CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1 Open-Label, Parallel-Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics and Pharmacodynamics of GS-9674 in Subjects with Normal and Impaired Hepatic Function
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND No.:	127960
Clinical Trials.gov Identifier:	NCT02808312
EudraCT No.:	Not Applicable
Indication:	Nonalcoholic Steatohepatitis (NASH)
Protocol ID:	GS-US-402-3885
Gilead Medical Monitor	Name: PPD Telephone: PPD Fax: PPD Mobile: PPD
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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 1 Open-Label, Parallel-Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics and Pharmacodynamics of GS-9674 in Subjects with Normal and Impaired Hepatic Function
IND Number:	127960
EudraCT Number:	Not Applicable
Study Centers Planned:	Multiple Sites in the United States and New Zealand
Objectives:	The primary objective of this study is as follows: • To evaluate the single-dose pharmacokinetics of GS-9674 in subjects with impaired hepatic function relative to matched, healthy controls with normal hepatic function The secondary objective of this study is as follows: • To evaluate the safety and tolerability of GS-9674 single dose administration in subjects with normal hepatic function, or mild, moderate, and severe hepatic impairment • To evaluate Farnesoid X Receptor (FXR) activation by GS-9674 as measured by pharmacodynamic (PD) markers in subjects with normal hepatic function, or mild, moderate and severe hepatic impairment
Study Design:	Phase 1, open-label, single-dose, parallel-group, staggered-cohort, pharmacokinetic (PK) study
Number of Subjects Planned:	Enroll approximately 60 subjects for 48 evaluable: Cohort 1: GS-9674: 20 [10 per group (mildly impaired and matched controls) for 8 evaluable per group] Cohort 2: GS-9674: 20 [10 per group (moderately impaired and matched controls) for total 8 evaluable per group] Cohort 3: GS-9674: 20 [10 per group (severely impaired and matched controls) for total 8 evaluable per group] A subject with normal hepatic function may serve as a matched control across cohorts evaluating the same GS-9674 dose.

Target Population:	Subjects with hepatic impairment will be enrolled based upon the Child-Pugh-Turcotte (CPT) classification system for mild hepatic impairment (CPT Class A; Cohort 1) moderate hepatic impairment (CPT Class B; Cohort 2) or severe hepatic impairment (CPT Class C; Cohort 3). The control group will consist of matched healthy subjects with normal hepatic function.
Duration of Dosing:	1 day
Study Duration:	Up to 15 Days (not including screening window)
Diagnosis and Main Eligibility Criteria:	Cohort 1: Male and nonpregnant/nonlactating female subjects aged ≥ 18 years with mildly impaired and normal hepatic function. Each subject in the control group will be matched for age (± 10 years), gender, race, and body mass index (± 15% 18 ≤ BMI ≤ 36 kg/m²) with a subject in the mild hepatic impairment group. Subjects with mild hepatic impairment must have a score of 5-6 on the CPT Classification at Screening without evidence of worsening clinical and/or laboratory signs of hepatic impairment within 2 months prior or within the screening period. Cohort 2: Male and nonpregnant/nonlactating female subjects aged ≥ 18 years with moderately impaired and normal hepatic function. Each subject in the control group will be matched for age (± 10 years), gender, race, and body mass index (± 15% 18 ≤ BMI ≤ 36 kg/m²) with a subject in the moderate hepatic impairment group. Subjects with moderate hepatic impairment must have a score of 7-9 on the CPT Classification at Screening without evidence of worsening clinical and/or laboratory signs of hepatic impairment within 2 months prior or within the screening period. Cohort 3: Male and nonpregnant/nonlactating female aged ≥ 18 years with severely impaired and normal hepatic function. Each subject in the control group will be matched for age (± 10 years), gender, race, and body mass index (± 15% 18 ≤ BMI ≤ 36kg/m²) with a subject in the severe hepatic impairment group. Subjects with severe hepatic impairment must have a score of 10-15 on the CPT Classification at Screening without evidence of worsening clinical and/or laboratory signs of hepatic impairment within 2 months prior or within the screening period.

Study Procedures/ Frequency:

Following screening procedures and Day -2 admission assessments, eligible subjects will be enrolled in 1 of three sequential cohorts. Subjects will undergo intensive sampling over 24 hours on Day -1 after administration of placebo-to-match (PTM) for baseline PD markers. On Day 1 subjects will receive a single dose of GS-967430 mg (3 x 10 mg tablet) orally for Cohorts 1 and 2 or 10 mg (1 x 10 mg tablet) for Cohort 3. In general, dosing in subjects with normal hepatic function will begin after a matched subject with hepatic impairment has completed PK assessments.

Cohorts 1 through 3 will be dosed in a sequential manner, with dosing of subjects in Cohort 2 (moderate hepatic impairment) and Cohort 3 (severe hepatic impairment) proceeding after review of safety and available preliminary pharmacokinetic data from hepatic impaired subjects in the previous cohorts. Based on the cumulative review of safety and PK data, sequential cohorts may or may not be initiated at the discretion of the investigator and Sponsor.

Study Visits and Confinement

Following screening assessments, eligible subjects will be admitted to the clinic on Day -2 and confined to the clinic for the duration of the study until discharge on Day 5.

Subjects will be required to return for a Follow-up (FU) visit 10-14 days after study drug dosing.

Study Drug Administration

The study drug will be supplied as GS-9674 tablets strengths of 10 mg or PTM. All study treatments will be administered with 240 mL of water.

Study Treatments will be administered in the fed state as described below.

Fed state dosing:

Study drugs will be administered following an overnight fast (no food or drinks except water) for at least 10 hours and within 5 minutes of completing a standardized meal (moderate-fat-calorie breakfast containing ~600 kcal and 25% to 30% fat will be provided). The meal should be initiated 30 minutes prior to study drug administration. Subjects will fast until after collection of the 4-hour PK/PD sample, relative to study drug dosing.

Additionally, subjects will be restricted from water consumption from 1 hour before through 2 hours after dosing, except for the water given with the study drugs and the standardized meal. A standardized meal may be provided to subjects after the 4-hour post-dose PK/PD draw.

Pharmacokinetic Assessments

Plasma PK Collection

Intensive PK sampling will occur relative to dosing of GS-9674 at the following time points for each cohort:

- Day 1: -0.5, 0 (pre-dose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours post-dose

Plasma concentrations of GS-9674 (and its metabolites, as applicable) will be determined and PK evaluated. Pharmacokinetic parameters will be estimated, as appropriate.

In addition, on Day 1 at the 3 and 5 hours post dose time-points, an additional plasma samples will be collected for plasma protein binding evaluation. Alternatively, pre-dose samples may be utilized for plasma protein binding evaluation.

A blood sample for PK analysis will also be collected at the Early Termination (ET) visit (if applicable) and may be analyzed.

Pharmacodynamic (PD) Assessments

Plasma and/or Serum PD Collection

Blood samples will be collected relative to dosing of GS-9674 or PTM to measure PD biomarkers including but not limited to FGF19 (fibroblast growth factor 19) and C4 (7-alpha-hydroxy-4-cholesten-3-one) for GS-9674 at the following time points for each cohort:

- Day -1: -0.5, 0 (predose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 16 (relative to Day 1 dosing time assignment)
- Day 1: -0.5, 0 (pre-dose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours post-dose

A single blood sample will be collected for analysis including but not limited to bile acids at the following time point:

Day 1: -0.5 hours predose

A blood sample for PD analysis will also be collected at the Early Termination (ET) visit (if applicable) and may be analyzed.

Genomic Sample

For subjects who provide consent, an additional blood sample will be collected for genetic research to identify or validate genetic markers that may be predictive of the safety and/or tolerability of study drug used in this protocol. This sample should be collected on Day 1, but

	may be collected at any time during the study or at a separate post-study visit, if necessary. **Safety Assessments-- Cohorts 1, 2, and 3** Complete Physical exam: Screening and ET visit (if applicable) Symptom-directed physical exam: Days -2, 5, and FU visit Vital signs (blood pressure, pulse, respiration rate, and temperature): Screening, Days -2, 1 (predose and at approximately 3 hours postdose), 5, and FU visit or ET visit (if applicable) Height, Weight, and BMI: Screening Clinical Laboratory Tests (hematology, fasting chemistry, and urinalysis: Screening, Days -2 (two sets of safety labs will be collected upon clinic admission; one will be sent to the central lab and another will be sent to the sites' local lab to obtain results in time for enrollment on Day 1) , 5, and FU visit or at ET visit (if applicable) Coagulation (PT, PTT, INR): Screening and FU Visit Urine drug/alcohol assessment: Screening, Day -2, and at the FU visit or at ET visit (if applicable). 12-lead ECG: Screening, Days -2, 5, and at the FU visit or ET visit (if applicable) Serum Pregnancy Test (female subjects of childbearing potential): Screening Urine Pregnancy Test (female subjects of childbearing potential): Days -2, 5, and at the FU visit or at ET visit (if applicable) FSH (female subjects ≤ 54 years old with amenorrhea > 12 months): Screening Serology (Hepatitis B surface antigen (HBVsAg), Hepatitis C antibody (HCV-Ab), Human immunodeficiency virus (HIV)-1/2: Screening Assessment of Adverse Events (AEs) and concomitant medications will continue throughout the study.
Test Product, Dose, and Mode of Administration:	Cohorts 1 and 2: A single oral dose of GS-9674 30 mg (3 x 10 mg tablet) administered on Day 1 Cohort 3: A single oral dose of GS-9674 10 mg (1 x 10 mg tablet) administered on Day 1

Reference Therapy, Dose, and Mode of Administration:	Cohorts 1 and 2: A single oral dose of PTM GS-9674 30 mg (3 x PTM 10 mg tablet) administered on Day -1 Cohort 3: A single oral dose of PTM GS-9674 10 mg (1 x PTM 10 mg tablet) administered on Day -1
Criteria for Evaluation:	
Safety:	Safety will be evaluated by physical examinations, vital signs, clinical laboratory tests and ECGs at various time points during the study, and by documentation of adverse events (AEs)
Efficacy:	Not applicable.
Pharmacokinetics:	The following plasma PK parameters will be calculated for GS-9674, as applicable: % AUC_{exp}, AUC_{last}, AUC_{inf}, C_{max}, T_{max}, Clast, T_{last}, λ_z, CL/F, V/F and $T_{½}$. Percent plasma protein binding will be determined and PK parameters adjusted for protein binding will be estimated.
Pharmacodynamics:	FXR activation will be evaluated by PD markers including but not limited to FGF19 and C4.
Statistical Methods:	GS-9674 plasma concentrations and PK parameters will be listed and summarized by hepatic function group within each cohort (normal and mildly impaired, moderately impaired, or severely impaired) using descriptive statistics (e.g., sample size, arithmetic mean, geometric mean, % coefficient of variation [%CV], standard deviation [SD], median, minimum, and maximum). An analysis of variance (ANOVA) appropriate for a parallel design with hepatic function group as a fixed effect will be fit to the natural logarithmic transformation of PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) for GS-9674. The 90% confidence intervals (CIs) will be constructed for the geometric least squares mean (GLSM) ratio of PK parameters for GS-9674 in the mild, moderate, or severe hepatic impairment group versus the control (normal hepatic function) group. Safety data will be listed by subject and summarized by hepatic function group and frequency of event/abnormality or descriptive statistical summaries, as appropriate. Pharmacodynamic and PK/PD relationships will be explored as appropriate. For each cohort, with 16 (8 per group) evaluable subjects, the estimated upper limit of one-sided 95% CI of the GLSM ratio of

