CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1 Open-Label Study to Evaluate the Pharmacokinetics of GS-9876 in Subjects with Impaired Renal Function
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND No.:	123903
EudraCT No.:	2016-003823-47
Indication:	Inflammatory Diseases
Protocol ID:	GS-US-379-1932
Gilead Medical Monitor	Name: PPD Telephone: PPD Fax: PPD Mobile: PPD Email: PPD
Protocol Version/Date:	Original: 10 October 2016 Amendment 1: 09 January 2017

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 1 Open-Label Study to Evaluate the Pharmacokinetics of GS-9876 in Subjects with Impaired Renal Function
IND Number: **EudraCT Number:**	123903 2016-003823-47
Study Centers Planned:	Multiple centers in the United States, Germany, and New Zealand
Objectives:	The primary objective of this study is as follows: • To evaluate the pharmacokinetics (PK) of GS-9876 in subjects with impaired renal function relative to matched, healthy controls The secondary objective of this study is as follows: • To evaluate the safety and tolerability of GS-9876 in subjects with normal and impaired renal function
Study Design:	Phase 1, open-label, parallel-group, adaptive, single-dose, multi-center, pharmacokinetic study
Number of Subjects Planned:	This study will target enrolling 20 subjects per cohort, and a maximum of 60 subjects using an adaptive design that includes up to 3 enrolled cohorts of subjects with renal impairment and matched healthy controls. Based on safety and PK results from subjects with moderate renal impairment (Cohort 1), subjects with severe renal impairment (Cohort 2) and/or mild renal impairment (Cohort 3) will be enrolled as follows: • Cohort 1 (Moderate Renal Impairment): Up to 20 subjects (10 per group, moderate renal impairment and matched healthy controls) for 8 evaluable subjects per group. • Adaptive Cohort 2 (Severe Renal Impairment): Up to 20 subjects (10 subjects with severe renal impairment and up to 10 matched healthy control subjects if none of the healthy subjects from a previous cohort is an appropriate match for a severe impairment subject) for 8 evaluable subjects per group.

- Adaptive Cohort 3 (Mild Renal Impairment): Up to 20 subjects (10 subjects with mild renal impairment and up to 10 matched healthy control subjects if none of the healthy subjects from a previous cohort is an appropriate match for a mild impairment subject) for 8 evaluable subjects per group.

Adaptive Cohorts 2 and/or 3 will be enrolled as determined by safety and/or PK data in Cohort 1. Specifically, Cohort 2 (Severe Renal Impairment) will be evaluated if supported by safety and/or PK data from Cohort 1 (Moderate Renal Impairment). Cohort 3 (Mild Renal Impairment) will be evaluated if supported by safety and if substantial changes (≥ 2-fold mean difference from matched controls) in the exposure of GS-9876 is observed in subjects with moderate renal impairment in Cohort 1. Cohorts 2 and 3 may not be enrolled or may be enrolled sequentially or in parallel, as governed by safety and PK data in Cohort 1. Each control subject may be matched to multiple renal impaired subjects across different cohorts and can be matched to only 1 renal impaired subject within a cohort.

Target Population:	Male and non-pregnant/non-lactating female subjects, ages ≥ 18 and ≤ 75 years, with normal or impaired renal function. Subjects with renal impairment must have a renal impairment classification (mild, moderate, or severe) at Screening that has been unchanged during the 3 months prior to first study drug. Subjects may not be taking moderate or strong inhibitors or inducers of CYP3A during the study or within 2 weeks prior to the first dose. Each subject in the control group will be matched for age (± 10 years), gender, and body mass index (± 20%, ≥ 18 kg/m^2 and ≤ 36 kg/m^2).
Duration of Dosing:	1 day
Study Duration:	15 days
Diagnosis and Main Eligibility Criteria:	Subjects will comprise those with normal and impaired renal function. Those with impaired renal function will be categorized based on estimated creatinine clearance (CLcr) using the Cockcroft-Gault (C-G) equation for renal function as recommended by the Food and Drug Administration (FDA) and international guidance documents. Classification of renal impairment is defined as follows: • Mild: CLcr 60-89 mL/min • Moderate: CLcr 30-59 mL/min • Severe: CLcr 15-29 mL/min Severe renal impairment subjects requiring or anticipated to require dialysis within 90 days of study entry are not eligible. The control group will consist of matched control subjects with normal renal function (CLcr ≥ 90 mL/min).

Subjects will also be categorized using the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) Study equation and select results from this study will also be analyzed using these criteria {National Institute of Diabetes and Digestive and Kidney Diseases (NIH) 2016}.

eGFR (mL/min/1.73 m^2) = 175 × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American)

- Normal: eGFR ≥ 90 mL/min/1.73 m^2
- Mild: eGFR 60-89 mL/min/1.73 m^2
- Moderate: eGFR 30-59 mL/min/1.73 m^2
- Severe: eGFR 15-29 mL/min/1.73 m^2

Study Procedures/ Frequency:

Following completion of Screening and Day -1 assessments, eligible subjects will receive a single oral dose of the following study drug on Day 1:

- 20 mg GS-9876 (2 × 10 mg tablet) in the fasted state

Dosing in a matched subject with normal renal function will occur after the corresponding subject with impaired renal function has completed his/her PK assessment, except for control subjects that were already matched to a subject with impaired renal function in a previous cohort, as permitted in adaptive Cohorts 2 and 3.

Study Visits and Confinement

Following screening and Day -1 procedures, eligible subjects will be confined to the study center beginning Day -1 until the completion of assessments on Day 6. Subjects will return 14 (± 1) days after last dose for an in-clinic follow up visit (ie. Day 15).

Study Drug Administration

Following an overnight fast of at least 8 hours (no food or drink except water), study drug will be administered in the morning with 240 mL of water. 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 1 hour before until 2 hours after dosing, except for the 240 mL given with the study treatment.

Pharmacokinetic Assessments

Plasma PK collection

Plasma concentrations of GS-9876 will be measured and PK parameters determined. Plasma concentrations of GS-9876 metabolites may be determined and pharmacokinetics explored, as applicable.

Intensive PK sampling will occur relative to dosing of GS-9876 at the following time points:

- Day 1: 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96 and 120 hours postdose

Protein binding of GS-9876 (and its metabolites, as applicable) will be assessed at or near their T_{max} timepoint(s) as well as another later time point.

Urine PK Sampling

Urine PK samples will be collected relative to dosing of GS-9876 at the following intervals:

- Day 1: Pre-dose void, 0-6, 6-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours postdose

Urine concentrations of GS-9876 and/or metabolites may be determined and PK parameters estimated.

Safety Assessments

Complete physical exam: Screening, Days -1, 6, and at the follow-up visit 14 (± 1) days after last dose or at the Early Termination (ET) visit, if applicable

Symptom driven physical exam: every day during confinement as needed, based on reported signs and symptoms

Vital signs (blood pressure, pulse, respiration rate, and temperature): Screening, Days -1, 1 (predose, 1, 3, 6, and 12 hours postdose), 2, 3, 4, 5, 6, and at the follow-up visit 14 (± 1) days after last dose or at the ET visit, if applicable

Height: Screening

Weight: Screening, Day -1

Clinical laboratory tests (blood chemistry, and urinalysis): Screening, Days -1, 1 (4 hours postdose), 2, 3, 6, and at the follow-up visit 14 (± 1) days after last dose or at the ET visit, if applicable

Clinical laboratory tests (hematology and coagulation): Screening, Days -1, 1 (4 hours postdose), 3, 6, and at the follow-up visit 14 (± 1) days after last dose or at the ET visit, if applicable.

