CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Proof-of-Concept Study to Evaluate Safety, Tolerability, and Efficacy of GS-9876 in Subjects with Active Rheumatoid Arthritis on Background Therapy with Methotrexate	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	IND 123903	
EudraCT Number:	2016-001496-75	
Clinical Trials.gov Identifier:	TBD	
Indication:	Rheumatoid Arthritis	
Protocol ID:	GS-US-379-1582	
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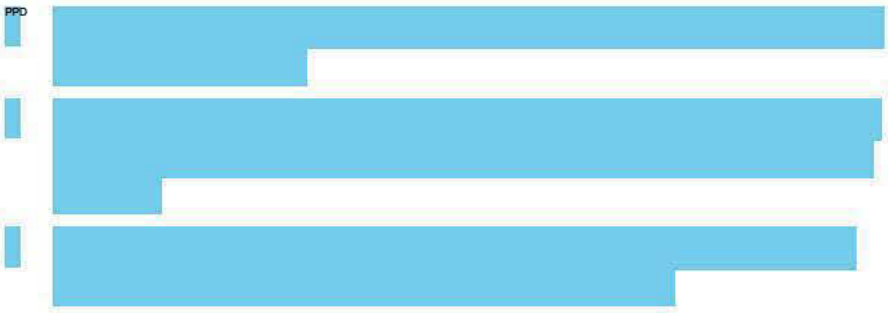
PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Proof-of-Concept Study to Evaluate Safety, Tolerability, and Efficacy of GS-9876 in Subjects with Active Rheumatoid Arthritis on Background Therapy with Methotrexate
IND Number:	IND 123903
EudraCT Number:	Not Available
Clinical Trials.gov Identifier:	Not Available
Study Centers Planned:	Approximately 30-40 centers globally
Objectives:	The primary objective of this study is as follows: • To evaluate the effect of GS-9876 versus placebo for the treatment of signs and symptoms of rheumatoid arthritis (RA) in subjects with active RA as measured by change from baseline in Disease Activity Score for 28 joint count using C-reactive protein (CRP) (DAS28 [CRP]) at Week 12 The secondary objective of this study is as follows: • To evaluate the safety and tolerability of GS-9876 in subjects with RA • To explore the effect of GS-9876 on other disease-specific outcomes in RA The exploratory objectives of this study are: 

Study Design:	This is a randomized, double-blind, placebo-controlled, proof-of-concept (POC) study evaluating the safety, tolerability, and efficacy of GS-9876 in adult male and female subjects with active RA despite MTX therapy who had an inadequate response to MTX (either alone or in combination with biological disease modifying anti-rheumatic drug [bDMARDs]). Approximately 60 subjects will be randomized in a 1:1:1 ratio to receive 30 mg GS-9876, 10 mg GS-9876 or placebo-to-match (PTM) in addition to background therapy with MTX for up to 12 weeks: • GS-9876 (30 mg QD) (N=20) • GS-9876 (10 mg QD) (N=20) • GS-9876 PTM (QD) (N=20) Randomization will be stratified by prior inadequate response to biologic therapy and geographic region. Subjects will be followed for 4 weeks after their last dose of study drug.
Number of Subjects Planned:	Approximately 60 subjects
Target Population:	Subjects with active RA on background MTX therapy who had an inadequate response to MTX (either alone or in combination with bDMARDs).
Duration of Treatment:	Up to 12 weeks
Diagnosis and Main Eligibility Criteria:	Male or non-pregnant female subjects with active RA, between 18 and 75 years of age (inclusive) ***Key Inclusion Criteria include:*** 1) Active RA disease as defined by: a tender joint count (TJC) of ≥ 6 (out of 68), a swollen joint count (SJC) of ≥ 6 (out of 66), and a CRP ≥ 5 mg/l 2) Inadequate response to treatment with oral or parenteral MTX 7.5 to 25 mg/week continuously for at least 12 weeks, with at least 6 weeks at a stable dose prior to the first dose of study drug 3) Subjects must be receiving a folic or folinic acid supplementation at a stable dose. Subjects who are not taking folic or folinic acid at Screening, should be initiated on an adequate dose of folic acid (≥5 mg/week total dose or as per local practice) or equivalent and maintained throughout the study.

	4) Use of oral corticosteroids of no more than 10 mg prednisone or its equivalent per day is allowed if the dose is stable for at least 28 days prior to the first dose of study drug 5) Nonsteroidal Anti-inflammatory Drugs (NSAIDs) or other analgesics (including aspirin ≤ 100 mg daily) are allowed if doses are stable for at least 14 days prior to the first dose of study drug ***Key Exclusion Criteria include:*** 1) Prior treatment with B-cell depleting agents (eg, rituximab), unless more than 6 months prior and documented return of CD19+ cells 2) Prior treatment with any commercially available or investigational SYK inhibitor 3) Current treatment with any other conventional DMARD (cDMARD) other than MTX and/or hydroxychloroquine (HCQ) (unless appropriate wash out as defined in Section 5.5) 4) Current treatment with any bDMARD (unless appropriate wash out as defined in Section 5.5) 5) QT interval corrected for heart rate using the Fredericia formula (QTcF) > 450 msec determined by the average of values at the Screening visit 6) History of any major bleeding event defined as Grade 3 severity and above [as defined by modified the Common Terminology Criteria for Adverse Events (CTCAE) 4.03] within the last year or personal or family history of bleeding disorder 7) If no history of a documented negative tuberculosis (TB) test within the last 12 months or documented course of adequate therapy for either latent or active TB, a Quantiferon must be performed according to local standards. Subjects with a positive Quantiferon at Screening are not eligible 8) Ongoing treatment with moderate or strong CYP3A inducers or inhibitors or within 2 weeks prior to study drug administration Additional inclusion and exclusion criteria are outlined in Section 4 Subject Population.
Study Procedures/ Frequency:	All subjects will complete the following study visits: Screening, Day 1 (first dose), and on-treatment visits at Weeks 2, 4, 8, and 12. All subjects will be followed for safety for an additional 4 weeks after their last dose of study drug. Screening assessments will be completed no more than 28 days prior to the Day 1 visit and will include a complete physical examination (PE), joint count assessment, medical history, vital signs, height and weight, electrocardiogram (ECG), adverse events (AEs) related to

	screening procedures, concomitant medications, safety laboratory tests (including hematology, chemistry, and coagulation), CRP, serology (HIV, HCV, HBV), leukocyte subsets, biomarkers, RNA, TB test as applicable and as outlined in the protocol, urinalysis, urine drug screen, and CD19 count as applicable and as outlined in the protocol. Pregnancy testing will be performed for females of childbearing potential. On-treatment assessments include a symptom driven PE, joint count assessment, disease-specific questionnaires and activity scales, vital signs, ECGs, AEs, concomitant medications, safety laboratory tests (including hematology, chemistry, and coagulation), leukocyte subsets (Day 1 and Week 12), quantitative immunoglobulins (Day 1 and Week 12 or ET), RNA (Day 1, Week 4, and Week 12 or ET), RF/CCP [Day 1 and Week 12 or ET], CRP, urine pregnancy test, and biomarkers (Day 1, Week 4, and Week 12 or ET). Additional testing will include PK sampling (Day 1, Weeks 2, 4, 8 and 12 or ET). Post-treatment assessments include symptom driven PE, vital signs, ECGs, AEs, concomitant medications, safety laboratory tests (including hematology, chemistry, and coagulation), CRP, and urine pregnancy test where indicated. For subjects who provide their additional and specific consent, PPD For subjects who provide their additional and specific consent, PPD
Test Product, Dose, and Mode of Administration:	GS-9876 30 mg (1 x 30 mg tablet), administered orally once daily GS-9876 10 mg (1 x 10 mg tablet), administered orally once daily
Reference Therapy, Dose, and Mode of Administration	GS-9876 PTM (1 tablet), administered orally once daily
Required Background therapy	MTX 7.5 to 25 mg, administered orally or parenterally once a week
Criteria for Evaluation:	
Safety:	Safety will be assessed through the reporting of AEs, clinical laboratory tests, PEs, vital sign assessments, and ECGs at various time points during the study. Concomitant medication usage will also be documented throughout the study.

Efficacy:	The primary endpoint is change from baseline in DAS28 (CRP) at Week 12. The secondary endpoints include: • The proportion of subjects who achieve ACR 20/50/70 at Week 12 • Change from baseline in Heath Assessment Questionnaire - Disability Index (HAQ-DI) score at Week 12
Pharmacokinetics:	Plasma concentrations of GS-9876 will be determined.
Exploratory:	PPD [redacted]
Statistical Methods:	The primary endpoint is change from baseline in DAS28 (CRP) at Week 12. The primary analysis will consist of a superiority test of each of the GS-9876 doses compared to placebo based on the change from baseline in DAS28 (CRP) at Week 12.
	All continuous endpoints will be summarized using an 8-number summary [n, mean, standard deviation (SD), median, 1st quartile (Q1), 3rd quartile (Q3), minimum, maximum] by treatment group. All categorical endpoints will be summarized by the number and percentage of subjects who meet the endpoint definition. Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, SD, median, Q1, Q3, minimum, maximum) for continuous data by treatment group. Sample size is determined based on the superiority test of one dose of GS-9876 compared to placebo based on the change from baseline in DAS28 (CRP) at Week 12. When assuming a difference of 1.2 between the two groups and a common standard deviation of 1.35, 20 subjects in each of the GS-9876 groups and 20 in the placebo group are required to obtain 78% power at a 2-sided 0.05-level. Therefore, the total sample size will be 60 (20 per treatment group).

