CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1 Open-Label, Parallel-Group, Single-Dose Study to Evaluate the Pharmacokinetics of GS-0976 or Fenofibrate in Subjects with Normal and Impaired Hepatic Function	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND No.:	124915	
Clinical Trials.gov Identifier:	NCT02891408	
Indication:	Nonalcoholic Steatohepatitis (NASH)	
Protocol ID:	GS-US-426-3988	
Gilead Medical Monitor:	Name: Telephone: Fax: Cell:	PPD PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1: Amendment 2:	03 August 2016 01 September 2017 18 December 2018

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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, Single-Dose Study to Evaluate the Pharmacokinetics of GS-0976 or Fenofibrate in Subjects with Normal and Impaired Hepatic Function
IND Number: **Clinical Trials.gov Identifier:**	124915 NCT02891408
Study Centers Planned:	Multiple Sites in the United States, Europe, and New Zealand
Objectives:	The primary objectives of this study are as follows: • To evaluate the single-dose pharmacokinetics (PK) of GS-0976 in subjects with normal hepatic function, and mild, moderate, or severe hepatic impairment • To evaluate the single-dose PK of fenofibrate in subjects with normal hepatic function and mild hepatic impairment The secondary objectives of this study are as follows: • To evaluate the safety and tolerability of GS-0976 single dose administration in subjects with normal hepatic function, and mild, moderate, or severe hepatic impairment • To evaluate the safety and tolerability of single dose fenofibrate administration in subjects with normal hepatic function and mild hepatic impairment
Study Design:	Phase 1, open-label, single-dose, parallel-group, multi-center, pharmacokinetic (PK) study
Number of Subjects Planned:	Approximately 80 subjects (for 64 evaluable): **Cohort 1 (Mild Hepatic Impairment):** Approximately 20 subjects (10 per group [mildly impaired and matched controls] for 8 evaluable per group) **Cohort 2 (Moderate Hepatic Impairment):** Approximately 20 subjects (10 per group [moderately impaired and matched controls] for 8 evaluable per group) **Cohort 3 (Severe Hepatic Impairment):** Approximately 20 subjects (10 per group [severely impaired and matched controls] for 8 evaluable per group)

	Cohort 4 (Mild Hepatic Impairment): Approximately 20 subjects (10 per group [mildly impaired and matched controls] for 8 evaluable per group) A subject with normal hepatic function may serve as a matched control in Cohorts 1 and 2 but may only serve as a matched control to one hepatic impaired subject within a cohort.
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 and 4), 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 and 4 (Mild Hepatic Impairment):** Male and non-pregnant/non-lactating female subjects, ages 18-70 years inclusive with mildly impaired and normal hepatic function. Subjects will be current non-smokers (no use of tobacco, nicotine-containing or THC-containing products within the last 14 days). Each subject in the control group will be matched for age (± 10 years), gender, race, and body mass index (± 15% 18 < body mass index (BMI) $\leq$ 36 kg/m^2) 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, have diagnosis of chronic (> 6 months), and stable hepatic impairment with no clinically significant changes within 3 months (or 90 days) prior to study drug administration (Day 1). **Cohort 2 (Moderate Hepatic Impairment):** Male and non-pregnant/non-lactating female subjects, ages 18-70 years inclusive with moderately impaired and normal hepatic function. Subjects will be current non-smokers (no use of tobacco, nicotine-containing or THC-containing products within the last 14 days). 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) 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, have diagnosis of chronic (> 6 months), and stable hepatic impairment with no clinically significant changes within 3 months (or 90 days) prior to study drug administration (Day 1).

Cohort 3 (Severe Hepatic Impairment): Male and non-pregnant/non-lactating female subjects, ages 18-70 years inclusive with severely impaired and normal hepatic function. Subjects will be current non-smokers (no smoking of tobacco, nicotine-containing or THC-containing products within the last 14 days). 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) 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, have diagnosis of chronic (> 6 months), and stable hepatic impairment with no clinically significant changes within 3 months (or 90 days) prior to study drug administration (Day 1).

Study Procedures/ Frequency:

Following completion of Screening and Day -2 admission assessments, eligible subjects will be enrolled in one of four cohorts and will be administered the following study treatment on Day 1:

- Cohorts 1 and 2: A single oral dose of 20 mg GS-0976 (2 × 10 mg capsules)
- Cohort 3: A single oral dose of 5 mg GS-0976 (1 × 5 mg tablet)
- Cohort 4: A single oral dose of 48 mg fenofibrate (1 x 48 mg tablet)

In general, dosing in subjects with normal hepatic function will begin after a matched subject with hepatic impairment has completed all Day 1 PK assessments (eg, 96 hours postdose).

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

Study Visits and Confinement

Following Screening and admission assessments, eligible subjects will be confined to the study center beginning Day -2 until the completion of assessments on Day 5. Subjects will return for a follow-up (FU) visit on Day 13 (± 2 days).

Study Drug Administration

Study drug will be administered on Day 1 with 240 mL of water following an overnight fast (no food or drinks except for water) for at least 10 hours. Subjects will continue to fast until after collection of the 4-hour PK 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 drug. A standardized meal may be provided to subjects after the 4-hour post-dose PK draw.

Pharmacokinetic Assessments

Plasma PK Collection

Intensive PK sampling will occur relative to dosing of GS-0976 or fenofibrate on Day 1 at the following time points for each cohort:

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

Plasma concentrations of GS-0976 or fenofibrate (and their metabolites, as applicable) will be determined and PK evaluated. Pharmacokinetic parameters will be estimated, as appropriate.

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

Exploratory Biomarker Assessments: CCI [redacted]

CCI [redacted]

Protein Binding Samples

Plasma protein binding sampling will occur relative to dosing of GS-0976 or fenofibrate on Day 1 at the following time points for each cohort:

- Day 1: 1 and 3 hours post-dose

Plasma protein binding of GS-0976 or fenofibrate (and their metabolites as applicable) will be determined and summarized descriptively.

Safety Assessments

Complete physical exam: Screening and at the early termination (ET) visit (if applicable).

Symptom-driven physical exam: Day -2, Day -1 (prior to biomarker sample collection), Day 1 (predose and approximately 4 hours postdose), Day 5, and at the FU visit.

Vital signs (blood pressure, heart rate, respiration rate, and body temperature): Screening, Day -2, Day -1 (prior to biomarker sample collection), Day 1 (predose and approximately 4 hours postdose), Day 5, and at the FU visit or ET visit (if applicable).

Height, Weight, and BMI: Screening

Clinical laboratory tests (hematology, chemistry, and urinalysis): Screening, Day -2, Day 1, Day 5, and at the FU visit or ET visit (if applicable).

Note: On Day -2 (clinic admission), two sets of safety labs will be collected. 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.

Coagulation tests (PT, PTT, INR): Screening and at the FU visit or ET visit (if applicable).

α-fetoprotein: Screening

Urine drug and alcohol assessments: Screening, Day -2, and at the FU visit or ET visit (if applicable).

12-lead electrocardiogram (ECG): Screening, Day -2, Day 1 (predose and approximately 4 hours postdose), Day 5, and at the FU visit or ET visit (if applicable).

Serum pregnancy test (females of childbearing potential only): Screening and Day -2, Day 5, and at the FU visit or 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. All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in protocol Appendix 3. CCI [redacted]
Test Product, Dose, and Mode of Administration:	For Cohort 1 and 2, a single oral dose of 20 mg GS-0976 (2 × 10 mg capsule) administered on Day 1 For Cohort 3, a single oral dose of 5 mg GS-0976 (1 × 5 mg tablet), administered on Day 1 For Cohort 4, a single oral dose of 48 mg fenofibrate (1 x 48 mg tablet), administered on Day 1
Reference Therapy, Dose, and Mode of Administration:	Not applicable
Criteria for Evaluation:	
Safety:	Safety will be evaluated by physical examinations, vital signs, clinical laboratory tests and ECGs at various timepoints during the study, and by documentation of AEs.
Efficacy:	Not applicable.
Pharmacokinetics:	The following plasma PK parameters will be calculated for GS-0976 and fenofibrate (and their metabolites as applicable), as appropriate: % AUC_{exp}, AUC_{last}, AUC_{inf}, C_{max}, T_{max}, C_{last}, T_{last}, λ_z, CL/F, Vz/F and $t_{½}$. Percent plasma protein binding will be determined and PK parameters adjusted for protein binding will be estimated.

Statistical Methods:

Pharmacokinetics:

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 (eg, 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 each analyte. The 90% confidence intervals (CIs) will be constructed for the geometric least squares mean (GLSM) ratio of PK parameters for each analyte in the mild, moderate or severe hepatic impairment group versus the matched control (normal hepatic function) group.

Safety:

The AE data will be listed by subject. Treatment-emergent AEs, serious adverse events (SAEs), and AEs leading to permanent study drug discontinuation will be summarized by hepatic function group (according to study drug received), system organ class, and preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

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 (according to study drug received), at scheduled visits. The incidence of treatment-emergent laboratory abnormalities will be summarized by hepatic function group (according to study drug received).

Vital signs and ECG data will be summarized by hepatic function group.

Sample Size:

For cohorts 1 to 3, 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_{inf} and C_{max}, would be less than 200% with ≥ 72 and $\geq 57\%$ probability, respectively, if the estimated GLSM ratio were 1.0. This is assuming a SD of no more than 0.588 for AUC_{inf} and 0.722 for C_{max} on a natural logarithm scale, supported by previous Gilead study 0976-101. With 25% overage, a total sample size of 60 subjects (10 per group, 20 per cohort) will be required.