	(mild, moderate or severe) hepatic impaired group vs control (normal hepatic function), with regards to AUC_{last}, AUC_{inf}, and C_{max}, would be less than 200% with ≥ 88% probability, if the estimated GLSM ratio were 1.0. This is assuming a SD of no more than 0.463 on a natural logarithm scale, supported by previous Gilead study GS-US-402-1851. With 25% overage, a total sample size of 60 subjects (10 per group, 20 per cohort) will be required.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
%CV	% coefficient of variation
AE	adverse event
AME	absorption, metabolism, and elimination
ALT	alanine aminotransferase (previously serum glutamic pyruvic transaminase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BID	twice a day
BLQ	below limit of quantitation
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
C4	7-alpha-hydroxy-4-cholesten-3-one
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CL	systemic clearance
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
CLss/F	apparent oral clearance at steady state after administration of the drug: $CLss/F = Dose/AUC_{tau}$, where "Dose" is the dose of the drug
C_{last}	last observed quantifiable concentration of the drug
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
CPK	creatine phosphokinase
CRF	case report form
CRO	contract (or clinical) research organization
CSR	clinical study report

CTA	clinical trial application
C_{tau}	observed drug concentration at the end of the dosing interval
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EudraCT	European Clinical Trials Database
eGFR	estimated glomerular filtration rate
ESA	erythropoiesis-stimulating agent
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
E2	depressed estradiol
FDA	Food and Drug Administration
FGF19	fibroblast growth factor 19
FSH	follicle-stimulating hormone
FU	follow-up
FXR	Farnesoid X Receptor
GCP	Good Clinical Practice
GCSF	Granulocyte colony stimulating factor
Gilead	Gilead Sciences, Inc.
GLSM	geometric least-squares mean
HBV	hepatitis B virus
HBsAb	hepatitis B surface antibody
HBSAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HIV, HIV-1	human immunodeficiency virus, type 1
HLGT	high-level group term
HLT	high-level term
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ID	identification

IEC	independent ethics committee
IND	investigational new drug (application)
IRB	institutional review board
IUD	intrauterine device
LDL	low-density lipoprotein
LLT	lower-level term
LLOQ	lower limit of quantitation
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MM	medical monitor
NDA	new drug application
PD	pharmacodynamic(s)
PG	pharmacogenomics
PI	principal investigator, package insert
PK	pharmacokinetic(s)
PR interval	electrocardiographic interval occurring between the onset of the P wave and the QRS complex representing time for atrial and ventricular depolarization, respectively
PT	preferred term, prothrombin time
PTT	partial thromboplastin time
QA	quality assurance
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave, representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTcF	QT interval corrected for heart rate using the Fridericia formulation
RBC	red blood cell
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
T_{last}	time (observed time point) of C_{last}
T_{max}	the time (observed time point) of C_{max}
TOST	two one-sided tests
TQT	thorough QT
TT	thrombin time
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural

	log of 2 by the terminal elimination rate constant (λ_z)
ULN	upper limit of normal
US, USA	United States, United States of America
V_z/F	apparent volume of distribution of the drug
WBC	white blood cell
WHO	World Health Organization
%AUCexp	percentage of AUC extrapolated between AUClast and AUCinf
λz	elimination phase of the log serum/plasma/PBMC concentration versus time curve of the drug

1. INTRODUCTION

1.1. Background

Chronic liver disease and the consequences of end-stage liver disease are increasing globally despite improved prevention and treatment of viral hepatitis. This is due to the emerging epidemics of obesity, metabolic syndrome, and diabetes mellitus that are leading to an increased incidence of nonalcoholic fatty liver disease (NAFLD). Nonalcoholic fatty liver disease is characterized by the excess accumulation of lipid droplets within the liver, also known as hepatic steatosis. Prevalence rates of NAFLD range from 6% to 37% worldwide {Vernon et al 2011}, {Ong et al 2007}. Nonalcoholic steatohepatitis (NASH), an aggressive form of NAFLD characterized by the presence of inflammation and hepatocellular ballooning, with or without fibrosis, is present in approximately 25% of patients with NAFLD. Nonalcoholic steatohepatitis is associated with increased liver-related mortality {Williams et al 2011}, {Ong et al 2007}. In the United States (US), it has been estimated that 3% to 6% of the population {Vernon et al 2011}, {Wanless et al 1990}, or the equivalent of up to 15 million adults, have NASH.NASH represents a significant and growing unmet medical need for which there are no currently approved therapies. Furthermore, as NASH is a manifestation of the metabolic syndrome, risk factors for cardiovascular disease (eg, atherosclerotic disease, cardiac arrhythmogenicity) frequently coexist in these patients {Faramawi et al 2008}, {Voulgari et al 2010}, {Dietrich et al 2014}. A treatment that targets the underlying metabolic disorder could potentially ameliorate these cardiovascular risks and associated morbidity and mortality.

Nonalcoholic steatohepatitis is primarily thought to occur as the result of the metabolic syndrome, the impact of obesity, insulin resistance, and dyslipidemia in the liver. Simple steatosis is not sufficient to cause liver injury; it is the presence of inflammation and hepatocellular injury on the background of steatosis that defines NASH and results in the progression to end-stage liver disease and its complications. The “2-hit” hypothesis of NASH suggests that in the setting of steatosis and metabolic dysfunction, increased oxidative stress and the generation of reactive oxygen species (ROS) likely mediate the inflammatory changes in the liver (steatohepatitis) that may lead to progressive fibrosis {Dowman et al 2010}, {Kannel et al 1982}, {Koek et al 2011}, {Sumida et al 2013}. The major pathways in NASH disease progression include those involved in metabolic dysfunction in the hepatocyte, and activation of hepatic stellate cells and macrophages leading to progressive inflammation and liver fibrosis. Advanced fibrosis and cirrhosis are characterized by extensive collagen deposition and remodeling of the extracellular matrix.

Over time, NASH may result in progressive liver fibrosis, ultimately leading to cirrhosis in 10-20% of affected patients. Advanced fibrosis (bridging fibrosis or cirrhosis) is associated with increased morbidity and mortality {Ekstedt et al 2015}, {Yeh et al 2014}. Patients with cirrhosis may develop hepatocellular carcinoma (HCC) and other complications of end-stage liver disease, including jaundice, fluid retention (edema and ascites), portal hypertension and variceal bleeding, impaired coagulation and hepatic encephalopathy. Decompensated liver disease, as defined by the development of one of the above complications, has a high mortality and the only

known effective treatment is liver transplantation. With the increasing prevalence of obesity and obesity-related diseases, NASH is expected to become the leading indication for liver transplantation, and the leading etiology of HCC among liver transplant recipients in the US {Wong et al 2014}, {Afzali et al 2012}.

1.2. GS-9674

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

1.2.1.1. General Information

For further information on GS-9674, refer to the current IB for GS-9674

1.2.2. Preclinical Pharmacology, Pharmacokinetics and Toxicology

The nonclinical toxicity profile of GS-9674 has been assessed in mice and cynomolgus monkeys administered GS-9674 orally for up to 4 weeks. GS-9674-related effects were limited to non-adverse findings in the liver for both species that are likely related to the pharmacology of the compound. In both mice and cynomolgus monkeys, mild increases in ALP activity, liver weight, and hepatocellular hypertrophy were observed. Minimal oval cell hyperplasia was also observed in the liver of cynomolgus monkeys. Additional findings in mice included mild decreases in cholesterol and triglycerides. Findings were observed at ≥ 100 mg/kg/day in mice and 300 mg/kg/day in cynomolgus monkeys. Because these findings were considered non-adverse, the no observed adverse effect levels (NOAELs) in mice and cynomolgus monkeys were the highest doses evaluated (600 and 300 mg/kg/day, respectively).

Preliminary steady-state PK data from Cohort 4 (administration of GS-9674 300 mg) in the ongoing First-in-Human study of GS-9674 (GS-SU-402-1851: Section 1.2.5) 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 300 mg GS-9674 QD under Fasting Conditions at Steady-State in Cohort 4 Compared to Exposures Observed at NOAEL doses in Mouse and Cynomolgous Monkey

Species	NOAEL		Exposure Margin[a]
	Dose mg/kg/day	AUC_{tau} µg•h/mL	
Mouse	600	189	15
Cynomolgus Monkey	300	148	12

a Calculated using observed AUC_{tau} of 12.5 µg•h/mL from Healthy Volunteers administered 300 mg GS-9674 QD

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 EC50 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 receptorsN 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/RXR response element (PC-402-2012). GS-9674 caused complete FXR activation with an EC50 value of 43 nM, which was more potent than chenodeoxycholic acid (EC50 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 (OST)α 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 indicate 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 /NaNO2 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 {Nakamoto et al 2009}, {Murakami et al 2013}. 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 NASH patients by inducing FGF19 production.

1.2.4. Nonclinical Pharmacokinetics

GS-9674 is expected to be poorly absorbed in humans based on low oral bioavailability in nonclinical species (approximately 10% and 20% when dosed as CCI [redacted]). 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.

Using the estimates of bioavailability, CL, and Vss in nonclinical species, and assuming linear kinetics, a 300-mg twice-daily dose of GS-9674 is projected to give a C_{max} of 3.8 μg/mL and AUC_{0-24} of 34.4 μg/mL•h in humans.

After oral dosing to albino and pigmented mice, [14C]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 [14C]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 [14C]GS-9674-derived radioactivity did not cross the blood:brain barrier. Fecal elimination was a predominant route of elimination of [14C]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 (IC50 > 25 μM). For CYP2C8, CYP2C9, and CYP3A, IC50 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 (IC50 2.8-7.7 μM). GS-9674 inhibited human OATP1B1, OATP1B3, and OATP2B1 with IC50 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

Ongoing clinical experience with GS-9674 includes a Phase 1 clinical study (GS-US-402-1851). A brief PK summary of results from this ongoing study is presented below.

1.2.5.1. GS-US-402-1851

Study GS-US-402-1851 is an ongoing Phase 1, randomized, single-blind, placebo-controlled, single- and multiple-dose study in healthy volunteers with 4 pre-specified staggered dose-escalation cohorts and 4 adaptive randomized, single-blind, placebo-controlled, single- and multiple dose cohorts with adaptive dose selection and dose frequency.

Approximately 60 subjects have been enrolled into the 4 pre-specified cohorts with preliminary data presented below.