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
β-hCG	beta-human chorionic gonadotropin
μM	micromolar
ACPA	anti-citrullinated protein antibody
ACR	American College of Rheumatology
ACR 20/50/70	American College of Rheumatology 20/50/70% improvement
ADP	adenosine di-phosphate
AE	adverse event
AhR	aryl hydrocarbon receptor
AKT	protein kinase B
ALT	alanine aminotransferase
APC	antigen-presenting cell
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
$AUC_{0\text{-last}}$	area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration
BCR	B-cell receptor
BCRP	breast cancer resistance protein
BDC	bile duct-cannulated
bDMARD	biological disease modifying anti-rheumatic drug
BLNK	B-cell linker protein
BLQ	below the limit of quantitation
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CCP	cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
CFR	Code of Federal Regulations
CG	Cockcroft-Gault
CIA	collagen-induced arthritis
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear cell concentration of drug
CMH	Cochran–Mantel–Haenszel
CNS	central nervous system
CRO	contract research organization
CRP	C-reactive protein

CTCAE	Common Toxicity Criteria for Adverse Events
CYP	cytochrome P450
DAS28	Disease Activity Score for 28 joint count
DMARD	disease modifying anti-rheumatic drug
DMC	Data Monitoring Committee
DSPH	Drug Safety and Public Health
EC_{50}	estimated concentration of drug for a half maximal response
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ERK	extracellular signal-regulated kinase
eSAE	electronic serious adverse event
ESR	erythrocyte sedimentation rate
ET	early termination
EU	European Union
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
g	gram
GCP	Good Clinical Practice
Gilead	Gilead Sciences, Inc.
GLP	Good Laboratory Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBV	hepatitis B virus
HCQ	hydroxychloroquine
HCV	hepatitis C virus
HDPE	high density polyethylene
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
IB	Investigator's Brochure
IC	immune complex
IC_{50}	concentration that results in 50% inhibition
ICH	International Conference on Harmonization
ICH E3	ICH Guideline for Structure and Content of Clinical Study Reports
ie	id est (that is)
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
IMP	investigational medicinal product

INR	International Normalized Ratio of prothrombin time
IR	inadequate response
IRB	Institutional Review Board
IU	international units
IUD	intrauterine device
IXRS	Interactive Web and Mobile Response System
kg	kilogram
L	liter
LAM	lactational amenorrhea method
LLT	lower-level term
MAPK	mitogen-activated protein kinase
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MEK	MAPK/ERK kinase
mg	milligram
MMRM	mixed model repeated measures
msec	millisecond
MTX	methotrexate
ng	nanogram
nM	nanomolar
NOEAL	no-observed-adverse-effect-level
NSAID	nonsteroidal anti-inflammatory drug
OATP	organic anion transporting polypeptide
PAR-1	protease-activated receptor
PD	pharmacodynamics
PE	physical examination
P-gp	P-glycoprotein
PK	pharmacokinetics
PKC	protein kinase C
POC	proof-of-concept
prn	pro re nata (as needed)
PT	preferred term or prothrombin time
PTM	placebo-to-match
PTT	partial thromboplastin time
PXR	pregnane X receptor
Q1	first quartile
Q3	third quartile
QD	quaque die (each day)

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	corrected QT interval
QTcF	QT interval corrected for heart rate using the Fridericia formula
RA	rheumatoid arthritis
RBC	red blood cell
RF	rheumatoid factor
RNA	ribonucleic acid
s	second
SADR	serious adverse drug reaction
SAE	serious adverse event
SD	standard deviation
SDAI	Simplified Disease Activity Index
SJC	swollen joint count
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNF	tumor necrosis factor
UGT	uridine disphosphate glucuronosyltransferase
ULN	upper limit of normal
US, USA	United States, United States of America
VAS	visual analog scale
WBC	white blood cell

1. INTRODUCTION

1.1. Background

Rheumatoid Arthritis is a chronic, systemic inflammatory disease that affects approximately 1.3 million adults in the United States (US) {Helmick et al 2008}. RA 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. Patients 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 patients respond adequately (or maintain response) to current therapies and some patients 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.

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 RA resulting in pleiotropic anti-inflammatory effects.

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 and Toxicology

1.2.2.1. Preclinical Pharmacology and Safety Pharmacology

In biochemical assays, GS-9876 is a selective and potent 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. The potency of GS-9876 to inhibit SYK activation was also assessed in human and rat whole blood. Levels of autophosphorylation and activation of SYK on tyrosines (Y)525/6 in blood samples preincubated with GS-9876 showed potent inhibition of phosphoSYK -Y525/6 levels in human and rat whole blood with EC_{50} values of 171 nM and 230 nM, respecitively. Studies with human whole blood also showed that GS-9876 inhibited anti-IgD/BCR-induced CD69 expression on B-cells (geometric mean EC_{50} = 301 nM) and anti-FceRI-stimulated CD63 expression on basophils (geometric mean EC_{50} = 73.2 nM in 25% human blood and 221.8 nM in 67% blood).

The ability of GS-9876 to inhibit SYK signaling in primary human B-cells, lymphocytes, and macrophages was assessed in vitro. GS-9876 inhibited anti-IgM-induced BCR/SYK-mediated phosphorylation and activation of multiple downstream signaling pathways in primary human B-cells including AKT, BLNK, BTK, ERK, MEK, and PKC with EC_{50} values ranging from 24 to 51 nM. GS-9876 also suppressed anti-IgM-induced CD69 and CD86 expression on human peripheral blood B-cells with EC_{50} values of 112 nM and 164 nM, respectively. BCR and CD40 costimulation of B-cell proliferation and anti-CD3/anti-CD28 costimulation of T-cell proliferation was also inhibited by GS-9876 with EC_{50} values of 108 nM and 1291 nM, respectively, demonstrating a 12-fold relative functional selectivity of GS-9876 for B-cells compared to T-cells. In immune complex (IC)-stimulated cytokine release assays in primary human monocyte differentiated macrophages, GS-9876 inhibited IC-stimulated TNF-α, IL-1, and IL-6 secretion with geometric mean EC_{50} values of 121 nM, 93 nM, and 909 nM, respectively, demonstrating that GS-9876 inhibition of SYK blocks B-cell and macrophage receptor signaling in vitro with similar potencies.

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, respiratory, and CNS systems. 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. Preclinical 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 highest proposed dose 30 mg dose, estimated exposure margins are 2.4-/5.9- fold based on exposures at the NOAELs in the 26 week study in male/female rats. Patients 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. However in the ongoing 39-week study, one 15 mg/kg/day monkey was euthanized moribund during Week 22 with persistent fecal changes, weight loss, deteriorating clinical condition, and large bowel inflammation. All other animals survived to their scheduled necropsy after 39-weeks dosing. For the highest proposed dose 30 mg dose, the estimated exposure margin is 2.7-fold based on exposures at the 15 mg/kg/day NOAEL in the 13-week monkey study. Although the relationship of the moribund animal to GS-9876 treatment is uncertain, Gilead considers it prudent to limit exposures to mean exposures achieved in monkeys at the 10 mg/kg/day mid-dose at Week 13 of the 39-week study (6750 ng.h/mL), which were 1.8-fold above estimated exposures at the highest proposed dose 30 mg dose.

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 30 mg once daily (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)	2.4/5.9 (male/female)
Cynomolgus Monkey	Once daily x 13 weeks	Oral	15[c]	10,100	2.7

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 observed steady-state exposure (AUC_{tau}) in humans of 3708 ng•h/mL at 30 mg once daily in study GS-US-379-1900.
c One animal was euthanized moribund during Week 22 at the 15 mg/kg/day dose level.

1.2.2.3. Preclinical Drug Metabolism and Pharmacokinetics

Consistent with the high absorption observed in nonclinical species, GS-9876 shows high permeability and low efflux transport across human Caco-2 cell monolayers. Efflux is likely mediated by P-gp and BCRP.

The whole blood to plasma ratios determined in rats, dogs, cynomolgus and rhesus monkeys, and humans ranged from 0.83 in rats to 2.38 in cynomolgus monkeys. GS-9876 plasma protein binding at 2 μM is moderate in all species with the free fraction ranging from 11.8% in rat to 38.5% in dog. In human plasma, GS-9876 has an average free fraction of 20.4%.

The oral bioavailability of GS-9876 is high in rat, dog, and cynomolgus monkey and is independent of the formulation used ($F \geq 60\%$). GS-9876 had low to intermediate clearance relative to liver blood flow in rats, dogs, and cynomolgus and rhesus monkeys. Across species, the in vivo clearance is similar to the predicted hepatic clearance obtained in primary hepatocytes leading to confidence in the human prediction based on in vitro hepatocyte data. The volume of distribution is approximately equal to (rat) or higher than (all other species) total body water (0.7 L/kg).

After oral dosing to albino and pigmented rats, [^{14}C]GS-9876-derived radioactivity was distributed to most of the tissues by the first collection time point (0.25 hours postdose). Most tissues reached maximum GS-9876 concentration by 1 hour postdose and concentrations of radioactivity were below the limit of quantitation by 168 hours postdose. The tissues showing the highest maximum concentrations of radioactivity included liver, adrenal glands, and kidney. The lowest levels of radioactivity were observed in the brain, bone, adipose, and testis. Generally

similar distribution patterns and tissue concentrations of [^{14}C]GS-9876-derived radioactivity were observed in albino and pigmented rats except for the pigmented skin and eye uveal tract where higher tissue/blood ratios were seen in melanin-containing tissues. Binding was reversible. In both strains, the brain/blood concentration ratio was low (< 0.1), suggesting [^{14}C]GS-9876-derived radioactivity was relatively excluded by the blood:brain barrier.

Recovery of radioactivity dosed orally to rats was high (≥ 97.8%). The main route of elimination of GS-9876 is likely hepatobiliary with ≤ 5.1% orally dosed radioactivity found in rat urine and 69.4% in bile of BDC rats.

GS-9876 undergoes slow oxidative metabolism in human hepatocytes. Comparison of metabolism in hepatocytes from rats, dogs, monkeys, and humans did not identify any metabolites unique to humans, supporting the selection of rat and cynomolgus monkey as toxicology species. No detectable turnover of GS-9876 by recombinant human CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4) was observed confirming the high metabolic stability in human hepatocytes. The clearance of GS-9876 may be increased by inducers of CYP enzymes.

GS-9876 had little inhibitory effect on the activities of human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A. GS-9876 was a weak inhibitor of human UGT1A1 (IC50 = 31.1 μM). The low systemic concentrations anticipated in the clinic for GS-9876 make it unlikely to cause drug-drug interactions in vivo through inhibition of human CYP enzymes or UGT1A1.

GS-9876 is a weak inhibitor of the efflux transporters P-gp (IC50 > 23.2 μM) and BCRP (IC50 > 100 μM) as well as the hepatic uptake transporters OATP1B1 (IC50 = 10.3 μM) and OATP1B3 (IC50 = 12.3 μM). The low dose and low systemic concentrations anticipated in the clinic for GS-9876 suggest that the potential for clinically relevant drug-drug interactions with GS-9876 as an inhibitor of these transporters is low.

GS-9876 is a substrate for P-gp and BCRP, but not OATP1B1 or OATP1B3. Inhibitors of intestinal P-gp and BCRP are unlikely to have a marked effect on GS-9876 absorption due to its high permeability and high oral bioavailability expected in the clinic.