For cohort 4, with 16 (8 per group) evaluable subjects, the estimated two-sided 90% CI of the GLSM ratio of mild hepatic impaired group vs control (normal hepatic function), with regards to AUC_{last}, AUC_{inf} and C_{max} would be within [0.5, 2.0] with ≥ 90% probability, if the estimated GLSM ratio were 1.0. This is assuming a SD of no more than 0.387 on a natural logarithm scale, supported by information from Food and Drug Administration (FDA) {U. S. Food and Drug Administration 2004}. With 25% overage, a total sample size of 20 subjects (10 per group) 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

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration versus time curve of the drug
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
%CV	percentage coefficient of variation
°C	degrees Celsius
°F	degrees Fahrenheit
ACC	acetyl coenzyme A (acetyl-CoA) carboxylases
AE	adverse event
ALT	alanine aminotransferase (previously serum glutamic pyruvic transaminase
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
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, 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
CPT	Child-Pugh-Turcotte
CRF	case report form
CRO	contract (or clinical) research organization
CSR	clinical study report
C_{tau}	observed drug concentration at the end of the dosing interval
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DNL	de novo lipogenesis
EC	ethics committee
ECG	electrocardiogram

eCRF	electronic case report form
EDC	electronic data capture
EudraCT	European Clinical Trials Database
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
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
HI	hepatic impairment
HIV, HIV-1	human immunodeficiency virus, type 1
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IEC	independent ethics committee
IND	investigational new drug (application)
IRB	institutional review board
IUD	intrauterine device
LDL	low-density lipoprotein
LLOQ	lower limit of quantitation
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MPR	metabolite-to-parent
NAFLD	Nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NDA	new drug application
NOAEL	no-observed-adverse-effects levels
NOEL	no-observed-effect level
PD	pharmacodynamic(s)

PK	pharmacokinetic(s)
PTT	partial thromboplastin time
PVE	Pharmacovigilance and Epidemiology
QA	quality assurance
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
ROS	reactive oxygen species
SAD	single ascending dose
SADR	serious adverse drug reaction
SAE	serious adverse event
SD	standard deviation
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TIPS	transjugular intrahepatic portosystemic shunt
T_{last}	time (observed time point) of C_{last}
T_{max}	the time (observed time point) of C_{max}
$t_{1/2}$	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

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 {Ong 2007, Vernon 2011}. 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 {Ong 2007, Williams 2011}. In the United States (US), it has been estimated that 3% to 6% of the population {Vernon 2011, Wanless 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 {Dietrich 2014, Faramawi 2008, Voulgari 2010}. 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 2010, Kannel 1982, Koek 2011, Sumida 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. In addition, evidence suggests that lipotoxic intermediates of fatty acids likely contribute to the etiology of NASH {Neuschwander-Tetri 2010}.

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 2015, Yeh 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 {Afzali 2012, Wong 2014}.

1.2. GS-0976

GS-0976 is a small molecule allosteric inhibitor that acts at the protein-protein homodimer interface of acetyl coenzyme A (acetyl-CoA) carboxylases (ACC) ACC1 and ACC2, to prevent dimerization. ACC1 and ACC2 are important regulators of fatty acid metabolism. ACC1 catalyzes the first step of de novo lipogenesis (DNL) by converting acetyl-CoA to malonyl-CoA while ACC2 regulates the entry of fatty acids into the mitochondria where beta oxidation can occur. Therefore, inhibition of ACC1 and ACC2 will reduce DNL and increase fatty acid beta oxidation. GS-0976 is being developed for the treatment of NASH.

1.2.1. General Information

For further information on GS-0976, refer to the investigator's brochure (IB), including information on the following:

- Nonclinical pharmacokinetic (PK) and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

1.2.2. Nonclinical Pharmacology

GS-0976 has been characterized in several biochemical and cellular assays to enhance the understanding of the mechanism of action and has been well characterized in vivo in several mechanistic models to demonstrate target engagement and in animal disease models to demonstrate specific activity on endpoints relevant to metabolic disease. Moreover, extensive safety pharmacology and receptor screening studies have been conducted.

The results of these pharmacodynamic (PD) studies indicate that GS-0976 can favorably affect the DNL, hepatic steatosis, insulin resistance, and body weight/body fat elevations produced in nonclinical models of metabolic disease without affecting food consumption or markers of liver function. In total, these studies confirm the potential for GS-0976 to impact important metabolic endpoints associated with NASH.

1.2.3. Nonclinical Toxicology

The toxicity of GS-0976 was evaluated in rats and dogs in acute and repeated dose nonclinical studies up to 13 weeks in duration. Selection of the test species was based on the in vitro and in vivo assessment of metabolism. In in vitro experiments using human hepatocytes, no human-specific metabolites were identified and all metabolites detected were also present in rat and/or dog hepatocytes.

There were no adverse findings in safety pharmacology studies (central nervous system, respiratory and cardiovascular studies) at exposures ~ 50 fold above the predicted steady-state clinical exposure (C_{max} ~110 ng/mL) after administration of 20 mg GS-0976 once daily fasted. The genotoxicity potential of GS-0976 was considered low as the compound is negative in the in vitro Ames, chromosome aberration studies and the in vivo mouse micronucleus study.

Single doses of GS-0976 up to 1000 mg/kg were tolerated in rats and dogs. In the 28-day studies, the no-observed-adverse-effects levels (NOAELs) for the rat and dog were 60 and 100 mg/kg/day respectively, the highest doses tested in the studies, affording exposure margins of at least 23 (rat) and 63 (dog) times above the predicted steady-state clinical exposure after administration of 20 mg GS-0976 once daily fasted (240 ng•h/mL). In the 13-week rat study, no dose limiting toxicity was observed and the NOAEL was 60 mg/kg/day, the highest dose tested, providing an exposure margin of 23-fold above predicted steady-state clinical exposure. In the 13-week dog study, bilateral posterior cortical cataracts and histological evidence of cataracts were observed at 90 mg/kg/day, with progression in severity after a 28-day recovery period. There was no evidence of cataracts at doses ≤ 30 mg/kg/day. In the 13-week dog study, the presence of cataracts was found at exposures approximately 82 times above the predicted steady-state clinical exposure. No evidence of cataracts was observed at doses ≤ 30 mg/kg/day. The NOAEL for the 13-week dog study was 30 mg/kg/day, providing an exposure margin of approximately 15 fold above the predicted steady-state clinical exposure at 20 mg.

In the rat embryo-fetal development dose-range finding study, maternal toxicity and fetal abnormalities (external and soft tissue malformations, and developmental variations) were observed at doses ≥ 50 mg/kg/day in a dose-dependent manner. The no-observed-effect level (NOEL) for the embryo-fetal rat study was 25 mg/kg/day at an approximate exposure margin of 5.8 times above the predicted steady-state clinical exposure. In the rabbit study, 100 mg/kg/day was not tolerated and maternal toxicity (decreased body weight gain and food consumption) was observed at doses ≥ 25 mg/kg/day. While decreases in fetal weights were observed at doses ≥10 mg/kg/day, no external malformations and developmental variations were observed at all doses. The NOEL for the embryo-fetal rabbit study was less than 10 mg/kg/day. At this dose, the predicted steady-state clinical exposure margin is approximately 53. The observed embryo-fetal effects were not unexpected as the deletion of ACC1 in mice is embryonically lethal.

1.2.4. Nonclinical Pharmacokinetics

GS-0976 is highly protein bound in plasma, and the volume of distribution of GS-0976 across nonclinical species is greater than total body water (0.7 L/kg), suggesting that GS-0976 is well distributed. A significant fraction of the absorbed parent compound is extracted by the liver indicating that GS-0976 is available to the target site (ie, the liver).

The metabolism of GS-0976 has been evaluated in in vitro incubations of rat, dog, Cynomolgus monkey, and human hepatocytes. No metabolites unique to the human were detected. In vivo metabolite identification studies in Sprague-Dawley rat and Beagle dog have demonstrated that the primary metabolite of GS-0976 is the glucuronide conjugate.

Neither GS-0976 nor the metabolite, NDI-011535, inhibits the cytochrome P450 (CYP) enzymes involved in drug metabolism. GS-0976 is not an inducer of CYP1A2 or CYP2B6 isozymes and is a mild inducer of CYP 3A4 in human hepatocytes in vitro.

A single nonclinical study to evaluate elimination of GS-0976 and the metabolite NDI-011535 was performed in bile duct cannulated Sprague-Dawley rats to profile concentrations over time in plasma, urine, and bile. Overall, the PK profile in plasma and bile indicates that GS-0976 is rapidly cleared from the plasma compartment, and the primary route of elimination is via the bile.

1.2.5. Clinical Trials of GS-0976

1.2.5.1. Study 0976-101: Single Ascending Dose Study

The first-in-human single ascending dose (SAD) study (Protocol Number 0976-101) was a randomized, placebo-controlled, double-blind study performed in normal, healthy adult subjects at one study center in the United States with a starting dose of 30 mg. The dosing in this study is completed with PK and tolerability data obtained following dosing of 30, 80, 200, 500, 800, and 1000 mg in the fasted state and 200 mg following a high fat meal (fed state) to cohorts of 8 subjects (6 active and 2 placebo control per group). Final data from the SAD study indicated that single doses of GS-0976 were tolerated across the dose range of 30 to 1000 mg. There were no deaths, serious adverse events (SAEs), or subject discontinuations due to adverse events (AEs) in this study. There were no clinically important treatment related or dose related trends in the incidence or severity of treatment emergent adverse events (TEAEs), clinical laboratory, vital sign, ECG, or physical examination assessments in this study. Abdominal discomfort, vessel puncture site pain, dizziness, and presyncope, reported by 2 subjects each (6% overall for fasted GS-0976), were the most frequently reported events in this study. Of the 27 TEAEs reported in the study, all were of Grade 1 severity. The principal investigator considered 2 TEAEs to be probably related (1 episode each of nausea and dyspepsia in placebo fasted subjects), 4 possibly related (1 episode of cough in the 30 mg GS-0976 fasted group and 1 episode each of discolored feces, abdominal discomfort, and diarrhea in the 500 mg GS-0976 fasted group), and 21 unrelated to study treatment.