Summary of subjects enrolled/dosed and safety data available for Cohorts 1-4 based on interim safety data from 13-April-2016:

Preliminary safety data for GS-9674 after single and multiple dose administration of 10, 30, 100, or 300 mg GS-9674 demonstrated no adverse events of grade 3 or higher, no serious adverse events, and no subjects discontinued GS-9674 due to adverse event. Overall rate of any adverse event was 4/15 (27%) in the 10mg cohort, 4/15 (27%) in the 30mg cohort, 3/15 (20%) in the 100mg cohort, and 4/15 (27%) in the 300mg cohort. All adverse events were grade 1 or 2 in severity, did not result in dose interruption or discontinuation and were not felt to be related to GS-9674 by the investigator.

Preliminary PK parameters for GS-9674 after single and multiple dose administration of 10, 30, 100 or 300 mg GS-9674 under fasting conditions in healthy volunteers are presented below in Table 1-2. GS-9674 was absorbed quickly with the maximum plasma concentration (C_{max}) occurring between 1.25 to 3.25 hours post dose (median T_{max}) with a bi-phasic decline after C_{max}. Across the doses tested, GS-9674 exhibited a median half-life ($T_{1/2}$) of 5.56 to 12.8 hours. The lower observed median half-life 5-6 hours in the 10 mg and 30 mg cohorts may be a result of plasma concentrations falling below the limit of quantitation during the distributional phase of the profile. In general, GS-9674 AUC and C_{max} increased less than dose proportionally above 10 mg upon single and multiple dosing. As expected based on the short GS-9674 $T_{1/2}$ and once daily dosing, minimal to no accumulation was observed for GS-9674 AUC, C_{max} or C_{24} from single to multiple dose administration.

Table 1-2. Preliminary Plasma Pharmacokinetic Parameters of GS-9674 Following Single and Multiple Dose Administration of GS-9674 Under Fasting Conditions in Healthy Volunteers (GS-US-402-1851).

	Parameter (N=12) Mean (%CV)	Cohort 1: 10 mg (N=12)	Cohort 2: 30 mg (N=12)	Cohort 3: 100 mg (N=12)	Cohort 4: 300 mg (N=12)
Single Dose	AUC_{inf} (ng*hr/ml)	1260 (30.3)	2480 (37.2)	7740 (93.9)	12,500 (33.9)
	C_{max} (ng/ml)	304 (41.6)	580 (48.9)	2590 (118)	3060 (66.2)
	C_{24} (ng/ml)	2.61 (49.9)[b]	6.04 (35.7)	23.5 (40.0)	76.0 (67.4)
	T_{max} (hr)[a]	3.00 (2.38, 4.00)	3.00 (2.38, 3.63)	1.75 (1.38, 2.63)	1.25 (1.00, 3.13)
	$T_{1/2}$ (hr)[a]	5.56 (5.46, 6.41)	8.10 (5.74, 9.58)	11.2 (8.30, 11.9)	12.4 (11.4, 13.9)
Mulitple Dose	AUC_{tau} (ng*hr/ml)	1280 (35.8)	2890 (23.5)	6720 (59.2)	8490 (48.8)
	C_{max} (ng/ml)	322 (42.4)	718 (32.8)	2230 (75.9)	2330 (81.5)
	C_{tau} (ng/ml)	2.75 (55.5)	7.90 (50.3)	36.3 (42.5)	70.1 (56.3)
	T_{max} (hr)[a]	2.50 (1.50, 3.50)	3.00 (1.88, 3.13)	1.50 (1.00, 2.63)	3.25 (1.00, 5.00)
	$T_{1/2}$ (hr)[a]	6.75 (5.64, 8.45)	5.95 (5.54, 6.55)	8.99 (6.84, 11.49)	12.8 (10.0, 14.7)

Pharmacokinetic parameters are presented as Mean (%CV), and shown to 3 significant digits
a T_{max} and $T_{1/2}$ are presented as median (Q1; Q3)
b N=11

1.2.5.2. GS-US-402-3885 (current study)

Study GS-US-402-3885 is an ongoing Phase 1, open-label, parallel-group, single dose study evaluating the safety, tolerability, PK, and PD of GS-9674 in subjects with normal hepatic function and mild, moderate, or severe hepatic impairment. Up to 60 subjects are planned for enrollment in 1 of 3 hepatic impairment cohorts: Cohort 1 (mild hepatic impairment, CPT Class A), Cohort 2 (moderate hepatic impairment, CPT Class B), and Cohort 3 (severe hepatic impairment, CPT Class C).

Within each cohort, each subject with impaired hepatic function (N=10 per cohort) will be matched for age (± 10 years), sex, race, and body mass index (BMI: ± 15%) with a control subject with normal hepatic function (N=10 per cohort). Data from healthy subjects may be used in >1 cohort if a subject was an appropriate match for a subject with hepatic function in >1 cohort. All subjects will receive a single oral dose of GS-9674 30 mg in the fed state on Day 1 with PD collected on Day -1 and Day 1.

1.2.5.2.1. Subject Disposition

As of 1 November 2017, a total of 37 subjects were enrolled and 36 subjects had completed study treatment. One subject prematurely discontinued study treatment due to quality issues at the site that justified a suspension in dosing at the site. No subjects prematurely discontinued due to an AE, withdrew consent, or were lost to follow-up.

1.2.5.2.2. Preliminary Safety Results

Overall, 8.8% of subjects had a treatment-emergent adverse event (TEAE) of Grade 1 or 2. There was 1 SAE of gastrointestinal bleed that was not related to study drug. This subject had a history of esophageal variceal bleeding and experienced bleeding requiring hospitalization and blood transfusion. There were no pregnancies or deaths.

In the mild hepatic impairment cohort, there were 2 subjects (20%) that had Grade 3 lab abnormalities of elevated GGT and low platelets. The Grade 3 GGT was stable from the subject's baseline. There was 1 healthy matched control subject (10%) who had Grade 3 lab abnormalities in total cholesterol and LDL cholesterol, which were stable from their baseline. In the moderate hepatic impairment cohort, 2 subjects (20%) had Grade 3 lab abnormalities. One subject had low lymphocytes, and the other subject had elevated total bilirubin and low platelets. The platelet count was not changed from the subject's baseline. One subject, who had a SAE of gastrointestinal bleeding in the moderate hepatic impairment cohort (described above), had a Grade 4 lab abnormality of low hemoglobin.

1.2.5.3. Preliminary PK Results

Preliminary PK results are presented below and in Table 1-3:

- Cohort 1 (mild hepatic impairment; CPT Class A): GS-9674 exposure (AUC_{inf} and C_{max}) was higher in subjects with mild hepatic impairment (approximately 76% and 57%, respectively) as compared to subjects with normal hepatic function. In subjects with mild hepatic impairment, exposure (AUC_{inf} and C_{max}) of the metabolite GS-716070 was similarly higher (approximately 64% and 25%, respectively). Both analytes had minor changes in plasma protein binding (unbound fraction [fu] increased ~30%). GS-9674 is a substrate of hepatic OATP and CYP2C8 expression/activity of these transporters and enzymes may be altered in patients with hepatic impairment and may contribute to the observed higher systemic exposure of GS-9674. At a dose of 30 mg QD in subjects with mild hepatic impairment, exposure margins relative to preclinical NOAEL exposures for both parent and metabolite are expected to remain adequate.

- Cohort 2 (moderate hepatic impairment; CPT Class B): GS-9674 exposure (AUC_{inf} and C_{max}) was higher in subjects with moderate hepatic impairment (approximately 2.3- and 1.6-fold, respectively) as compared to subjects with normal hepatic function. Exposure (AUC_{inf}) of the metabolite GS-716070 was also higher (approximately 1.6-fold) with minimal change in C_{max}. Plasma unbound fraction (fu) of GS-9674 and GS-716070 was increased ~96% and ~85%, respectively, in moderate hepatic impairment, leading to a > 4-fold and > 3-fold increase in free drug exposures of parent and metabolite, respectively.

Preliminary PD results for Cohort 1 are also available for change from baseline (Day 1) in plasma FGF19 and serum 7-alpha-hydroxy-4-cholesten-3-one (C4) levels following a single 30 mg dose of GS-9674. Changes in FGF19 and C4 following a single dose of GS-9674 were similar in the mild hepatic impairment subjects as compared to the healthy matched controls as indicated by the PD parameter ratios (mild hepatic impairment/healthy) for C_{max} and $AUC_{2\text{-}12hr}$ for FGF19 (1.1 and 1.1, respectively) and for C_{min} and $AUC_{2\text{-}12hr}$ for C4 (0.82 and 0.87, respectively) in that the ratios were not significantly different from 1.

Based on the preliminary PK and PD data from this study as well as the overall safety profile of GS-9674, dose adjustments are not considered necessary in subjects with mild hepatic impairment.

Table 1-3. GS-US-402-3885: Preliminary GS-9674 and GS-716070 PK Parameters Following a Single Dose of GS-9674 30 mg in Subjects with Hepatic Impairment or Normal Hepatic Function

Cohort	Analyte	Mean (%CV) PK Parameter	Matched Healthy Control (N=10)	Hepatic Impairment (N=10)	%GMR (90% CI)
1	GS-9674	AUC_{inf} (hr ng/mL)	3030 (40.5)	5410 (40.2)	176 (127, 253)
		AUC_{last} (hr ng/mL)	2970 (41.4)	5380 (40.4)	178 (128, 247)
		C_{max} (ng/mL)	604 (45.6)	994 (53.7)	157 (108, 229)
	GS-716070	AUC_{inf} (hr ng/mL)	1440 (49.7)	2330 (44.8)	164 (104, 259)
		AUC_{last} (hr ng/mL)	1400 (51.1)	2300 (44.8)	169 (115, 247)
		C_{max} (ng/mL)	179 (42.6)	234 (50.8)	125 (85.0, 188)
2	GS-9674	AUC_{inf} (hr ng/mL)	2810 (30.3)	8280 (91.4)	230 (163, 324)
		AUC_{last} (hr ng/mL)	2460 (30.9)	8220 (91.1)	249 (169, 367)
		C_{max} (ng/mL)	496 (40.2)	909 (52.5)	164 (115, 233)
	GS-716070	AUC_{inf} (hr ng/mL)	1380 (47.7)	3160 (81.8)	163 (95.1, 280)
		AUC_{last} (hr ng/mL)	1340 (48.8)	3090 (80.9)	197 (117, 329)
		C_{max} (ng/mL)	168 (51.6)	181 (61.5)	89.5 (54.3, 147)

Data reported to 3 significant figures

1.3. Rationale for This Study

Hepatic disease may alter absorption, disposition and elimination of drugs resulting in PK and subsequently PD changes. As such, the objective of this study is to investigate potential clinically relevant differences in the pharmacokinetics and safety of administration of the single dose of GS-9674 to subjects with mild (Class A), moderate (Class B) or severe (Class C) hepatic impairment as determined by Child-Pugh-Turcotte (CPT) classification {Pugh et al 1973}, compared to matched subjects with normal hepatic function with the goal to provide dosing recommendations to subjects with hepatic impairment. Administration of GS-9674 as a single-dose is expected to accurately predict PK under steady-state conditions and is thus deemed satisfactory for an evaluation in this study.