It is unlikely that GS-9876 would activate PXR- or AhR-regulated genes at the maximum plasma concentrations expected in the clinic. Thus, the potential of GS-9876 to cause drug-drug interactions through induction is low.

1.2.3. Clinical Trials of GS-9876

As of 08 April 2016, 62 healthy volunteers have been dosed with GS-9876 in two clinical studies.

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).

Ongoing Clinical Trial

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.

1.3. Information about Methotrexate

Subjects will continue to receive stable weekly doses of MTX. Further information regarding side effects, dosage and administration is available in the current local prescribing information.

1.4. Rationale for Current Study

Over the last decade, changes in RA treatment strategies accompanied by advances in drug development and the addition of targeted biological therapies have greatly improved the outcomes for subjects with RA. Despite these developments, therapeutic challenges remain. The current conventional and biological DMARDs may be ineffective, produce only partial responses or loose therapeutic response over time due to development of neutralizing antibodies in some subjects and are associated with significant safety and tolerability concerns. There is an unmet medical need for simple, orally administered therapies with novel and targeted mechanisms of action that can effectively improve the disease course while being safe and well tolerated.

Given its central role in immune cell signaling, inhibition of SYK is expected to have pleiotropic anti-inflammatory effects and affect multiple steps in RA pathogenesis. B cells have been implicated as playing a critical role in the pathogenesis of RA as demonstrated by the clinical activity of the anti-CD20 monoclonal antibody, rituximab, in RA patients {Leandro et al 2006, Navarro-Millan et al 2013}. B cells contribute to the pathogenesis of RA through their ability to act as antigen presenting cells (APCs) presenting self-antigens to auto-reactive T cells {Shlomchik 2008}, and through the production of autoantibodies and pro-inflammatory cytokines {Martin et al 2006, Song et al 2010}. As a critical mediator of BCR signaling, SYK inhibition suppresses BCR-stimulated proliferation, co-stimulatory molecule expression, and autoantibody production in B cells {Braselmann et al 2006, Coffey et al 2012}.

Additionally, SYK inhibition suppresses IC-stimulated cytokine release from monocytes/macrophages and prevents osteoclastogenesis {Liao et al 2013}. Spleen tyrosine kinase is expressed in the rheumatoid synovium {Cha et al 2006} and SYK inhibition reduces cellular infiltrates into synovial tissue {Coffey et al 2012}. Pharmacologic inhibition of SYK has been shown to inhibit disease progression and reduce inflammation in multiple animal models of RA, and has demonstrated disease modifying anti-rheumatic drug (DMARD) activity on endpoints such as cartilage destruction and bone erosion {Coffey et al 2012, Liao et al 2013, Pine et al 2007}. A consistent finding in these nonclinical studies is that significant efficacy can be achieved with minimum plasma concentrations (C_{min}) that result in target coverage less than 50% {Liao et al 2013}.

Taken together, the in vitro and in vivo data suggest that inhibition of SYK may decrease several pathologically active mechanisms implicated in RA including B-cell activation, T-cell costimulation, and cytokine release.

This study is designed to evaluate the efficacy, safety, tolerability, PK, and PPD

1.5. Rationale for Dose Selection

In the rat CIA model, predicted GS-9876 exposure at the 30 mg and 10 mg QD doses are estimated to provide 75% and 37% of the maximal treatment response observed with GS-9876, respectively. The maximal treatment response observed with GS-9876 in this model was similar to the positive control dexamethasone. In the multiple ascending dose study (GS-US-379-1900), doses up to 30 mg QD of GS-9876 for 7 days were well tolerated in healthy volunteers. Therefore both doses (10 mg QD and 30 mg QD) are expected to be safe and have the potential to be efficacious in RA.

1.6. Risk/Benefit Assessment for the Study

As of 08 April 2016, GS-9876 has been well tolerated by 62 healthy subjects. In the clinical studies GS-US-379-1372 (single ascending dose) and GS-US-379-1900 (cohorts 1 and 2; multiple ascending dose over 7 days), no risks were identified, and observed AEs were mainly Grades 1 and 2 in severity. The majority of AEs were assessed by the investigator as not related to GS-9876. The majority of graded laboratory abnormalities was Grade 1 or Grade 2 and mostly related to cholesterol. No prolongation of bleeding time duration was noted during the study. No clinically significant changes in vital signs, physical findings, or ECGs were reported during this study and no clinically relevant QTcF interval prolongation was noted in time matched ECGs in cohort 1 and cohort 2.

In the repeat dose toxicology studies, 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 $\geq$ 10 mg/kg/day, and hemorrhage and thrombosis in monkeys at $\geq$ 20 mg/kg/day. At higher doses in rats ($\geq$ 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 NOAEL in rats was 10 mg/kg/day after 26 weeks dosing. For the proposed 30 mg dose in planned Study GS-US-379-1582, estimated exposure margins are 2.4-/5.9- fold based on exposures at the NOAELs in the 26 week study in male/female rats. Patients will be closely monitored for any infection, changes in the differential CBC and cell subsets.

In monkeys, the NOAEL in the 28-day study was identified at 10 mg/kg/day, which was associated with $AUC_{0\text{-}24\ hr}$ 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. However in the ongoing 39-week study, one 15 mg/kg/day monkey was euthanized moribund during Week 22

with persistent fecal changes, weight loss, deteriorating clinical condition, and large bowel inflammation. Gilead considers it prudent to limit exposures in Study GS-US-379-1582 to mean exposures achieved in monkeys at the 10 mg/kg/day mid-dose at Week 13 of the 39-week study (6750 ng•h/mL). For the highest proposed dose of 30 mg in this study the estimated exposure margin is 2.7- fold based on exposures at the NOAEL in the 13-week monkey study.

In clinical studies GS-US-379-1372 and GS-US-379-1900 (cohorts 1 and 2) no change in platelets numbers, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ration (INR) as well as bleeding time were observed. The risk for bleeding at the doses proposed for this POC study is therefore considered to be low.

An independent and experienced Data Monitoring Committee (DMC) appointed to monitor the study will provide an additional level of risk mitigation. Refer to Section 8.9 Data Monitoring Committee.

The overall risk:benefit balance of this study is considered favorable. For additional information about the risks of GS-9876, reference is made to the investigator brochure.

1.7. Compliance

This study will be conducted in compliance with this protocol, GCP, and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the effect of GS-9876 versus placebo for the treatment of signs and symptoms of RA in subjects with active RA as measured by change from baseline in DAS28 (CRP) at Week 12

The secondary objectives of this study are:

- To evaluate the safety and tolerability of GS-9876 in subjects with RA
- To explore the effect of GS-9876 on other disease-specific outcomes in RA

The exploratory objectives of this study are:

3. STUDY DESIGN

3.1. Endpoints

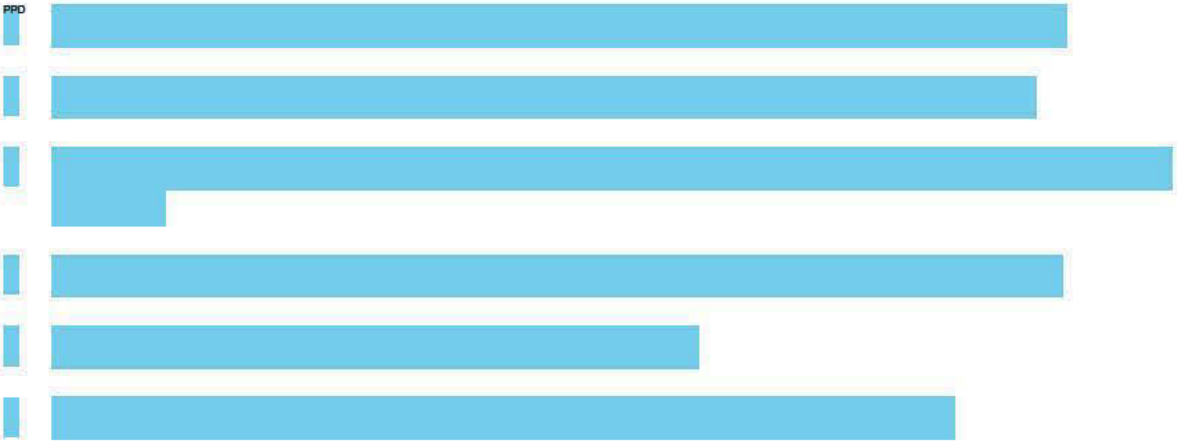
The primary endpoint of this study is:

- Change from baseline in DAS28 (CRP) at Week 12

The secondary endpoints of the study are:

- The proportion of subjects who achieve ACR 20/50/70 at Week 12
- Change from baseline in HAQ-DI score at Week 12

The exploratory endpoints include:

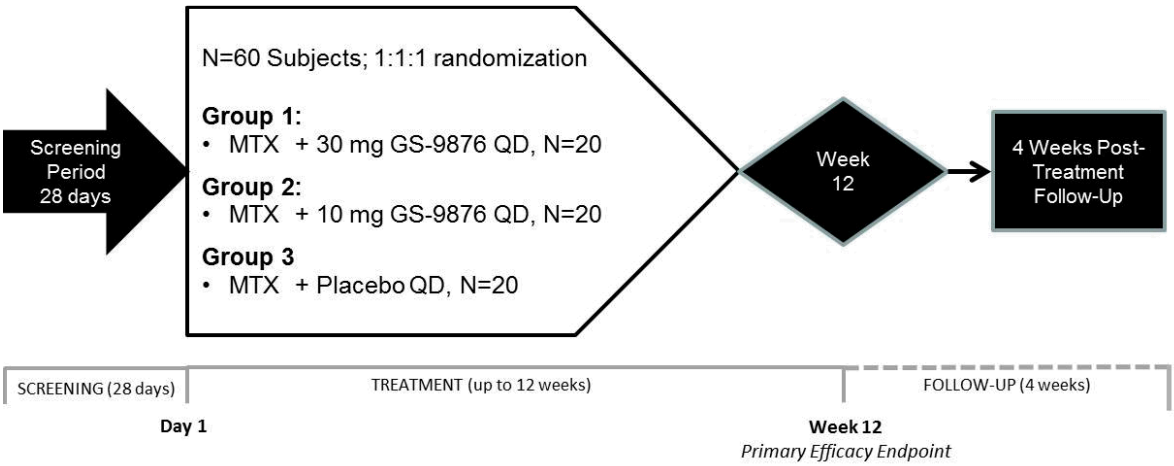


3.2. Study Design

This is a randomized, double-blind, placebo-controlled, POC study evaluating the safety, tolerability, and efficacy of GS-9876 in adult male and female subjects with active RA despite MTX therapy who had an inadequate response to MTX (either alone or in combination with bDMARDs).

