow-up visit, whichever occurs later.

6.13.1. Sample Storage

PPD

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

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

An AE does not include the following:

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

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

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

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

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

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

For specific information on handling of clinical laboratory abnormalities in this study, please refer to (Section 7.5).

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 GS-9674 therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the GS-9674. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

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

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event 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 adverse event has an etiology other than the study procedure.

- **Yes:** The adverse event 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) Version 4.03, which can be found at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (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 adverse event should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

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

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of GS-9674; AEs must be reported to the eCRF database as instructed.

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

Serious Adverse Events

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

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

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

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

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead DSPH	Email:	PPD
	Fax:	PPD

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

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

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

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

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

7.4. Gilead Reporting Requirements

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

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure 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.

To minimize the possibility of exposing study subjects to unusual risk, the safety information from this study will also be reviewed periodically by an independent Data Monitoring Committee (DMC). The DMC may have access to partially blinded or unblinded data and will make recommendations regarding the study according to the DMC charter. See Section 8.12 for additional details regarding the DMC.

7.5. Toxicity Management

Observation for Drug Induced Liver Injury (DILI):

Although subjects randomized in this study will have baseline liver disease, their hepatic function should not be significantly impaired. However, at baseline, some may have liver biochemistry levels above the upper limit of normal (ULN). Baseline values for liver tests (ALT, AST, and total bilirubin) will be determined by averaging the values obtained at screening and Baseline/Day 1.

For subjects with ALT and/or AST below ULN at study start, close observation for DILI (as described below) will be performed in subjects with any of the following criteria (all labs confirmed by repeat testing), unless an alternative cause for the combination of laboratory abnormalities is apparent in the opinion of the principal investigator:

- ALT or AST > 3 x ULN
- Total bilirubin > 2 x ULN
- INR >1.5 (except for subjects on anticoagulant therapy)
- Clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant discomfort, fever, nausea, vomiting, jaundice, rash, or eosinophilia > 5%)

For subjects with ALT and/or AST between 1 and 5 x ULN at study start, close observation for DILI (as described below) will be performed in subjects with any of the following criteria (all labs confirmed by repeat testing), unless an alternative cause for the combination of laboratory abnormalities is apparent in the opinion of the principal investigator:

- ALT or AST > 2 x baseline at any time
- Total bilirubin > 2 x ULN
- INR >1.5 (except for subjects on anticoagulant therapy)
- Clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant discomfort, fever, nausea, vomiting, jaundice, rash, or eosinophilia > 5%).

Close observation includes:

- Repeating liver biochemistries (ALT, AST, ALP, total bilirubin, INR) and obtaining creatine phosphokinase (CPK) levels within 2 working calendar days upon receipt of the laboratory 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 primary investigator)

- Continue to monitor liver biochemistries twice weekly. Frequency can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and subject is asymptomatic

During a period of close observation, study drug can be continued, if desired, at the discretion of the Gilead Medical Monitor and the principal investigator during the DILI evaluation.

However, for all subjects, study drug should be withheld if any of the following criteria are met:

- ALT or AST > 5 x baseline
- ALT or AST >10 x ULN
- ALT or AST >3 x baseline with 1 or more of the following:
  - Total bilirubin > 2 x ULN or 1.5 x baseline
  - INR >1.5 (except for subjects on anticoagulant therapy)
  - Appearance of clinical signs or symptoms that are, in the opinion of the investigator, consistent with drug-induced hepatotoxicity
- ALT or AST > baseline with any 2 or more of the following:
  - Total bilirubin > 2 x ULN or 1.5 x baseline
  - INR >1.5 (except for subjects on anticoagulant therapy)
  - Appearance of clinical signs or symptoms that are, in the opinion of the investigator, consistent with drug-induced hepatotoxicity

  AND

- No other cause for the combination of laboratory abnormalities is immediately apparent (e.g. prolonged INR with warfarin use). Important potential causes or contributors to abnormal AST/ALT or total bilirubin values include, but are not limited to:
  - Obstructive gall bladder or bile duct disease
  - Viral or alcoholic hepatitis (e.g. hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella)
  - Autoimmune hepatitis
  - Concomitant administration of other hepatotoxins, including excessive doses of acetaminophen, drugs that inhibit bilirubin glucuronidation (e.g. indinavir, atazanavir, irinotecan), or herbal or dietary supplements
  - Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right-sided heart failure

— Wilson disease

— Nonalcoholic fatty liver disease (NAFLD)

— Progression of malignancy involving the liver (note that metastatic disease to the liver, by itself, should not be used as an explanation for significant AST/ALT elevations)

If study drugs are withheld, they may be reintroduced with approval from the Medical Monitor if another etiology for elevated liver tests is present. Study drug must be discontinued if close monitoring of a patient for DILI is not possible or if total bilirubin, ALT or AST elevation recurs following re-challenge with study drug.