This study design is consistent with recommendations as outlined in the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER) 2003}. All subjects in the impairment group will have clinically manifested, confirmed, primary liver disease (and not hepatic impairment due to some other cause). Evaluation of pharmacokinetics and safety of GS-9674 in moderate or severe liver impairment will commence after the review of safety and available PK

data from subjects with mild, or moderate hepatic impairment respectively. The trial will also enroll healthy controls, matched for body mass index, age, and sex.

1.3.1. Rationale for the Dose Selection

This study will evaluate the impact of hepatic impairment on the single dose PK of 30 mg (Cohorts 1 and 2) and 10 mg (Cohort 3) GS-9674 administered under fed conditions (moderate fat breakfast based on results from food effect evaluations in study GS-US-402-1851). These doses were selected based on the observed PK of single- and multiple-dose administration of GS-9674 up to 300 mg in study GS-US-402-1851 in healthy subjects and on the preliminary data from Cohorts 1 and 2 of this study, which showed increased unbound exposure with degree of hepatic impairment. Based on the PK of GS-9674 across the range of doses evaluated, and GS-9674 exposure and PD response observed in study GS-US-402-1851, alterations of GS-9674 PK observed in this study as a result of hepatic impairment are expected to reflect the magnitude of alteration of steady-state GS-9674 pharmacokinetics in subjects with NASH.

Short-term safety data from clinical study GS-US-402-1851 and GS-US-402-2102 indicate that GS-9674 exposures higher than those expected in this study are well tolerated in healthy subjects with no clinically significant or treatment limiting adverse events or laboratory abnormalities.

This study will proceed in three sequential cohorts starting with mild (CPT Class A), then moderate (CPT Class B), followed by severe (CPT Class C) hepatic impairment with evaluation of preliminary safety and PK data from hepatic impaired subjects from each cohort prior to initiation of subsequent cohorts. In addition, the proposed 30 mg dose of GS-9674 in Cohorts 1 and 2 is 10-fold lower than the highest dose level previously evaluated (300 mg) in study GS-US-402-1851 which provided GS-9674 exposures 12- to 15- fold lower than those observed at the NOAEL in the 4-week repeat dose toxicity studies in the mouse and cynomolgous monkey (Section 1.2.21.2.2). Based on the preliminary exposures observed in Cohort 1 and 2 (Section 1.2.5.2) and expected further increases in unbound exposure in Cohort 3, the dose of GS-9674 is being reduced to 10 mg in subjects with severe hepatic impairment to cautiously maintain adequate exposure margins.

With the proposed doses, it is unlikely that plasma exposures of GS-9674 in hepatic impairment subjects would exceed previously observed exposures in healthy volunteers or exceed exposures observed at the NOAEL in the toxicity studies.

1.4. Risk/Benefit Assessment for the Study

Potential risks of a participant's study involvement include unknown AEs, general risks associated with frequent clinic visits and laboratory blood draws, and the associated pain and discomfort of phlebotomy. Strategies to mitigate these risks include close monitoring of lab values as well as AEs. Parameters for discontinuation of the study drug due to AEs will be well-defined and closely followed.

There is no direct benefit to subjects participating in this study; however, data from this study will support the development of GS-9674 for the treatment of NASH. Potential benefits may include the participant's contribution to understanding the safety and tolerability of a single-dose of GS-9674, how much GS-9674 gets into the blood stream, and how these may differ in those with hepatic insufficiency.

Considering the above, the benefit-risk balance for this study is considered positive.

1.5. Compliance

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

2. OBJECTIVES

The primary objectives of this study are as follows:

- To evaluate the single-dose pharmacokinetics of GS-9674 in subjects with impaired hepatic function relative to matched, healthy controls with normal hepatic function

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of GS-9674 single dose administration in subjects with normal hepatic function, or mild, moderate, and severe hepatic impairment

- To evaluate FXR activation by GS-9674 as measured by PD markers in subjects with normal hepatic function, or mild, moderate and severe hepatic impairment

3. STUDY DESIGN

3.1. Study Design

This protocol describes a Phase 1, open-label, adaptive, single-dose, parallel-group, staggered-cohort, PK study to evaluate the single-dose pharmacokinetics of GS-9674 in subjects with normal and impaired hepatic function. Up to approximately 60 subjects will be enrolled.

Cohort 1: GS-9674: 20 [10 per group (mildly impaired and matched controls) for 8 evaluable per group]

Cohort 2: GS-9674: 20 [10 per group (moderately impaired and matched controls) for total 8 evaluable per group]

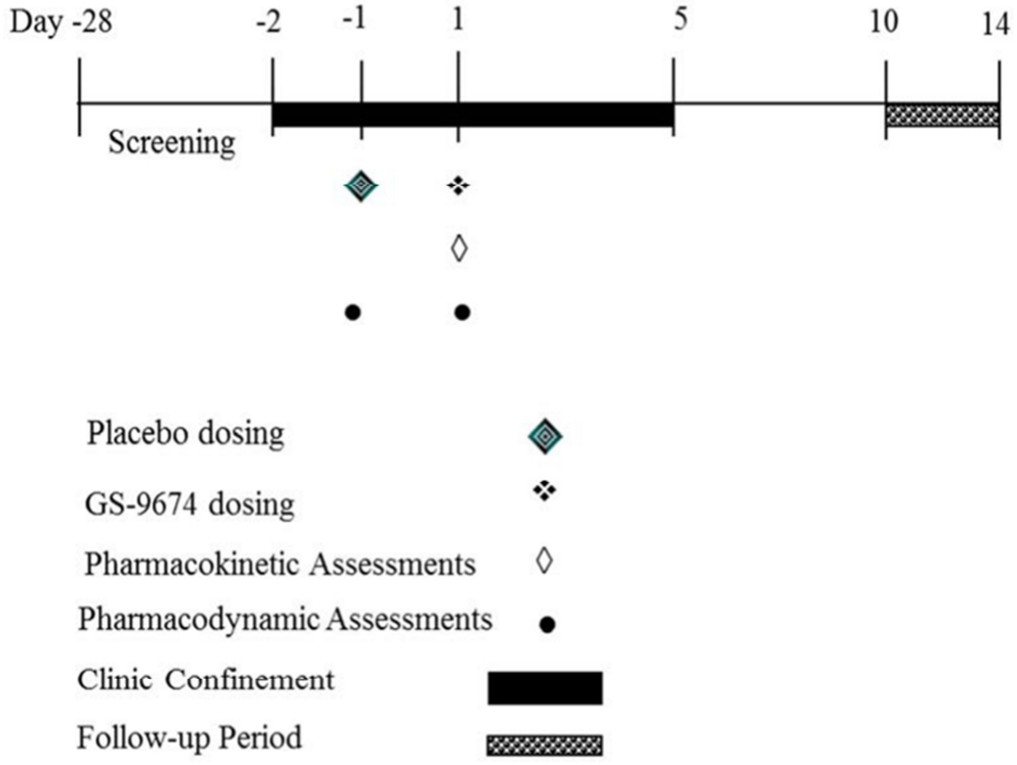
Cohort 3: GS-9674: 20 [10 per group (severely impaired and matched controls) for total 8 evaluable per group]

Eligible subjects include male and nonpregnant/nonlactating female subjects, aged $\geq$ 18 years with mildly, moderately impaired, severely impaired, and normal hepatic function will be enrolled into the study. Each subject in the control group will be matched for age (± 10 years), gender, race and body mass index (± 15% 18 $\leq$ BMI $\leq$ 36 kg/m^2) to a subject in the hepatic impairment group. A subject with normal hepatic function in a cohort may serve as a match to a subject with hepatic impairment in another cohort.

Cohorts 1 through 3 will be dosed in a sequential manner, with dosing of subjects in Cohort 2 (moderate hepatic impairment) and Cohort 3 (severe hepatic impairment) proceeding after review of safety and available preliminary pharmacokinetic data from hepatic impaired subjects in the previous cohorts. Based on the cumulative review of safety and PK data, sequential cohorts may or may not be initiated at the discretion of the investigator and Sponsor.

In general, dosing in subjects with normal hepatic function will begin after a matched subject with hepatic impairment has completed PK assessments. The study design is presented in Figure 3-1.

Figure 3-1. Cohorts 1, 2, and 3 Study Schema



3.2. Study Drug Administration

The study drug will be supplied as GS-9674 tablets or placebo to match, in strengths of 10 mg. All study treatments will be administered with 240 mL of water.

Study Treatments will be administered in the fed state as described below.

Fed state dosing:

Study drugs will be administered following an overnight fast (no food or drinks except water, for at least 10 hours) and within 5 minutes of completing a standardized meal (moderate-fat-calorie breakfast containing ~600 kcal and 25% to 30% fat will be provided). The meal should be initiated 30 minutes prior to study drug administration. Subjects will l fast until after collection of the 4-hour PK/PD sample, relative to study drug dosing.

Additionally, subjects will be restricted from water consumption from 1 hour before through

2 hours after dosing, except for the water given with the study drugs and the standardi zed meal. A standardized meal may be provided to subjects after the 4-hour post-dose PK/PD draw.

Please refer to Section 5.3 for additional information for study drug dosage and administration.

3.3. Clinic Confinement

Eligible subjects will be confined beginning on Day -2 until the completion of assessments on Day 5. Subjects will be required to return for a Follow-up visit 10-14 days after study drug dosing.

3.4. Pharmacokinetic Assessments

PK assessments will occur on assigned study days as outlined in Table 6-1.

3.4.1. Plasma Pharmacokinetic Collection

Plasma concentrations of GS-9674 (its major metabolites, as applicable) will be determined and PK evaluated. PK parameters will be estimated as appropriate.

3.5. Safety Assessments

Safety assessments will be performed through the study as outlined in Table 6-1.

3.6. Pharmacodynamic Biomarker Assessments

PD assessments will be performed throughout the study as outlined in Table 6-1 and in Section 6.9.

3.7. Optional Genomic Research

CCI

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

3.8. End of Study

The end of this study will be the last subject's last observation (or visit).

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A total of up to approximately 60 unique subjects will be enrolled in the study. Eligible subjects include male and nonpregnant/nonlactating female subjects at least 18 years of age with mildly impaired, moderately impaired, severely impaired, and normal hepatic function. If necessary, replacement subjects may be enrolled if subjects do not complete all intensive PK procedures with Sponsor approval. Replacement subjects will not be enrolled for subjects who discontinue the study due to treatment-related adverse events.

Classification of hepatic impairment will be assigned as follows:

- **Mild:** Class A, CPT score 5-6
- **Moderate:** Class B, CPT score of 7-9
- **Severe:** Class C, CPT score of 10-15

Based on CPT classification, subjects with hepatic impairment and healthy matched controls will be enrolled as described in Section 5.1. The control group will consist of matched healthy subjects with normal hepatic function. Each subject in the hepatic impairment group will be matched for age (± 10 years), gender, and BMI (± 15%, 18 ≤ BMI ≤ 36 kg/m²) with a subject in the healthy control group.