Urine Drug and Alcohol Assessments: Screening, Day -1

12-lead ECG: Screening, Days -1, 1 (postdose), 6, and at the follow-up visit 14 (± 1) days after last dose or at the ET visit, if applicable

Serum Pregnancy Test (women of childbearing potential only): Screening, Day -1, 6, and at the follow-up visit 14 (± 1) days after last dose or at the ET visit, if applicable

	Serology Test (HBV, HCV, HIV): Screening Assessment of adverse events and concomitant medications will continue throughout the study.
Test Product, Dose, and Mode of Administration:	GS-9876 2 × 10 mg tablet, oral, administered fasted
Criteria for Evaluation:	
Safety:	Safety will be assessed during the study through the reporting of AEs, and by clinical laboratory tests, physical examinations, vital signs, and ECGs at various time points during the study. Concomitant medication usage will be assessed throughout the study.
Efficacy:	Not applicable.
Pharmacokinetics:	The following plasma PK parameters will be calculated, as appropriate: C_{max}, T_{max}, C_{last}, T_{last}, λ_z, AUC_{last}, AUC_{0-24}, AUC_{inf}, $\%AUC_{exp}$, $t_{½}$, CL/F, and V_z/F. PK of predominant GS-9876 metabolites (if applicable) may be explored. In addition, urine parameters (e.g. renal clearance and percentage of dose excreted in urine) may be estimated.
Statistical Methods:	**Pharmacokinetics**: Pharmacokinetic parameters for GS-9876 will be listed and summarized by renal function group (normal, mild, moderate, and severe impairment) using descriptive statistics. An analysis of variance appropriate for a parallel design will be fit to the natural logarithm-transformed PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) for GS-9876. Two-sided 90% confidence intervals (CIs) will be constructed for the geometric least-squares means (GLSM) ratio of PK parameters for GS-9876 in groups of subjects with renal impairment versus matched controls. **Safety**: Safety data will be listed by subject and summarized by renal function group and the frequency of event/abnormality or descriptive statistical summaries, as appropriate.Sample Size: With 16 (8 per group) evaluable subjects, the estimated two-sided 90% CI of the GLSM ratio of test versus reference groups, with regards to PK parameters (AUC and C_{max}) would be within (50%, 200%) with over 95% probability. This calculation is based on a two

	group t-test of equivalence in means at the significance level of 0.05, assuming the expected geometric means ratio of 1.0 and inter-subject standard deviation (SD) of no more than 0.35 on a natural logarithm scale. The assumption about the inter-subject SD is supported by previous Gilead study GS-US-379-1372 using the maximum variability for AUC and C_{max} from the closest dose levels (15 mg and 30 mg) of the dose in this study. An overage of 2 subjects per group will be enrolled to accommodate subject drop-outs, thus requiring a total enrollment of 20 subjects (10 per group) for each cohort.

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}
°C	degrees Celsius
ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
AhR	aryl hydrocarbon receptor
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
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
AUC_{0-24}	area under the concentration versus time curve during 24 hours
BCR	B-cell receptor
BCRP	breast cancer resistance protein
BLQ	below limit of quantitation
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
CBC	complete blood count
CD	Cluster of differentiation
CFR	Code of Federal Regulations
C-G	Cockcroft-Gault
CI	confidence interval
CIA	collagen-induced arthritis
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
CNS	central nervous system
CPK	creatine phosphokinase
CRF	case report form
CRO	contract (or clinical) research organization

CTCAE	Common Terminology Criteria for Adverse Events
C_{tau}	observed drug concentration at the end of the dosing interval
CYP	cytochromes P450
DMARD	disease modifying antirheumatic drugs
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health
EC_{50}	half maximal effective concentration
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
ED_{50}	median effective dose
EDC	electronic data capture
EudraCT	European Clinical Trials Database
eGFR	estimated glomerular filtration rate
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
FceRI	Fc epsilon receptor I alpha
FDA	Food and Drug Administration
FU	follow-up
GCP	Good Clinical Practice
Gilead	Gilead Sciences, Inc.
GLP	Good Laboratory Practice
GLSM	geometric least-squares mean
GN	glomerulonephritis
HBV	hepatitis B virus
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HIV, HIV-1	human immunodeficiency virus, type 1
HLGT	high-level group term
HLT	high-level term
IB	investigator's brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ID	identification

IEC	independent ethics committee
Ig	immunoglobulin
IL	interleukins
IMP	investigational medicinal product
IND	investigational new drug (application)
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
LAM	lactational amenorrhea method
LDH	lactic acid dehydrogenase
LDL	low-density lipoprotein
LLT	lower-level term
LLOQ	lower limit of quantitation
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MM	medical monitor
mTOR	mammalian target of rapamycin
nM	nanometers
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NSAID	nonsteroidal anti-inflammatory drug
OATP	organic anion-transporting polypeptide
PD	pharmacodynamic(s)
PG	pharmacogenomics
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)
PR interval	electrocardiographic interval occurring between the onset of the P wave and the QRS complex representing time for atrial and ventricular depolarization, respectively
PT	preferred term
PTT	partial thromboplastin time
PXR	pregnane X receptor
Q1	first quartile
Q3	third quartile
QA	quality assurance
QD	quaque die (every day or once daily)
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave, representing time for ventricular depolarization

QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected
QTcF	QT interval corrected for heart rate using the Fridericia formulation
RA	rheumatoid arthritis
RBC	red blood cell
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	International system of units
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SYk	spleen tyrosine kinase
TEAE	treatment-emergent adverse event
T_{last}	time (observed time point) of C_{last}
T_{max}	the time (observed time point) of C_{max}
TNF	tumor necrosis factor
TOST	two one-sided tests
TQT	thorough QT
TV	television
$t_{1/2}$	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
µM	micrormeter
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

GS-9876 is a potent and selective inhibitor of SYK and is being developed by Gilead Sciences, Inc. (Gilead) as an oral agent for the treatment of inflammatory diseases. Spleen tyrosine kinase is a nonreceptor cytoplasmic tyrosine kinase primarily expressed in cells of hematopoietic lineage, where it functions as a key signaling molecule mediating immunoreceptor signaling in a range of cells involved in inflammatory disease. Given its central role in immune cell signaling, inhibition of SYK is expected to affect multiple steps in the pathogenesis of several autoimmune diseases such as rheumatoid arthritis (RA) resulting in pleiotropic anti-inflammatory effects.

Rheumatoid Arthritis is a chronic, systemic inflammatory disease that affects approximately 1.3 million adults in the United States (US) {Helmick et al 2008}. Rheumatoid Arthritis manifests principally as an attack on peripheral joints and may lead to marked destruction and deformity of joints, with considerable disability and impact on quality of life. It is characterized by the production of autoantibodies, synovial inflammation with formation of pannus tissue, and erosion of underlying cartilage and bone. Although people of any age can be affected, the onset of RA is most frequent between the age of 40 and 50 years, and women are affected 3 times more often than men. While the cause of RA is still not completely understood, aberrant B-cell activation, T-cell co-stimulation, osteoclast differentiation, and cytokine release all have been implicated in its pathogenesis. Subjects with RA experience a high risk of disability and mortality {Arthritis Foundation 2008}.

Despite the currently available treatment options for RA, there is still a need for new treatments because not all subjects respond adequately (or maintain response) to current therapies and some subjects experience toxicities and/or intolerance that limit the use of such therapies. All currently available treatments have safety considerations that can develop during chronic use that may require a change to a different therapy. The unmet medical need for new therapeutic options with a favorable efficacy and safety profile that do not require injection/infusion have prompted efforts to develop oral small molecule inhibitors of protein kinases involved in cellular signaling associated with the underlying RA disease pathology.

There are several potential causes of nephropathy in patients with RA: drug-related renal disease, where drugs such as NSAIDs and DMARDs, secondary renal amyloidosis and various types of glomerulonephritis (GN) {Karie et al 2008}. Kidney disease and impairment is thought to be highly prevalent in the RA population and therefore a renal impairment study is indicated.

1.2. GS-9876

1.2.1. General Information

For further information on GS-9876 refer to the current investigator's brochure (IB).

1.2.2. Preclinical Pharmacology, Pharmacokinetics and Toxicology

1.2.2.1. Nonclinical Pharmacology and Safety Pharmacology

GS-9876 is a selective and potent adenosine triphosphate (ATP)-competitive inhibitor of SYK with an IC_{50} value of 9.5 nM. Overall, GS-9876 is at least 7-fold more selective biochemically for SYK relative to all other protein kinases assayed. Functionally, GS-9876 inhibited anti-IgM-induced BCR/SYK-mediated phosphorylation and activation of multiple downstream signaling pathways in primary human B-cells, suppressed anti-IgM mediated CD69 and CD86 activation marker expression on B-cells, and proliferation of peripheral B cells. GS-9876 showed a 12-fold selectivity for B-cell proliferation versus anti-CD3/anti-CD28 costimulation of T-cell proliferation. Furthermore, GS-9876 inhibited immune-complex stimulated TNFα and IL-1β release from primary human monocytes. In human blood, GS-9876 inhibited SYK autophosphorylation, anti-IgD/BCR-induced CD69 expression on B-cells, and anti-FceRI-stimulated CD63 expression on basophils with geometric mean EC_{50} values ranging from 171 nM to 301 nM.