A total of approximately 60 subjects will be randomized in this study.

Figure 3-1. Study Schema



3.3. Study Treatments

Following completion of Screening assessments, eligible subjects will be randomized in a blinded fashion in a 1:1:1 ratio as follows:

Group 1:
GS-9876 (30 mg QD) (N=20)

Group 2:
GS-9876 (10 mg QD) (N=20)

Group 3:
GS-9876 PTM (QD) (N=20)

Randomization will be stratified by prior inadequate response to biologic therapy and geographic region.

3.4. Duration of Treatment

Subjects will be treated for up to 12 weeks and then followed for 4 weeks after their last dose of study drug.

3.5. Discontinuation Criteria

When medically feasible, the Medical Monitor should be consulted prior to subject discontinuation. Study medication may be discontinued in the following instances:

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

- 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
- Subjects use of non-permitted concurrent therapy
- Serious infections (those requiring parenteral antimicrobial therapy or hospitalization)
- Any opportunistic infections
- Complicated herpes zoster infection (multi-dermatomal, disseminated, ophthalmic or CNS involvement)
- Pregnancy during the study; refer to Appendix 5
- Investigator discretion
- Discontinuation of the study at the request of Gilead, regulatory agency or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)
- Laboratory abnormalities:
    - 2 sequential total WBCs <2000 cells/mm^3 (SI: <2.0x10^9 cells/L).
    - 2 sequential neutrophil counts <1000 neutrophils/mm^3 (SI: <1.0x10^9 cells/L).
    - 2 sequential lymphocyte counts <750 lymphocytes/mm^3 (SI: <0.75x10^9 cells/L).
    - 2 sequential hemoglobin values <8.0 g/dL (SI: <80 g/L).
    - 2 sequential platelet counts <75,000 platelets/mm^3 (SI: <75.0x10^9 cells/L).
    - 2 sequential AST or ALT elevations >3xULN with ≥1 total bilirubin value >2xULN.[1]
    - 2 sequential AST or ALT elevations >3xULN accompanied by elevated international normalized ratio (INR).[1]

[1] In each case, there is a need for additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with the study Medical Monitor.

- 2 sequential AST or ALT elevations >5xULN, regardless of total bilirubin or accompanying symptoms.[1]
- 2 sequential increases in serum creatinine >50% over the average of Screening and Day 1 values.[2]
- After becoming aware of any of the above described abnormal laboratory changes occurring at any one time, an unscheduled visit (i.e. second sequential) must occur to retest within 3 to 5 days. Subjects who stop study medication for any reason will not be replaced. Subjects withdrawing from the study will be encouraged to complete the same final evaluations as subjects completing the study according to the protocol, particularly safety evaluations in the subject's interest so that data can

3.6. End of Study

End of Study is defined as when the last patient has completed up to 12 weeks of treatment and 4 weeks of follow-up.

3.7. Post Study Care

Subjects may be offered the opportunity to enroll into an open-label extension of GS-9876 at a future date. At this time there are no confirmed post study care options to subjects that have participated on this study and the long term care of subjects will remain the responsibility of their primary treating physician.

3.8. Pharmacokinetic (PK) Assessments

Plasma concentrations of GS-9876 will be measured and PK parameters determined. Plasma concentrations of GS-9876 metabolites may be determined and PK parameters may be explored, as applicable. PK sampling will occur relative to study drug dosing at Weeks 2, 8, and 12 or ET, corresponding to a trough concentration taken approximately 24 hours after the previous dose of GS-9876, but prior to the next dose of GS-9876. At Week 4, PK sampling will occur at 2 hours postdose. The samples will be used to evaluate PK of GS-9876 and may also be used to measure protein binding of GS-9876. Plasma concentrations of GS-9876 metabolites and/or MTX may be determined.

PPD

[2] At the time of study completion or discontinuation, if a subject should exhibit elevations in serum creatinine ≥33 % above the average of Screening and Day 1 values, they should be re-tested every 1 to 2 weeks until the serum creatinine elevation is fully reversed to within 10% of the average of Screening and Day 1 values.

3.9. Biomarker Testing

PPD

Sampling for markers relevant to inflammation (including but not limited to disease-associated markers of RA and/or the SYK pathway) may be performed at Baseline, Day 1, Week 4, and Week 12 or ET. Sampling time points may be modified by the Sponsor based upon emerging data and assay feasibility. Samples for CRP will be drawn at every visit.

The testing outlined in this protocol is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of knowledge. Samples may be stored at Gilead Sciences for a period of up to 15 years after the end of the study.

3.9.1. Optional Genomic Research

PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 60 subjects will be enrolled in this study with active RA who have an inadequate response to MTX (either alone or in combination with bDMARDs). In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

4.2. Inclusion Criteria

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

1) Male or female subjects who are between 18 and 75 years of age, inclusive, on the day of signing informed consent

2) Have a diagnosis of RA as defined by the 2010 American College of Rheumatology - European League Against Rheumatism Collaborative Initiative Classification Criteria for Rheumatoid Arthritis (Appendix 6)

3) Active RA disease as defined by a TJC of ≥ 6 (out of 68), a SJC of ≥ 6 (out of 66), and a CRP ≥ 5 mg/l

4) Inadequate response to treatment with oral or parenteral MTX 7.5 to 25 mg/week continuously for at least 12 weeks, with at least 6 weeks at a stable dose prior to the first dose of study drug

5) Subjects must be receiving a folic or folinic acid supplementation at a stable dose. Subjects who are not taking folic or folinic acid at Screening should be initiated on an adequate dose of folic acid (≥5 mg/week total dose or as per local practice) or equivalent and maintained throughout the study.

6) Use of oral corticosteroids of no more than 10 mg prednisone or its equivalent per day is allowed if the dose is stable for at least 28 days prior to the first dose of study drug

7) NSAIDs or other analgesics (including aspirin ≤ 100 mg daily) are allowed if doses are stable for at least 14 days prior to the first dose of study drug

8) Able and willing to sign the informed consent as approved by the IRB/IEC. Written consent must be provided before initiating any Screening evaluations. Subjects must have read and understood the informed consent form (ICF), must fully understand the requirements of the study, and must be willing to comply with all study visits and assessments.

9) A negative serum pregnancy test is required for female subjects

10) Lactating females must agree to discontinue nursing before the investigational medicinal product (IMP) is administered.

11) 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 5.

4.3. Exclusion Criteria

1) Prior treatment with B-cell depleting agents (eg, rituximab), unless more than 6 months prior and documented return of CD19+ cells

2) Prior treatment with any commercially available or investigational SYK inhibitor

3) Current treatment with any other cDMARD other than MTX and/or HCQ (unless appropriate wash out as defined in Section 5.5)

4) Current treatment with any bDMARD (unless appropriate wash out as defined in Section 5.5). Prior failure to treatment with bDMARDs is not an exclusion criterion.

5) QT interval corrected for heart rate using the Fredericia formula (QTcF) > 450 msec determined by the average of values at the Screening visit

6) History of any major bleeding event defined as Grade 3 severity and above [as defined by modified the Common Terminology Criteria for Adverse Events (CTCAE) 4.03] within the last year or personal or family history of bleeding disorder

7) If no history of a documented negative TB test within the last 12 months or documented course of adequate therapy for either latent or active TB, a Quantiferon must be performed according to local standards. Subjects with a positive Quantiferon at Screening are not eligible

8) Ongoing treatment with moderate or strong CYP3A inducers or inhibitors or within 2 weeks prior to study drug administration

9) Joint injections within 4 weeks prior to the first dose of study drug

10) Administration of a live or attenuated vaccine within 30.

11) Participation in any investigational drug/device clinical study within 4 weeks or 5 half-lives prior to Screening, whichever is longer. Exposure to investigational biologics should be discussed with the sponsor.

12) Have a diagnosis of any generalized musculoskeletal disorder (eg, generalized osteoarthritis, or systemic inflammatory condition other than RA such as, but not limited to: juvenile idiopathic arthritis, Felty's syndrome, ankylosing spondylitis, reactive arthritis, psoriatic arthritis, inflammatory bowel disease associated arthropaties, systemic lupus erythematosus, scleroderma inflammatory myopathy, mixed connective tissue disease, any overlap syndrome, systemic vasculitis or gout [participants with secondary Sjogren's syndrome or secondary limited cutaneous vasculitis with RA are not excluded]).

13) History of or current moderate to severe congestive heart failure (New York Heart Association [NYHA] class III or IV), or within the last 6 months, a cerebrovascular accident, myocardial infarction, unstable angina, unstable arrhythmia or any other cardiovascular condition which, in the opinion of the investigator, would put the subject at risk by participation in the study.

14) History of malignancy within the past 5 years prior to Screening (except for adequately treated or excised basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ with no evidence of recurrence).

15) History of lymphoproliferative disease or possible current lymphoproliferative disease

16) History of demyelinating disease or current signs and symptoms suggestive of demyelinating disease, or immediate family history of demyelinating disease.

17) History of organ or bone marrow transplant.

18) Positive serology for human immunodeficiency virus (HIV) 1 or 2, hepatitis B virus (i.e., surface antigen [Ag] or core antibody [Ab] positive) or hepatitis C virus (i.e., HCV Ab positive) or any history of infectious hepatitis from any cause with the exception of hepatitis A.

19) History of opportunistic infection or immunodeficiency syndrome.

20) Known active infection of any kind (excluding fungal infections of nail beds) or any major episode of infection requiring hospitalization or treatment with IV anti-infectives within 4 weeks of Screening or 8 weeks of Day 1 visit or completion of oral anti-infectives within 2 weeks of the Screening or 6 weeks of Day 1 visit.

21) Currently on any therapy for chronic infection (such as pneumocystis, cytomegalovirus, herpes zoster, and atypical mycobacteria). Past history of disseminated Staphylococcus aureus or disseminated Herpes simplex infection.

22) History of symptomatic herpes zoster or herpes simplex infection within 12 weeks prior to Screening or have history of disseminated/complicated herpes zoster infection (multi-dermatomal involvement, ophthalmic zoster, central nervous system involvement or postherpetic neuralgia).

23) History of an infected joint prosthesis or other implanted device with retention of the prosthesis or device in situ.