4.2. Inclusion Criteria

4.2.1. All Subjects

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

1. Have the ability to understand and sign a written informed consent form (ICF), which must be obtained prior to initiation of study procedures.
2. Must be ≥ 18 years of age, inclusive at Screening.
3. Must be able to comply with the smoking restrictions at the study site.
4. Have a calculated body mass index (BMI) from 18 to 36 kg/m², inclusive, at study Screening.

5. Have a creatinine clearance (CL_{cr}) ≥ 80 mL/min (using the Cockcroft-Gault method {Cockcroft et al 1976}) based on serum creatinine and actual body weight as measured at Screening

$$\text{Male:} \quad \frac{(140 - \text{ageinyears}) \times (\text{wtinkg})}{72 \times (\text{serum creatinine in mg/dL})} = \text{CrCl (mL/min)}$$

$$\text{Female:} \quad \frac{(140 - \text{ageinyears}) \times (\text{wtinkg})}{72 \times (\text{serum creatinine in mg/dL})} \times 0.85 = \text{CrCl (mL/min)}$$

6. Females of childbearing potential (as defined in Appendix 3) must have a negative serum pregnancy test at Screening and negative urine pregnancy at Day -2 unless permanently sterile or greater than two years post-menopausal

7. Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified highly effective method(s) of contraception as described in Appendix 3.

8. Male subjects must refrain from sperm donation from clinic admission, throughout the study period, and continuing for at least 90 days following the last dose of study drug.

9. Subjects have not donated blood within 56 days of study entry or plasma within 7 days of study entry and must refrain from blood donation from clinic admission, throughout the study period, and continuing for at least 30 days following the last dose of study drug.

10. Have either a normal 12-lead electrocardiogram (ECG) or one with abnormalities that are considered clinically insignificant by the investigator.

11. Must be willing and able to comply with all study requirements.

4.2.2. Subjects with Impaired Hepatic Function

Subjects with mild, moderate, or severe hepatic impairment must also meet the following additional inclusion criteria to be eligible for participation in this study:

12. Aside from hepatic insufficiency, the subject must, in the opinion of the investigator, be sufficiently healthy for study participation based upon medical history, physical examination, vital signs, and screening laboratory evaluations

13. Must have diagnosis of chronic (> 6 months), stable hepatic impairment with no clinically significant changes within 3 months (90 days) prior to study drug administration (Day -1)

14. Must meet all of the following laboratory parameters at Screening:

    - ALT value ≤ 10 × ULN
    - AST value ≤ 10 × ULN
    - Absolute neutrophil count ≥ 1,000/mm3
    - Platelets ≥ 25,000/mm3
    - Hemoglobin ≥ 8 g/dL
    - α-fetoprotein ≤ 50 ng/mL

15. Subjects with severe hepatic impairment must have a score on the Child Pugh Turcotte scale of 10-15 at Screening. If a subject's score changes during the course of the study, the score at Screening will be used for classification.

16. Subjects with moderate hepatic impairment must have a score on the Child Pugh Turcotte scale of 7-9 at Screening. If a subject's score changes during the course of the study, the score at Screening will be used for classification.

17. Subjects with mild hepatic impairment must have a score on the Child Pugh Turcotte scale of 5-6 at Screening. If a subject's score changes during the course of the study, the score at Screening will be used for classification

18. Subjects with hepatic impairment with comorbid diseases not associated with hepatic impairment requiring medication(s) must be taking the medication(s) without a change in dose for at least 4 weeks (or 5 half-lives, whichever is longer) prior to Screening. Any change in the dosage during this timeframe should be reviewed and approved by the Sponsor.

4.2.3. Healthy Matched Control Subjects

Healthy matched control subjects must also meet the following additional inclusion criteria to be eligible for participation in this study:

19. Must, in the opinion of the Investigator, be in good health based upon medical history, physical examination, vital signs, and screening laboratory evaluations.

20. Must meet all of the following laboratory parameters at Screening:

    - INR ≤ 1 × ULN
    - Albumin ≥ 1 × LLN
    - Total bilirubin ≤ 1 × ULN

- AST value ≤ 1 × ULN
- ALT value ≤ 1 × ULN
- Alkaline phosphatase ≤ 1 × ULN
- α-fetoprotein ≤ 1 × ULN

21. Must match in age (± 10 years), gender, race, and BMI (± 15% of ≥ 18 and ≤ 36) with the respective subject in hepatic impairment group.

4.3. Exclusion Criteria

4.3.1. All Subjects

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

1. Pregnant or lactating subjects.
2. Have received any investigational compound within 30 days prior to study dosing (Day -1).
3. Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance or subject safety.
4. A positive test result for human immunodeficiency virus (HIV-1/2) antibody
5. Have poor venous access that limits phlebotomy.
6. Have been treated with systemic steroids, immunosuppressant therapies, or chemotherapeutic agents within 3 months prior to Screening or expected to receive these agents during the study (eg, corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies).
7. Significant serious skin disease, such as but not limited to rash, food allergy, eczema, psoriasis, or uticaria.
8. Significant drug sensitivity or drug allergy (such as anaphylaxis or hepatoxicity).
9. Known hypersensitivity to the study drugs their metabolites or to formulation excipients (see Section 5.2.1).
10. Significant cardiac disease including history of myocardial infarction based on ECG and/or clinical history, any history of ventricular tachycardia, congestive heart failure, or dilated cardiomyopathy with left ventricular ejection fraction < 40%, implanted defibrillator or pacemaker), a family history of Long QT Syndrome, or unexplained death in an otherwise healthy individual between the ages of 1 and 30 years.

11. Syncope, palpitations, or unexplained dizziness.

12. Severe peptic ulcer disease, gastroesophageal reflux disease, or other gastric acid hypersecretory conditions.

13. Medical or surgical treatment that permanently alters intestinal absorption (eg, gastric or intestinal surgery). A history of cholecystectomy is not exclusionary.

14. Are unable to comply with study requirements or are otherwise believed, by the study investigator, to be inappropriate for study participation for any reason.

4.3.2. Subjects with Impaired Hepatic Function

Subjects with mild, moderate, or severe hepatic impairment meeting any of the following additional exclusion criteria are not to be enrolled in this study:

15. Aside from hepatic insufficiency, serious or active medical or psychiatric illness that, in the opinion of the Investigator, would interfere with subject treatment, assessment, or compliance with the protocol. This would include renal, cardiac, hematological, unstable hepatic, pulmonary (including chronic asthma), endocrine (eg, diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders, active infection, or malignancy that are clinically significant or requiring treatment.

16. Chronic hepatitis B virus (HBV) infection, defined as a positive test for hepatitis B surface antigen (HBsAg), unless the patient has been treated with a nucleos(t)ide analog (eg, tenofovir or entecavir) for at least 6 months and the HBV DNA by polymerase chain reaction (PCR) assay has been persistently undetectable for at least 6 months.

17. Positive test for drugs of abuse, including alcohol at Screening or on Day -2/check-in, with the exception of opioids and tetrahydrocannabinol (THC, marijuana) under prescription and Investigator verification for pain management. Subjects who screen positive for benzodiazepines may be allowed if prescribed under the care of a physician and after review by Investigator and Sponsor.

18. Requires paracentesis > 1 time per month.

19. Subjects with hepatic impairment with co-morbid diseases not associated with hepatic impairment requiring medication(s) must be taking the medication(s) without a change in dose for > 3 months prior to Screening.

20. Changes in concomitant medications or dosage used to treat symptoms of hepatic impairment or associated co-morbid conditions that could lead to clinically significant changes in medical conditions during the course of the study that would affect the ability to interpret potential drug-drug interactions within 28 days prior to dosing.

All concomitant medications including over-the-counter and herbal products must be approved by the Investigator and Medical Monitor prior to study enrollment and study drug administration.

21. Prior placement of a portosystemic shunt (such as TIPS), unless vascular imaging indicates the shunt has no current blood flow.

4.3.3. Healthy Control Subjects

Healthy matched controlled subjects meeting any of the following additional exclusion criteria are not to be enrolled in this study:

22. A positive test result for HCV antibody or HBVsAg.

23. Positive test for drugs of abuse, including alcohol at Screening or on Day -2/check-in.

24. Have any serious or active medical or psychiatric illness (including depression) which, in the opinion of the Investigator, would interfere with subject treatment, assessment, or compliance with the protocol. This would include renal, cardiac, hematological, hepatic, pulmonary (including chronic asthma), endocrine (including diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders, active infection, or malignancy that are clinically significant or requiring treatment.

25. History of liver disease.

26. Have taken any prescription medications or over-the-counter medications including herbal products within 28 days of commencing study drug dosing (Day -1) with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptive medications.

5. STUDY DRUGS

5.1. Enrollment and Blinding

It is the responsibility of the Investigator to ensure that the subject is eligible for the study prior to enrollment. Subjects will be assigned a Screening number at the time of consent.

At Screening, study participants will be assigned to a cohort within their respective part. Once eligibility has been confirmed, eligible subjects will be assigned a subject number starting on Day 1 and will receive the study treatments as described in Section 5.3.

All Screening and Day -2 tests and procedures must be completed prior to the administration of the first dose of study drug on starting on Day -1. Once a subject number has been assigned to a subject, it will not be reassigned to another subject. If necessary, replacement subjects may be enrolled after discussion and approval from Sponsor. A new unique subject number will be assigned to the replacement subject.

A subject number list will be provided to the study center by the Sponsor.

5.2. Description and Handling of GS-9674

5.2.1. Formulation

GS-9674 is supplied as 10 mg strength (as free form equivalent) tablets. The tablets contain CCI [redacted] GS-9674 tablets 10 mg, are round, plain-faced, film-coated, orange tablets.

Placebo-to-match (PTM) GS-9674 tablets are identical in size, shape, color and appearance to their corresponding strength of active GS-9674 tablets. Placebo-to-match GS-9674 tablets contain the following inactive ingredients: CCI [redacted]

5.2.2. Packaging and Labeling

GS-9674 tablets, 10 mg, and PTM GS-9674 are packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, a silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

Study drugs to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the 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

GS-9674 tablets and PTM GS-9674 tablets should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25ºC (77ºF); excursions are permitted between 15ºC and 30ºC (59ºF and 86ºF). Storage conditions are specified on the label.

Until study drug tablets are 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, the drug products 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 through inhalation when handling GS-9674 tablets.

5.3. Dosage and Administration of Study Drug

The study drugs will be supplied as GS-9674 tablets, in strengths of 10 mg and PTM GS-9674. All study treatments will be administered with 240 mL of water. Study treatments will be administered in the fed state.

5.4. Fed State Dosing

Study drugs will be administered following an overnight fast (no food or drinks except water, for at least 10 hours). Study drugs will be administered within 5 minutes of completing a standardized meal (moderate-fat-calorie breakfast containing ~600 kcal and 25% to 30% fat will be provided). The meal should be initiated 30 minutes prior to study drug administration. Subjects will fast until after collection of the 4-hour PK/PD sample, relative to study drug dosing.

Additionally, subjects will be restricted from water consumption from 1 hour before through 2 hours after dosing, except for the water given with the study drugs and the standardized meal. A standardized meal may be provided to subjects after the 4-hour post-dose PK/PD draw.