In two independent rat collagen-induced arthritis (CIA) models in animals with established disease, treatment with GS-9876 caused significant and dose-dependent amelioration of clinical and histopathology parameters when dosed either early (at initiation of ankle swelling) or late (at time of peak ankle swelling) after disease onset. Histological evaluation of joints in the animals from the study demonstrated that GS-9876 treatment reduced pannus formation, cartilage damage, bone resorption, and periosteal bone formation with an effective dose inducing a 50% inhibitory effect (ED_{50}) of < 6.25 mg/kg, QD and 11.6 mg/kg, QD in the early and late CIA models, respectively. Significant efficacy was seen with GS-9876 doses that produced C_{ave} exposures that were calculated to inhibit SYK phosphorylation by 50% (EC_{50}). GS-9876 was well tolerated at all doses and there were no treatment-related adverse effects on body weight, food and drink intake, in-life observations or clinical pathology parameters.

Safety pharmacology studies were conducted to examine the potential effects of GS-9876 on the cardiovascular system, respiratory system, and central nervous system (CNS). There were no clinically-relevant effects on the respiratory, and CNS systems after single oral doses up to 300 mg/kg. Cardiovascular effects in telemetered cynomolgus monkeys at ≥ 20 mg/kg included prolonged QTc interval from 5 through 25 hours postdose, slightly higher systolic, diastolic, and mean arterial pressure with lower heart rate through 6 hours postdose, and higher heart rate from 9 through 25 hours postdose. While differences in QTc interval were generally small, the changes were of sufficient magnitude to be considered biologically relevant. There were no inhibitory effects on the hERG potassium current when GS-9876 was tested up to a free drug concentration of 30 μM, approximately 207-fold above the observed steady state C_{max} at a 30 mg QD clinical dose. Further, no cardiovascular effects were observed in telemetered cynomolgus monkeys administered GS-9876 for 13 weeks at doses up to 15 mg/kg/day. The potential for GS-9876 to prolong the QTc interval was assessed with intensive time matched ECG monitoring in Gilead studies GS-US-379-1372 and GS-US-379-1900 (cohorts 1 and 2), and no clinical significant change in time matched QTc intervals was observed. No clinical significant changes in vital signs during serial vital sign measurements were observed.

1.2.2.2. Nonclinical Toxicology

In the repeat-dose studies, the toxicity profile of GS-9876 was assessed in rats and monkeys administered GS-9876 orally for up to 26 weeks. Dose-dependent effects on lymphocytes in both rats and monkeys were consistent with the expected pharmacology of SYK inhibition. Effects on hemostasis were observed in rats and monkeys, with increased erythrocyte turnover in rats at ≥ 10 mg/kg/day, and hemorrhage and thrombosis in monkeys at ≥ 20 mg/kg/day. At higher doses in rats (≥ 30 mg/kg/day), mortality associated with bacterial infections, likely resulting from the immunomodulatory activity of GS-9876, was seen. Additional findings included lymphoid depletion in the thymus, changes in the pancreas, with secondary effects related to the immunomodulatory activity of GS-9876, and likely opportunistic bacterial infection, observed in several tissues. The no-observed-adverse-effect level (NOAEL) in rats was 10 mg/kg/day after 26 weeks dosing. For the 20 mg single dose proposed in this study, estimated exposure margins are 3.1-/7.6- fold based on exposures at the NOAELs in the 26 week study in male/female rats. Subjects will be closely monitored for any infection and changes in the differential CBC.

In monkeys, the NOAEL in the 28-day study was identified at 10 mg/kg/day, which was associated with $AUC_{0\text{-}24hr}$ of 4290 ng•hr/mL. In the 13-week monkey study, there were no effects on hemostasis, and the NOAEL was the high dose of 15 mg/kg/day. In the 39-week monkey study, there was no evidence of effects on hemostasis at the high dose of 15 mg/kg/day, and the NOAEL was 15 mg/kg/day, associated with an AUC0-24hr of 8040 ng•h/mL. For the 20 mg single dose proposed in this study, the estimated exposure margin is 2.8-fold based on exposures at the 15 mg/kg/day NOAEL in the 39-week monkey study.

In GLP range-finding developmental toxicity studies in pregnant rats and rabbits, no Caesarean-sectioning, litter parameters, or gross external or visceral alterations were affected by GS-9876 at dose levels up to 100 mg/kg/day in rats, or up to 30 mg/kg/day in rabbits. In rabbits at 100 mg/kg/day, mortality, clinical observations, reduced body weights and food consumption in does were associated with increased resorptions and reduced fetal body weights. In rats, the maternal no-observed-effect level (NOEL) was 30 mg/kg/day, and the embryo-fetal development NOEL was 100 mg/kg/day. In rabbits, the maternal and embryo-fetal development NOEL was 30 mg/kg/day.

GS-9876 was negative in the bacterial reverse mutation (Ames) assay, in vitro chromosomal aberration assay, and in vivo rat micronucleus assay and is therefore considered to be nongenotoxic. In the in vitro chromosome aberration assay in human lymphocytes, slight, but statistically significant increases in the number of polyploid cells was observed at the highest GS-9876 dose level evaluated. GS-9876 did not induce structural chromosome breakage when evaluated in the in vitro assay.

Table 1-1. Margins for GS-9876 Based on Systemic Exposure Relative to the Observed Human Exposure at 20 mg (AUC)

Species	Duration	Route	NOAEL (mg/kg/day)	AUC_{0-24} (ng•h/mL)[a]	Margin [b]
Rat	Once daily x 26 weeks	Oral	10	8800/21,800 (male/female)	3.1/7.6 (male/female)
Cynomolgus Monkey	Once daily x 39 weeks	Oral	15[c]	8040	2.8

a NOAEL, no observed adverse effect level. Week 4 male and female rat AUC and week 13 Cynomolgus monkey AUC (combined sex)
b Margins of exposure were calculated using predicted 20 mg single dose exposure in humans of 2865 ng•h/mL (extrapolated from 30 mg single dose data in study GS-US-379-1372).
c One animal was euthanized moribund during Week 22 at the 15 mg/kg/day dose level.

1.2.2.3. Nonclinical Drug Metabolism and Pharmacokinetics

GS-9876 exhibits high absorption in rats, dogs and monkeys. Plasma protein binding is moderate in all species with the mean free fraction in humans being of 20.4%.

After oral dosing to albino and pigmented rats, [^{14}C]GS-9876-derived radioactivity was rapidly distributed to most tissues and concentrations of radioactivity were below the limit of quantitation by 168 hours postdose. The lowest levels of radioactivity were observed in the brain, bone, adipose, and testis. Melanin containing tissues exhibited higher concentrations than their non-pigmented counterparts but binding was reversible. Recovery of radioactivity was high ($\geq$ 97.8%) and the main route of elimination of GS-9876 was hepatobiliary with $\leq$ 5.1% orally dosed radioactivity found in urine and 69.4% in bile.

In vitro, GS-9876 exhibits high metabolic stability with human hepatocytes, liver fractions and individual metabolizing enzymes. GS-9876 had little inhibitory effect on the activities of the major human drug metabolizing CYP enzymes and was a weak inhibitor of human UGT1A1. GS-9876 is a weak inhibitor of P-gp and BCRP and is a substrate for those efflux transports. It is a weak inhibitor of the hepatic uptake transporters OATP1B1 and OATP1B3 but is a substrate for neither. Drug-drug interactions in vivo are unlikely through inhibition of human CYP enzymes, UGT1A1, or efflux or uptake transporters. The potential of GS-9876 to cause drug-drug interactions through induction is low as there is little activation of PXR or AhR in vitro.

1.2.3. Additional Clinical Studies of GS-9876

As of 12 February 2016, 62 healthy volunteers have been dosed with GS-9876 in two clinical studies.

1.2.3.1. Completed Clinical Trial

GS-US-379-1372: This was a first-in-human, Phase 1, single-dose ranging study of GS-9876 in healthy adult volunteers to evaluate the safety, tolerability, PK, PD, food effect, and drug-drug

interaction potential using a representative acid reducing agent (omeprazole). No risks were identified and no grade 3 or 4 AEs were reported. There were no clinically significant changes in vital signs, physical findings, bleeding times, or ECGs. For further information, refer to the current IB.