24) History within the previous 2 years or current evidence of drug or alcohol abuse.

25) Any condition including active fibromyalgia that based on the investigator's opinion would make it difficult to appropriately assess RA activity for the purposes of this study.

26) Any condition or circumstances which in the opinion of the investigator or sponsor may make a subject unlikely or unable to complete the study or comply with study procedures and requirements.

27) Significant blood loss (>450 mL) or transfusion of any blood product within 12 weeks prior to Day 1.

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

29) Female subjects must refrain from egg donation or harvest throughout the study period and continuing for at least 30 days after last dose.

30) 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.

31) The results of the following laboratory tests performed at the central laboratory at Screening meet any of the criteria below:

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

   b) White blood cells $<3.0 \times 10^3$ cells/mm^3 (SI: $<3.0 \times 10^9$ cells/L);

   c) Neutrophils $<1.5 \times 10^3$ cells/mm^3 (SI: $<1.5 \times 10^9$ cells/L);

   d) Lymphocytes $<0.5 \times 10^3$ cells/mm^3 (SI: $<0.5 \times 10^9$ cells/L);

   e) Platelets $<100 \times 10^3$ cells/mm^3 (SI: $<100 \times 10^9$ cells/L);

   f) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥1.5x ULN;

   g) Total bilirubin level ≥ 2x ULN unless the subject has been diagnosed with Gilbert's disease and this is clearly documented;

   h) Creatinine clearance < 60 mL/min based on the Cockcroft-Gault (CG) formula[3]

[3] Creatinine clearance (mL/min) = [(140 – age) * weight in kg] / [815 * serum creatinine in mmol/L]

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

An Interactive Web and Mobile Response System (IXRS) will be employed to manage subject randomization and treatment assignments. 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.

5.1.1. Procedures for Breaking Treatment Codes

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

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

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

5.2. Description and Handling of GS-9876 and Placebo-To-Match (PTM) GS-9876

5.2.1. Formulation

GS-9876 will be supplied as 10 or 30 mg tablets that are round, biconvex, plain-faced and film-coated blue. Each tablet contains either 10 mg or 30 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.

Matching placebo tablets will be supplied that are identical in physical appearance to the 10 or 30 mg GS-9876 tablets and contain the following inactive ingredients: microcrystalline cellulose, lactose, 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, 10 mg or 30 mg, and PTM 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 shall 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 and PTM tablets should be stored at controlled room temperature of 25ºC (77ºF); excursions are permitted between 15ºC and 30ºC (59ºF and 86ºF). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

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

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

5.3. Dosage and Administration of GS-9876

GS-9876 30 mg (1 x 30 mg tablet), GS-9876 10 mg (1 x 10 mg tablet), or GS-9876 PTM (1 tablet) will be provided by Gilead Sciences, Inc. and are to be administered orally once daily with water. The study drug should be swallowed whole. GS-9876 may be taken with or without food. Each subject will be given instructions to maintain approximately the same daily dosing interval between study drug doses. Subjects will be instructed to take study drug at approximately the same time each morning. On Day 1, subjects will be instructed to take their dose in clinic as the last in-clinic study procedure (after all other procedures for that visit have been completed). At Weeks 2, 8 and 12, subjects will be instructed to take their dose after predose assessments have been completed (eg, PK sample collection). At Week 4, subjects will be instructed to take their dose in clinic as the first study procedure prior to any others scheduled for that visit.

For missed dose(s) of study medication, subject should be instructed to take the missed dose(s) of study medication, as soon as possible, during the same day. If more than 8 hours has elapsed since the scheduled time of the missed dose, the subject should be instructed to wait and take the next dose at the regularly scheduled time. Subjects should be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

5.4. Other Medication Administered

Methotrexate should be administered weekly at a dose of 7.5 to 25 mg.

5.5. Prior and Concomitant Medications

At Screening, all medication taken up to 30 days prior to the Screening visit will be recorded on the eCRF. At each study visit, the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription, non-prescription medications, therapies, dietary supplements, and minerals.

Allowed Medications:

- Subjects must have taken oral or parenteral MTX 7.5 to 25 mg/week continuously for at least 12 weeks, with at least 6 weeks of stable dose prior to first study dose and throughout the duration of the study. Subjects will continue to receive stable weekly doses of MTX. Further information regarding side effects, dosage and administration is available in the current local prescribing information.

- Subjects are allowed to remain on hydroxychloroquine, with at least 8 weeks of stable dose prior to first study dose

- Chronic use of systemic corticosteroids up to a maximum of 10 mg/day of prednisone or equivalent is allowed if dose is stable for at least 28 days prior to first study dose and maintained at a stable dose throughout the study.

- NSAIDs or other analgesics (including aspirin ≤ 100 mg) are allowed if doses are stable for at least 14 days prior to first study dose.

- For pain while on study, the patient may take acetaminophen or other non-NSAID pain medications as directed by the treated physician. Any scheduled or pro re nata (prn) pain medication should be taken after the Baseline and Week 12 visits are completed.

Prohibited Medications:

- Any herbal/natural supplements, unless approved by the Medical Monitor

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

- Changes in the doses of background MTX, anti-malarial therapy, corticosteroids and/or NSAIDS are not permitted during the study period except to avoid adverse effects

- Use of moderate or strong CYP3A4 inhibitors or moderate or strong CYP3A4 inducers within 2 weeks prior to the first dose of study drug and while on study drug is prohibited

- The following medications are prohibited from 4 weeks prior to the first dose of study drug and throughout the study:

  — minocycline, penicillamine, sulfasalazine, anakinra, etanercept, etanercept biosimilar, azathioprine, cyclosporine, tacrolimus, sirolimus, everolimus, mycophenolate mofetil, tofacitinib

- The following medications are prohibited within 10 weeks of the first dose of study drug and throughout the study:

  — infliximab, infliximab biosimilar, golimumab, certolizumab pegol, abatacept, tocilizumab, adalimumab

- Treatment with antibiotics for a clinical infection or other medical condition within 30 days prior to first dose

- Previous treatment with B-cell depleting agents (ie, rituximab) within 6 months of treatment

- Treatment with any other investigational study drug within 1 month prior or within 5 half-lives of the prior investigational agent (whichever is longer) prior to Screening

- Prior treatment with any commercially available or investigational SYK inhibitor

- Joint injections during the course of the study are not permitted. If a joint injection has been used within 6 weeks of first dose, the joint will be considered unevaluable throughout the study.

- 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

Vaccine Guidelines:

Vaccination with live components is prohibited during the study and for 6 weeks after the last dose of study medication. Also routine household contact with persons vaccinated with live vaccine components should be avoided. These vaccines include varicella, oral polio and inhaled flu vaccine. General guidelines suggest that exposure should be avoided following vaccination with these vaccines for the stated time period:

- varicella or attenuated typhoid fever vaccination for 4 weeks following vaccination

- oral polio vaccination for 6 weeks following vaccination

- attenuated rotavirus vaccine for 10 days following vaccination
- inhaled flu vaccine for 1 week following vaccination

When inactivated flu vaccines are to be used during the study, it should be borne in mind that vaccination responses have not been studied during the administration of GS-9876. Currently, there are no available data on continuous use of IMP and its impact on immune responses following vaccination.

Examples of representative medications which are prohibited are listed below:

Table 5-1. Examples of Disallowed Medications

Drug Class	Agents Disallowed
Strong CYP3A4 Inhibitors[a]	clarithromycin, conivaptan, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole, ritonavir, cobicistat, telaprevir, boceprevir, grapefruit juice, idelalisib,
Strong CYP3A4 Inducers[b]	carbamazepine, phenytoin, rifampin, fosphenytoin, pentobarbital, primidone, rifabutin, rifapentine, phenobarbital, mitotane, avasimibe, St. John's Wort
Moderate CYP3A4 Inhibitors[a]	fluconazole, erythromycin, diltiazem, dronedarone, aprepitant, imatinib, verapamil, tofisopam, ciprofloxacin, cimetidine, cyclosporine, Schisandra sphenanthera
Moderate CYP3A4 Inducers[b]	efavirenz, tipranavir/ritonavir, bosentan, thioridazine, nafcillin, talviraline, lopinavir, modafinil, etravirine, lersivirine, semagacestat, genistein
Immunosuppressants	mycophenolate mofetil, azathioprine, quinacrin, gold, leflunomide
Calcineurin inhibitor	cyclosporine, tacrolimus
mTOR inhibitor	sirolimus, everolimus
Herbal/Natural Supplements[d]	grapefruit juice[a], St. John's Wort[b], fish oil, borage oil, Schisandra sphenanthera
Anti-platelet	adenosine diphosphate(ADP) receptor inhibitors, phosphodiesterase inhibitors, PAR-1 antagonists, Glycoprotein 2b/3a inhibitorsc
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
d Herbal/Natural supplements not listed require Medical Monitor review and approval.

5.6. Investigational Medicinal Product Accountability and Disposal or Return

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

GS-9876 accountability records will be provided to each study site to:

- Record the date received and quantity of IMP;
- Record the date, subject number, subject initials, and the IMP number dispensed; and
- Record the date, quantity of used and unused IMP returned, along with the initials of the person recording the information.

For additional information about study drug accountability and return, refer to Section 9.1.7.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled are presented in tabular form in Appendix 2 and described in the text that follows. The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

The study center will not initiate dosing until:

- The IRB and IEC and 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 informed consent of each subject, using the study-specific, IRB-approved Informed Consent Forms (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 informed consent has been obtained, all screening tests and procedures have been assessed, and study eligibility has been confirmed, eligible subjects will be randomized to study treatment as described in Section 5.1.

6.2. Pretreatment Assessments

6.2.1. Screening Visit (within 28 days prior to randomization)

Written informed consent must be obtained from each subject before initiation of any visit procedures. After a subject has provided informed consent, the investigator will determine if the subject is eligible for participation in the study. Subjects will be screened within 28 days before randomization to determine eligibility for participation in the study. The assessment will include a review of the Inclusion/Exclusion criteria and completion of all Screening Visit procedures as outlined in Appendix 2. A sufficient number of subjects will be screened to identify approximately 60 subjects for enrollment.