5.5. Meals

All meals and/or snacks given to subjects during their stay in the clinical study facility will be standardized for all subjects and should be similar in calorie and fat content and taken at approximately the same time each day. All meals provided must be approved by the Sponsor. Components of meals (eg, margarine, jelly, bread) should be given to subjects in individual portions (eg, 1 tablespoon) per the approved meal schedule. The provision of meal components in bulk (eg, a jar of jelly for subjects to share) should not be practiced. All meals should be given at approximately the same time each day (eg, 07:30, 12:00, and 18:00).

5.6. Dispensing, Accountability, and Disposal or Return of Study Drug

The Investigator (or designee, eg, study center pharmacist) will acknowledge receipt of the study drug (after reviewing the shipment's content and condition) from Gilead (or designee). The Investigator will maintain an accurate inventory of all study drug(s). Each dose of the study drug(s) administered at the study center will be administered by qualified study center staff. The dose of study drug(s) administered to subjects in the clinic under the supervision of staff will be accurately recorded on the Study Drug Accountability Form provided by Gilead (or on equivalent documentation maintained by the study center), which indicates the date and quantity of each dosage formulation dispensed to individual subjects.

Gilead recommends that used and unused study drug supplies, including empty containers, be returned to the shipping facility from which it came or Gilead Sciences for destruction following drug accountability and drug inventory reconciliation.

If returning drug supplies to the shipping facility from which it came or to Gilead Sciences is not possible, the monitor will evaluate the site's SOP for study drug disposal/destruction in order to ensure that it complies with Gilead's requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures.

5.7. Concomitant Medications and Other Protocol Restrictions

5.7.1. Concomitant Medications

5.7.1.1. Hepatic Impairment Group

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

Concomitant medications taken within 30 days of Screening through the follow-up visit need to be recorded in the source documents and electronic Case Report Forms (eCRFs).

Subjects with hepatic impairment with co-morbid diseases requiring medication(s) must be taking the medication(s) without a change in dose within 28 days of Day 1. All concomitant medications including over-the-counter and herbal products must be approved by the Investigator and Medical Monitor prior to study enrollment and study drug administration.

The following medications are prohibited from 28 days prior to Day -1 through discharge:

- 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 (e.g., infliximab)
- Investigational agents or devices for any indication
- Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters P-gp, BCRP, or OATP, or the drug metabolizing enzyme 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 Day -1 through discharge are listed below in Table 5-1:

Table 5-1. List of Disallowed Medications

Drug Class	Agents Disallowed
Antibiotics	Azithromycin, Clarithromycin, Erythromycin
Acid Reducing Agents	Proton-Pump Inhibitors, H2-Receptor Antagonists, Antacids[a]
Anticonvulsants[b]	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine
Antifungals	Itraconazole, Ketoconazole
Antimycobacterials[b]	Rifamycins, Isoniazid
Cardiac Medications	Amiodarone, Digoxin, Dronedarone, Felodipine, Verapamil, Quinidine, Ranolazine, Bosentan, Olmesartan, Telmisartan, Valsartan
Herbal/Natural Supplements[b]	St. John's Wort, Echinaccea. Milk thistle (i.e. silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
HMG-CoA Reductase Inhibitors[c]	fluvastatin, lovastatin, pitavastatin , pravastatin, rosuvastatin
Selective Serotonin Reuptake Inhibitors	Fluvoxamine
Other	Modafinil

a Proton pump inhibitors can be taken up to 7 days before study drug dosing (Day 1). H2 receptor antagonists can be taken up to 3 days before study drug dosing (Day 1). 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.
b May result in a decrease in the concentrations of study drugs.
c Use with study drug may result in an increase in the concentration of the HMG-CoA Reductase Inhibitors. The 28 day washout period does not apply to HMG-CoA Reductase inhibitors, which can be taken up to the day before Day -1.

Medications for disease conditions **excluded** from the protocol (e.g., HIV-1 infection, active cancer, transplantation) are not listed under this Concomitant Medication section and are disallowed in the study.

5.7.1.2. Subjects with Normal Hepatic Function

The following medications are excluded while subjects with normal hepatic function are participating in the study:

- Any prescription medications or over-the-counter medications including herbal products within 28 days of commencing study drug dosing (Day -1) with the exception of vitamins, acetaminophen, ibuprofen and/or hormonal contraceptives. However, the short term use of topical hydrocortisone cream or A&D ointment to treat minor skin irritation due to ECG leads will be allowed. If a subject requires use of a disallowed medication, a request for such use must be reviewed by the Sponsor and if approved, subjects may continue to participate in the study.

- Any and all illegal or illicit drug use, including use of prescription drugs outside the care of the prescribing physician.

5.7.2. Other Protocol Restrictions

- Subjects will be required to refrain from the consumption of food and beverages containing alcohol products 72 hours prior to the first dose of study drug and during the course of the study through the follow-up visit.

- Subjects will be required to refrain from the use of nicotine or nicotine-containing products 90 days prior to first dose of study drug and during the course of the study through the follow-up visit.

- Subjects will be required to refrain from consumption of grapefruit juice, grapefruits, and Seville orange juice 72 hours prior to the first dose of study drug and during the course of the study through the follow-up visit.

- While confined at the study center, tea, coffee, chocolate, and other foods and beverages containing caffeine and other methyl xanthines will be prohibited on each dosing day. At all other times, caffeine-containing beverages and foodstuffs may be served or withheld in accordance with normal study center practice. Caffeine-containing beverages and foodstuffs will not be restricted while subjects are outside of the clinic.

- Subjects will be encouraged to avoid strenuous or prolonged exercise, as well as saunas, steambaths, and sunbathing or other prolonged ultraviolet exposure, eg, in a tanning salon, from the screening evaluation until completion of the follow-up visit, as these activities are known to affect certain clinical laboratory test parameters, (eg, creatine kinase) and will provide false indicators of a potentially treatment-related toxicity.

Upon every admission to the clinic, each subject will be questioned as to their compliance with the above protocol restrictions**.** If a subject is unable to comply with any of the restrictions described above, the subject's continued participation in the study will be reevaluated by the investigator in consultation with the sponsor.

6. STUDY ASSESSMENTS

The study procedures to be conducted for each subject enrolled in the study are detailed below.

Any deviation from protocol procedures should be noted in the subject's clinical chart and appropriate electronic case report forms (eCRFs). In addition, the sponsor should be promptly notified of any protocol deviations.

The study center will not initiate dosing until the following have all been met:

- The institutional review board (IRB)/ethics committee (EC)/other applicable regulatory agencies have reviewed and approved the study and the informed consent document.
- All requested regulatory documents have been submitted to and approved by Gilead.
- A master services agreement and/or study agreement is executed.
- The study initiation meeting has been conducted by the Gilead (or designee).

The initiation meeting will include but is not limited to a review of the protocol, the IB, study drugs, and investigator responsibilities.

Documentation of the personally signed and dated ICF for each subject, using the study-specific, IRB/EC-approved ICF, is required before initiating the screening process.

6.1. Subject Enrollment and Treatment Assignment

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

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

Once the ICF has been obtained, all screening and admission tests and assessments have been assessed, and study eligibility has been confirmed, subjects will be enrolled to receive study drug on Day 1.

Subjects will receive the study treatments as described in Section 5.3.

Table 6-1. Schedule of Assessments

Study Procedure	Screen[a]	Day -2	Day -1	Day 1	Day 4	Day 5[b]	Day 10-14 FU Period	ET[d]
Written Informed Consent	X							
Medical History	X							
Complete Physical Exam	X							X
Symptom-Driven Physical Examination[e]		X						
Height	X							
Weight	X							
BMI	X							
Vital Signs[f]	X	X		X		X	X	X
HIV-1, HBV, and HCV Testing[h]	X							
Hematology[g, h]	X	X				X	X	X
Serum Chemistry[h]	X	X				X	X	X
Coagulation	X							
A-fetoprotein	X							
Urinalysis	X	X				X	X	X
Serum Pregnancy Test[i]	X							X
Urine Pregnancy Test[i]		X				X	X	X
FSH[j]	X							

Study Procedure	Screen[a]	Day -2	Day -1	Day 1	Day 4	Day 5[b]	Day 10-14 FU Period	ET[d]
Urine Drug and Alcohol Screen[h]	X	X					X	X
12-Lead ECG	X	X				X	X	X
Enrollment			X					
Placebo Administration			X					
GS-9674 Administration				X				
PK Assessments[k]								X
PD Assessments[l]			X	X				X
Genetic Sample[m]				X				
Review Study Restrictions	X	X				X	X	X
Clinic Confinement		X ---------- X						
Review AEs & Concomitant Medications[n]	X	X ---------- X					X	X

a. Prospective subjects should be screened no more than 28 days prior to administration of the first dose of study drugs.

b. Subjects will be discharged from the clinic on Day 5 following all morning assessments.

c. Subjects will be required to return for a Follow-up visit 10-14 days after study drug dosing.

d. Assessments will be performed within 72 hours of early termination from the study.

e. Symptom-driven PEs will be performed on Day 1 (predose), 4, and at the Follow-up Visit

f. Vital signs include blood pressure, pulse rate, respiration rate, and body temperature. To be performed on Day -2, 1 (predose and at approximately 3 hours postdose), 5, and at the Follow-up Visit.

g. Hematology: CBC with differentials

h. Fasting serum chemistry: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, GGT, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, total cholesterol, HDL, LDL, triglycerides, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 x ULN).

i. Female subjects of child-bearing potential.

j. Female subjects ≤ 54 years old with amenorrhea > 12 months as outlined in Appendix 3 kIntensive PK sampling will occur relative to the dosing at the following timepoints:

k. Day 1: -0.5, 0 (pre-dose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours post-dose

   In addition, on Day 1 at the 3 and 5 hours post dose timepoints, an additional plasma sample will be collected for plasma protein binding evaluation. Alternatively, pre-dose samples may be utilized for plasma protein binding evaluation

l. Blood samples will be collected relative to dosing of GS-9674 to measure PD biomarkers for FGF19 and C4 GS-9674 at the following timepoints for each cohort: Day -1: -0.5, 0 (pre-dose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 16 (relative to Day 1 dosing time assignment)

   Day 1: -0.5, 0 (pre-dose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours post-dose

   A single blood sample will be collected on Day 1, -0.5 hours predose for the determination including but not limited to individual bile acids.

m. For subjects who provide consent, an additional blood sample will be obtained. This sample should be collected on Day 1, but may be collected at any time during the study or at a separate post-study visit, if necessary.

n. From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any non-serious adverse events related to protocol-mandated procedures on the AE 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 CRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Prospective subjects should be screened no more than 28 days prior to administration of the first dose of study drug. If a subject does not begin the treatment phase within this 28-day window, all screening evaluation procedures must be repeated. Screening laboratory assessments may be repeated once within 28 days prior to administration of study drug to rule out laboratory error.

A sufficient number of subjects will be screened to identify planned number of subjects for enrollment.

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

Written informed consent must be obtained from each subject before initiation of any screening procedure. After a subject has provided informed consent, the investigator and other study personnel will determine if the subject is eligible for participation in the study. This assessment will include a review of the inclusion/exclusion criteria and completion of all screening procedures as outlined in Table 6-1 and described in the following text.