Pharmacokinetic parameters of GS-0976 are presented in Table 1-1. Plasma GS-0976 maximum plasma concentration (C_{max}) and overall exposure (AUC_{inf}) generally increased in a dose proportional manner across the range of 30 to 500 mg, under fasted conditions, with greater than dose-proportional increases above 500 mg. Similar results were observed for plasma NDI-011535 (glucuronide metabolite of GS-0976). The apparent total body clearance (CL/F) and apparent volume of distribution (V_z/F) of GS-0976 decreased with increasing GS-0976 doses of 800 mg and 1000 mg. Urinary excretion of unchanged GS-0976 was negligible. GS-0976 C_{max} was approximately 68% lower under fed compared to fasted conditions; however, overall plasma GS-0976 exposure (based on AUC_{0-t} and AUC_{0-inf}) was only approximately 9% to 14% lower under fed compared to fasted conditions, which may not be a clinically significant difference. The median T_{max} and mean $t_{1/2}$ values were similar under fed and fasted conditions, although there was a delay in the first quantifiable concentration and a prolonged absorption/distribution phase observed under fed compared to fasted conditions. Similar results were observed for plasma NDI-011535. Mean plasma NDI-011535 exposure was < 10% of GS-0976 plasma exposure, based on metabolite-to-parent (MPR) C_{max} and MPR AUC_{inf}.

Table 1-1. Summary of Single Dose Pharmacokinetic Parameters of GS-0976 Following Administration of 30 mg to 1000 mg GS-0976 Under Fasting Conditions and 200 mg GS-0976 Under Fed Conditions

PK Parameter Mean ± SD	GS-0976 Dose (mg)						
	30 mg Fasted (N=6)[a]	80 mg Fasted (N=6)[a]	200 mg Fasted (N=6)[a]	200 mg Fed (N=6)[a]	500 mg Fasted (N=6)[b]	800 mg Fasted (N=6)[b]	1000 mg Fasted (N=6)
Plasma							
AUC_{0-t} (ng*h/mL)	176 ± 104	363 ± 215	1210 ± 537	1160 ± 613	2930 ± 2440	6420 ± 3180	17,400 ± 8400
AUC_{0-inf} (ng*h/mL)	179 ± 115	402 ± 225	1250 ± 616	1260 ± 683	2960 ± 2460	6460 ± 3190	17,500 ± 8410
C_{max} (ng/mL)	79.7 ± 65.9	101 ± 47.8	416 ± 211	134 ± 70.1	1110 ± 1150	2570 ± 1880	8380 ± 3210
T_{max} (h)[c]	1.26 (0.23, 2.00)	2.00 (1.50, 2.00)	1.50 (1.01, 4.00)	2.00 (1.50, 24.0)	1.75 (1.01, 3.00)	2.01 (1.01, 3.00)	2.50 (1.02, 4.01)
$t_{1/2}$ (h)	4.47 ± 1.56	6.98 ± 2.81	11.7 ± 1.35	8.70 ± 2.10	10.2 ± 2.13	8.24 ± 3.26	9.46 ± 2.60
CL/F (L/h)	250 ± 178	251 ± 124	189 ± 76.5	212 ± 131	290 ± 188	146 ± 57.4	65.2 ± 21.3
V_z/F (L)	1730 ± 1510	2360 ± 1390	3150 ± 1270	2500 ± 1290	4190 ± 2570	1620 ± 561	904 ± 469
Urine							
A_{e0-48} (µg)	9.72 ± 8.73	25.8 ± 11.7	48.8 ± 21.3	N/C	135 ± 106	1030 ± 924	636 ± 600
F_e (%)	0.032 ± 0.029	0.032 ± 0.015	0.024 ± 0.011	N/C	0.027 ± 0.021	0.129 ± 0.115	0.064 ± 0.060
CL_{Renal} (mL/h)	50.0 ± 45.1	109 ± 96.2	46.2 ± 15.5	N/C	77.5 ± 65.7	135 ± 62.2	42.6 ± 36.5

PK parameters are presented to 3 significant digits, N/C = Not Calculated
a N=5 for AUC_{0-inf}, $t_{1/2}$, CL/F, and V_z/F
b N=5 for A_{e0-48}, F_e, and CL_{renal}
c T_{max} is presented as median (minimum, maximum)
The A_{e0-48}, F_e, and Cl_{renal} for PPD (500 mg GS-0976) were missing, because this subject was unable to provide urine samples during the 12-24 hour, 24-36 hour, and 36-48 hour intervals, due to an AE.
The A_{e0-48}, F_e, CL_{renal} for PPD (800 mg GS-0976) were excluded from the summary statistics, because the urine sample for the 24-36 hour collection interval was partially spilled prior to volume measurement (ie, calculations were based off an approximate urine volume)

1.2.5.2. Study 0976-102: Multiple Ascending Dose (MAD) Study

The multiple ascending dose (MAD) study (Protocol Number 0976-102) was a randomized, double-blind, placebo-controlled, clinical study conducted in healthy adult subjects at one study center in the United States. Five (5) cohorts of 8 subjects (6 active and 2 placebo) were evaluated at the following GS-0976 doses: 50 mg twice a day (BID) (100 mg daily) or placebo, 100 mg once daily (100 mg daily) or placebo, 100 mg BID (200 mg daily) or placebo, 200 mg once daily (200 mg daily) or placebo, or 150 mg once daily (150 mg daily) or placebo. In each cohort, subjects received multiple oral doses of GS-0976 or placebo BID (every 12 hours) or once daily for 9 consecutive days (Days 1 through 9), with a single oral dose of GS-0976 or placebo on the morning of Day 10. Doses were administered approximately 30 minutes after meals. Preliminary safety and PK data are available for the first 4 dose groups.

Each of the first 4 dose groups was fully enrolled and, overall, 24 subjects received GS-0976 and 8 subjects received placebo. The majority of these 32 subjects who received GS-0976 (19/24, 79%) and placebo (4/8, 50%) had at least 1 treatment-related AE as assessed by the principal investigator. The incidence of treatment-related AEs appeared to increase with higher doses and BID dosing of GS-0976: 50% of subjects at 50 mg BID, 62.5% at 100 mg once daily, 75% at 200 mg once daily, and 100% at 100 mg BID. One subject in the 200 mg once daily cohort discontinued due to an AE on study Day 7 for Grade 4 elevated triglycerides. No deaths or SAEs were reported.

The most frequently reported TEAEs were gastrointestinal disorders and involved nausea (33% of all subjects who received GS-0976 vs. 0% of all subjects who received placebo), abdominal distension (25% GS-0976 vs. 13% placebo), constipation (21% GS-0976 vs. 13% placebo), diarrhea (21% GS-0976 vs. 0% placebo), and vomiting (13% GS-0976 vs. 0% placebo). In addition, TEAEs of increased blood triglycerides were reported (25% GS-0976 vs. 0% placebo) and involved Grade 3 events in 5 subjects (3 subjects in the 100 mg BID cohort and 2 subjects in the 50 mg BID cohort), and a Grade 4 event in 1 subject in the 200 mg once daily cohort (discontinued treatment).

There were no clinically important treatment-related or dose-related trends in vital signs, ECG, or physical examination assessments in this study.

Preliminary single (Day 1) and (Day 10) multiple dose PK parameters for GS-0976 and ND-011535 after administration of 50 mg BID, 100 mg once daily, 100 mg once daily, and 200 mg once daily GS-0976 under fed conditions are presented Table 1-2 and Table 1-3, respectively. In general, GS-0976 AUC and C_{max} increased in a dose proportional manner across the doses evaluated. GS-0976 AUC accumulated approximately 2-fold on Day 10 compared to Day 1 with minimal accumulation of C_{max}. Median GS-0976 T_{max} occurred between 3 and 6 hours, in agreement with the food effect observed in study 0976-101. The mean $t_{1/2}$ of GS-0976 ranged from 3.5-10.3 hours with higher variability contributing to the higher mean estimates from Day 10 in the 50 mg BID and 100 mg once daily cohorts. Mean plasma NDI-011535 exposure was < 10% of GS-0976 plasma exposure, based on MPR for AUC and C_{max}. The PK profile of NDI-011535 was consistent with the PK profile of GS-0976, as seen by the consistent MPR for AUC_{inf} and C_{max} on Day 1 and Day 10 as well as across the doses evaluated. NDI-011535 exhibits formation rate limited kinetics as the mean $t_{1/2}$ of NDI-011535 was consistent with that observed for GS-0976.