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

- Other than in the case of the liver enzymes noted above, Grade 3 or 4 clinically significant laboratory 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.

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

- Any questions regarding toxicity management should be directed to the Medical Monitor.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of AEs associated with product complaints, occupational exposure with an AE, pregnancy reports regardless of an associated AE, and AE in an infant following exposure from breastfeeding.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

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

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

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

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure with an AE: exposure to a medicinal product as a result of one's professional or non-professional occupation.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

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.

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

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

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

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should

continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, fax number PPD or email PPD

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

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

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

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.

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

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

8. STATISTICAL CONSIDERATIONS

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

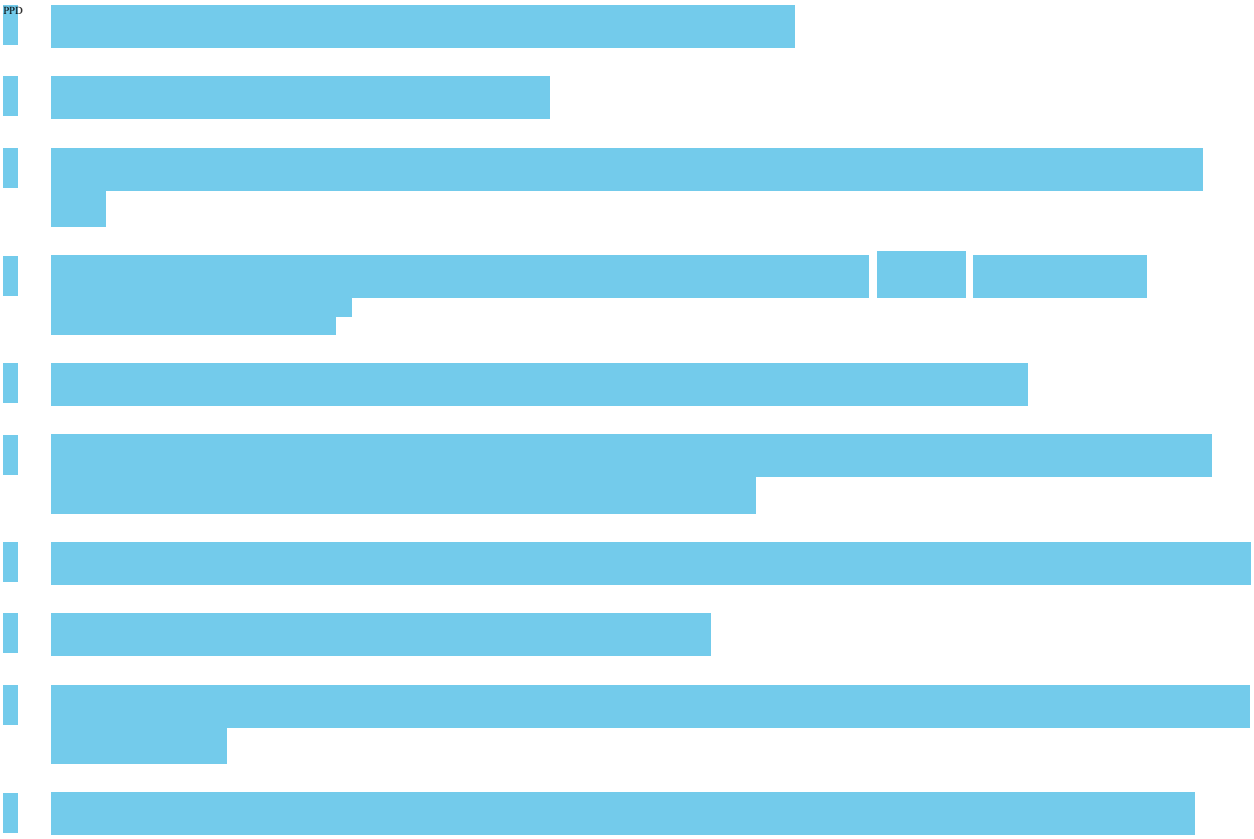
8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To evaluate the safety and tolerability of GS-9674 in subjects with PBC

The exploratory objectives of this study are:



8.1.2. Primary Endpoint

The primary endpoint is the safety of GS-9674 in subjects with PBC without cirrhosis. The safety and tolerability of GS-9674 will be evaluated by examining the incidence of treatment-emergent adverse events, including serious adverse events, clinical laboratory tests, and vital signs assessments at various time points during the study.