Eligible subjects meeting all of the inclusion criteria and none of the exclusion criteria will be instructed on all protocol requirements, including the restrictions on concomitant medication usage and other substances as well as consumption of food or beverages containing alcohol, caffeine, or xanthine. Subjects will be asked to arrive at the study center on Day -2 for admission assessments.

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 adverse events related to protocol-mandated procedures on the adverse events case report form (AE 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.

6.2.2. Admission Assessments

6.2.2.1. Admission

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

Subjects meeting all eligibility criteria following the screening evaluation will return to the clinic for admission assessments on Day -2. The admission evaluations and/or procedures are outlined in Table 6-1.

Prior to dosing on Day -1, the results of the clinical and laboratory evaluations (as described in Table 6-1 must be reviewed by the investigator to confirm the continued eligibility of each subject to participate in the study. At the time of enrollment subjects will be assigned a sequential subject number as described in Section 5.1. Subjects will remain confined to the study clinic for the duration as described in Section 6.2.2.2 and Table 6-1.

Prior to study drug administration, record any SAEs and all AEs related to protocol-mandated procedures. After drug administration, report all AEs and SAEs.

6.2.2.2. Clinic Confinement

Subjects will be confined to the study clinic starting on Day -2 until completion of assessments on Day 5.

6.3. Check-in Assessments

Following completion of screening and Day -1 assessments, eligible subjects will be assigned a subject number and receive study treatments as shown in Section 5.3.

6.4. Treatment Assessments

Study procedures and assessments are outlined in Table 6-1.

6.5. Posttreatment Assessments

Subjects will be required to return for a Follow-up visit 10-14 days after study drug dosing.

6.6. Assessments for Premature Discontinuation from Study

If the subject discontinues from the study, the ET evaluations and/or procedures outlined in Table 6-1 should be performed within 72 hours of permanently discontinuing the study.

6.7. Criteria for Discontinuation of Study Drug for Multiple Dose Studies

Study treatment 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
- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest
- Subject request to discontinue for any reason
- Subject noncompliance

- Pregnancy during the study (refer to Appendix 4)
- Investigator discretion
- Discontinuation of the study at the request of Gilead, regulatory agency, or an IRB/EC

6.8. Pharmacokinetic Assessments

6.8.1. Plasma PK Collection

Plasma concentrations of GS-9674 (and its metabolites, as applicable) will be determined and PK evaluated. PK parameters will be estimated, as appropriate.

Intensive PK sampling will occur relative to the morning dose of GS-9674 at the following time points:

- Day 1: -0.5, 0 (pre-dose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours post-dose

In addition, on Day 1 at the 3 and 5 hours post dose time-points, an additional plasma samples will be collected for plasma protein binding evaluation. Alternatively, pre-dose samples may be utilized for plasma protein binding evaluation.

A blood sample for PK analysis will also be collected at the Early Termination (ET) visit (if applicable) and may be analyzed.

6.9. Pharmacodynamic Assessments

Blood samples will be collected relative to dosing of GS-9674 to measure PD biomarkers including but not limited to FGF19 and C4 for GS-9674 at the following time points for each cohort:

- Day-1: -0.5, 0 (pre-dose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 16 (relative to Day 1 dosing time assignment)
- Day1: -0.5, 0 (predose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours post-dose

For analysis including but not limited to individual bile acids a single blood sample will be collected at the following time point for each cohort:

- Day1: -0.5 hours predose

A blood sample for PD analysis will also be collected at the Early Termination (ET) visit (if applicable) and may be analyzed.

6.10. Optional Genomic Sample

CCI [redacted]

6.11. Safety Assessments

Safety will be evaluated throughout the study. Refer to Table 6-1 for a schedule of assessments.

6.11.1. Electrocardiogram Assessment

Subjects should rest quietly in the supine position for a minimum of 10 minutes prior to each scheduled ECG acquisition and should remain in that position until the recording is complete.

There should be no environmental distractions (including TV, radio, video games, and conversation) while the subjects are resting prior to and during the recordings. Electrocardiograms will be recorded using the site's standard ECG equipment. All ECGs will be obtained using instruments that analyze data using the same algorithms and produce the same data for interpretation. Electrode placement will be performed according to the method of Wilson, Goldberger, and Einthoven with a check to confirm that the aVR lead is not inverted.

The investigator or other qualified individuals at the study center will review ECGs to assess for changes in ECG intervals and morphology as compared with pretreatment ECGs. ECG interval measurements output by the machine will be used for bedside safety monitoring.

Collection of additional ECGs for routine safety monitoring at additional time points or days is at the discretion of the investigator based on GCP.

6.11.2. Physical Examination

Physical examinations conducted throughout the study will be a complete physical examination or a symptom-directed physical examination, as outlined in Table 6-1. The complete physical examination conducted at screening will also include the following assessments:

- Review medical history, including history of allergies, prior and current use of nicotine or nicotine-containing products, alcohol and illegal drug use, and prior (within 30 days) and current medication use

6.11.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiration rate, and temperature and should be taken once subjects have been seated or in the supine position. Subject position for measurement should be kept consistent throughout the study. Refer to Table 6-1 for vital signs collection time points.

6.11.4. Body Mass Index

Height and weight will be collected at screening for calculation of BMI for inclusion criteria.

6.11.5. Clinical Laboratory Tests/Assessments

Blood and urine samples for safety evaluations will be collected throughout the study as outlined in Table 6-1.

6.11.5.1. Blood Sampling

Blood samples will be collected for the following laboratory analyses:

- Hematology: CBC with differential
- Serum chemistry (fasting): alkaline phosphatase, AST, ALT, GGT total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, total cholesterol, HDL, LDL, triglycerides, and amylase (reflex lipase testing is performed in subjects with total amylase
- > 1.5 × ULN).
- •HIV-1/2, HBVsAg, and HCV-Ab testing (Screening only)
- •Coagulation (PT, PTT, INR; Screening and FU Visit only)
- α-fetoprotein test (Screening only)
- Serum pregnancy test (females of childbearing potential only)
- FSH (Female subjects ≤ 54 years old with amenorrhea > 12 months, Screening only)

6.11.5.2. Urine Samples

Urine samples will be collected for urinalysis and alcohol and drug screen assessments.

6.11.6. Creatinine Clearance

Weight will be collected at Screening to calculate creatinine clearance (eGFR) for inclusion criteria.

6.11.7. Adverse Events/Concomitant Medications/Protocol Restrictions

Evaluation for AEs, review of concomitant medications, and review of protocol restrictions will occur at the times shown in Table 6-1. See Section 7 for more information regarding AEs and Sections 4.3 and 5.7.1 for more information about concomitant medications.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a study drug, 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 study drug, whether or not considered related to the study drug. Adverse events may also include pre- or posttreatment 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 AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.8.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and that is not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

A 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.)
- Inpatient 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.

7.1.2.1. Protocol-Specific Serious Adverse Event Instructions

Protocol-specific SAEs: In this study, is to be considered medically important and, therefore, "serious."

Protocol-specific SAE reporting exemptions:

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes**: There is reasonable possibility that the event may have been caused by the study drug.

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

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

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

AE severity should be recorded and graded according to the modified GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (see Appendix 4 for moreinformation). 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.

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.

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

7.3.1. 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 (CRF/eCRF): all SAEs and AE related to protocol-mandated procedures.

7.3.1.1. Adverse Events

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

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

7.3.1.2. 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 CRF/eCRF database and Gilead 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 but within 30 days of the last dose of study drug, regardless of causality, should also be reported.

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

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

7.3.1.3. 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 SAE reporting form and submit within 24 hours as described below.

Gilead DSPH:	Fax: E-mail:	PPD 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 CRF/eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to

worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

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

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

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

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, X-rays, 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 (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities as described in Appendix 4. The GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities has been modified to be more appropriate for healthy volunteers and patients with inflammatory diseases (eg, rheumatoid arthritis, asthma, psoriasis). 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.

7.6. Toxicity Management

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor (MM), who will have a discussion with the investigator and decide the appropriate course of action. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal Grade 3 or 4 clinically significant laboratory abnormalities should be managed as outlined in Appendix 2.

Any questions regarding toxicity management should be directed to the Gilead MM.

7.7. Study Specific Stopping Criteria

Study drug dosing of a cohort will be suspended and, based on full review of the clinical data by the MM and in discussion with the investigator, may be halted when:

- 2 healthy control subjects dosed with GS-9674 within a cohort experience elevations in liver function tests of ALT and/or AST > 5 x the upper limits of normal (ULN); or ALT > 3 x ULN and total bilirubin > 2 x ULN, confirmed by immediate repeat testing.

- 2 hepatic impairment subjects dosed with GS-9674 within a cohort experience elevation of baseline liver function tests of ALT and/or AST > 3 x baseline; or ALT > 2 x baseline and total bilirubin > 2 x baseline.

- 1 subject experiences a SAE possibly related to the study drug

- The sponsor unilaterally requests it.

Decisions to reinitiate the study will be made in consultation with the sponsor and pending a safety review.

7.8. Special Situations Reports

7.8.1. 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 an 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 that 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.

7.8.2. Instructions for Reporting Special Situations

7.8.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study drug and throughout the study, including the poststudy 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 Section 7.3. 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 by emailing PPD or faxing 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 pregnancy should continue until its conclusion. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH by faxing PPD or emailing PPD

Refer to Appendix 3, Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.8.2.2. Reporting Other Special Situations

All special situations reports (SSRs) will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.

Electronic Special Situations Report (eSSR) Reporting Process

- Site personnel record all SSR data in the eCRF database and from there transmit the SSR 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 SSR information electronically, i.e., the eCRF database is not functioning, record the SSR on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead DSPH:	E-mail: Fax:	PPD PPD

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

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

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 CRF/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 CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is as follows:

- To evaluate the single-dose PK of GS-9674 in subjects with normal hepatic function, or mild, moderate and severe hepatic impairment

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of GS-9674 single dose administration in subjects with normal hepatic function, or mild, moderate, and severe hepatic impairment

- To evaluate FXR activation by GS-9674 as measured by PD markers in subjects with normal hepatic function, or mild, moderate and severe hepatic impairment

8.1.2. Primary Endpoint

The primary endpoints are single dose plasma PK parameters of GS-9674 AUC_{last}, AUC_{inf}, and C_{max}. Additional PK parameters calculated include: $\%AUC_{exp}$, C_{last}, T_{max}, T_{last}, λ_z, CL/F, Vz/F, and $T_{1/2}$ as appropriate.

8.1.3. Secondary Endpoint

The secondary endpoints are the incidences of AEs and laboratory abnormalities, physical examinations, vital signs, ECGs, and PD markers including but not limited to FGF19 and C4.

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Safety

The Safety Analysis Set will include all enrolled subjects who received at least 1 dose of study drug. Subjects who received treatment other than that to which they were assigned will be analyzed according to the treatment received.