Table 1-2. Summary of Single and Multiple Dose Pharmacokinetic Parameters of GS-0976 Following Administration of 50 mg BID, 100 mg once daily, 100 mg BID, or 200 mg once daily GS-0976 Under Fed Conditions

Plasma PK Parameter Mean ± SD	GS-0976 Dose			
	50 mg BID Fed (N=6)	100 mg once daily Fed (N=6)	100 mg BID Fed (N=6)	200 mg once daily Fed (N=6)
Day 1				
$AUC_{0\text{-}12or24}$ (ng*h/mL)	143 ± 29.1	268 ± 95.7	345 ± 77.0	868 ± 221
$AUC_{0\text{-}inf}$ (ng*h/mL)	178 ± 40.7[a]	278 ± 110[a]	671[b]	979 ± 286[a]
C_{max} (ng/mL)	41.3 ± 14.3	64.9 ± 31.7	61.6 ± 14.7	152 ± 68.4
T_{max} (h)[c]	2.50 (1.50, 3.02)	3.50 (1.00, 6.00)	5.02 (3.00, 8.00)	5.00 (2.00, 6.00)
$t_{1/2}$ (h)	3.50 ± 1.63[a]	4.33 ± 0.741[a]	5.58[b]	5.86 ± 3.59[a]
CL/F (L/h)	292 ± 61.6[a]	403 ± 139[a]	149[b]	219 ± 64.0[a]
V_z/F (L)	1350 ± 333[a]	2560 ± 1180[a]	1120[b]	1710 ± 720[a]
Day 10				
$AUC_{0\text{-}tau}$ (ng*h/mL)	305 ± 77.0	369 ± 160	742 ± 217	1770 ± 573[a]
RAUC	2.13 ± 0.279	1.37 ± 0.323	2.23 ± 0.766	2.10 ± 0.636[a]
C_{max} (ng/mL)	49.4 ± 15.2	53.5 ± 22.4	121 ± 56.3	198 ± 86.6[a]
C_{ave} (ng/mL)	25.4 ± 6.42	15.4 ± 6.68	61.8 ± 18.1	73.7 ± 23.9[a]
C_{trough} (ng/mL)	12.4 ± 5.04	3.16 ± 2.24	56.1 ± 22.7	33.9 ± 42.9[a]
T_{max} (h)[c]	4.01 (2.05, 8.00)	3.01 (2.00, 12.0)	6.00 (2.00, 6.00)	4.00 (1.50, 6.00)[a]
$t_{1/2}$ (h)	10.3 ± 6.66	7.92 ± 4.52	6.83 ± 1.62	5.91 ± 0.987[a]
CL_{ss}/F (L/h)	173 ± 41.5	312 ± 116	145 ± 43.5	125 ± 46.4[a]

PK parameters are presented to 3 significant digits
RAUC = Ratio of Day 10 $AUC_{0\text{-}tau}$ / Day 1 $AUC_{0\text{-}t}$
a N=5
b N=1
c T_{max} is presented as median (minimum, maximum)

Table 1-3. Summary of Single and Multiple Dose Pharmacokinetic Parameters of ND-011535 Following Administration of 50 mg BID, 100 mg once daily, 100 mg BID, or 200 mg once daily GS-0976 Under Fed Conditions

	GS-0976 Dose			
Plasma PK Parameter Mean ± SD	**50 mg BID Fed (N=6)**	**100 mg once daily Fed (N=6)**	**100 mg BID Fed (N=6)**	**200 mg once daily Fed (N=6)**
Day 1				
$AUC_{0\text{-}12or24}$ (ng*h/mL)	11.6 ± 3.57[a]	23.7 ± 0.891[b]	29.9 ± 15.1[a]	78.8 ± 43.3[c]
MPR AUC	0.064 ± 0.022[c]	0.042[d]	0.063 ± 0.027[a]	0.0636 ± 0.027[c]
C_{max} (ng/mL)	3.14 ± 1.39	3.98 ± 2.29	4.36 ± 2.63	9.54 ± 6.66
MPR C_{max}	0.057 ± 0.013	0.051 ± 0.023	0.054 ± 0.028	0.048 ± 0.020
T_{max} (h)[e]	2.50 (1.50, 302)	3.50 (1.50, 6.00)	6.00 (4.00, 11.9)	6.00 (4.00, 6.00)
$t_{1/2}$ (h)	5.13 ± 2.93[a]	3.59 ± 0.895[b]	N/C	7.55 ± 2.06[c]
Day 10				
$AUC_{0\text{-}tau}$ (ng*h/mL)	28.5 ± 8.89	46.0 ± 22.6[f]	67.0 ± 31.6	129 ± 74.3[a]
RAUC	2.49 ± 0.32[a]	2.50 ± 0.150[b]	1.93 ± 0.752[a]	2.41 ± 1.03[f]
MPR AUC	0.072 ± 0.013	0.073 ± 0.015 N=3	0.050 ± 0.020	0.052 ± 0.016[a]
C_{max} (ng/mL)	4.92 ± 1.90	4.52 ± 3.82	6.62 ± 2.84	12.2 ± 5.33[a]
C_{ave} (ng/mL)	2.37 ± 0.741	1.92 ± 0.943[f]	3.95 ± 1.64	5.38 ± 3.09[a]
MPR C_{max}	0.075 ± 0.014	0.057 ± 0.028	0.046 ± 0.019	0.051 ± 0.02[a]
C_{trough} (ng/mL)	1.20 ± 0.383	0.575 ± 0.078[b]	3.76 ± 1.45	3.21 ± 3.18[c]
T_{max} (h)[e]	3.50 (2.05, 6.00)	4.51 (2.00, 6.02)	6.00 (1.50, 6.04)	6.00 (3.00, 6.00)[a]
$t_{1/2}$ (h)	4.61 ± 1.30[a]	6.00 ± 0.225[b]	5.67 ± 0.40[b]	5.14 ± 2.14[f]

PK parameters are presented to 3 significant digits
RAUC = Ratio of Day 10 $AUC_{0\text{-}tau}$ / Day 1 $AUC_{0\text{-}t}$
MPR = Metabolite to Parent Ratio corrected for molecular weight
N/C = Not Calculated
a N=5
b N=2
c N=4
d N=1
e T_{max} and $t_{1/2}$ are presented as median (minimum, maximum)
f N=3

1.2.5.3. Study 0976-103: Single Ascending Dose Pharmacodynamic Study

The single ascending dose PD study (Study 0976-103) was a two-period, two-treatment, crossover, randomized, double-blind, study to determine the PD activity on fractional DNL of a single oral dose of 20, 50, or 200 mg of GS-0976 compared to placebo in 3 cohorts of 10 adult male subjects who were overweight and/or obese, but otherwise healthy, at each dose level (total 30 subjects). Subjects were randomized in Period 1 to receive a single oral dose of either GS-0976 or matched placebo followed by a washout and administration of the opposite study medication in Period 2.

The objectives of the study were to assess the following after a single oral dose of GS-0976 in overweight and/or obese, but otherwise healthy, adult male subjects: PD effects of GS-0976 on fractional DNL, safety and tolerability of GS-0976, correlation of PK and PD effects, and PK parameters.

Fractional DNL was evaluated by utilizing a qualified method that measured the appearance of de novo synthesis of palmitate in very-low density lipoproteins in response to oral fructose using [^{13}C] acetate incorporation into palmitate and mass isotopomer distribution analysis. Review of the data demonstrated mean inhibition of fractional DNL (71%, 87%, and 98% by AUC) by GS-0976 at 20, 50, and 200 mg, respectively, compared to matched placebo.

A total of 41 TEAEs were experienced by 15 (52%) subjects following administration of GS-0976 (28 considered possibly related); 22 TEAEs were experienced by 12 (40%) pooled placebo subjects (17 considered possibly related), and 4 TEAEs were experienced by 4 (13%) subjects following the [^{13}C] acetate infusion. Gastrointestinal events including diarrhea (11/29, 38% GS-0976 vs. 9/30, 30% placebo) and flatulence (5/29, 17% GS-0976 vs. 3/30, 10% placebo) were the most common TEAEs following both active and placebo treatments. The incidence of treatment emergent AEs did not increase with rising GS-0976 dose levels. Most TEAEs in the study were of Grade 1 severity (39/41, 95 %) and were resolved by study completion. Three subjects experienced 4 TEAEs of Grade 2 severity including headache and nausea (placebo), arthralgia (GS-0976 20 mg), and dyspepsia (GS-0976 20 mg). No deaths or SAEs were reported.

Overall, no clinically important trends in changes over time were noted in the laboratory results for GS-0976 active groups compared to placebo.

1.2.5.4. Study GS-US-426-4074: Drug-Drug Interaction Study

Study GS-US-426-4074 is an ongoing, open-label, multiple-cohort study designed to evaluate transporter and CYP-mediated drug-drug interactions (DDIs) between GS-0976 (20 or 50 mg) and various probe drugs in healthy subjects.

Preliminary PK results from the following cohorts are presented below and in Table 1-4. The differences in PK parameters between subjects with hepatic impairment (test) versus healthy subjects (reference) were assessed using percent geometric mean ratios (%GMRs) and 90% confidence intervals (CIs).

Cohort 1: Impact of OATP/MPR2/P-gp inhibition (single dose cyclosporine 600 mg: CsA) or OATP1B1/1B3 inhibition (single dose rifampin 600 mg: RIF) on single dose of GS-0976 20 mg (N=28). Single doses of CsA and RIF significantly increased GS-0976 exposure (21.2- and 18.4-fold, respectively) and resulted in even greater increases in GS-834773 exposures (64.5- and 55.4-fold, respectively). These data indicate GS-0976 is a sensitive substrate of hepatic OATP with intestinal P-gp playing a minimal role in GS-0976 absorption as seen by a smaller increase in GS-0976 C_{max} by CsA compared to single dose RIF.

Cohort 2: Impact of pan-UGT inhibition (probenecid 500 mg: PBC) and CYP3A4 inhibition (voriconazole 200 mg: VORI) on single dose administration of GS-0976 20 mg (N=14). Coadministration of GS-0976 with PBC resulted in a moderate increase in GS-0976 exposure

(61%) indicating UGTs are involved in the metabolism of GS-0976. The moderate increase in GS-834773 exposure (74%) with PBC may be due to inhibition of other enzymes/transporters involved in the clearance of GS-834773. Coadministration of GS-0976 with VORI increased GS-0976 and GS-834773 exposures (37% and 44%, respectively) indication CYP3A4 plays a small role in the elimination of both parent and metabolite.

Cohort 5: Impact of single and multiple doses of GS-0976 50 mg once daily on a sensitive CYP3A4 probe substrate (midazolam 2 mg: MDZ; N=12). Neither single dose nor multiple doses of GS-0976 altered MDZ exposure (90% CIs of the %GMR for AUC and C_{max} with lack of effect bounds of 70-143%) indicating GS-0976 is not an inhibitor or inducer of CYP3A4.