The following will be performed and documented at Screening:

- Obtain written informed consent
- Obtain medical history including but not limited to RA, prior RA medication history any personal or family histories of bleeding disorders
- Perform complete physical examination (refer to Appendix 9)
- Obtain vital signs, to include height and weight at Screening (refer to Appendix 9)
- Complete 12-lead ECG (refer to Appendix 9)
- Perform 66 swollen and 68 tender joint count assessment (refer to Appendix 7 and Appendix 9)
- Obtain blood samples for (refer to Appendix 3):
  - Hematology, Chemistry, and Coagulation
  - CRP
  - Leukocyte subsets
  - Serology (HIV, HCV, and HBV)
  - Serum pregnancy test
  - RNA
- Perform Quantiferon test, as applicable (refer to exclusion criteria)
- Obtain a CD19 count, as applicable (refer to exclusion criteria)
- Obtain urine for urinalysis and urine drug screen (refer to Appendix 3)
- Collect biomarker samples
- Record any serious adverse events (SAEs) and all AEs related to protocol mandated procedures occurring after signing of the consent form (refer to Section 7).
- Record any prior and concomitant medications

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

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all SAEs, as well as any AEs related to protocol-mandated procedures

on the adverse events 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.

Screening labs may be repeated once within 28 days prior to administration of study drug to rule out laboratory error.

6.3. Randomization (Day 1)

Subjects who meet all inclusion and exclusion criteria and complete screening will return for randomization into one of the three treatments as described in Section 3.3. Randomization will be completed as described in Section 5.1.

6.4. Treatment Assessments

6.4.1. Day 1

Study procedures and assessments are outlined in Appendix 2. The HAQ-DI, Patient's Assessment of Pain, and Patient's Global Assessment of Disease Activity are recommended to be done prior to the 66 swollen and 68 tender joint count assessments and before any invasive study procedures. Blood draws should be done at the end of the study visit prior to dosing.

The following will be performed and documented on Day 1, within a $\pm$ 3-day window:

- Confirm study eligibility
- Perform symptom driven physical examination
- Obtain vital signs
- Perform 12-lead ECG (predose)
- Assess AEs and concomitant medications
- Subject completes disease specific questionnaires and activity scales (refer to Appendix 9):
  - HAQ-DI
  - Patient's Assessment of Pain
  - Patient's Global Assessment of Disease Activity
- Perform 66 swollen and 68 tender joint count assessment (refer to Appendix 9)
- Investigator completes Physician's Global Assessment of Disease Activity (refer to Appendix 9)

- Obtain blood samples for:
  - Hematology, Chemistry, and Coagulation
  - CRP
  - Leukocyte subsets
  - RF/CCP
  - IgA, IgG, and IgM
  - RNA
- Obtain urine sample for urine pregnancy test for females of childbearing potential only
- Collect biomarker samples
- PPD .
- Drug Administration
  - Dispense study drugs as directed by the IXRS
  - Instruct the subject on the packaging, storage and administration of all study drugs
  - Observe the subject taking the first dose of study drug and record the time of the first dose. Study drug should be administered as the last study procedure on Day 1.
  - Instruct subjects not to take study drug until after predose assessments at Week 2, Week 8, and Week 12 visits. Instruct subjects not to take study drug until in clinic and instructed to do so at Week 4.

6.4.2. Week 2 (± 3 days)

Study procedures and assessments are outlined in Appendix 2. The following will be performed and documented at Week 2, within a ± 3-day window:

- Perform symptom driven physical examination
- Obtain vital signs
- Perform 12-lead ECG
- Assess AEs and concomitant medications
- Subject completes disease specific questionnaires and activity scales:

- HAQ-DI
- Patient's Assessment of Pain
- Patient's Global Assessment of Disease Activity

- Perform 66 swollen and 68 tender joint count assessment
- Investigator completes Physician's Global Assessment of Disease Activity
- Obtain blood samples for:
  - Hematology, Chemistry, and Coagulation
  - CRP
- Obtain urine sample for urine pregnancy test for females of childbearing potential only
- Collect PK sample (predose)
- Study drug administration after predose assessments completed (eg, PK sample collection).
- Complete medication pill count
- Review study drug compliance and drug administration instructions with subject.

6.4.3. Week 4 (± 3 days)

Study procedures and assessments are outlined in Appendix 2. The following will be performed and documented at Week 4, within a ± 3-day window:

- Study drug administration prior to other study procedures (PPD)
- Perform symptom driven physical examination
- Obtain vital signs
- Perform 12-lead ECG
- Assess AEs and concomitant medications
- Subject completes disease specific questionnaires and activity scales:
  - HAQ-DI
  - Patient's Assessment of Pain
  - Patient's Global Assessment of Disease Activity

- Perform 66 swollen and 68 tender joint count assessment
- Investigator completes Physician's Global Assessment of Disease Activity
- Obtain blood samples for:
  - Hematology, Chemistry, and Coagulation
  - CRP
  - RNA
- Obtain urine sample for urine pregnancy test for females of childbearing potential only
- Collect biomarker samples
- Collect PK sample (2 hours postdose)
- PPD
- Study drug will be dispensed as directed by IXRS.
- Complete medication pill count
- Review study drug compliance and drug administration instructions with subject.

6.4.4. Week 8 (± 3 days)

Study procedures and assessments are outlined in Appendix 2. The following will be performed and documented at Week 8, within a ± 3-day window:

- Perform symptom driven physical examination
- Obtain vital signs
- Perform 12-lead ECG
- Assess AEs and concomitant medications
- Subject completes disease specific questionnaires and activity scales:
  - HAQ-DI
  - Patient's Assessment of Pain
  - Patient's Global Assessment of Disease Activity
- Perform 66 swollen and 68 tender joint count assessment

- Investigator completes Physician's Global Assessment of Disease Activity
- Obtain blood samples for:
  - Hematology, Chemistry, and Coagulation
  - CRP
- Obtain urine sample for urine pregnancy test for females of childbearing potential only
- Collect PK sample (predose)
- PPD .
- Study drug administration after predose assessments completed (eg, PK sample collection).
- Study drug will be dispensed as directed by IXRS.
- Complete medication pill count
- Review study drug compliance and drug administration instructions with subject.

6.4.5. Week 12 (± 3 days)

Study procedures and assessments are outlined in Appendix 2. The HAQ-DI, Patient's Assessment of Pain, and Patient's Global Assessment of Disease Activity are recommended to be done prior to the 66 swollen and 68 tender joint count assessments and before any invasive study procedures. Blood draws should be done at the end of the study visit.

The following will be performed and documented on Day 1, within a ± 3-day window:

- Perform symptom driven physical examination
- Obtain vital signs
- Perform 12-lead ECG
- Assess AEs and concomitant medications
- Subject completes disease specific questionnaires and activity scales:
  - HAQ-DI
  - Patient's Assessment of Pain
  - Patient's Global Assessment of Disease Activity

- Perform 66 swollen and 68 tender joint count assessment (prior to Physician's Global Assessment of Disease Activity)
- Investigator completes Physician's Global Assessment of Disease Activity
- Obtain blood samples for:
  - Hematology, Chemistry, and Coagulation
  - CRP
  - Leukocyte subsets
  - RF/CCP
  - IgA, IgG, and IgM
  - RNA
- Obtain urine sample for urine pregnancy test for females of childbearing potential only
- Collect biomarker samples
- Collect PK sample (predose)
- PPD
- Study drug administration after predose assessments completed (eg, PK sample collection).
- All study drug must be returned by subject. Study drug not previously returned by the subject should also be collected.
- Complete medication pill count
- Review study drug compliance and drug administration instructions with subject.

6.5. Early Termination (± 3 days)

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to perform the required study-related follow-up and procedures (see Section 3.5, Discontinuation Criteria).

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 discontinues prematurely from the study, the ET evaluations and/or procedures should be completed as outlined in Appendix 2 within 72 hours of subject's early termination from the study. The following will be performed and documented at ET, within a ± 3-day window:

- Perform symptom driven physical examination
- Obtain vital signs
- Perform 12-lead ECG
- Assess AEs and concomitant medications
- Subject completes disease specific questionnaires and activity scales:
  - HAQ-DI
  - Patient's Assessment of Pain
  - Patient's Global Assessment of Disease Activity
- Perform 66 swollen and 68 tender joint count assessment
- Investigator completes Physician's Global Assessment of Disease Activity
- Obtain blood samples for:
  - Hematology, Chemistry, and Coagulation
  - CRP
  - RF/CCP
  - IgA, IgG, and IgM
  - RNA
- Obtain urine sample for urine pregnancy test for females of childbearing potential only
- Collect biomarker samples
- Collect PK sample

6.6. Post-Treatment Assessments (± 5 days)

Study procedures and assessments are outlined in Appendix 2. The 4 Weeks Post-Treatment Follow-Up Visit will occur 28 days (± 5 days) from the last administration of study drug. The following will be performed and documented:

- Perform symptom driven physical examination
- Obtain vital signs
- Perform 12-lead ECG
- Assess AEs and concomitant medications
- Obtain blood samples for:
  - Hematology, Chemistry, and Coagulation
  - CRP
- Obtain urine sample for urine pregnancy test for females of childbearing potential only

6.7. Sample Storage

From subjects who provide additional consent, residual samples from blood drawn at all visits will be frozen and stored. These stored samples may be used by Gilead or our research partners to help answer questions about the RA and related diseases, study drug, or clinical laboratory testing to provide additional safety data. No human genetic testing will be performed without express consent of the study subjects. At the conclusion of this study, these samples and samples collected for RNA may be retained in storage for Gilead for a period of up to 15 years.

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 medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, 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 adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the Screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.2.2)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

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

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

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

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigator 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 sub-investigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

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

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

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

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

7.2.2. Assessment of Severity

The severity grading of AEs will be assessed as Grade 1, 2, 3 or 4 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 informed consent, but prior to initiation of study medication, the following types of events should be reported on the eCRF: all SAEs and adverse events related to protocol-mandated procedures.

7.3.1.1. Adverse Events

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

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

7.3.1.2. Serious Adverse Events

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

Any SAEs and deaths that occur after the post treatment follow-up visit but within 4 weeks of the last dose of study drug, regardless of causality, should also be reported.

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

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

7.3.1.3. Electronic Serious Adverse Event (eSAE) Reporting Process

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

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

Gilead DSPH	Email: Safety_FC@gilead.com Fax: +1 650-522-5477

- 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.