1.2.3.2. Ongoing Clinical Trials

GS-US-379-1582: This is a 12 week proof of concept trial of GS-9876 in patients with RA to evaluate efficacy, safety, tolerability and PK of GS-9876.

GS-US-379-1900: This is a single- and multiple-dose Phase 1 study of GS-9876 in healthy volunteers to evaluate the safety, tolerability, PK and PD of GS-9876. No risks were identified; all AEs were Grade 1 in severity. No dose relationships were observed between GS-9876 and any AE. No AE was assessed by the investigator as related to study drug .There were no clinically significant changes in vital signs, physical findings, laboratory parameters, or ECGs.

1.3. Rationale for This Study

Renal dysfunction may alter the elimination of drugs resulting in PK and subsequently pharmacodynamic changes. Available data indicate the disposition of GS-9876 is primarily via hepatic metabolism and elimination with minimal excretion expected in urine. In a nonclinical ADME study in rat (AD-379-2001), 2.7% to 5.1% of the administered radioactivity was excreted in urine. In study GS-US-379-1372 in humans, 0.6% to 4.1% of the dose of GS-9876 was excreted unchanged in urine following single oral doses from 2 to 50 mg. However, renal impairment may alter the disposition of hepatically cleared drugs due to possible changes in hepatic/gut drug metabolism, absorption and plasma protein binding. Thus, the objective of this study is to investigate the potential for clinically relevant alterations in the PK and safety of GS-9876 in subjects with renal impairment.

This study will be conducted in accordance with regulatory guidance and good scientific practice. This study will enroll subjects with moderate renal impairment (Cohort 1) with a screening estimated creatinine clearance (CL_{cr}) of 30-59 mL/min using the Cockcroft-Gault (C-G) equation for renal function as recommended by the Food and Drug Administration (FDA) and international guidance documents. Data from these subjects will be compared to matched subjects with normal renal function ($CL_{cr} \geq 90$ mL/min). Subjects with severe renal impairment (Cohort 2; CL_{cr} 15-29 mL/min) will be evaluated if supported by safety and/or PK data from Cohort 1. Should substantial changes in exposure be observed in Cohort 1, these data would inform the need for an expanded study including subjects with lesser degrees of renal dysfunction (Cohort 3; CL_{cr} 60-89 mL/min).

As renal impairment may be associated with changes in protein binding, a measurement of plasma protein binding will be conducted at or near T_{max} and at another later timepoint following GS-9876 dosing. Administration of GS-9876 as a single-dose is expected to accurately predict PK under steady-state conditions and is thus deemed satisfactory for evaluation in this study.

1.4. Rationale for the Dose Selection

The dose of GS-9876 to be used in this study is a 20 mg single dose in the fasted state. Results from study GS-US-379-1372 indicated that GS-9876 was safe and well tolerated when administered as a single dose of 2 mg to 50 mg. Similarly, preliminary results from study GS-US-379-1900 have indicated that GS-9876 was safe and well tolerated following 7 days dosing of GS-9876 15 mg QD, 30 mg QD or 50 mg QD. GS-9876 doses of 10 mg QD and 30 mg QD are currently under investigation in subjects with rheumatoid arthritis in study GS-US-379-1582. Thus a single dose of 20 mg GS-9876 represents a safe dose that's clinically relevant and allows for potential increase of GS-9876 exposures in subjects with renal impairment. Although food (high fat breakfast) only had minimal impact (reducing C_{max} by 13% and delaying T_{max} but no effect on AUC, on GS-9876 PK study GS-US-379-1372), GS-9876 will be administered in the fasted state in this study to avoid any potential confounding effect of food on assessing the effect of renal impairment on GS-9876 PK.

1.5. Risk/Benefit Assessment for the Study

While there is no direct benefit for the subject participating in the renal impairment study of GS-9876, the risks are considered to be minimal for the following reasons:

GS-9876 has been in a battery of nonclinical animal studies, and no renal toxicity was identified.

GS-9876 has been tested in humans as a single ascending dose over a dose range of 2 to 50 mg (GS-US-379-1372) and as a multiple ascending dose over a dose range of 15 to 50 mg (GS-US-379-1900) and no evidence of nephrotoxicity has been observed. In general GS-9876 was well tolerated at all dose levels. The planned single dose of 20 mg of GS-9876 is well below the highest dose given in the healthy volunteers and is expected to be tolerated well.

As discussed in Section 1.3, the disposition of GS-9876 is primarily via hepatic metabolism and elimination with minimal excretion expected in urine and the impact on renal impairment on GS-9876 PK is expected to be limited. Subjects in this study will receive a single 20 mg dose of GS-9876, which is expected to provide a margin of 2.8-fold to the NOAEL exposure in the 39-week Cynomolgus monkey toxicology study.

Evidence of deterioration in kidney function in humans can readily be detected and monitored using routine laboratory tests. For this study, frequent assessments of kidney function will be performed from the collection of both blood and urine samples. While subjects with renal impairment will be enrolled, the risk of further kidney injury in these subjects should be minimized by this close renal monitoring. Further, this study will enroll subjects with moderate renal impairment (Cohort 1) with a screening estimated creatinine clearance (CL_{cr}) of 30-59 mL/min first. Data from these subjects will be compared to matched subjects with normal renal function ($CL_{cr} \geq 90$ mL/min). Subjects with severe renal impairment (Cohort 2; CL_{cr} 15-29 mL/min) will only be evaluated if supported by safety and/or PK data from Cohort 1.

There are several potential causes of nephropathy in patients with chronic autoimmune diseases: primary autoimmune attack on the kidney, secondary renal amyloidosis, drug-related renal disease due to necessary drugs used to treat the primary autoimmune disease. Kidney disease and

impairment is thought to be highly prevalent in patients with autoimmune disease and therefore a renal impairment study is indicated and is in line with the FDA draft guidance Pharmacokinetics in patients with Impaired Renal Function indicating that a PK study in patients with renal impairment should be conducted for most drugs intended for chronic use.

The benefit-risk assessment for this study is favorable.

1.6. Compliance

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

2. OBJECTIVES

The primary objective of this study is as follows:

- To evaluate the pharmacokinetics (PK) of GS-9876 in subjects with impaired renal function relative to matched healthy controls.

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of GS-9876 in subjects with normal and impaired renal function.

3. STUDY DESIGN

3.1. Study Design

This protocol describes a Phase 1, open-label, parallel-group, adaptive, single-dose, multi-center, pharmacokinetic study in subjects with renal impairment and matched healthy controls. A maximum of 60 subjects using an adaptive design that includes up to 3 enrolled cohorts.

- Cohort 1 (Moderate Renal Impairment): Up to 20 subjects (10 per group, moderate renal impairment and matched healthy controls) for 8 evaluable subjects per group.

- Adaptive Cohort 2 (Severe Renal Impairment): Up to 20 subjects (10 subjects with severe renal impairment and up to 10 matched healthy control subjects if none of the healthy subjects from a previous cohort is an appropriate match for a severe impairment subject) for 8 evaluable subjects per group.

- Adaptive Cohort 3 (Mild Renal Impairment): Up to 20 subjects (10 subjects with mild renal impairment and up to 10 matched healthy control subjects if none of the healthy subjects from a previous cohort is an appropriate match for a mild impairment subject) for 8 evaluable subjects per group.

Adaptive Cohorts 2 and/or 3 will be enrolled as determined by safety and/or PK data in Cohort 1. Specifically, Cohort 2 (Severe Renal Impairment) will be evaluated if supported by safety and/or PK data from Cohort 1 (Moderate Renal Impairment). Cohort 3 (Mild Renal Impairment) will be evaluated if supported by safety and if substantial changes (≥ 2-fold mean difference from matched controls) in the exposure of GS-9876 is observed in subjects with moderate renal impairment in Cohort 1. Cohorts 2 and 3 may not be enrolled or may be enrolled sequentially or in parallel, as governed by safety and PK data in Cohort 1. Each control subject may be matched to multiple renal impaired subjects across different cohorts and can be matched to only 1 renal impaired subject within a cohort.

Male and nonpregnant, nonlactating female subjects 18 to75 years of age, inclusive, with normal or impaired renal function will be enrolled into the study. Each subject in the control group will be matched for age (± 10 years), gender, and body mass index (± 20%, ≥ 18 kg/m^2 and ≤ 36 kg/m^2).