Table 1-4. Preliminary Pharmacokinetic Results from Study GS-US-426-4074 Evaluating DDIs with GS-0976 (20 mg or 50 mg)

Inhibitor/Inducer Drug	GS-0976 %GMR (90% CIs)		GS-834773 %GMR (90% CIs)	
	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
CsA	2120 (1810, 2480)	2000 (1590, 2520)	6450 (5260, 7900)	7870 (6130, 10100)
RIF	1840 (1570, 2150)	2710 (2160, 3400)	5540 (4520, 6790)	10100 (7890, 13000)
PBC	161 (144, 180)	160 (132, 195)	174 (148, 204)	176 (145, 214)
VORI	137 (123, 152)	145 (119, 176)	144 (123, 170)	140 (116, 171)
	MDZ + SD GS-0976 %GMR (90% CIs)		MDZ + MD GS-0976 %GMR (90% CIs)	
	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
GS-0976 (50 mg)	111 (99.8, 123)	102 (91.6, 115)	102 (91.4, 113)	106 (94.9, 119)

SD = single dose
MD = multiple dose
Data reported to 3 significant figures

1.3. Information about Fenofibrate

Fenofibrate is a pro-drug of the active chemical moiety fenofibric acid which is a PPARα activator. Fenofibrate is indicated as an adjunct to diet to reduce elevated LDL-C, Total-C, triglyceride and ApoB, and to increase HDL-C in adult patients with primary hypercholesterolemia and for treatment of adult patients with severe hypertriglyceridemia. Fenofibrate is available as 48 or 145 mg tablets for once daily oral administration without regard to meals. The use of fenofibrate has not been evaluated in formal hepatic impairment studies; as such fenofibrate usage is contraindicated in subjects with active liver disease. However, use of fibrates (including fenofibrate) has been described in subjects with liver disease, including those with cirrhosis, due to primary biliary cholangitis. In these studies, the safety of fibrate therapy has been consistent with data in subjects without pre-existing liver disease {Corpechot 2018}. Myopathy and rhabdomyolysis have been reported in patients taking fenofibrate (>2% and at least 1% greater than placebo. The risk for myopathy and rhabdomyolysis are increased when fibrates are co-administered with a statin, particularly in elderly patients and patients with

diabetes, renal failure, or hypothyroidism. Fenofibrate can increase serum transaminases and reversibly increase serum creatinine (>2% and at least 1% greater than placebo). Liver tests including ALT should be monitored periodically during therapy. Renal function should be monitored periodically in patients with renal impairment. Fenofibrate increases cholesterol excretion into the bile, which may lead to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Concomitant oral coumarin anticoagulants should be used with caution with fenofibrate. Dose of coumarin anticoagulants should be adjusted to maintain prothrombin time/INR at the desired level to prevent bleeding complications.

Further information regarding fenofibrate is available in the prescribing information.

1.4. 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 a single dose of GS-0976 to subjects with mild (Class A), moderate (Class B) or severe (Class C) hepatic impairment (HI) as determined by Child-Pugh-Turcotte (CPT) classification {Pugh 1973}, compared to matched subjects with normal hepatic function with the goal to provide dosing recommendations for subjects with HI. Administration of GS-0976 as a single-dose is expected to accurately reflect alterations in PK under steady-state conditions and is thus deemed satisfactory for evaluation in this study.

The effect of hepatic impairment on the PK of fenofibrate has not been previously evaluated. Thus, this study's aim is to characterize the effect of mild hepatic impairment on fenofibrate PK by administration of fenofibrate as a single-dose to mild hepatic impaired subjects and matched control subjects with normal hepatic function. Administration of fenofibrate as a single-dose is expected to accurately reflect alterations in PK under-steady-state conditions and is thus deemed satisfactory for evaluation in this study.

This study design is consistent with recommendations as outlined in the FDA (Food and Drug Administration) 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 HI due to some other cause).

Evaluation of PK and safety of GS-0976 in mild and moderate HI will commence in parallel, followed by evaluation of PK and safety of GS-0976 in subjects with severe HI.

The design of this study is supported by cumulative safety data in healthy subjects (Section 1.2.5) including administration of single doses of GS-0976 up to 1000 mg administered under fasted conditions (Study 0976-101). As described in Section 1.2.5, single doses of GS-0976 up to 1000 mg or multiple daily doses (10 days) up to 200 mg were well tolerated by healthy subjects in these studies.

Additionally, the trial will enroll healthy controls, matched for body mass index, age, race, and gender.

1.5. Rationale for the Dose Selection of GS-0976

The proposed dose of GS-0976 (20 mg) in this study was selected for evaluation in an ongoing Phase 2 study in patients with NASH for 24 weeks (GS-US-426-3989), supported by the safety, tolerability and effects of GS-0976 from studies 0976-101, 0976-102, and 0976-103, and is 50-fold lower than the highest single dose level previously evaluated (1000 mg) in study 0976-101. Short-term safety data from clinical studies to date indicate that doses of GS-0976 up to 1000 mg (50-fold higher than the dose proposed in this study) were well tolerated with no clinically significant or treatment limiting adverse events or laboratory abnormalities.

Based on preliminary data from studies 0976-101 (Section 1.2.5.1) and 0976-102 (Section 1.2.5.2), GS-0976 exposures after administration of 20 mg GS-0976 are expected to remain > 15 to 23-fold lower than the GS-0976 exposures observed at the NOAELs in the 13-week rat and dog studies, respectively.

Thus, it is unlikely that plasma exposures of GS-0976 in subjects with mild or moderate hepatic impairment would exceed previously observed exposures in healthy volunteers or exceed exposures observed at the NOAEL in the toxicity studies. Based on preliminary PK data, GS-0976 plasma exposure was increased ~1.8- and ~8.7-fold in mild and moderate hepatic impairment, respectively. While GS-0976 20 mg was generally well-tolerated in the first 2 cohorts, a dose of 5-mg GS-0976 was selected for the severe hepatic impairment cohort to maintain adequate exposure margins. GS-0976 plasma exposures following a 5-mg dose of GS-0976 in subjects with severe hepatic impairment are unlikely to exceed previously observed exposures in healthy volunteers or those observed at the NOAEL in the toxicity studies and the exposure differences observed at 5-mg GS-0976 can be extrapolated to other dose levels of GS-0976.

Based on the known PK of GS-0976 across the range of doses evaluated, alterations of GS-0976 PK observed in this study as a result of hepatic impairment are expected to reflect the magnitude of alteration of steady-state GS-0976 pharmacokinetics in subjects with NASH and HI.

1.6. Rationale for Dose Selection of Fenofibrate

The dose of fenofibrate (48 mg) proposed for use in this study is the lowest dosage available, and is currently under evaluation in an ongoing Ph 2 study (GS-US-384-3914) in subjects with NASH. Only modest changes in exposure of fenofibrate or its metabolites are expected in subjects with mild hepatic impairment based on the known clearance mechanisms of fenofibrate and the effect of mild hepatic impairment on these mechanisms. In Gilead's previous studies with simtuzumab in subjects with advanced fibrosis due to NASH (GS-US-321-0105, GS-US-321-0106), 32 out of 477 subjects (6.7%) were treated with fibrates during the trials. No clear safety signals were attributed to fibrate therapy in these subjects.

1.7. 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. For this study, frequent assessments of hepatic function will also be performed from the collection of both blood and urine samples. 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-0976 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-0976 and fenofibrate, how much GS-0976 and fenofibrate 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.

1.8. 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 PK of GS-0976 in subjects with normal hepatic function, and mild, moderate, or severe hepatic impairment
- To evaluate the single-dose PK of fenofibrate in subjects with normal hepatic function and mild hepatic impairment

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of GS-0976 single dose administration in subjects with normal hepatic function, and mild, moderate, or severe hepatic impairment
- To evaluate the safety and tolerability of single dose fenofibrate administration in subjects with normal hepatic function and mild hepatic impairment

3. STUDY DESIGN

3.1. Study Design

This protocol describes a Phase 1, open-label, single-dose, parallel-group, PK study to evaluate the single-dose PK of GS-0976 or fenofibrate in subjects with normal and impaired hepatic function and to evaluate the safety and tolerability of GS-0976 or fenofibrate single-dose administration in subjects with normal and impaired hepatic function. Approximately 80 subjects will be enrolled (for 64 evaluable).

Cohort 1 (Mild Hepatic Impairment): Approximately 20 subjects (10 per group [mildly impaired and matched controls] for 8 evaluable per group)

Cohort 2 (Moderate Hepatic Impairment): Approximately 20 subjects (10 per group [moderately impaired and matched controls] for 8 evaluable per group)

Cohort 3 (Severe Hepatic Impairment): Approximately 20 subjects (10 per group [severely impaired and matched controls] for 8 evaluable per group)

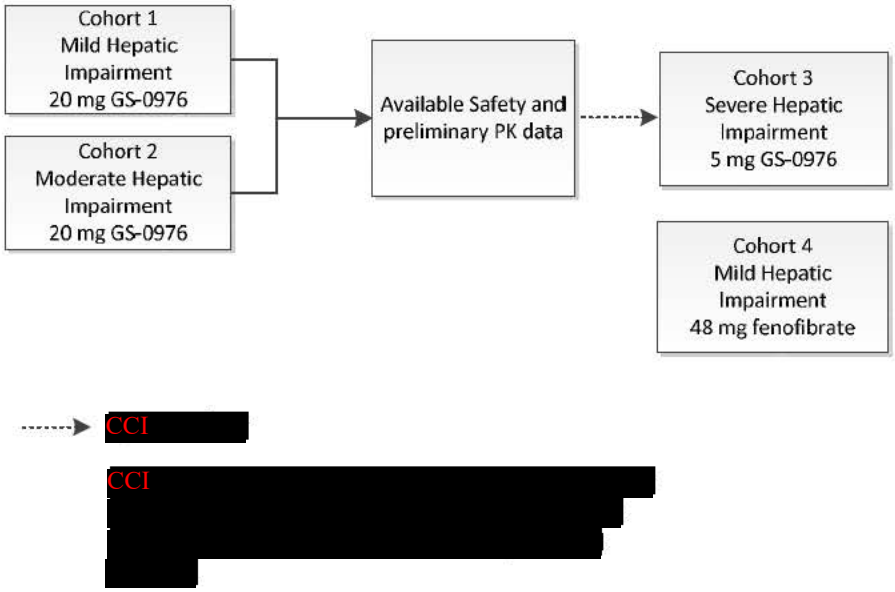
Cohort 4 (Mild Hepatic Impairment): Approximately 20 subjects (10 per group [mildly impaired and matched controls] for 8 evaluable per group)

Eligible subjects include male and non-pregnant/non-lactating female subjects, ages 18-70 years inclusive with mildly impaired, moderately impaired, severely impaired, and normal hepatic function. Subjects will be current non-smokers (no use of tobacco, nicotine-containing or THC-containing products within the last 14 days). 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) with a subject in the hepatic impairment group. A subject with normal hepatic function may serve as a matched control in Cohorts 1 and 2 but may only serve as a matched control to one hepatic impaired subject within a cohort.