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

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

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

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

7.4. Gilead Reporting Requirements

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

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

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

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

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 7.3.1.1 and 7.3.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the modified CTCAE Grading Scale as described in Appendix 4. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.5.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.5.2. Grades 3 and 4 Laboratory Abnormality or Clinical Event

For a Grade 3 and 4 clinical event or clinically significant Grade 3 and 4 laboratory abnormality confirmed by repeat testing (preferably within 3 calendar days after receipt of the original test results), study drug should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically

significant Grade 3 and 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

7.6. Toxicity Management

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead Sciences Medical Monitor or designee. 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 confirmed by repeat testing as soon as possible, and preferably within 3 calendar days after receipt of the original test results. Grade 3 or 4 clinically significant laboratory abnormalities should be managed as outlined in Section 7.5.2.

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

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events 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 which 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).

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

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

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

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

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in 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 Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows:
Email: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, fax number +1 650 522-5477 or email Safety_FC@gilead.com.

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP 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 3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective is:

- To evaluate the effect of GS-9876 versus placebo for the treatment of signs and symptoms of RA in subjects with active RA as measured by change from baseline in DAS28 (CRP) at Week 12

The secondary objectives are:

- To evaluate the safety and tolerability of GS-9876 in subjects with RA
- To explore the effect of GS-9876 on other disease-specific outcomes in RA

The exploratory objectives are:

PPD

8.1.2. Primary Endpoint

The primary endpoint is change from baseline in DAS28 (CRP) at Week 12.

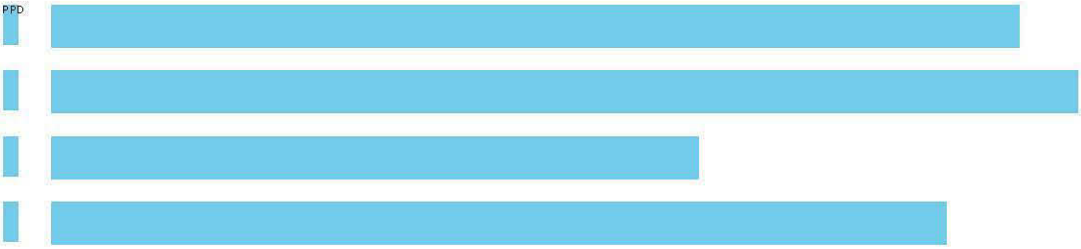
8.1.3. Secondary Endpoint

The secondary endpoints include:

- The proportion of subjects who achieve ACR 20/50/70 at Week 12
- Change from baseline in HAQ-DI score at Week 12

8.1.4. Exploratory Endpoints

PPD



8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Randomized

The all randomized analysis set includes all subjects who are randomized in the study. This is the primary analysis set for by-subject listings.

8.2.1.2. Efficacy

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

8.2.1.3. Safety

The primary analysis set for safety analyses will be the Safety Analysis Set, which includes all subjects who received at least 1 dose of study drug.

8.2.1.4. Pharmacokinetics

8.2.1.4.1. PK Substudy Analysis Set

The primary analysis set for intensive PK analyses will be the PK substudy analysis set, which includes all subjects in the Safety Analysis Set who have enrolled into the PK substudy, and have intensive PK concentration data to provide interpretable results for the specific parameters of interest for the analyte under evaluation.

8.2.1.4.2. PK Analysis Set

The primary analysis set for general PK analyses will be the PK analysis set, which includes all subjects in the Safety Analysis Set who have at least 1 non-missing PK concentration data for GS-9876 and/or its metabolite(s).

8.3. Data Handling Conventions

PK concentration values and PK parameter values below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listings. BLQ values that occur prior to the first dose will be treated as 0, BLQ values at all other time points will be treated as 1/2 of the lower limit of quantitation (LLOQ).

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

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized using standard descriptive methods including sample size, mean, SD, median, Q1, Q3, minimum, and maximum for continuous variables and frequency and percentages for categorical variables.

Demographic data will include sex, race, ethnicity, and age.

Baseline characteristics will include DAS28 (CRP), HAQ-DI, SDAI, and CDAI.

8.5. Efficacy Analysis

The primary endpoint for the study is change from baseline in DAS28 (CRP) at Week 12, which will be analyzed using a mixed model repeated measures (MMRM) approach. The model may include the fixed effects of treatment, visit, treatment by visit interaction, and baseline value. Subjects will be included as a random effect.

Secondary endpoints include proportion of subjects who achieve ACR20/50/70 at Week 12 and change from baseline in HAQ-DI score at Week 12. The ACR20/50/70 response rates between each of the 2 GS-9876 treated groups and the placebo group will be compared using a stratified Cochran-Mantel-Haenszel (CMH) Chi-square test adjusting for stratification factor in randomization. The difference in response rates between treatment groups and the corresponding 95% confidence intervals will be presented. The difference in change from baseline in HAQ-DI between treatment groups will be analyzed using a similar MMRM approach.

Sensitivity analyses may be performed for the efficacy assessment.

Details on efficacy analyses will be described in the statistical analysis plan.

8.6. Safety Analysis

All safety analyses will be performed using the safety analysis set.

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements at various time points during the study, and by the documentation of AEs.

All safety data collected on or after the first dose of study drug administration up to 30 days after the last dose of study drug, unless specified otherwise, will be summarized by treatment group according to the study drug received.

8.6.1. Extent of Exposure

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

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of the study drug, inclusive, regardless of temporary interruptions in study drug administration and summarized by treatment group.

8.6.2. Adverse Events

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

Treatment-emergent adverse events (TEAEs) are defined as one or both of the following:

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

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

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group. Absolute values and change from baseline at all scheduled timepoints will be summarized.

Graded laboratory abnormalities will be defined using CTCAE 4.03 grading scale (Appendix 4).

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post baseline up to the date of last dose of study drug plus 30 days, will be summarized by treatment.

8.6.4. Other Safety Evaluations

Individual data for physical examination findings, prior and concomitant medications and medical history will be provided. Twelve-lead ECGs and vital signs will be listed by subject or summarized by descriptive statistics as appropriate.

8.7. Pharmacokinetic Analysis

Plasma concentrations of GS-9876 will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum).

PPD

Plasma concentrations of GS-9876 metabolite(s) and/or MTX may also be determined and analyzed.

8.8. Biomarker Analysis

PPD

8.9. Data Monitoring Committee

An external multidisciplinary DMC will review the progress of the study and perform interim reviews of safety data in order to protect subject welfare and preserve study integrity. The DMC is to recommend to the sponsor whether the nature, frequency, and severity of adverse effects associated with treatment warrant the early termination of the study, whether the study should continue as planned, or the study should continue with modifications.

DMC will review unblinded safety data. The initial DMC review will be conducted after the 21st subject in the study has been treated for 4 weeks. Unblinded safety data will be reviewed quarterly thereafter.

The DMC will provide recommendations as needed regarding study design, conduct and the need for additional meetings or an alternative meeting schedule. While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

8.10. Sample Size

Sample size is determined based on the superiority test of one dose of GS-9876 compared to placebo based on the change from baseline in DAS28 (CRP) at Week 12. When assuming a difference of 1.2 between the two groups and a common standard deviation of 1.35, 20 subjects in each of the GS-9876 groups and 20 in the placebo group are required to obtain 78 percent power at a 2-sided 0.05-level. Therefore, the total sample size will be 60 (20 per treatment group).

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the 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, as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable sub-investigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any sub-investigator's) participation in the study. The investigator and sub-investigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

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

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

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The

investigator must use the most current IRB/IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC or local requirements. The consent form will inform subjects about pharmacogenomics testing and sample retention, and their right to receive clinically relevant pharmacogenomics analysis results.

9.1.4. Confidentiality

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

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

9.1.5. Study Files and Retention of Records

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

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

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

- Subject identification (name, date of birth, gender);

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

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

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. Electronic CRFs

should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the 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 timepoints as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF 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 trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Where possible, 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.

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

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, 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 trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.

STUDY ACKNOWLEDGEMENT

A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Proof-of-Concept Study to Evaluate Safety, Tolerability, and Efficacy of GS-9876 in Subjects with Active Rheumatoid Arthritis on Background Therapy with Methotrexate

GS-US-379-1582, Original Protocol, 08 April 2016

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

PPD

Franziska Matzkies, MD

Medical Monitor Name (Printed)

April - 14 - 2016

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed) Signature

Date Site Number

Appendix 2. Study Procedures Tables

Visit	Screening[a]	Day 1	Week 2	Week 4	Week 8	Week 12	ET[b]	4-weeks Post-Treatment Follow-Up[c]
Window in Days	**-28**		**±3**	**±3**	**±3**	**±3**	**±3**	**±5**
Written Informed Consent for Main Study	X							
PPD	X							
Medical History [d]	X							
Physical Examination [e]	X	X	X	X	X	X	X	X
Vital Signs [f]	X	X	X	X	X	X	X	X
12-Lead ECG	X	X[g]	X	X	X	X	X	X
66 swollen and 68 tender joint count assessment [h]	X	X	X	X	X	X	X	
Hematology, chemistry and coagulation [h, i, j]	X	X	X	X	X	X	X	X
CRP [h, i, j]	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Test [h, i, j, k]	X	X	X	X	X	X	X	X
Biomarkers [h, j, l]	X	X		X		X	X	
RNA Sample [h, i, j]	X	X		X		X	X	
Leukocyte subsets [h, i, j]	X	X				X		
Serology [i]	X							
Urinalysis and Urine Drug Screen [i]	X							
Quantiferon [i, m]	X							
CD19 Count [i, m]	X							
Randomization		X						
Disease-specific questionnaires and activity scores [h, n]		X	X	X	X	X	X	