An overview of the study design is described below and shown in Figure 3-1 and Figure 3-2.

Figure 3-1. High Level Schema

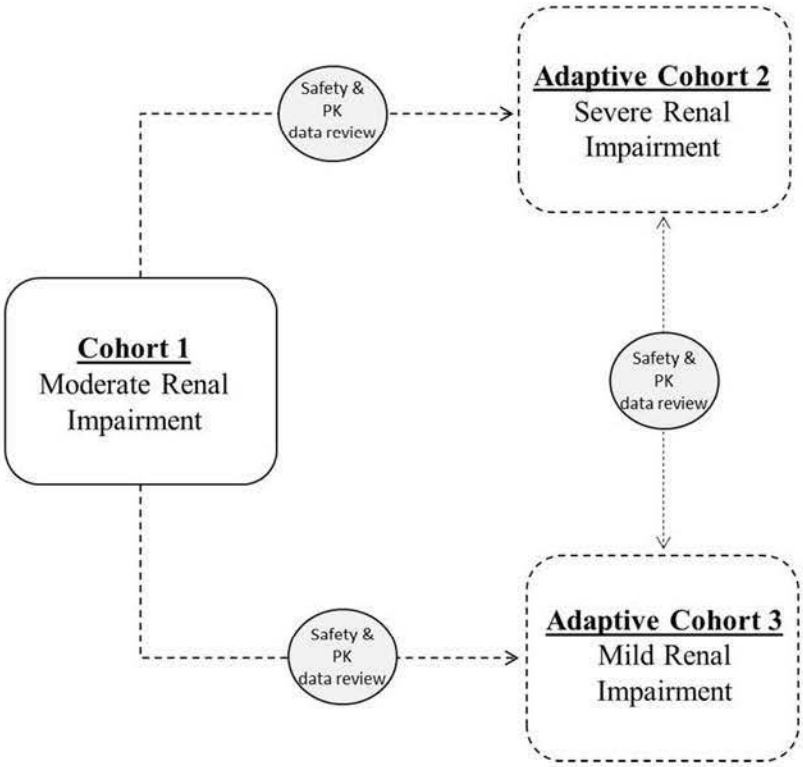
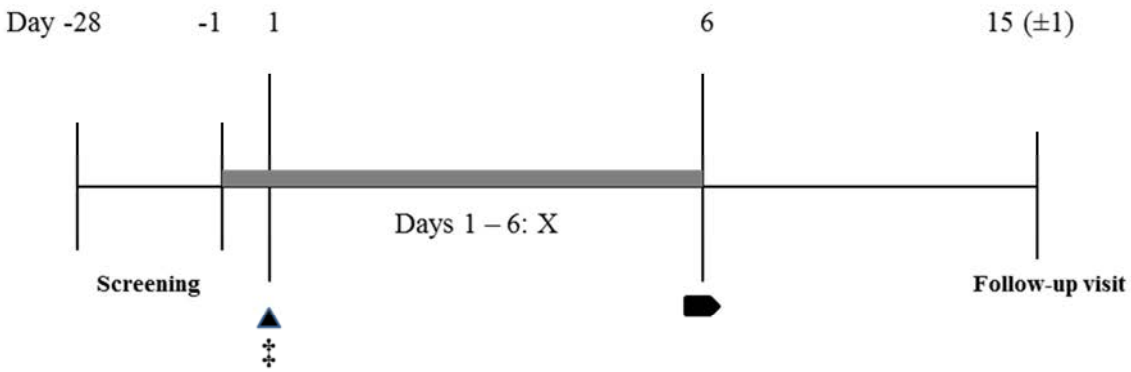


Figure 3-2. Study Schema



▲ GS-9876 20 mg
Clinic Confinement
X Intensive PK Samples
Discharge
‡ Matched healthy control subjects will begin dosing after completion of PK assessments (Day 6) for the subject with renal impairment.

3.2. Study Drug Administration

Following an overnight fast of at least 8 hours (no food or drink except water), study drug will be administered in the morning with 240 mL of water. 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 1 hour before until 2 hours after dosing, except for the 240 mL given with the study treatment.

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

3.3. Clinic Confinement

Following screening and Day -1 procedures, eligible subjects will be confined to the study center beginning Day -1 until completion of assessments on Day 6. Subjects will return 14 (± 1) days after last dose for an in-clinic follow up visit (ie. Day 15).

3.4. Pharmacokinetic Assessments

Pharmacokinetic assessments will occur on assigned study days as outlined in Table 6-1 and Section 6.7.

3.4.1. Plasma Pharmacokinetic Collection

Plasma concentrations of GS-9876 will be measured and PK parameters determined. Plasma concentrations of GS-9876 metabolites may be determined and pharmacokinetics explored, as applicable.

3.4.2. Urine Pharmacokinetic Collection

All urine voided will be collected and pooled for the determination of PK parameters as outlined in Section 6.8.2. Urine concentrations of GS-9876, as well as its metabolites, may be analyzed.

3.5. Safety Assessments

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

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

A total of up to 60 subjects will be enrolled in the study (up to 20 subjects per cohort), consisting of healthy male and nonpregnant, nonlactating female subjects of 18 through 75 years of age, inclusive. If necessary, replacement subjects may be enrolled if subjects do not complete all intensive PK procedures with sponsor approval. Replacement subjects will not be enrolled for subjects who discontinue the study due to study drug-related AEs. Each control subject may be matched to multiple renal impaired subjects across different cohorts and can be matched to only 1 renal impaired subject within a cohort.

Subjects will comprise those with normal and impaired renal function. Those with impaired renal function will be categorized based on estimated creatinine clearance (CL_{cr}) using the Cockcroft-Gault (C-G) equation for renal function as recommended by the Food and Drug Administration (FDA) and international guidance documents. Classification of renal impairment is defined as follows:

- Mild: CL_{cr} 60-89 mL/min
- Moderate: CL_{cr} 30-59 mL/min
- Severe: CL_{cr} 15-29 mL/min

Severe renal impairment subjects requiring or anticipated to require dialysis within 90 days of study entry are not eligible. The control group will consist of matched control subjects with normal renal function ($CL_{cr} \geq 90$ mL/min).

Each subject in the control group will be matched for age (± 10 years), gender, and body mass index (± 20%, ≥ 18 kg/m^2 and ≤ 36 kg/m^2).

4.2. Inclusion Criteria

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

4.2.1. All Subjects

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 between 18 through 75 years of age, inclusive at screening

3) Must be able to comply with the smoking restrictions at the study site.

4) Have a calculated body mass index (BMI) of ≥ 18 kg/m^2 and ≤ 36 kg/m^2 at screening

5) Females of childbearing potential (as defined in Appendix 3) must have a negative serum pregnancy test at screening and clinic admission (Day -1).

6) Female subjects must refrain from egg donation and in vitro fertilization during treatment and until at least 36 days after the last dose of study drug.

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 3.

8) Male subjects must refrain from sperm donation from clinic admission (eg, Day −1), 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 in consultation with the sponsor

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

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

13) Subjects must have the following laboratory parameters at screening:

   a) Hemoglobin ≥ 8.0 g/dL (International System of Units [SI]: ≥ 80 g/L)

   b) White blood cells ≥ 3.0 x 10^3 cells/mm^3 (SI: ≥ 3.0 × 10^9 cells/L)

   c) Neutrophils ≥ 1.5 x 10^3 cells/mm^3 (SI: ≥ 1.5 × 10^9 cells/L)

   d) Lymphocytes ≥ 0.5 x 10^3 cells/mm^3 (SI: ≥ 0.5 × 10^9 cells/L)

   e) Platelets ≥ 100 x 10^3 cells/mm^3 (SI: ≥ 100 × 10^9 cells/L)

   f) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) < 1.5 × ULN

   g) Total bilirubin level < 2 × ULN

4.2.2. For Subjects with Renal Impairment

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

1) Must have diagnosis of chronic (> 6 months), stable renal impairment with no clinically significant change in renal function status within 90 days prior to study drug administration (Day 1).