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

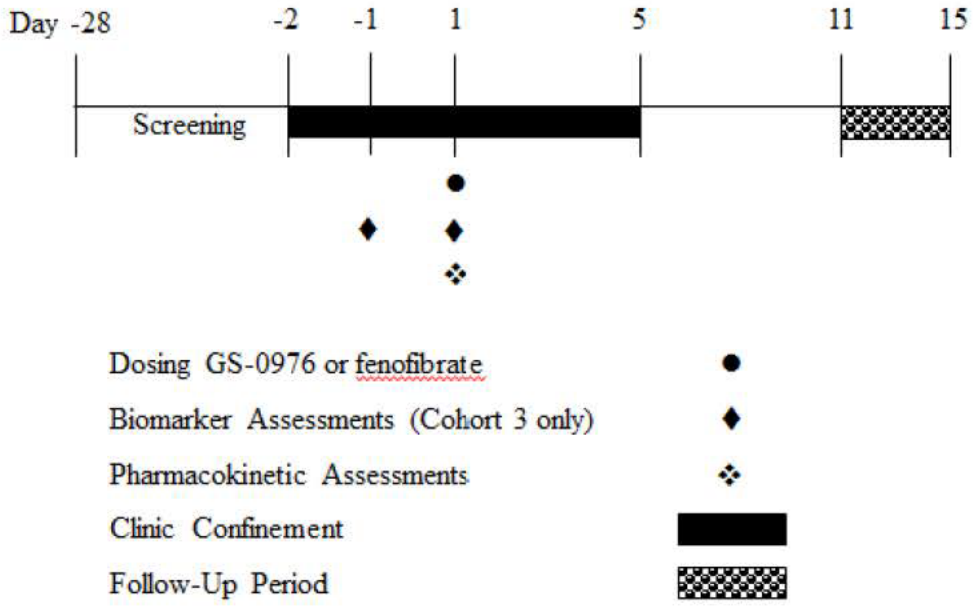
Dosing in subjects with normal hepatic function will begin after a matched subject with hepatic impairment has completed all Day 1 PK assessments (eg, 96 hours postdose). An overview of the study design is described below and shown in Figure 3-1.

Figure 3-1. High-Level Study Schema



An overview of the cohort study design is described below and shown in Figure 3-2.

Figure 3-2. Cohort Study Schema



3.2. Study Drug Administration

Study drug will be administered on Day 1 with 240 mL of water following an overnight fast (no food or drinks except for water) for at least 10 hours. Subjects will continue to fast until after collection of the 4-hour PK 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 drug. A standardized meal may be provided to subjects after the 4-hour post-dose PK draw.

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

3.3. Clinic Confinement

Following screening and admission procedures, eligible subjects will be confined to the study center beginning Day -2 until the completion of assessments on Day 5. Subjects will return for a follow-up (FU) visit on Day 13 (± 2 days).

3.4. Pharmacokinetic Assessments

Pharmacokinetic assessments will occur on assigned study days as outlined in Table 6-1 and Section 6.8.

3.4.1. Plasma Pharmacokinetic Collection

Plasma concentrations of GS-0976 or fenofibrate (and their metabolites, as applicable) will be determined and PK parameters estimated. Pharmacokinetic parameters will be estimated, as appropriate.

3.4.2. Safety Assessments

Safety assessments will be performed through the study as outlined in Table 6-1 and in Section 6.10.

3.5. Biomarker Testing

3.5.1. Biomarker Samples to Address the Study Objectives:

CCI [redacted]

Biomarker samples will be collected as described in Table 6-1. Samples will be destroyed 15 years after the end of the study.

CCI [redacted]

[redacted]

[redacted]

[redacted]

3.6. 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

Approximately 80 subjects will be enrolled in the study. Eligible subjects include healthy male and non-pregnant, non-lactating female subjects of 18 through 70 years of age, inclusive, with varying degrees of hepatic impairment and matched healthy controls. If necessary, replacement subjects may be enrolled with sponsor approval if subjects do not complete all intensive PK procedures. Replacement subjects will not be enrolled for subjects who discontinue the study due to study drug-related AEs.

Those subjects with hepatic impairment will be categorized based upon the CPT classification system for hepatic impairment as recommended by the United States FDA and international guidance documents {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}. Within the CPT system, subjects will be assigned to Class A, B, or C (CPT Class A, B, or C) based on a cumulative score evaluating the presence and severity of hyperbilirubinemia, hypoalbuminemia, prolongation of INR for coagulation time, ascites, and hepatic encephalopathy. Classification of hepatic impairment will be assigned as follows:

- Mild: Class A, CPT score of 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, race, and BMI (± 15%, 18 ≤ BMI ≤ 36 kg/m^2) 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) Be aged 18 through 70 years of age, inclusive at Screening.

3) Have a calculated body mass index (BMI) of ≥ 18.0 and ≤ 36.0 kg/m^2 at Screening.

4) Have a creatinine clearance (CL_{cr}) ≥ 80 mL/min (using the Cockcroft-Gault method {Cockcroft 1976}) based on serum creatinine and actual body weight as measured at screening, ie,

Male: $$\frac{(140 - \text{Age [years]}) \times (\text{Weight [kg]})}{72 \times (\text{Serum Creatinine [mg/dL]})} = CL_{cr}\ (\text{mL/min})$$

Female: $$\frac{(140 - \text{Age [years]}) \times (\text{Weight [kg]})}{72 \times (\text{Serum Creatinine [mg/dL]})} \times 0.85 = CL_{cr}\ (\text{mL/min})$$

5) Be a non-smoker (no use of tobacco, nicotine-containing or THC-containing products within the last 14 days)

6) Females of childbearing potential (as defined in Appendix 2) must have a negative serum pregnancy test at Screening and on Day -2 (unless permanently sterile or greater than 2 years postmenopausal)

7) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 2

8) Male subjects must refrain from sperm donation from clinic admission (eg, Day -2), 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 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 the 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 (or 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/mm^3
- Platelets ≥ 25,000/mm^3
- Hemoglobin ≥ 8 g/dL
- α-fetoprotein ≤ 50 ng/mL

15) 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

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 ***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.

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 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

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

21) Must, in the opinion of the investigator, be in good health based upon medical history and physical examination, including vital signs.

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 study drug or investigational compound within 30 days prior to study dosing

3) Have current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance or subject safety

4) Have a positive test result for human immunodeficiency virus type 1 (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 is expected to receive these agents during the study (eg, corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies)

7) Have a history of any of the following:

   a) Significant serious skin disease, such as but not limited to rash, food allergy, eczema, psoriasis, or urticaria

   b) Significant drug sensitivity or drug allergy (such as anaphylaxis or hepatoxicity)

   c) Known hypersensitivity to the study drugs their metabolites or to formulation excipients (see Section 5)

   d) 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%), a family history of long QT syndrome, or unexplained death in an otherwise healthy individual between the ages of 1 and 30 years

   e) Syncope, palpitations, or unexplained dizziness

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

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

h) Implanted defibrillator or pacemaker

8) 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:

9) 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.

10) 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.

11) Positive test for drugs of abuse, including alcohol at Screening or admission, 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.

12) Requires paracentesis > 1 time per month.

13) 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.

14) 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.

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

16) For cohort 4, any contraindication to fenofibrate (other than mild hepatic impairment) per the approved package insert

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.

4.3.3. Healthy Matched Control Subjects

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

17) A positive test result for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody

18) Positive test for drugs of abuse, including alcohol at Screening or admission.

19) Have any serious or active medical or psychiatric illness (including depression) that, 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.

20) History of liver disease

21) Have taken any prescription medications or over-the-counter medications, including herbal products, within 28 days prior to start of study drug dosing, with the exception of vitamins and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications.

5. STUDY DRUGS

5.1. Enrollment

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 following completion of the admission study procedures, eligible subjects will be assigned a subject number starting on Day 1 for Cohorts 1, 2 and 4 or on Day -1 for Cohort 3, and will receive the study treatments as described in Section 5.3.

All screening and admission (Day -2) tests and procedures must be completed and reviewed by the investigator prior to the administration of the first dose of study drug 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-0976

5.2.1. Formulation

GS-0976 capsules are white opaque size 0 hard gelatin capsules containing 10 mg of GS-0976. In addition to the active ingredient, GS-0976 capsules contain the following inactive ingredients: lactose monohydrate, stearoyl polyoxylglycerides and croscarmellose sodium, which are common pharmaceutical excipients.

GS-0976 tablets are round, plain-faced, film-coated white tablets containing 5 mg GS-0976. In addition to the active ingredient, GS-0976 tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc, which are common pharmaceutical excipients.

5.2.2. Packaging and Labeling

GS-0976 capsules are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 or 200 capsules. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

GS-0976 tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

GS-0976 capsules and tablets should be stored at controlled room temperature of 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Description and Handling of Fenofibrate

5.3.1. Formulation

Commercially available fenofibrate 48 mg will be used for the study. Information regarding the formulation of commercially available fenofibrate can be found in the prescribing information.

5.3.2. Packaging and Labeling

Commercially available product of fenofibrate will be used for the study. Fenofibrate 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.

5.3.3. Storage and Handling

Commercial product of fenofibrate will be used for the study. Further information regarding storage and handling are available in the Prescribing Information for commercial products.

5.4. Dosage and Administration of Study Drug

On Day 1 of Cohorts 1 and 2, subjects will receive a single oral dose of 20 mg GS-0976 (2 × 10 mg capsule). On Day 1 of Cohort 3, subjects will receive a single oral dose of 5 mg GS-0976 (1 × 5 mg tablet). On Day 1 of Cohort 4, subjects will receive a single oral dose of 48 mg fenofibrate (1 × 48 mg tablet). Dosing in subjects with normal hepatic function will begin after a matched subject with hepatic impairment has completed all Day 1 PK assessments (eg, 96 hours postdose).

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

5.5. Fasting and Meals

Study drug will be administered on Day 1 with 240 mL of water following an overnight fast (no food or drinks except for water) for at least 10 hours. Subjects will continue to fast until after collection of the 4-hour PK 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 drug. A standardized meal may be provided to subjects after the 4-hour post-dose PK draw.

On Day -1 of Cohort 3, the timing of meals and meal compositions will be matched to Day 1.

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.

Where possible, IMP should be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead Sciences, the site may destroy used (empty or partially empty) and unused IMP supplies. A copy of the site's IMP Disposal SOP or written procedure (signed and dated by the PI or designee) will be obtained for Gilead site files. If the site does not have acceptable procedures in place for drug destruction, study drug supplies can be sent back to GENCO Pharmaceutical Services.

For both options, the study monitor must first perform drug accountability during an on-site monitoring visit.

5.7. Concomitant Medications and Other Protocol Restrictions

5.7.1. Concomitant Medications

5.7.1.1. Hepatic Impairment Groups

Concomitant use of certain medications or herbal/natural supplements with study drug may result in PK 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 Case Report Form (CRF)/electronic Case Report Forms (eCRFs).

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.

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:

- Any and all illegal or illicit drug use, including use of prescription drugs outside the care of the prescribing physician.
- Hematologic stimulating agents (eg, erythropoiesis-stimulating agents [ESAs]; granulocyte colony stimulating factor [GCSF]; thrombopoietin [TPO] mimetics)
- Chronic systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (eg, infliximab). Use for ≤ 2 weeks total is allowed.
- Investigational agents or devices for any indication
- Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters P-gp, or OATP1B3 or 1B3 or inhibitors/inducers of UGT enzymes) with GS-0976 may result in PK interactions resulting in increases or decreases in exposure of GS-0976 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 Prohibited 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	Bosentan
Herbal/Natural Supplements[b]	St. John's Wort, Echinaccea. Milk thistle (i.e. silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
Other	Modafinil, Probenecid

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 (ie, Tums, Maalox) are permitted but may not be taken within 4 hours (before or after) of study drug administration.
b May result in a decrease in the concentrations of study drug.

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

5.7.1.2. Medications to be used with Caution with Fenofibrate

The prescribing information for fenofibrate should be consulted for medications that are prohibited and/or to be used with caution with fenofibrate.

Examples of representative medications that should be used with caution are listed in Table 5-2.

Table 5-2. List of Medications to be Used with Caution

Drug Class	Use with Caution
Anticoagulants[a]	Coumarin, coumadin, warfarin
Anti-gout agents[b]	Colchicine
Bile acid sequestrants[c]	Cholestyramine, colestipol, colesevelem
Lipid modifying agents[d]	Simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin, pitavastatin

a Fenofibrate can increase PT/INR. Increased frequency of PT/INR assessments when the subject is started on fenofibrate is at the investigators discretion. Monitor and adjust anticoagulant dose as necessary based on prescribing information.
b Concomitant use of colchicine with fenofibrates can increase the risk of rhabodmyolysis
c Bile acid sequestrants are permitted but may not be taken within 4 hours (before or after) study drug administration.
d Concomitant use of statins with fenofibrates can increase the risk of rhabodmyolysis

5.7.1.3. 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 and antacids 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 smoking nicotine or nicotine-containing products and THC-containing products for at least 14 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 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 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 CRFs/ 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 informed consent 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	Days 2-4	Day 5[b]	Day 13 (± 2 days)[c]	ET[d]
Written Informed Consent	X							
Medical History	X							
Complete Physical Exam	X							X
Symptom-Driven Physical Examination[e]		X	X[q]	X[f]		X	X	
Height, Weight, BMI	X							
Vital Signs[g]	X	X	X[q]	X[f]		X	X	X
HIV-1, HBV, and HCV Testing	X							
Hematology[h]	X	X[k]		X		X	X	X
Chemistry[h]	X	X[k]		X		X	X	X
Coagulation[h]	X						X	X
α-fetoprotein	X							
Urinalysis	X	X[k]		X		X	X	X
Serum Pregnancy Test[i]	X	X[k]				X	X	X
FSH[j]	X							
Urine Drug and Alcohol Screen	X	X[k]					X	X
12-Lead ECG	X	X		X[f]		X	X	X
Enrollment			X[l]	X				
Study Drug Administration				X				
PK Assessments[m]				X				X
Biomarker Assessments[p]			X	X				
CCI								
Review Study Restrictions	X	X				X	X	X

Study Procedure	Screen[a]	Day -2	Day -1	Day 1	Days 2-4	Day 5[b]	Day 13 (± 2 days)[c]	ET[d]
Clinic Confinement		X						
Review AEs & Concomitant Medications[o]		X						

a Prospective subjects should be screened no more than 28 days prior to administration of the first dose of study drug.
b Subjects will be discharged from the clinic on Day 5, following all morning assessments.
c Subjects will return for a follow-up visit on Day 13 (± 2 days).
d Assessments will be performed within 72 hours of early termination from the study.
e Symptom-driven PEs will be performed during confinement as needed, based on reported signs and symptoms.
f Predose and approximately 4 hours postdose
g Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
h Hematology, Chemistry, Coagulation: See Section 6.10.5.1 for specifics.
i Females of child-bearing potential only.
j Female subjects ≤ 54 years old with amenorrhea > 12 months as outlined in Appendix 2
k 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.
l Subjects of Cohort 3 will be enrolled on Day -1.
m Intensive PK sampling will occur relative to dosing of GS-0976 or fenofibrate on Day 1 at the following time points for each cohort:
Day 1: 0 (pre-dose, ≤ 5 minutes prior to dosing), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours post-dose
A blood sample for PK analysis will be collected at the Early Termination (ET) visit (if applicable) and may be analyzed.
Plasma protein sampling will occur relative to dosing of GS-0976 or fenofibrate on Day 1 at the following time points for each cohort:
Day 1: 1 and 3 hours post-dose
n [redacted]
o From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any nonserious AEs related to protocol-mandated procedures on the AE CRF/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/eCRF. See Section 7, Adverse Events and Toxicity Management for additional details.
p Biomarker sampling will be collected relative to the planned or actual dosing time of GS-0976 at the following time points for Cohort 3 only:
Day -1: 0, 1, 2, 3, 4, 6, 8, 12, and 16 hours postdose (relative to planned Day 1 dosing time)
Day 1: 0 (*pre-dose, ≤ 5 minutes prior to dosing), 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours postdose
*Pre-dose sample on Day 1 will also serve as 24 hour postdose sample on Day -1.
q Prior to biomarker sample collection (Cohort 3 only)

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 up to 80 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 study drug, record all SAEs, as well as any AE related to protocol-mandated procedures on the AE CRF/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/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.

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. Subjects will return for a FU visit on Day 13 (± 2 days).

6.3. Check-in Assessments

Following completion of screening and Day -2 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 return for a FU visit on Day 13 (± 2 days). Posttreatment assessments are outlined in Table 6-1.

6.6. Assessments for Premature Discontinuation from Study

If the subject discontinues prematurely 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 drug.

6.7. Pharmacokinetic Assessments

6.7.1. Plasma Pharmacokinetic Collection

Intensive PK sampling will occur relative to dosing of GS-0976 or fenofibrate on Day 1 at the following time points for each cohort:

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

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

Plasma concentrations of GS-0976 or fenofibrate (and their metabolites, as applicable) will be determined and PK evaluated. Pharmacokinetic parameters will be estimated, as appropriate.

6.7.2. Protein Binding Samples

Plasma protein binding sampling will occur relative to dosing of GS-0976 or fenofibrate on Day 1 at the following time points for each cohort:

- Day 1: 1 and 3 hours post-dose

Plasma protein binding of GS-0976 or fenofibrate (and their metabolites, as applicable) will be determined and summarized descriptively.

6.8. Exploratory Biomarker Assessments

CCI [redacted]

CCI [redacted]

6.10. Safety Assessments

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

6.10.1. 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.

6.10.2. 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

6.10.3. Vital Signs

Vital sign measurements include blood pressure, heart rate, 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.

6.10.4. Body Mass Index

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

6.10.5. Clinical Laboratory Tests/Assessments

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

On Day -2 (clinic admission), two sets of safety labs will be collected. 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.

6.10.5.1. Blood Sampling

Blood samples will be collected for the following laboratory analyses:

- Hematology: CBC with differentials
- Chemistry (fasting): alkaline phosphatase, AST, ALT, creatine phosphokinase (CPK) **(Cohort 4 only)**, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine (see below), glucose, phosphorus, magnesium, potassium, sodium, uric acid, total cholesterol, high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein--cholesterol (LDL-c), triglycerides, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × upper limit of normal [ULN]
- Coagulation: PT, PTT, INR
- α-fetoprotein
- HIV-1/2, HBVaAg, and HCV-Ab testing
- Serum pregnancy test (females of childbearing potential only)
- Follicle-stimulating hormone (FSH) testing (Female subjects ≤ 54 years old with amenorrhea > 12 months)

6.10.5.2. Urine Samples

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

6.10.6. Creatinine Clearance

Weight will be collected at Screening to calculate creatinine clearance (CL_{cr}) for inclusion criteria.

6.10.7. 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 7.7.1)
- 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 CRF/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.

7.2. 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 3 for more information). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

The distinction between the seriousness and the severity of an 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.

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 obtaining informed consent, but prior to initiation of study drug, all SAEs and AEs related to protocol-mandated procedures should be reported on the CRF/eCRF.

7.3.1.1. Adverse Events

Following initiation of study treatment, 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 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 posttreatment follow-up period, must be reported to the CRF/eCRF database and Gilead Pharmacovigilance and Epidemiology (PVE) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 30 days weeks 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 an investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead PVE.

- 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 Reporting Process

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

- If for any reason it is not possible to record the SAE information electronically (eg, the CRF/eCRF database is not functioning), record the SAE on the paper SAE reporting form and submit within 24 hours as described below.

Gilead PVE:	Fax:	PPD
	E-mail:	PPD

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

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

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

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by email or fax when requested and applicable. Transmission of such documents should occur without personal 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 United States (US) FDA Code of Federal Regulations, the European Union (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 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 independent ethics committee (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, electrocardiogram, X rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the modified GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities as described in Appendix 3. 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, 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 laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Grade 3 and 4 clinically significant laboratory abnormalities should be repeated to confirm toxicity grade and followed until resolution or until stable, if possible.

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

7.7. Special Situations Reports

7.7.1. 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.

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

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. 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 PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

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

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE 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 PVE 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 PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE by faxing PPD or emailing PPD

Refer to Appendix 2, Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

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

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

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

Refer to Section 7.3 and the 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 objectives of this study are as follows:

- To evaluate the single-dose PK of GS-0976 in subjects with normal hepatic function, and mild, moderate, or severe hepatic impairment
- To evaluate the single-dose PK of fenofibrate in subjects with normal hepatic function and mild hepatic impairment

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of GS-0976 single dose administration in subjects with normal hepatic function, and mild, moderate, or severe hepatic impairment
- To evaluate the safety and tolerability of single dose fenofibrate administration in subjects with normal hepatic function and mild hepatic impairment

8.1.2. Primary Endpoint

The primary endpoints are the PK parameters AUC_{last}, AUC_{inf}, and C_{max} of GS-0976 or fenofibrate (and their metabolites, as applicable). Additional PK parameters calculated include: % AUC_{exp}, T_{max}, C_{last}, T_{last}, λ_z, CL/F, Vz/F, and $t_{½}$ as appropriate.

8.1.3. Secondary Endpoint

The secondary endpoints include the incidence of AEs and laboratory abnormalities.

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 will include all enrolled subjects who received at least 1 dose of study drug and had at least 1 nonmissing PK concentration datum reported by PK lab for each respective analyte.

8.3. Data Handling Conventions

For summary statistics, PK concentration values below the limit of quantitation will be treated as zero at predose and 1-half of the lower limit of quantitation (LLOQ) for postdose time points.

Laboratory data that are continuous in nature but are less than the LLOQ or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus 1 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 study 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 by hepatic function groups (according to the study drug received).

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 CRF/eCRF. Exposure data will be listed.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the MedDRA. System organ class (SOC), high-level group term, high-level term, preferred term (PT), and lower-level term will be attached to the clinical database.

Adverse event data will be listed by subject. Treatment-emergent AEs (TEAEs), serious TEAEs, and TEAEs leading to discontinuation of treatment will be summarized by hepatic function group (according to the study drug received), SOC, and PT using the current version of 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 (according to the study drug received) at scheduled visits. The incidence of treatment-emergent graded laboratory abnormalities will be summarized by hepatic function group (according to the study drug received).

8.6.4. Other Safety Evaluations

Vital signs and ECG data will be listed by subject and visit and will be summarized by hepatic function group (according to the study drug received) and visit.

8.7. Pharmacokinetic Analysis

Plasma concentrations and PK parameters will be listed and summarized for GS-0976 or fenofibrate (and their metabolites as appropriate) using descriptive statistics by hepatic function group.

In addition, an analysis of variance 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 each analyte within each cohort. Two-sided 90% CIs will be calculated for the ratios of GLSMs of PK parameters for each analyte 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 each analyte compared with subjects with normal hepatic function will be rejected.

GS-0976 or fenofibrate 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 (according to the study drug received). Relationships between measures of hepatic function (ie, CPT score, serum albumin, total bilirubin, prothrombin time and INR) and PK parameters will be evaluated.

8.8. Sample Size

For cohorts 1 to 3, 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_{inf} and C_{max}, would be less than 200% with ≥ 72 and ≥ 57% probability, respectively, if the estimated GLSM ratio were 1.0. This is assuming a SD of no more than 0.588 for AUC_{inf} and 0.721 for C_{max} on a natural logarithm scale, supported by previous Gilead study 0976-101. With 25% overage, a total sample size of 60 subjects (10 per group, 20 per cohort) will be required.

For cohort 4, with 16 (8 per group) evaluable subjects, the estimated two-sided 90% CI of the GLSM ratio of mild hepatic impaired group vs control (normal hepatic function), with regards to AUC_{last}, AUC_{inf} and C_{max} would be within [0.5, 2.0] with ≥ 90% probability, if the estimated GLSM ratio were 1.0. This is assuming a SD of no more than 0.387 on a natural logarithm scale, supported by information from FDA {U. S. Food and Drug Administration 2004}. With 25% overage, a total sample size of 20 subjects (10 per group) 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 Harmonization (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 EU 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 (GCP), as outlined in 21 Code of Federal Regulations (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, ICF, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/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 ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB/EC local requirements. The consent form will inform subjects about PG testing and sample retention, and whether they will receive clinically relevant PG 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 study. Subject data will be processed in accordance with all applicable regulations.

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

9.1.5. 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/eCRF, IRB/EC and governmental approval with correspondence, ICF, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each 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 CRF/eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. The CRF/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 CRF/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 CRF/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

Gilead recommends that used and unused study drug supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies. If the site has an appropriate SOP for drug destruction as determined by Gilead quality assurance (QA), the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

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.

9.3. 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 CRF/eCRF.

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

Both Gilead 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 subjects, 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.
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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 1 Open-Label, Parallel-Group, Single-Dose Study to Evaluate the Pharmacokinetics of GS-0976 or Fenofibrate in Subjects with Normal and Impaired Hepatic Function

GS-US-426-3988, Amendment 2, 18 December 2018

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

PPD

Medical Monitor

19 December 2018

Date

PPD

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a) Definitions of Childbearing Potential

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

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

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

b) Definitions of Male Fertility

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

2) Contraceptive Requirements for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

No formal studies have been conducted to evaluate the reproductive toxicity of GS-0976; therefore, the reproductive toxicity of GS-0976 in humans is unknown. However, mutant mice lacking ACC1, one of the targets of GS-0976, are embryonically lethal. Therefore, GS-0976 is contraindicated in pregnancy. Preclinical data in human hepatocytes indicate that GS-0976 is a mild inducer of CYP3A4 isoenzymes. Clinical data demonstrates no decrease in exposure of a representative oral hormonal contraceptive indicating no loss of contraceptive efficacy is expected upon administration of GS-0976 with hormonal contraceptives. Information regarding fenofibrate is available in the fenofibrate prescribing 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 at the check-in visit prior to enrollment; subsequently, serum pregnancy tests will be performed on Day 5, and at the FU visit or ET visit (if applicable). Female subjects must agree to one of the following from screening until 30 days after the last dose of study drug.

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

  Or

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

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

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

  — Tubal sterilization

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

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

  Or

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

  — Barrier methods

    ■ Diaphragm with spermicide

    ■ Cervical cap with spermicide

    ■ Male condom (with or without spermicide)

  — Hormonal methods

    ■ Oral contraceptives (either combined or progesterone only)

    ■ Injectable progesterone

    ■ Implants of levonorgestrel

    ■ Transdermal contraceptive patch

    ■ Contraceptive vaginal ring

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

3) Contraceptive 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 until 90 days after the last dose of study drug.

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.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days (90 days for female partners of male subjects) of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

Appendix 3. 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
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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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
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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypouricemia **Adult and Pediatric ≥ 1 year** **Infant < 1 Year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN N/A	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L 1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L 0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 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** **Pediatric < 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN NA	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L 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 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 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
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) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA 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** **≥ 16 years**	- 3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < LLN g/dL 20 to < LLN g/L 2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L < 2.0 g/dL < 20 g/L	NA 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 (e.g., 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	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	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	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	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)
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.

Appendix 4. Child-Pugh Classification of Severity for Liver Disease

Child-Pugh classification of severity of liver disease

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/liter)	2-3 mg/dL (34.2 to 51.3 micromol/liter)	>3 mg/dL (>51.3 micromol/liter)
Albumin	>3.5 g/dL (35 g/liter)	2.8-3.5 g/dL (28 to 35 g/liter)	<2.8 g/dL (<28 g/liter)
Prothrombin time			
Seconds over control	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease). These grades correlate with one- and two-year patient survival: grade A - 100 and 85 percent; grade B - 80 and 60 percent; and grade C - 45 and 35 percent.