8.2.1.2. Pharmacokinetics

The PK Analysis Set for GS-9674 will include all enrolled subjects who received at least 1 dose of GS-9674 and had at least 1 non-missing PK concentration data reported by PK lab for each respective analyte.

8.2.1.3. Pharmacodynamics

Each PD analysis set will include all enrolled subjects who received at least 1 dose of study drug and have at least 1 non-missing PD value for each respective PD parameter.

8.3. Data Handling Conventions

For summary statistics, PK concentration values below the limit of quantitation (BLQ) will be treated as zero at predose and one-half of the lower limit of quantitation (LLOQ) for postdose time points.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus one significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned; if the result of a continuous laboratory test is < 20.0, a value of 19.9 will be assigned).

Missing data can have an impact upon the interpretation of the trial data. As this study is of short duration, it is anticipated that missing data will be minimal. In general, values for missing data will not be imputed. However, a missing pretreatment laboratory result would be treated as normal (ie., no toxicity grade) for the laboratory abnormality summary.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized and descriptive statistics will be provided.

8.5. Interim Analysis

There is no formal interim analysis in this study.

8.6. Safety Analysis

All safety data collected on or after the date that study drug was first administered up to the date of last dose of study drug plus 30 days will be summarized by hepatic function group (according to the study drug received) using safety analysis set.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug data will be generated from the study drug administration page in eCRF. Exposure data will be listed.

8.6.2. Adverse Events

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

Adverse event data will be listed by subject. Treatment-emergent AE (TEAE), Serious TEAE, and TEAE leading to discontinuation of treatment will be summarized by hepatic function group, system organ class, and preferred term using the current version the Medical Dictionary for Regulatory Activities (MedDRA).

8.6.3. Laboratory Evaluations

Listings of individual subject laboratory results will be provided. Laboratory results and change from predose values for selected lab tests will be summarized by hepatic function group at scheduled visits. The incidence of treatment-emergent graded laboratory abnormalities will be summarized by hepatic function group.

8.6.4. Other Safety Evaluations

Vital signs and ECG data will be listed by subject and visit, and summarized by hepatic function group and visit.

8.7. Pharmacokinetic Analysis

Plasma concentrations and PK parameters will be listed and summarized for GS-9674 using descriptive statistics by hepatic function group (normal and mildly impaired, moderately impaired, or severely impaired) within cohort.

In addition, an ANOVA model with hepatic function group as a fixed effect will be fitted to the natural logarithmic transformation of PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) for GS-9674 for each cohort. Two-sided 90% CIs will be calculated for the ratios of GLSM of PK parameters for GS-9674 between mild, moderate or severe hepatic impairment group and the control (normal hepatic function) group. If the upper bound of the two-sided 90% CIs of the GLSM ratio for AUC_{last}, AUC_{inf}, and C_{max} is smaller than 2.0, the null hypothesis that subjects with mild, moderate or severe hepatic impairment exhibit average PK parameter increases of at least 100% for GS-9674 compared with subjects with normal liver function will be rejected.

GS-9674 percent protein binding will be summarized by hepatic function group and data for individual subjects will be presented in a listing. Unbound PK parameters such as CL_u/F, and Vz_u/F will be calculated and summarized by hepatic function group. Relationships between measures of hepatic function (ie, CPT score, serum albumin, total bilirubin, prothrombin time and INR) and GS-9674 PK parameters will be evaluated.

8.8. Pharmacodynamics Analysis

Pharmacodynamics data will be listed and summarized using descriptive statistics by hepatic function within and across cohorts.

8.9. Pharmacokinetics and Pharmacodynamics Analysis

The PK/PD relationship may be explored using a graphic approach and correlation coefficients as appropriate.

8.10. Sample Size

For each cohort, with 16 (8 per group) evaluable subjects, the estimated upper limit of one-sided 95% CI of the GLSM ratio of (mild, moderate or severe) hepatic impaired group vs control (normal hepatic function), with regards to AUC_{last}, AUC_{inf}, and C_{max}, would be less than 200% with ≥ 88% probability, if the estimated GLSM ratio were 1.0. This is assuming a SD of no more than 0.463 on a natural logarithm scale, supported by previous Gilead study GS-US-402-1851. With 25% overage, a total sample size of 60 subjects (10 per group, 20 per cohort) will be required.

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 (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), 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, "Protection of Human Subjects", and 21 CFR, part 56, "Institutional Review Boards".

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, "Financial Disclosure by Clinical Investigators", providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the study 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/Independent Ethics Committee 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/EC. The investigator will not begin any study subject activities until approval from the IRB/IEC 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/EC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/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/EC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by local requirements. The consent form will inform subjects about genomic testing and sample retention, and their right to receive clinically relevant genomic analysis results.

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/EC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions or in accordance with local regulations. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled 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, CRF/eCRF, the study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. 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 2 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/EC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

- Subject identification (name, date of birth, gender)
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end dates (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end dates, and including causality and severity)
- Concomitant medication (including start and end dates, dose if relevant, and dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, 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 enrolled, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. The eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data, whenever possible. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received and the subject has been enrolled. Subsequent to data entry, a study monitor will perform source data verification within the electronic data capture (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 login credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF captures the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the study, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Study Drug Accountability and Return

Where possible, Gilead recommends that used and/or unused study drug supplies be destroyed at the site. If the site has an appropriate SOP for drug destruction as determined by Gilead Sciences, the site may destroy used (empty or partially empty) and/or unused study drug supplies in accordance with that site's approved SOP. A copy of the site's IMP Disposal SOP or written procedure (signed and dated by PI or designee) will be obtained for Gilead's site files. If the site does not have acceptable procedures in place for drug destruction, study drug supplies can be returned to the designated depot. The study monitor will provide instructions for the return.

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.

For both options, the study monitor must first perform drug accountability during an on-site monitoring visit. Additionally, 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 study to Gilead's appointed study monitors, to IRB/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 IRB/EC in accordance with local requirements and receive documented IRB/EC approval before modifications may be implemented.

9.2.2. Study Report and Publications

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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 authority(ies), IRBs, and ECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 1 Open-Label, Parallel-Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics and Pharmacodynamics of GS-9674 in Subjects with Normal and Impaired Hepatic Function

GS-US-402-3885, Amendment 2, 23 March 2018

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

PPD

Name (Printed)
Medical Monitor

PPD

Signature

30 March 2018

Date

INVESTIGATOR STATEMENT

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

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

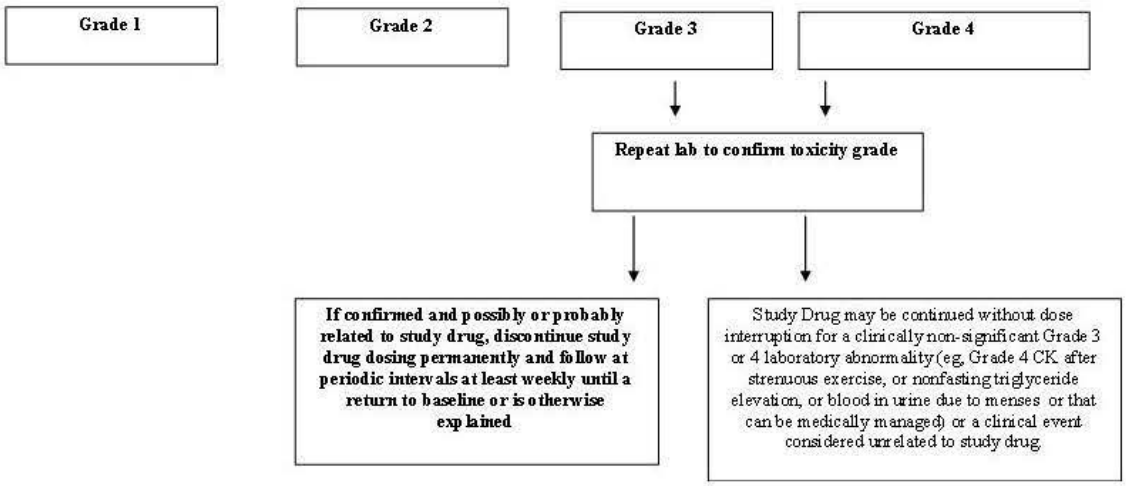
Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Management of Clinical and Laboratory Adverse Events



Appendix 3. 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. There are no preclinical data available to determine whether GS-9674 is teratogenic or fetotoxic in early human pregnancy. There are insufficient data to exclude the possibility of a clinically relevant interaction between GS-9674 and hormonal contraceptives that result in reduced contraception efficacy. Therefore, the use of hormonal contraception with GS-9674 is not recommended.

Therefore, in the GS-9674 clinical studies, women of childbearing potential must use a highly effective contraceptive measure or choose continuous heterosexual abstinence from intercourse from screening throughout the study period and for 30 days after last dose of GS-9674.

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 -2 visit prior to randomization. At minimum, a pregnancy test will be performed at the end of relevant system exposure. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is even true for women of childbearing potential with

infrequent or irregular periods. Female subjects must agree to one of the following from Screening until 30 days after last dose of 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)

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after last dose of 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 during treatment and for 90 days after last dose of GS-9674.

Male subjects must agree to avoid sperm donation from baseline throughout the study period and for 90 days after last dose of 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 and discontinue study drug immediately, 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 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 7.3.

Appendix 4. Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Antiviral Toxicity Grading Scale Version: 01 April 2015

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months#**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

An overlap between the Grade 1 scale and the Lab's normal range for absolute neutrophils may result for pediatric subjects. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Infant <1 Year	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to <3.0 mmolL	2.0 to < 2.5 mEq/L 2.0 t o <2.5 mmolL	< 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Infant <1 Year	>ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL < 1.64 mmol/L
Infant, < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia **Adult and Pediatric ≥ 1 year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine**	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate **Adult and Pediatric ≥ 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Pediatric < 4 Years	NA	11.0 mEq/Lto <LLN 11.0 mmol/L to <LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting) Adult	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
LDL (Fasting) Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL

** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for Male subjects >70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin **Pediatrics <16 years**	-	2.0 to < LLN g/dL 20 to < LLN g/L	< 2.0 g/dL < 20 g/L	NA
≥ 16 years	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below Females	>ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Males	6-10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection **Adult and Pediatric ≥ 10 Years**	200 to 999 mg/24 h	>999 to 1999 mg/24 h	>1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m^2/24 h	>499 to 799 mg/m^2/24 h	>799 to 1000 mg/m^2/24 h	> 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:

- Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.
- With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.
- If the severity of a clinical AE could fall under either one of two grades (eg, the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit) **Pediatric ≤ 17 Years** (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic NA	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic 91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	> 179 mmHg systolic OR > 109 mmHg diastolic ≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss **Pediatric < 21 Years**	BMD t-score or z-score –2.5 to –1.0 BMD z-score –2.5 to –1.0	BMD t-score or z-score < –2.5 BMD z-score < –2.5	Pathological fracture (including loss of vertebral height) Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years **Pediatric ≤ 15 Years**	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2) **Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter**	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2) **Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)**	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage **Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage**	Necrosis (involving dermis and deeper tissue) **Necrosis (involving dermis and deeper tissue)**
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.