2) Have a creatinine clearance (CL_{cr}) < 90 mL/min (using the Cockcroft-Gault method {Cockcroft et al 1976}) based on serum creatinine and actual body weight as measured at screening, ie,

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

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

- Mild: CL_{cr} 60-89 mL/min
- Moderate: CL_{cr} 30-59 mL/min
- Severe: CL_{cr} 15-29 mL/min

4.2.3. For Healthy Matched Controlled Subjects (Subjects with Normal Renal Function)

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

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

2) Have a creatinine clearance (CL_{cr}) ≥ 90 mL/min (using the Cockcroft-Gault method {Cockcroft et al 1976}) based on serum creatinine and actual body weight as measured at screening, ie,

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

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

3) Match in age (± 10 years), gender, and body mass index (± 20%, ≥ 18 kg/m^2 and ≤ 36 kg/m^2).

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) Be a lactating female

2) Have received any 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 as judged by the investigator

4) Have a positive test result for human immunodeficiency virus type 1 (HIV-1) antibody, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) 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) Implanted defibrillator or pacemaker

   g) Liver disease, including Gilbert disease

   h) Severe peptic ulcer disease, gastroesophageal reflux disease, or other gastric acid hypersecretory conditions requiring prolonged (> 6 months) medical treatment.

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

   j) History of any major bleeding event defined as Grade 3 severity and above (as defined by the modified CTCAE 4.03[Appendix 4]) within the last year or personal or family history of bleeding disorder

   k) Current use of chronic anticoagulant or anti-platelet agent, not including daily aspirin for cardiac prophylaxis.

8) 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 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.

9) Recent significant changes in the use of nicotine or nicotine containing products (ie, initiation, substantial increase or decrease or cessation of use) in the 90 days prior to study drug dosing, or anticipated significant changes in the use of nicotine or nicotine containing products during the course of the study through the follow-up visit.

4.3.2. For Subjects with Renal Impairment

1) Require or are anticipated to require dialysis within 90 days of study dosing

2) Require during the study or have received moderate or strong inhibitors or inducers of CYP3A within 2 weeks prior to study drug administration.

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

4.3.3. For Healthy Matched Controlled Subjects (Subjects with Normal Renal Function)

1) Have taken any prescription medications or over-the-counter medications, including herbal products and antacids, 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 and/or stable hormone replacement therapy in peri- /post-menopausal females

5. STUDY DRUGS

5.1. Enrollment and Treatment Code

This is a non-randomized, open-label study.

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.

Once eligibility has been confirmed following completion of the study procedures on Day -1, subjects will be enrolled and assigned a subject number.

All Day -1 tests and procedures must be completed prior to the administration of the first dose of GS-9876 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. Study drug will be dispensed by the study pharmacist, or designee, in an open-label fashion to subjects.

5.2. Description and Handling of GS-9876

5.2.1. Formulation

GS-9876 will be supplied as 10 mg tablets that are round, plain-faced and film-coated blue. Each tablet contains 10 mg of GS-9876 free base as the succinate form (GS-9876-02). The GS-9876 tablets contain commonly used excipients including microcrystalline cellulose, mannitol, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and FD&C blue #2/indigo carmine aluminum lake.

5.2.2. Packaging and Labeling

GS-9876 tablets are packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

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

5.2.3. Storage and Handling

GS-9876 tablets should be stored at controlled room temperature of 25 ºC (77 ºF); excursions are permitted between 15 ºC and 30 ºC (59 ºF and 86 ºF). Storage conditions are specified on the label.

Until dispensed to the subjects, all drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drugs and to ensure proper product identification, the drug products should not be stored in a container other than the containers in which they are 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. Dosage and Administration of Study Drug

Following completion of Screening and Day -1 assessments, eligible subjects will be enrolled in 1 of the 3 cohorts and receive a single oral dose of GS-9876 20 mg (2 × 10 mg tablet) in a fasted state on Day 1.

5.4. Fasting and Meals

Study drug will be administered in the morning with 240 mL of water. 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 1 hour before and 2 hours after dosing, except for the 240 mL given with the study drug. Water may be freely consumed following the 2-hour blood draw and for the remainder of the collection period.

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).

5.5. Accountability for Study Drug

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

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

- Record the date received and quantity of study drug bottles

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

5.5.1. Investigational Medicinal Product Return or Disposal

Please refer to Section 9.1.7

5.6. Concomitant Medications and Other Protocol Restrictions

5.6.1. Concomitant Medications

5.6.1.1. Subjects with Normal Renal Function

The following medications are excluded while subjects are participating in the study (from screening until discharge). This list does not include medications such as anti-HIV agents that would be contraindicated for other exclusion criteria.

- Any prescription medications and over-the-counter medications, including herbal products and antacids, with the exception of vitamins, and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications and/or stable hormone replacement therapy in peri- / post-menopausal females. 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.

5.6.1.2. Subjects with Renal Impairment

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 electronic Case Report Forms (eCRFs).

The following medications are excluded while subjects are participating in the study (from screening until discharge). This list does not include medications such as anti-HIV agents that would be contraindicated for other exclusion criteria.

- Any and all illegal or illicit drug use, including use of prescription drugs outside the care of the prescribing physician.
- Current alcohol or substance abuse judged by the Investigator to potentially interfere with subject compliance (eg. amphetamines, cocaine, opiates).
- Moderate or strong CYP3A4 inhibitors or inducers within 2 weeks prior to study drug administration and through the follow up visit.

- Concurrent therapy with any anti-coagulant (eg, coumadin [warfarin], any Vitamin K antagonist, any novel oral anticoagulant, any heparin or low molecular heparins, inhibitors of factor Xa)
- Concurrent therapy with any anti-platelet therapy (eg, adenosine diphosphate [ADP] receptor inhibitors, phosphodiesterase inhibitors, PAR-1 antagonists, Glycoprotein 2b/3a inhibitors) with the exception of ≤ 100 mg daily of aspirin and other NSAIDs
- Subjects with renal impairment with co-morbid diseases requiring medication(s) must be taking the medication(s) without a change in dose for > 3 months prior to screening.

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

Table 5-1 includes examples of prohibited medicines in subjects with renal impairment.

Table 5-1. Examples of Prohibited Medications for Subjects with Renal Impairment

Drug Class	Agents Disallowed
Strong CYP3A4 Inhibitors[a]	clarithromycin, conivaptan, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole, telaprevir, boceprevir, grapefruit juice, idelalisib, Viekira Pak (ombitasvir, paritaprevir, ritonavir, dasabuvir), troleandomycin, mibefradil
Strong CYP3A4 Inducers[b]	carbamazepine, phenytoin, rifampin, fosphenytoin, pentobarbital, primidone, rifabutin, rifapentine, phenobarbital, mitotane, avasimibe, St. John's Wort, enzalutamide
Moderate CYP3A4 Inhibitors[a]	fluconazole, erythromycin, diltiazem, dronedarone, aprepitant, casopitant, imatinib, verapamil, tofisopam, ciprofloxacin, cimetidine, cyclosporine, Schisandra sphenanthera, crizotinib, netupitant, nilotinib, isavuconazole
Moderate CYP3A4 Inducers[b]	bosentan, thioridazine, nafcillin, modafinil, semagacestat, genistein
Anti-platelet[c]	adenosine diphosphate (ADP) receptor inhibitors, phosphodiesterase inhibitors, PAR-1 antagonists, Glycoprotein 2b/3a inhibitors
Anti-coagulant	warfarin, any Vitamin K antagonist, any novel oral anticoagulant, any heparin or low molecular heparins, inhibitors of factor Xa

a In vitro data indicate GS-9876 is a substrate of CYP3A4. Co-administration of CYP3A4 inhibitors may increase GS-9876 exposure. These agents are prohibited while subject is on study drug and 2 weeks prior to study drug administration.
b In vitro data indicate GS-9876 is a substrate of CYP3A4. Co-administration of CYP3A4 inducers may decrease GS-9876 exposure. These agents are prohibited while subject is on study drug and 2 weeks prior to study drug administration.
c ≤ 100 mg aspirin and NSAIDs are permitted

5.6.2. Other Protocol Restrictions

- Subjects will be required to refrain from the consumption of food and beverages containing alcohol products 72 hours prior to the first dose of study drug and during the course of the study through the follow-up visit.
- Subjects must be able to comply with the smoking restrictions at the study site.