Visit	Screening[a]	Day 1	Week 2	Week 4	Week 8	Week 12	ET[b]	4-weeks Post-Treatment Follow-Up[c]
Window in Days	**-28**		**±3**	**±3**	**±3**	**±3**	**±3**	**±5**
RF/CCP [h, i, j]		X				X	X	
IgA, IgG, and IgM [h, i, j]		X				X	X	
[redacted] PPD		X						
PK Samples [p]			X	X	X	X	X	
[redacted] PP					X			
Study Drug Dispensation		X		X	X			
Study Drug Administration (In-Clinic) [r]		X	X	X	X	X		
Adverse Events [s]	Continuous							
Concomitant Medications [t]	Continuous							

a Prospective subjects should be screened no more than 28 days prior to administration of the first dose of study drug.
b Early Termination assessments should be performed within 72 hours of early termination from the study.
c 28 (±5) days after the last administration of study drug, all subjects will return for an in-clinic follow-up visit.
d Medical history, including but not limited to, RA, prior RA medication history, and any personal or family histories of bleeding disorders
e Screening visit includes complete PE as outlined in Appendix 9. All other PEs are symptom driven. A symptom driven PE should be performed after Screening when a subject reports a new symptom or a worsening symptom at a study visit. If a subject reports no change in symptoms, then no PE is necessary.
f Vital signs include resting blood pressure, pulse, respiration rate, temperature (obtained orally), height and weight. Height and weight will be collected at Screening only.
g Conduct Day 1 ECG predose (prior to study drug administration).
h At Day 1 and Week 12 visits, the HAQ-DI, Patient's Assessment of Pain, and Patient's Global Assessment of Disease Activity are recommended to be done prior to the 66 swollen and 68 tender joint count assessments and before any invasive study procedures. Blood draws should be done at the end of the study visit.
i Refer to Appendix 3 for complete laboratory assessments.
j Samples to be collected prior to dosing, except at Week 4 visit.
k At Screening, a serum pregnancy test will be collected. At all other visits, a urine pregnancy test will be collected. If a urine pregnancy test is positive, a serum pregnancy test will also be collected.
l Samples will be collected at Day 1, Week 4, and Week 12 or ET visits for exploratory disease and/or pathway markers relevant to rheumatoid arthritis. Sampling timepoints and assessments may be modified during the study based on assay availability and/or emerging data.
m As needed per exclusion criteria (refer to Section 4.3)
n Disease-specific questionnaires and activity scales include the HAQ-DI, Patient's Assessment of Pain, Patient's Global Assessment of Disease Activity, and Physician's Global Assessment of Disease Activity.
o PPD

p PK samples will be collected prior to study drug administration (pre-dose) at Weeks 2, 8, and 12 or ET. At Week 4, PK samples will be collected 2 hours post dose.

q PPD

r On Day 1, study drug administration (in-clinic) should be the last study procedure performed. On Week 4, study drug administration (in-clinic) should be the first study procedure performed (with the exception of predose PK for PPD subjects only). At all other treatment visits, study drug administration should occur after predose assessments are completed.

s After informed consent, but prior to initiation of study medication, all SAEs and adverse events related to protocol-mandated procedures shall be collected. Following initiation of study medication, all SAEs and all AEs, regardless of cause or relationship, shall be collected. Refer to Section 7.3 for more detail.

t At Screening, all medication taken up to 30 days prior to the Screening visit will be recorded on the eCRF.

Appendix 3. Laboratory Assessments Table

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count White blood cell (WBC) count Differentials (absolute and percentage), including: Leukocytes Monocytes Neutrophils Eosinophils Basophils Reticulyte count Mean corpuscular volume (MCV)	Alkaline phosphatase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct and indirect bilirubin Total protein Albumin Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Serum creatinine Glucose Phosphorus Magnesium Potassium Sodium Amylase Lipase	Appearance Blood Color Glucose Leukocyte esterase pH Protein Urobilinogen Reflex to microscopic urinalysis if dipstick result is abnormal.	Urine drug screen for: Amphetamines Cocaine Methadone Opiates Leukocyte subsets IgA, IgG, IgM C-reactive protein (CRP) Rheumatoid factor and cyclic citrullinated peptide (RF/CCP) Quantiferon (if required per exclusion criteria) CD19 (if required per exclusion criteria) RNA
Coagulation		**Serology**	**Pregnancy**
Activated partial thromboplastin time (aPTT) Prothrombin time (PT) International normalized ratio (INR)		Hepatitis BsAg and core Ab Hepatitis C Ab HIV	*In females of childbearing potential:* Serum β-hCG (Screening and if positive urine β-hCG) Urine β-hCG (all other visits)

Ab = antibody
β-hCG = beta-human chorionic gonadotropin
BsAg = B surface antigen
IgA, IgG, IgM = immunoglobulins A, G, M

Appendix 4. Common Terminology Criteria for Adverse Events (CTCAE) v4.03

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).

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a) Definition of Childbearing Potential

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

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause.

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 fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

GS-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. Therefore, 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 version of the investigator's brochure 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 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 (Appendix 2).

Female subjects of childbearing potential must agree to one of the following from Screening until 30 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 3 months after procedure)

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

3) Contraception Requirements for Male Subjects

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

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

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

Appendix 6. The 2010 American College of Rheumatology –European League Against Rheumatism Collaborative Initiative Classification Criteria for Rheumatoid Arthritis {Aletaha et al 2010}

Target population (Who should be tested?): Patients who have at least 1 joint with definite clinical synovitis (swelling)[a] with the synovitis not better explained by another disease[b]	
Classification criteria for RA (score-based algorithm: add score of categories A - D; a score of ≥ 6/10 is needed for classification of a patient as having definite RA)[c]	
A. Joint involvement[d]	
1 large joint[e]	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)[f]	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)[g]	5
B. Serology (at least 1 test result is needed for classification)[h]	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)[i]	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms[j]	
<6 weeks	0
≥6 weeks	1

a The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

b Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

c Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

d Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

e "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

f "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

g In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (eg, temporomandibular, acromioclavicular, sternoclavicular).

h Negative refers to IU values that are less than or equal to the ULN for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti-citrullinated protein antibody.

i Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

j Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (eg, pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Appendix 7. American College of Rheumatology Response Evaluations/ Preliminary Definition of Improvement in Rheumatoid Arthritis {Felson et al 1995}

ACR 20/50/70 Requires ≥ 20%/50%/70% improvement in tender joint count, AND
≥ 20%/50%/70% improvement in swollen joint count, AND
≥ 20%/50%/70% improvement in at least 3 of the following 5:

- Patient's Assessment of Pain
- Patient's Global Assessment of Disease Activity
- Physician's Global Assessment of Disease Activity
- Patient's assessment of physical function (HAQ-DI)
- Acute-phase reactant (CRP)

The following lists the disease activity measure followed by the method of assessment

1. Tender joint count

ACR tender joint count is an assessment of 68. The joint count should be done by scoring several different aspects of tenderness, as assessed by pressure and joint manipulation on physical examination. The information on various types of tenderness should then be collapsed into a single tender-versus-nontender dichotomy.

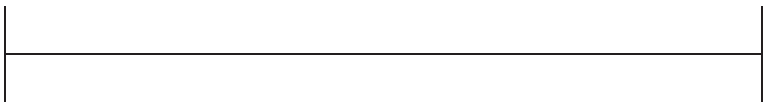
2. Swollen joint count

ACR swollen joint count is an assessment of 66. Joints are classified as either swollen or not swollen.

3. Patient's Assessment of Pain

A horizontal visual analog scale (VAS) will be used to assess the patient's current level of pain.[4]

How much pain have you had because of your condition over the past week? Place a mark on the line below to indicate how severe your pain has been:



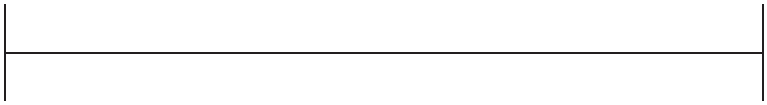
No Pain **Unbearable Pain**

[4] Visual analog scales provided in this protocol are not to scale and should not be utilized for assessments.

4. Patient's Global Assessment of Disease Activity

A horizontal VAS will be used to provide the patient's overall assessment of how the arthritis is doing.

Place a mark on the line below to indicate how you assess your current arthritis disease activity:

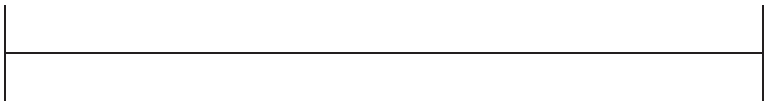


No arthritis activity **Extremely active arthritis**

5. Physician's Global Assessment of Disease Activity

A horizontal VAS will be used to measure the physician's assessment of the patient's current disease activity.

Place a mark on the line below to indicate disease activity (independent of the subject's self-assessment):



No Disease Activity **Maximum Disease Activity**

6. Patient's Assessment of Physical Function

The HAQ-DI will be used to provide a patient's self-assessment of physical function.

7. Acute-phase reactant value

C-reactive protein level

Appendix 8. Disease Activity Score for 28 Joint Count (DAS28) {Prevoo et al 1995}

Assessments of RA in patients by the Disease Activity Score (modified to include the 28 joint counts according to Smolen* 1995) will be conducted at the measured timepoints**.** The DAS28 consists of a composite score of the following variables: tender joint count, swollen joint count, CRP, and Patient's Global Assessment of Disease Activity score. The following equation will be used to calculate the DAS28 (CRP)

- DAS28 (CRP) = $0.56 \sqrt{TJC28} + 0.28\sqrt{SJC28} + 0.36\ln(CRP + 1) + 0.014 \times (\textit{Patient's Global Assessment of Disease Activity}) + 0.96$

  — TJC28 = number of joints tender out of 28

  — SJC28 = number of joints swollen out of 28

  — CRP = C-reactive protein

  — Patient's Global Assessment of Disease Activity on a 100 mm VAS recorded by the patient

Appendix 9. Procedures and Specifications

Complete Physical Examination

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

Vital Signs

Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate, and temperature. Body weight and height will also be included at Screening only.

Blood pressure will be measured using the following standardized process:

- Subject should sit for ≥ 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level;
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery;
- Measure and record the blood pressure to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

12-Lead ECG

Subjects will be required to rest in a supine position for ≥ 5 minutes prior to making a recording.

The investigator (or qualified designee) should review the ECG traces recorded in real time for clinically significant abnormalities. On treatment ECGs should be compared to the subject's Baseline as part of routine safety monitoring.

Fredericia Formula (QTcF)

QTc = QT/(RR^0.33)

Health Assessment Questionnaire – Disability Index

The HAQ-DI is a patient reported questionnaire specific for RA. It consists of 20 questions referring to 8 component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Physician's and Patient's Global Assessment of Disease Activity and Patient's Global Assessment of Pain

The physician's and the patient's global assessment of disease activity will be recorded on a 100-mm horizontal VAS that ranges from "none" (0 mm, symptom free and no RA symptoms) to "maximum" (100 mm, maximum RA activity). The patient's global assessment of pain will be recorded on a 100-mm horizontal VAS that ranges from "none" (0 mm) to "unbearable" (100 mm).

Joint Assessment

An assessment of 66 joints for swelling and 68 joints for tenderness will be performed. Joints will be assessed and classified as swollen or not swollen and tender or not tender by pressure and joint manipulation upon physical examination. Joint exams should be performed by a trained and experienced joint assessor. Every effort should be made for the same joint assessor to perform the joint exams on the same subject particularly during the blinded phase of the study.