8.1.3. Exploratory Endpoints

PPD

PPD

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

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

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

8.2.1.2. Safety

The primary analysis set for safety analyses will include all subjects who received at least one 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. Subjects who received study drug other than that to which they were assigned will be analyzed according to the study drug received.

8.2.1.3. Pharmacokinetics

There are two pharmacokinetic analysis sets: 1) the PK analysis set which includes concentration data from the single samples drawn at each visit PPD

The PK analysis set will include all randomized subjects who took at least one dose of study drug and for whom concentration data of analytes GS-9674 (and its metabolites as applicable) are available. The PK analysis set will be used for analyses of population PK.

PPD

8.2.1.4. Pharmacodynamics

There are two pharmacodynamics analysis sets: 1) The PD analysis set which includes concentration data from the single samples drawn at each visit PPD

The PD analysis set will include all randomized subjects who took at least one dose of study drug and for whom concentration data of FGF19, C4, and bile acids are available. The PD analysis set may be used for descriptive and/or population based PD analyses as applicable.

PPD

8.2.1.5. Biomarkers

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

8.2.2. Analysis by Study Phase

Result of statistical analysis for the randomized phase will be presented by treatment groups. Safety data from the OLE Phase will be summarized for overall subjects who roll-over into the OLE Phase for safety review, supporting regulatory document update or publication purposes.

An administrative interim analysis will be performed after first 30 subjects finish 12 weeks of treatment.

8.3. Data Handling Conventions

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

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

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

8.5. Efficacy Analysis

The biological activity of GS-9674 will be evaluated using biomarker variables. Because efficacy endpoints will be evaluated for exploratory purpose, formal statistical comparisons will not be made for these endpoints. Point estimates and ninety-five percent confidence intervals (95% CI) will be provided if applicable.

8.6. Exploratory Analyses

PPD

8.7. Safety Analysis

All safety data collected on or after the date that GS-9674 was first dispensed up to the date of last dose of GS-9674 plus 30 days will be summarized by treatment group. Data for the pretreatment and follow-up periods will be included in data listings.

8.7.1. Extent of Exposure

Data for a subject's extent of exposure to GS-9674 will be generated from the study drug administration eCRF. Exposure data will be summarized by treatment group.

8.7.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database. Adverse event severity will be graded using the CTCAE Version 4.03.

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

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

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

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

8.7.3. Laboratory Evaluations

Selected laboratory 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 Version 4.03 (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.

8.7.4. Other Safety Evaluations

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

8.8. Pharmacokinetic Analysis

Plasma concentrations and pharmacokinetic parameters (eg, AUCtau, Cmax and Ctau) will be listed and summarized as appropriate for GS-9674 (and its metabolites as applicable) using descriptive statistics.

Details of the analysis plan will be provided in the pharmacokinetic reporting and analysis plan.

8.9. Pharmacodynamics Analysis

Primary PD parameters ($AUC_{partial}$, C_{max}, C_{min} as applicable) of FGF19 and C4 will be listed and summarized as appropriate for GS-9674 using descriptive statistics.

Details of the analysis plan will be provided in the pharmacodynamics reporting and analysis plan.

8.10. Biomarker Analysis

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

PPD

PPD

8.11. Sample Size

Due to the exploratory nature of this study, no formal power calculations were used to determine sample size. The number of subjects was chosen based on clinical experience with other similar proof of concept studies.

8.12. Data Monitoring Committee

An independent, external data monitoring committee (DMC) that consists of two hepatologists and a PhD statistician will review the progress of the study and perform reviews of safety data. The DMC will convene once 20 subjects have been randomized and will meet every 3 to 4 months thereafter to monitor the study for safety events in Blinded Study Phase and every 6 months in the OLE Phase. The DMC will meet on an ad hoc basis if there are at least 3 similar Grade ≥ 3 serious, treatment-related Common Terminology Criteria for Adverse Events (CTCAE) observed in the trial. In the event of two similar treatment related Grade 4 CTCAE events or one treatment related Grade 5 CTCAE, the DMC will review the data and advise the sponsor regarding stopping or continuing the trial. The DMC will provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment 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. The DMC may also provide recommendations as needed regarding study design.

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

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any 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 subject completes the protocol-defined activities.

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

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

9.1.3. 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 and before undertaking any study-related procedures. The investigator must use the most current IRB/IEC/EC -approved consent form for documenting

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

9.1.4. Confidentiality

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

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, 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.