- Subjects will be required to refrain from consumption of grapefruit juice, grapefruits, and Seville orange juice 96 hours prior to the first dose of study drug and during the course of the study through the follow-up visit.
- While confined at the study center, tea, coffee, chocolate, and other foods and beverages containing caffeine and other methyl xanthines will be prohibited on each dosing day. At all other times, caffeine-containing beverages and foodstuffs may be served or withheld in accordance with normal study center practice. Caffeine-containing beverages and foodstuffs will not be restricted while subjects are outside of the clinic.
- Subjects will be encouraged to avoid strenuous or prolonged exercise, as well as saunas, steambaths, and sunbathing or other prolonged ultraviolet exposure, eg, in a tanning salon, from the screening evaluation until completion of the follow-up visit, as these activities are known to affect certain clinical laboratory test parameters, (eg, creatine kinase) and will provide false indicators of a potentially treatment-related toxicity.

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

6. STUDY ASSESSMENTS

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

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

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

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

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

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

6.1. Subject Enrollment and Treatment Assignment

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

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

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

Table 6-1. Schedule of Assessments

Study Procedure	Screen[a]	Day −1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6[b]	Day 15 (±1) Follow-Up[c]	ET[d]
Written Informed Consent	X									
Medical History	X									
Complete Physical Exam	X	X						X	X	X
Symptom-Driven Physical Examination[e]			X	X	X	X	X			
Height	X									
Weight	X	X								
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X
HIV-1, HBV, and HCV Testing	X									
Hematology[g]	X	X	X		X			X	X	X
Coagulation	X	X	X		X			X	X	X
Chemistry[h]	X	X	X	X	X			X	X	X
Urinalysis	X	X	X	X	X			X	X	X
Serum Pregnancy Test[i]	X	X						X	X	X
Creatinine Clearance	X	X								
Urine Drug and Alcohol Screen	X	X								
12-Lead ECG	X	X	X					X	X	X
Study Drug Administration			X							
Intensive Plasma PK[j]			X	X	X	X	X	X		
Urine PK[k]			X	X	X	X	X	X		

Study Procedure	Screen[a]	Day −1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6[b]	Day 15 (±1) Follow-Up[c]	ET[d]
Review Study Restrictions	X	X						X	X	
Clinic Confinement		X	X	X	X	X	X			
Review AEs & Concomitant Medications[l]	X	X	X	X	X	X	X	X	X	X

a Prospective subjects should be screened no more than 28 days prior to administration of the first dose of study drug.
b Subjects will be discharged from the clinic on Day 6, following all morning assessments.
c 14(± 1) days after the last administration of study drug, all subjects will return for an in-clinic follow-up visit and complete procedures as outlines.
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 Vital signs include blood pressure, heart rate, respiration rate, and temperature.
g Hematology: CBC with differential.
h See Section 6.9.5 for specifics.
i Females of child-bearing potential only.
j Intensive PK sampling will occur relative to the morning dosing of GS-9876 at the following time points:
Day 1: 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96 and 120 hours postdose.
k All urine voided will be collected and pooled relative to dosing of GS-9876 at the following collection intervals:
Day 1: Predose void, 0-6, 6-12, 12-24, 24-48, 48-72, 72-96, and 96-120 hours postdose
l 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 eCRF.

All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7, Adverse Events and Toxicity Management for additional details.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

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

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

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

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

Eligible subjects meeting all of the inclusion criteria and none of the exclusion criteria will be instructed on all protocol requirements, including the restrictions on concomitant medication usage and other substances as well as consumption of food or beverages containing alcohol, caffeine, or xanthine. Subjects will be asked to arrive at the study center on Day -1 for admission assessments.

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 -1. 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

Clinic confinement is outlined in Section 3.3, as well as in Table 6-1.

6.3. Check-in Assessments

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

6.4. Treatment Assessments

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

6.5. Posttreatment Assessments

All subjects will return 14 days (±1) after last dose of study drug for an in-clinic follow-up visit. Study procedures and assessments are outlined in Table 6-1.

6.6. Assessments for Premature Discontinuation from Study

If a subject discontinues study treatment dosing, for example as a result of an AE, every attempt should be made to keep the subject in the study and continue to perform the required study-related procedures until stabilization per the investigator. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. Evaluations indicating abnormal results believed to be possibly or probably related to study treatment at the ET visit should be repeated weekly or as often as deemed appropriate by the investigator until the abnormality resolves, returns to baseline visit levels, or is otherwise explained.

If the subject withdraws 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. Criteria for Discontinuation of Study

Study confinement may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest
- Subject request to discontinue for any reason
- Subject noncompliance

- Pregnancy during the study (refer to Appendix 3)
- Investigator discretion
- Discontinuation of the study at the request of Gilead, regulatory agency, or an IRB/EC

6.8. Pharmacokinetic Assessments

6.8.1. Plasma PK Collection

Plasma concentrations of GS-9876 will be determined and PK parameters estimated. Plasma concentrations of GS-9876 metabolites may be determined, if necessary. Intensive PK sampling will occur relative to the morning dose of GS-9876 at the following time points:

Intensive PK sampling will occur relative to dosing of GS-9876 at the following time points:

Day 1: 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96 and 120 hours postdose

Protein binding of GS-9876 (and its metabolites, as applicable) will be assessed at or near their T_{max} timepoint(s) as well as another later time point.

6.8.2. Urine Pharmacokinetic Collection

All urine voided will be collected and pooled relative to dosing of GS-9876 at the following collection intervals:

Day 1: Pre-dose void, 0-6, 6-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours postdose

Urine concentrations of GS-9876 and/or metabolites may be determined and PK parameters estimated.

6.9. Safety Assessments

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

6.9.1. 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.

6.9.2. 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:

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

- 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.

6.9.3. 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 for a minimum of 5-10 minutes. Subject position for measurement should be kept consistent throughout the study. Refer to Table 6-1 for vital signs collection time points.

6.9.4. Body Mass Index

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

6.9.5. Clinical Laboratory Tests/Assessments

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

6.9.5.1. Blood Sampling

Blood samples will be collected for the following laboratory analyses:

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

- Coagulation panel: D-Dimer, prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR)

- Chemistry (fasting): alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, total protein, albumin, lactic acid dehydrogenase (LDH), creatine phosphokinase (CPK), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine (see below), glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × upper limit of normal [ULN])

- Serum pregnancy test (females of childbearing potential only)

- HIV-1, HBV(HbsAg and HBcAb), and HCV testing (screening only)

6.9.5.2. Urine Samples

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

6.9.6. Creatinine Clearance and Estimated Glomerular Filtration Rate

Weight will be collected at screening and upon admission to calculate creatinine clearance (CL_{cr}) and estimate glomerular filtration rate (eGFR), however CL_{cr} will be used for inclusion criteria.

eGFR (mL/min/1.73 m^2) = 175 × $(*S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American)

*S_{cr} – serum creatinine

6.9.7. 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 5.6.1 for more information about concomitant medications.

6.10. Sample Storage

PPD

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An 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, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.4)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and that is not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

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

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

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

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to 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

The severity grading of AEs will be assessed as Grade 1, 2, 3, 4 or 5 using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. 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 only modification to the CTCAE criteria is the addition of a Grade 1 upper respiratory, as described in Appendix 4.

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 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 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 eCRF database and Gilead DSPH as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

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

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if 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 DSPH.

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

7.3.1.3. Electronic Serious Adverse Event (eSAE) Reporting Process

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

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

Gilead DSPH	Email: PPD Fax: PPD

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

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

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by 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 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.

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

7.5. Toxicity Management

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead Sciences 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 or 4 clinically significant laboratory abnormalities should be managed as outlined in Appendix 2.

Severity should be recorded and graded according to the modified CTCAE Grading Scale as described in (Appendix 4).

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

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

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

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

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

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 labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

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

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

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

Refer to the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

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

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

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

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH by emailing PPD or faxing PPD

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

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

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPHwithin 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 7.6.2 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is as follows:

- To evaluate the PK of GS-9876 in subjects with impaired renal function relative to matched, healthy controls

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of GS-9876 in subjects with normal and impaired renal function

8.1.2. Primary Endpoint

The primary endpoints are PK parameters AUC_{last}, AUC_{inf}, and C_{max} for GS-9876.

8.1.3. Secondary Endpoint

The secondary endpoints include incidences of AEs, laboratory abnormalities, abnormal findings in vital signs and safety ECG monitoring.

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Enrolled

The All Enrolled Analysis Set includes all subjects enrolled into the study after screening. This is primary analysis set for listings.

8.2.1.2. Safety

The Safety Analysis Set will include all enrolled subjects who received 1 dose of GS-9876.