9.1.5. Study Files and Retention of Records

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

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

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

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

- 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 adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

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

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

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

9.1.6. Case Report Forms

For each subject consented, an electronic case report form (eCRF) will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as

any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Where possible, study drug should be destroyed at the site. If the site does not have acceptable procedures in place for drug destruction, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies. The study monitor will provide instructions for return.

The study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, 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 drug 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. Refer to the pharmacy binder for study drug disposal/return instructions.

The study monitor will review study drug supplies and associated records at periodic intervals.

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met: the results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

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

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, e.g. attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the 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 subject records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-9674 in Subjects with Primary Biliary Cholangitis Without Cirrhosis

GS-US-427-4024, Amendment 3, 09 February 2017

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

PPD

Medical Monitor

09 Feb 2017

Date

PPD

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 for GS-US-427-4024

		Blinded Study Phase Treatment Weeks (±3 days)							OLE Weeks (±3 days weeks 1-12 and ±5 days weeks 24-96)	
	Screening [a]	**Baseline (Day 1)**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12 /ET** [b]	**Blinded Study Phase follow-up visit** [c] **(±5 days)**	**OLE Baseline/Day1,Weeks 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96/ET** [b]	**OLE follow-up** [d]
Subject Fasting		X	X	X	X	X	X	X	X	
Written Informed Consent [e]	X									
Review Inclusion/Exclusion Criteria	X	X								
Medical History	X									
Pruritus VAS &5D-Itch [f]		X	X	X	X	X	X	X	X	X
QoL SF-36, & PBC-40[f]		X					X	X	X	
Symptom-directed PE[g]	X	X	X	X	X	X	X	X	X	X
Vital Signs[h]	X	X	X	X	X	X	X	X	X	X
Height and weight[i]	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X
Coagulation Panel	X	X	X	X	X	X	X	X	X	X
Cirrhosis Assessments	X									
Lipid Profile		X	X		X	X	X	X	X	X

		Blinded Study Phase Treatment Weeks (±3 days)							OLE Weeks (±3 days weeks 1-12 and ±5 days weeks 24-96)	
	Screening [a]	Baseline (Day 1)	Week 1	Week 2	Week 4	Week 8	Week 12 /ET [b]	Blinded Study Phase follow-up visit [c] (±5 days)	OLE Baseline/Day1,Weeks 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96/ET [b]	OLE follow-up [d]
C-Peptide, hemoglobin A1C and insulin		X					X			
Blood for Biomarkers [j]	X	X	X		X		X	X	X	
Single PK and PD Sampling		X [k]	X	X	X					
HIV-1, HBV and HCV Serology	X									
Pregnancy Test [l]	X	X	X		X	X	X	X	X	X
Serum FSH [m]	X									
PPD										
12- lead ECGs		X					X			
Fibroscan [o]		X					X			
MRE [p]		X							X	
Urine drug screening	X									
Urine collection [q] (Biomarkers)		X	X		X		X	X	X	
Stool collection [r] (Biomarkers)		X					X	X	X	
PPD										

		Blinded Study Phase Treatment Weeks (±3 days)							OLE Weeks (±3 days weeks 1-12 and ±5 days weeks 24-96)	
	Screening [a]	**Baseline (Day 1)**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12 /ET** [b]	**Blinded Study Phase follow-up visit** [c] **(±5 days)**	**OLE Baseline/Day1,Weeks 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96/ET** [b]	**OLE follow-up** [d]
Dispense GS-9674/ PTM GS-9674[t]		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
Take GS-9674/ PTM GS-9674 Tablets		X – Daily (Baseline/ Day 1 to Week 12)[u]							X-Daily (OLE Baseline/ Day 1 to Week 96)	

a The visit window may be extended under special circumstances with explicit approval of the Medical Monitor. Subjects who fail to meet eligibility criteria due to an abnormal laboratory result may undergo re-testing of the abnormal analyte during the screening window. This will be done at the discretion of the investigator and also with prior approval of the Medical Monitor.

b Blinded Study Phase subjects discontinuing the study at any time for any reason (Early Termination – ET) should complete the procedures listed for the Week 12/ Visit AND the follow-up visit. OLE Phase subjects discontinuing the study at any time for any reason (Early Termination – ET) should complete the procedures listed for the Week 96/ Visit AND the follow-up visit if possible.

c After completing 12 weeks of treatment in the Blinded Study Phase, subjects will return for the follow-up visit 4 weeks post the last dose of the study drug. and at that time they can begin their OLE Phase follow-up visit for Blinded Study Phase and Baseline/Day 1 OLE visit can occur on the same day if convenient. If OLE Baseline/Day 1 and Blinded study follow-up visit is on the same day subjects should only complete OLE Baseline /Day 1 assessments.

d Follow-up visit should be completed during the Blinded Study Phase as well as the OLE Phase.

e Obtain written informed consent before initiation of any screening procedure.

f QoL questionnaires and pruritus assessments should be completed prior to any study procedures being performed and prior to the subject seeing a health care provider. Refer to the Study Reference Binder for guidance on QoL questionnaire administration. During OLE, QoL questionnaires are required at OLE Baseline/Day 1, Weeks 4, 12 and every 12 weeks thereafter.

g Complete PE at screening and symptom-directed PE for other visits. The focus of a symptom-driven physical examination will be determined by the investigator based on subject complaint.

h Vital signs include (heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature)

i Height should be collected at Screening and Baseline/Day 1 only. Weight should be collected at all visits. Refer to the Study Reference Binder for specific instructions on how weight should be measured.

j Biomarker analyses include, but are not limited to, the tests listed in Section 6.12.1. PPD

k PD sampling only at Baseline/Day 1.

l Females of childbearing potential only (see Appendix 4). Serum pregnancy test at Screening and Urine pregnancy tests at all Blinded Study Phase visits, except Week 2 and at OLE Baseline/Day 1 and every 4 weeks thereafter.
m Only required for some female subjects – see Appendix 4.
PPD
o Subject should be in fasted state for FibroScan® collection. Refer to the study reference binder for further details. If FibroScan® is not available at a site the test may be omitted.
p Subject should be in fasted state for MRE scan. Refer to the study reference binder for further details. If MRE is not available at a site the test may be omitted. MRE scan should be performed at Blinded Study Phase Baseline /Day 1 and OLE weeks 48 and 96.
q Urine Biomarker sample collection at Blinded Study Phase Baseline/Day 1, week 1, weeks 4, 12 and at the Follow up and Early term visits. Urine Biomarker sample collection during OLE at OLE Baseline/Day 1, Weeks 24, 48, 72 and 96 only.
r Stool sample collection at Blinded Study Phase Baseline/Day 1, week 12 and at the Follow up and Early term visits. Stool sample collection during OLE at OLE Baseline/Day 1, Week 48 and Week 96 visit.
PPD
t Study drug will be assigned via the IWRS system every 4 weeks from Baseline/Day 1 through Week 8 in Blind Study Phase and at OLE Baseline/Day 1, Weeks 1, 4, 8, 12 and every 12 weeks thereafter.
u Subjects to self-administer the study drug at the investigative site at the conclusion of the Blinded Study Phase Baseline/Day 1 and Week 12 visit.

Appendix 3. CTCAE Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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

1. Definitions

a. Definition of Childbearing Potential

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

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

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

b. Definition of Male Fertility

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

2. Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

GS-9674 has not yet been studied in pregnant women. In the initial dose range-finding studies in pregnant mice and rabbits 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 are likely secondary to maternal toxicity rather than a direct effect of GS-9674. The NOEL for embryo/fetal development is 300 mg/kg/day in mice and 200 mg/kg/day in rabbits. These doses were associated with exposures that are > 50-fold higher than the anticipated human exposure at the maximum proposed human dose of 100 mg once daily. 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 Investigator's Brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to randomization. At minimum, a pregnancy test will be performed at all study visits except Blinded Study Phase Week 2 and OLE Weeks 1 and 2 and at 30 days after the last dose of the study drug. Female subjects must also agree to one of the following from Screening until 30 days following the last dose of the study drug GS-9674.

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

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
  - Intrauterine device (IUD) with a failure rate of <1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

  Or

- Consistent and correct use of one hormonal method and one barrier method.
  - Barrier methods
    - Diaphragm with spermicide
    - Cervical cap with spermicide
    - Male condom (with or without spermicide)
  - Hormonal methods
    - Oral contraceptives (either combined or progesterone only)
    - Injectable progesterone
    - Implants of levonorgestrel
    - Transdermal contraceptive patch
    - Contraceptive vaginal ring

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the last dose of the study drug, GS-9674.

3. Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms (plus spermicide) during treatment and until 90 days after last dose of GS-9674. Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male subjects must agree to avoid sperm donation during treatment and until at least 90 days after the last dose of study drug, GS-9674.

4. Unacceptable Birth Control Methods

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

5. Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days (90 days of partner of male subject) of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.