8.2.1.3. Pharmacokinetics

The PK Analysis Set will include all enrolled subjects who received 1 dose of GS-9876 and had at least 1 nonmissing PK concentration datum reported by PK lab.

8.3. Data Handling Conventions

For summary statistics, PK concentration values below the limit of quantitation (BLQ) will be treated as zero at predose and 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.

Demographic summaries will include sex, race/ethnicity, enrollment, and age.

8.5. Interim Analysis

Review of available safety and PK data will be conducted by the sponsor to facilitate the decision of enrolling adaptive cohorts.

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 renal function group using Safety Analysis Set.

8.6.1. Extent of Exposure

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

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be attached to the clinical database.

Adverse event data will be listed by subject. Treatment-emergent AEs (TEAEs), serious TEAEs, and TEAEs leading to discontinuation of treatment will be summarized by treatment, 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 renal function group at scheduled visits. The incidence of treatment-emergent graded laboratory abnormalities will be summarized by treatment.

8.6.4. Other Safety Evaluations

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

8.7. Pharmacokinetic Analysis

Plasma concentrations and PK parameters for GS-9876 will be listed and summarized by renal function group using descriptive statistics (eg, sample size, mean, SD, % coefficient of variation, median, first quartile [Q1], third quartile [Q3], minimum, and maximum).

In addition, an analysis of variance appropriate for a parallel design will be fitted to the natural logarithmic transformation of PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) for GS-9876. Two-sided 90% CIs will be calculated for the GLSM ratios of PK parameters between renal impairment group versus the control (normal renal function) group.

If determined, urine concentrations of GS-9876 over sampling time will be listed and summarized by renal function group using descriptive statistics. Urine concentrations versus time profiles of GS-9876 and its metabolites (if applicable) may be displayed by renal function group, as appropriate. When possible, urinary PK parameters (Ae, CLr and % $Dose_{excreted}$) will be calculated.

Protein binding of GS-9876 in plasma (at or near T_{max} and a later timepoint) will also be summarized by renal function group using descriptive statistics.

The PK of GS-9876 metabolites (if applicable) may also be evaluated.

8.8. Sample Size

With 16 (8 per group) evaluable subjects, the estimated two-sided 90% CI of the GLSM ratio of test versus reference groups, with regards to PK parameters (AUC and C_{max}) would be within (50%, 200%) with over 95% probability. This calculation is based on a two group t-test of equivalence in means at the significance level of 0.05, assuming the expected geometric means ratio of 1.0 and inter-subject SD of no more than 0.35 on a natural logarithm scale. The assumption about the inter-subject SD is supported by previous Gilead study GS-US-379-1372 using the maximum variability for AUC and C_{max} from the closest dose levels (15 mg and 30 mg) of the dose in this study. An overage of 2 subjects per group will be enrolled to accommodate subject drop-outs, thus requiring a total enrollment of 20 subjects (10 per group) for each cohort.

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/EChas 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- or 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.

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, 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, 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 eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. The eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data, whenever possible. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received and the subject has been enrolled. Subsequent to data entry, a study monitor will perform source data verification within the electronic data

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

9.1.7. Study Drug Accountability and Return

Where possible, IMP should be destroyed at the site. At the start of the study, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for disposal or return of unused IMP supplies. 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 as long as performed in accordance with the site's SOP. This can occur only after the study monitor has performed drug accountability during an on-site monitoring visit.

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, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMPs destroyed. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

Both 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.

10. REFERENCES

Arthritis Foundation. Rheumatoid Arthritis Fact Sheet. 2008.

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

Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum 2008;58 (1):15-25.

Karie S, Gandjbakhch F, Janus N, Launay-Vacher V, Rozenberg S, Mai Ba CU, et al. Kidney disease in RA patients: prevalence and implication on RA-related drugs management: the MATRIX study. Rheumatology (Oxford) 2008;47 (3):350-4.

National Institute of Diabetes and Digestive and Kidney Diseases (NIH). Estimating Glomerular Filtration Rate (GFR). Available at: https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx. Accessed 06 October. 2016:

11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 1 Open-label Study to Evaluate the Pharmacokinetics of GS-9876 in Subjects with Impaired Renal Function

GS-US-379-1932, Amendment 1 Protocol, 09 January 2017

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

PPD

PPD

Medical Monitor

12-Jan-2017

Date

INVESTIGATOR STATEMENT

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

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

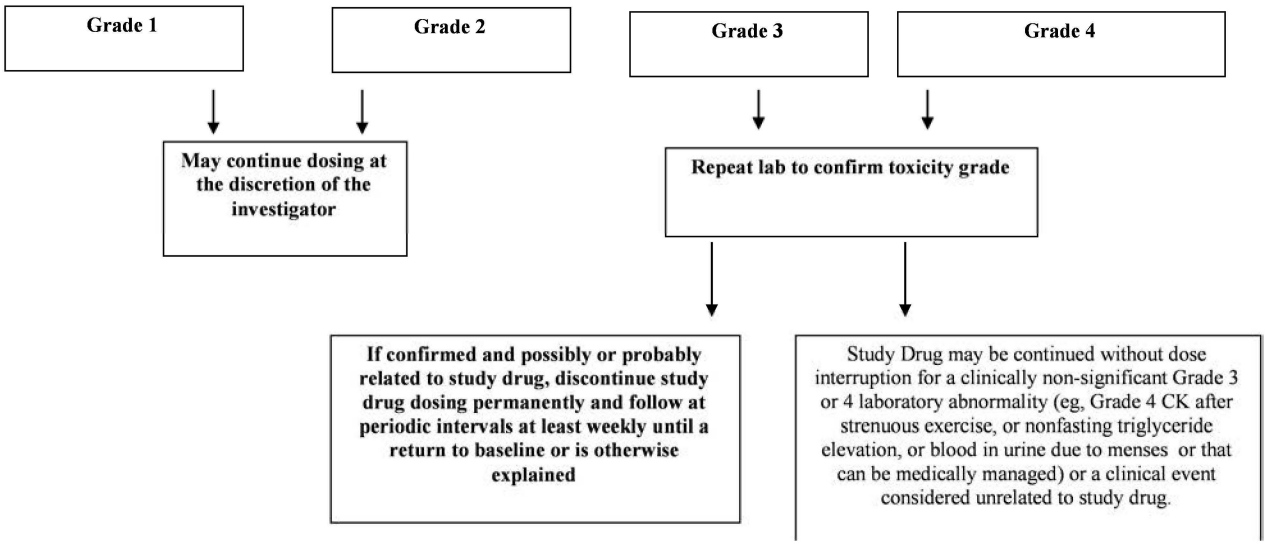
Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Management of Clinical and Laboratory Adverse Events



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

1) Definitions

a) Definition of Childbearing Potential

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

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

b) Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

GS-9876 is contraindicated in pregnancy as its teratogenicity/fetotoxicity profile is unknown.

GS-9876 has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. In this study, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Subjects may remain on their hormonal contraception if they prefer to do so, but will still be required to choose from contraceptive methods delineated below as the efficacy of their hormonal contraception during study dosing is unknown.

Please refer to the latest versions of the GS-9876 IBs for additional information.

b) Contraceptive Methods Permitted for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of *highly effective* contraceptive measures. Women must agree to also not rely on hormone-containing contraceptives as a form of birth control during the study, though they may continue hormonal contraception if they prefer to do so. Women must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Day -1 visit prior to first dose of study drug. Pregnancy tests will be performed as defined by the schedule of assessments (Table 6-1).

Female subjects of childbearing potential must agree to one of the following from Screening until 36 days following 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
- 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 at least 3 months after procedure)

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 36 days after the last dose of study drug.

c) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must agree to use condoms during treatment and until 90 days after the last dose of study drug. Additional contraception recommendations should also be considered if the female partner is of childbearing potential.

Male subjects must also 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.

d) Unacceptable Birth Control Methods

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

e) 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 36 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study or up to 90 days after the last dose of study drug must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1

Appendix 4. Common Terminology Criteria for Adverse Events (CTCAE) v 4.03

CTCAE v4.03 can be accessed from the below link:

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

The only modification to the CTCAE criteria is the addition of a Grade 1 upper respiratory infection as follows:

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.03 AE Term Definition
Upper respiratory infection	Mild symptoms; symptomatic relief (eg, cough suppressant, decongestant)	Moderate symptoms; oral intervention indicated (eg, antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea).