CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 2 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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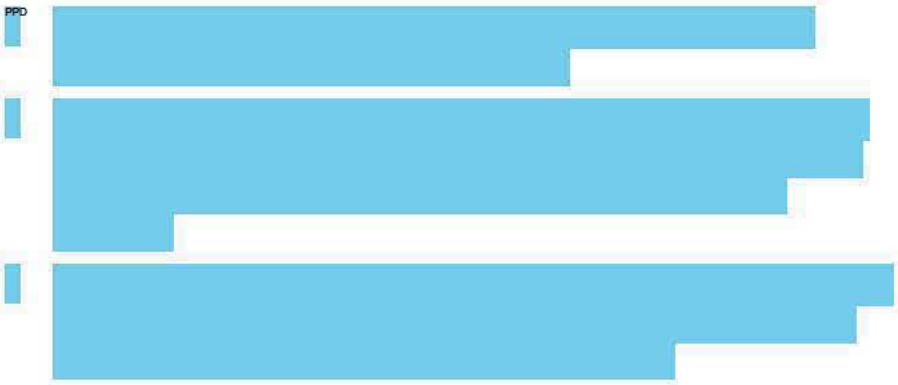
PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 2 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: **EudraCT Number:** **Clinical Trials.gov Identifier:**	IND 123903 2016-001496-75 TBD
Study Centers Planned:	Approximately 60 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: PPD 

Study Design:	This is a randomized, double-blind, placebo-controlled, multicenter, Phase 2 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 80 subjects will be randomized in a 1:1:1:1 ratio to receive daily doses of 30 mg GS-9876, 10 mg GS-9876, 200 mg filgotinib, or placebo-to-match (PTM) in addition to background therapy with MTX for up to 12 weeks: • **GS-9876 30 mg:** GS-9876 (1 x 30 mg tablet QD) + PTM filgotinib (2 x placebo tablets QD) (N=20) • **GS-9876 10 mg:** GS-9876 (1 x 10 mg tablet QD) + PTM filgotinib (2 x placebo tablets QD) (N=20) • **Filgotinib 200 mg:** filgotinib (2 x 100 mg tablets QD) + PTM GS-9876 (1 x placebo tablet QD) (N=20) • **Placebo only:** PTM GS-9876 (1 x placebo tablet QD) + PTM filgotinib (2 x placebo tablets 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 80 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:	For a complete list of inclusion and exclusion criteria, please refer to Section 4 of the protocol. 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) at Screening and Day 1 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 (defined as no change in prescription) 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 (defined as no change in prescription) 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 (defined as no change in prescription) for at least 14 days prior to the first dose of study drug; pro re nata (PRN) use for other indications is allowed.

6) No evidence of active or latent TB as demonstrated by a negative QuantiFERON® TB-Gold In-Tube test at Screening. Tests with inconclusive results may be repeated one time. If an inconclusive test is repeated and is returned with inconclusive results a second time, the subject will be excluded from the study. Any prior history of active or latent TB (regardless of treatment) is exclusionary.

Key Exclusion Criteria include:

1) Prior treatment with B-cell depleting agents (eg, rituximab), unless more than 6 months prior to the first dose of study drug and documented return of CD19+ cells at Screening

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

3) Concurrent treatment at Screening with any other conventional synthetic DMARD (csDMARD) other than MTX and/or hydroxychloroquine (HCQ) (prior csDMARD treatment allowed if appropriate wash out as defined in Section 5.7)

4) Concurrent treatment at Screening with any bDMARD (prior bDMARD treatment allowed if appropriate wash out as defined in Section 5.7). Prior failure to treatment with bDMARDs is not an exclusion criterion.

5) QT interval corrected for heart rate using the Fridericia 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[Appendix 4]) within the last year or personal or family history of bleeding disorder

   OR

   Current use of chronic anticoagulant, not including daily aspirin for cardiac prophylaxis

7) Treatment with moderate or strong CYP3A inducers or inhibitors within 2 weeks prior to the first dose of study drug (examples are provided in Section 5.7)

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, coagulation, and lipid panel), CRP, serology (HIV, HCV, HBV), QuantiFERON® TB-Gold In-Tube test, urinalysis, urine drug screen, thyroid-stimulating hormone (TSH), HbA1c, and CD19 count as applicable and as outlined in the protocol . Serum pregnancy testing will be performed for females of childbearing potential (as defined per protocol).

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, coagulation, and lipid panel [fasting on Day 1 and Week 12]), B and T cell panels (Day 1, Week 4, and Week 12), 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, inflammation and pathway biomarkers (Day 1, Week 4, and Week 12 or ET), whole blood samples for mechanism of action (MoA) studies (Day 1, Week 4 and Week 12), and urine bone marker samples (Day 1 [fasting], Week 4, and Week 12 [fasting]). Additional testing will include PK sampling (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 applicable. 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 Filgotinib 200 mg (2 x 100 mg tablets), administered orally once daily
Reference Therapy, Dose, and Mode of Administration	PTM GS-9876 (1 x placebo tablet), administered orally once daily PTM filgotinib (2 x placebo tablets), administered orally once daily
Required Background Therapy	MTX 7.5 to 25 mg, administered orally or parenterally once a week and folic acid supplementation
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, filgotinib and the active metabolite of filgotinib (GS-829845) will be determined.

Exploratory:	PPD
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 sizes for GS-9876 and placebo groups are 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. PPD Therefore, the total sample size will be 80 (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
CES	carboxylesterase
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
CPK	creatine phosphokinase

CRO	contract research organization
CRP	C-reactive protein
csDMARD	conventional synthetic disease modifying anti-rheumatic drug
CTCAE	Common Toxicity Criteria for Adverse Events
CYP	cytochrome P450
DAS28	Disease Activity Score for 28 joint count
DMARD	disease modifying anti-rheumatic drug
DSPH	Drug Safety and Public Health
DSS	dextran sulphate sodium
EC_{50}	half maximal effective concentration
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
GFR	glomerular filtration rate
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBV	hepatitis B virus
HCQ	hydroxychloroquine
HCV	hepatitis C virus
HDL	high-density lipoprotein
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
INR	International Normalized Ratio of prothrombin time
IR	inadequate response
IRB	Institutional Review Board
IU	international units
IUD	intrauterine device
IV	intravenous
IXRS	Interactive Web and Mobile Response System
JAK	Janus kinase
kg	kilogram
L	liter
LAM	lactational amenorrhea method
LDL	low-density lipoprotein
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
MoA	mechanism of action
msec	millisecond
MTX	methotrexate
ng	nanogram
nM	nanomolar
NOAEL	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
SLE	systemic lupus erythematosus
SOC	system organ class
SOP	standard operating procedure
SS	Sjogren's syndrome
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected serious adverse reaction
SYK	spleen tyrosine kinase
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
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}. Rheumatoid Arthritis manifests principally as an attack on peripheral joints and may lead to marked destruction and deformity of joints, with considerable disability and impact on quality of life. It is characterized by the production of autoantibodies, synovial inflammation with formation of pannus tissue, and erosion of underlying cartilage and bone. Although people of any age can be affected, the onset of RA is most frequent between the age of 40 and 50 years, and women are affected 3 times more often than men. While the cause of RA is still not completely understood, aberrant B-cell activation, T-cell co-stimulation, osteoclast differentiation, and cytokine release all have been implicated in its pathogenesis. Subjects with RA experience a high risk of disability and mortality {Arthritis Foundation 2008}.

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

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.

Filgotinib (GS-6034, formerly GLPG0634) is being developed by Gilead as an oral agent, and is a potent and selective inhibitor of JAK1. While the pan JAK inhibitor tofacitinib (Xeljanz®) has shown an early onset of action and long-term efficacy in RA as monotherapy and in combination with background csDMARD therapy, dose levels were limited by side effects potentially mediated by its effect on JAK 2 and JAK 3. This highlights the need for more selective and targeted therapies with improved immunomodulatory and hematologic effects. JAK1 is thought to be an integral part of RA pathogenesis due its role in transmitting inflammatory cytokine signaling. Hence, targeted inhibition of JAK1 has great potential for the treatment of RA with an improved safety and side effect profile.

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. Nonclinical Pharmacology and Toxicology

1.2.2.1. Nonclinical Pharmacology and Safety Pharmacology

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

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

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

GS-9876 to prolong the QTc interval was assessed with intensive time matched ECG monitoring in Gilead studies GS-US-379-1372 and GS-US-379-1900 (cohorts 1 and 2), and no clinical significant change in time matched QTc intervals was observed. No clinical significant changes in vital signs during serial vital sign measurements were observed.

1.2.2.2. Nonclinical Toxicology

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

In monkeys, the NOAEL in the 28-day study was identified at 10 mg/kg/day, which was associated with $AUC_{0\text{-}24hr}$ of 4290 ng•hr/mL. In the 13-week monkey study, there were no effects on hemostasis, and the NOAEL was the high dose of 15 mg/kg/day. 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. Nonclinical Drug Metabolism and Pharmacokinetics

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

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

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

1.2.3. Clinical Trials of GS-9876

As of 14 June 2016, 74 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). No risks were identified and no grade 3 or 4 AEs were reported. There were no clinically significant changes in vital signs, physical findings, bleeding times, or ECGs. For further information, refer to the current IB.

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. Filgotinib

1.3.1. General Information

For further information on filgotinib, refer to the current IB.

1.3.2. Nonclinical Pharmacology, Absorption, Distribution, Metabolism, and Excretion (ADME) and Toxicology

Filgotinib and its metabolite, GS-829845 have been extensively characterized in nonclinical studies. This program includes cellular assays demonstrating potency and selectivity of the compound against JAK1, efficacy studies in rats and mice, repeat dose toxicity studies (up to 26 weeks in the rat and 39 weeks in the dog), *in vitro* and *in vivo* safety pharmacology and genetic toxicology studies, and reproductive toxicology studies in rats and rabbits. Additional toxicology studies conducted include phototoxicity studies and dose-range finding studies in support of a definitive rat juvenile toxicity study and a 6 month carcinogenicity study in transgenic (TgrasH2) mice. A 2 year rat oral carcinogenicity study is ongoing.

1.3.2.1. Primary and Secondary Pharmacology

Filgotinib is an ATP-competitive inhibitor of JAK1. It is highly selective for inhibition of JAK1 over 451 other kinases evaluated *in vitro*. In cellular assays, it inhibits JAK/STAT-driven processes with half maximal inhibitory concentration (IC_{50}) values from 179 nM onwards. In human whole blood, JAK1 is inhibited by filgotinib with an IC_{50} of 629 nM and exhibits approximately 30-fold selectivity over JAK2. Filgotinib demonstrated significant efficacy in the rat CIA model as well as in the mouse dextran sulphate sodium (DSS)-induced colitis model.

Metabolite GS-829845 exhibits a similar JAK1 selectivity profile but is approximately 10 to 20-fold less potent than the parent filgotinib in *in vitro* assays. GS-829845 was as effective as filgotinib in the rat CIA model, but at doses that required a 10-fold higher exposure.

1.3.2.2. Safety Pharmacology

Filgotinib and GS-829845 had no effects on the respiratory system and CNS up to respectively 40- and 5-fold the exposure in RA subjects given filgotinib 200 mg QD.

Filgotinib and GS-829845 had no relevant effects on cardiovascular parameters (hERG and dog telemetry studies), apart from a slight non-adverse increase in heart rate and arterial pressure with GS-829845 at exposures 7-fold that of the C_{max} in subjects with RA dosed with 200 mg QD filgotinib. There were no relevant effects on ECG and QT.

1.3.2.3. Nonclinical ADME

Filgotinib demonstrates good oral bioavailability in mice, rats, dogs, and mini-pigs but less in monkeys. Plasma protein binding is low (< 70%) in all species, including humans.

The PK of filgotinib is generally dose proportional without gender differences. No accumulation occurs with repeated dosing. The mean terminal half-life after oral administration is 4 and 5 hours in rats and dogs, respectively.

In the rat, filgotinib showed a rapid and even distribution throughout the body. High concentrations were observed only in the gastrointestinal tract and urinary bladder. Filgotinib does not penetrate into CNS tissues. The distribution of filgotinib indicates some affinity for melanin-containing tissues.

Excretion is nearly complete within 24 hours (rat) and 48 hours (dog) post-dosing. In the rat, fecal and urinary excretion accounted for 40% and 53% of the administered dose, respectively, with a bile secretion of about 15%. In the dog, fecal excretion was the primary route of excretion, accounting for 59% of the administered dose, with urinary excretion accounting for 25%.

In vitro metabolism studies in all species revealed one major metabolite (GS-829845). The formation of GS-829845 is mediated by carboxylesterases (CES) and is not dependent on CYP.

In vitro experiments have shown that drug-drug interactions with filgotinib and GS-829845 are unlikely. There is no inhibition or induction of CYPs or UGTs, and no relevant inhibition of key drug transporters, including the organic anion transporters involved in the renal elimination of MTX, by filgotinib or GS-829845.

1.3.2.4. Nonclinical Toxicology

In repeat oral dose toxicity studies in both rats and dogs, the primary target tissues identified for filgotinib were the lymphoid tissues which are expected based on the pharmacology of JAK inhibition. Additional filgotinib-related findings were observed in the male reproductive organs of both species, and in the incisor teeth of rats only. Effects on the lymphoid system were fully reversible. Testicular toxicity demonstrated reversibility, however sperm counts remained low; this may have been a result of a recovery period of insufficient duration. A dose of 200 mg/day of filgotinib results in an estimated mean clinical AUC of 2.80 µg·h/mL, which represents an

exposure margin of 2.7-fold when considering the mean AUC in male dogs at the NOELs across studies of ≥ 26 weeks in duration (mean AUC of 7.5 μg·h/mL).

GS-829845-related findings in general repeat dose toxicity studies were similar to those of the parent filgotinib, however no testicular toxicity was noted following administration of GS-829845.

Filgotinib and GS-829845 were non-genotoxic when evaluated in the bacterial mutagenicity assay, the *in vitro* mouse lymphoma mutagenicity assay, and the rat bone marrow micronucleus assay.

In embryofetal development studies, filgotinib and GS-829845 caused embryolethality and teratogenicity in rats and rabbits at exposures similar to the human exposure at 200 mg/day of filgotinib in subjects with RA. Administration of filgotinib did not affect female fertility but impaired fertility was observed in male rats at exposures approximately 15-fold the human exposure at 200 mg of filgotinib in subjects with RA. GS-829845 did not have any effects on fertility parameters in either male or female rats.

In an *in vitro* phototoxicity study in 3T3 cells, the metabolite GS-829845 was positive for phototoxic potential and results with filgotinib were equivocal. A follow-up *in vivo* rat phototoxicity assay revealed a lack of phototoxic potential for both compounds.

1.3.3. Clinical Trials of Filgotinib

As of January 2016, filgotinib has been administered to 153 healthy subjects, 1004 RA subjects, and 130 subjects with Crohn's disease. The main Phase 2b studies are listed below. A detailed description of all clinical studies can be found in the IB.

GLPG0634-CL-203: In this study, subjects with active RA on stable dose of MTX were randomized to receive either placebo or one of three total daily doses of filgotinib (50 mg, 100 mg, or 200 mg) on a once or twice daily schedule for 24 weeks. The primary objective of the study was to evaluate the efficacy of different doses and dose regimens of filgotinib compared to placebo at Week 12.

GLPG0634-CL-204: This study evaluated filgotinib administered as a monotherapy in RA subjects. The primary objective of study GLPG0634-CL-204 was to evaluate the efficacy of three doses of daily filgotinib compared to placebo at Week 12.

In both 24-week, Phase 2b, randomized, double-blind, placebo-controlled studies in 594 (Study GLPG0634-CL-203) and 283 subjects (Study GLPG0634-CL-204) with moderately to severely active RA who had insufficient response to MTX, filgotinib added to a stable dose of background MTX or administered as monotherapy was efficacious in a dose-dependent manner in treating the signs and symptoms of active RA. In Study GLPG0634-CL-203, an ACR20 response was achieved by a statistically significantly higher percentage of subjects in the 100-mg once-daily, 200-mg once-daily, and 100-mg filgotinib twice-daily groups (63.5%, 68.6%, and 78.6%, respectively) compared with placebo (44.2%) ($p = 0.0435$, 0.0068, and < 0.0001,

respectively). In Study GLPG0634-CL-204, an ACR20 response at Week 12 was achieved by a statistically significantly higher percentage of subjects in all filgotinib dose groups compared with placebo (66.7%, 65.7%, and 72.5% in the 50-mg once-daily, 100-mg once-daily, and 200-mg filgotinib once-daily groups, respectively, compared with 29.2% on placebo) ($p < 0.0001$ for all comparisons). In both studies, the ACR20 appeared to plateau at Week 8 and was maintained through Week 24. In addition, at Week 12, filgotinib showed a beneficial effect across the following secondary efficacy parameters: ACR50, ACR70, ACR-N, DAS28 (CRP), CDAI, and SDAI. A dose-dependent fast onset of efficacy was reported, and the responses were maintained or continued to improve through 24 weeks. No significant difference in efficacy was observed between 100-mg and 200-mg once-daily dosing regimens.

1.4. 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.

1.5. 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 subjects {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.

Filgotinib is an orally administered, small molecule inhibitor of JAK1, an intracellular tyrosine kinase dysregulated in subjects with inflammatory disorders including RA. Filgotinib has demonstrated clinical activity and a favorable safety and tolerability profile in Phase 2 studies in subjects with moderately to severely active RA.

This study is designed to evaluate the efficacy, safety, tolerability, PK, and PPD of GS-9876 in subjects with RA. PPD .

1.6. 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.

Results from Phase 2a studies (GLPG-CL-201 and GLPG-CL-202) and Phase 2b studies (GLPG-CL-203 and GLPG-CL-204) showed that 200 mg QD filgotinib was well tolerated and demonstrated promising clinical efficacy (ACR20/50/70 and DAS28[CRP]) in subjects with RA. Exposure-response analysis based on data from all Phase 2 studies indicated a dose-dependent increase in efficacy (ACR20/50/70, DAS28[CRP]), with a plateau at the 200 mg total daily dose on the dose-response curve. These results are consistent with the relationship observed between filgotinib exposures and pSTAT1 activation (ex-vivo) following single and multiple filgotinib doses, where maximal inhibition of pSTAT1 (~78%) was achieved at or above 200 mg total daily dose {Namour et al 2015}. Based on the overall risk-benefit observed in Phase 2b studies, 200 mg QD filgotinib is expected to be safe and efficacious in subjects with RA, and is considered an appropriate dose to investigate the mechanism of action of a JAK inhibitor in comparison to a SYK inhibitor.

1.7. Risk/Benefit Assessment for the Study

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease that affects approximately 1% of the population {Helmick et al 2008}. Despite the currently available medications for RA, there is still a need for new treatments because not all patients respond adequately (or maintain

response) to current therapies and some experience toxicities and/or intolerance that limit the use of such therapies. The need for new, non-injectable therapeutic options with a favorable efficacy and safety profile have prompted efforts to develop orally administered, small molecules. The development of these drugs is important because in addition to RA, other inflammatory diseases, such as systemic lupus erythematosus (SLE) and Sjogren's syndrome (SS), also have a need for additional therapeutic options.

GS-9876 is a highly selective spleen tyrosine kinase (SYK) inhibitor with once daily dosing; SYK is a key signaling molecule involved in innate and adaptive immune system responses. It is important in various cell types, including platelets, phagocytes, fibroblasts, and osteoclasts, and in the generation of the inflammasome. Nonclinical studies show that SYK inhibition may have therapeutic value in the treatment of RA, SLE, SS, autoimmune cytopenias, and allergic and autoinflammatory diseases. Clinical trials with fostamatinib (an experimental SYK inhibitor) have demonstrated responses in RA and in idiopathic thrombocytopenic purpura.

In repeat dose toxicity studies of GS-9876 (in rats for up to 26 weeks and in cynomolgus monkeys for up to 39 weeks), the primary observed effects were reversible, dose-dependent decreases in circulating lymphocytes, and decreased lymphocytes in various tissues (spleen, lymph nodes, thymus, and/or bone marrow), consistent with the expected pharmacology of SYK inhibition {Barr et al 2012}. Additionally, effects on erythrocyte turnover were seen in rats, and effects on hemostasis (hemorrhage and thrombosis) were seen in monkeys. In clinical studies of GS-9876 in healthy volunteers (GS-US-379-1372, single ascending dose, completed, and GS-US-379-1900, multiple ascending dose, ongoing), no risks were identified and no grade 3 or 4 AEs were reported. There were no clinically significant changes in vital signs, physical findings, or ECGs. Given the role of SYK in platelet activation and aggregation, bleeding time was evaluated in the study subjects; no prolongation was noted.

In addition to GS-9876, filgotinib, a once-daily, oral, potent JAK-1 inhibitor, has the potential to address the medical needs of RA. As of January 2016, filgotinib has been administered to 1004 subjects with RA and 152 subjects with Crohn's disease (CD) at daily doses ranging from 50 to 200 mg. Dose-dependent decreases in mean neutrophil counts and platelet counts were observed in the RA Phase 2b studies (but mean levels of both remained within normal laboratory reference ranges), and there were no decreases in mean lymphocytes or lymphocyte subsets. However, a potential increased risk of infection may be considered consistent with the mechanism of JAK inhibition. In the filgotinib RA program, three deaths have been reported, all due to infectious etiologies. One subject in the Phase 2b study died of community acquired pneumonia and septic shock; two subjects had entered the open-label extension study, one died of meningococcal meningitis, and the other of pneumonia.

Nonclinical studies in rats and dogs identified lymphoid tissues and testes as target organs for filgotinib; microscopic findings in the testes included germ cell depletion and degeneration in both species, with reduced sperm content and reduced fertility in male rats. The clinical relevance of the testicular findings is unknown. A male safety study is planned to specifically address the effect (if any) of filgotinib on the human testes.

Both GS-9876 and filgotinib are contraindicated in pregnancy; highly effective contraception is to be used across all clinical studies to mitigate this risk. Measures to minimize other potential risks to subjects will include site/investigator training regarding monitoring for infection, and collection of AEs of special interest, including major adverse cardiac events, malignancies, infections, and specific laboratory abnormalities.

Preclinical and clinical data support the further clinical development of GS-9876 and filgotinib due to their potential benefit as novel therapies in inflammatory diseases, with an acceptable level of risk consistent with immunomodulation in these patient populations. Controlled trials will be utilized to minimize risk to subjects, while gaining understanding of the lowest effective doses of these drugs. With respect to GS-9876 and filogotinib, given the early clinical data, as well as the beneficial findings in nonclinical models and overall safety, tolerability, and PK characteristics of these drugs, there is a favorable benefit:risk profile for continued development as treatments for autoimmune/inflammatory diseases. The development of GS-9876 and filgotinib are expected to provide a valuable addition and alternative to existing treatments for RA, SLE, SS, and related diseases.

1.8. Compliance

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

2. OBJECTIVES

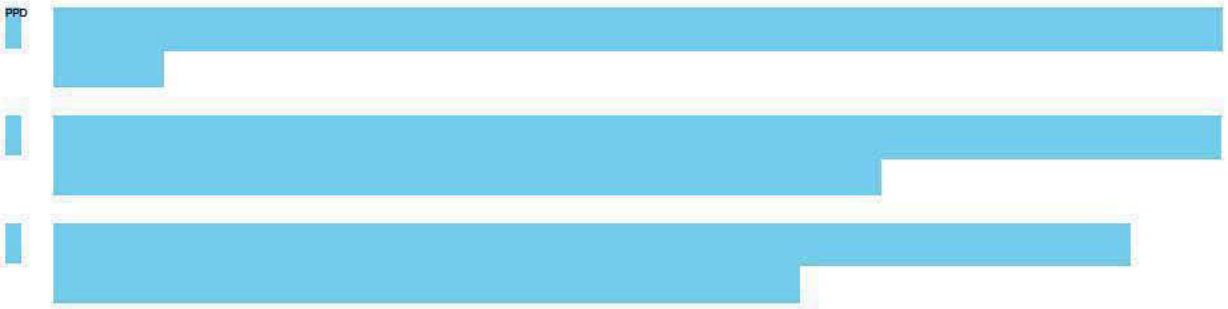
The primary objective of this study is:

- 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

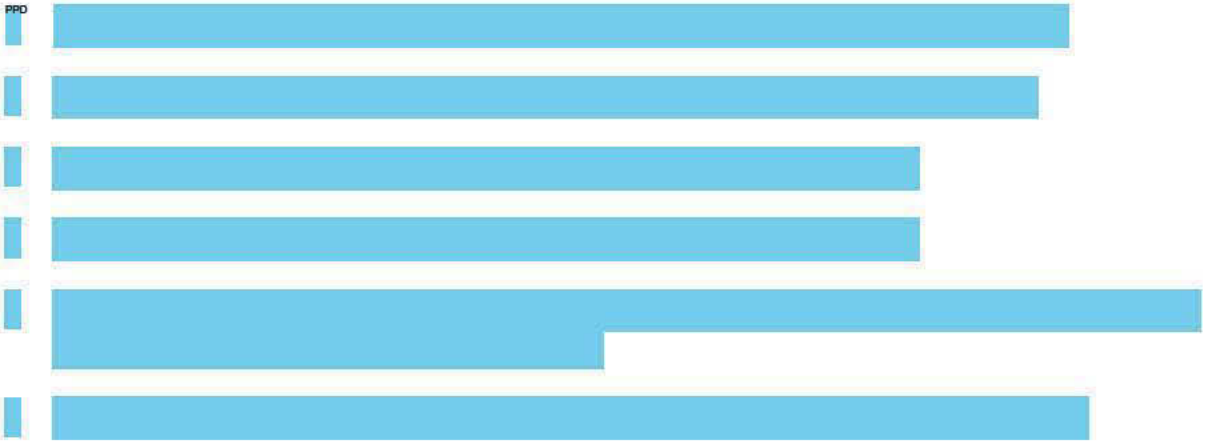
The primary endpoint of this study is:

- 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:

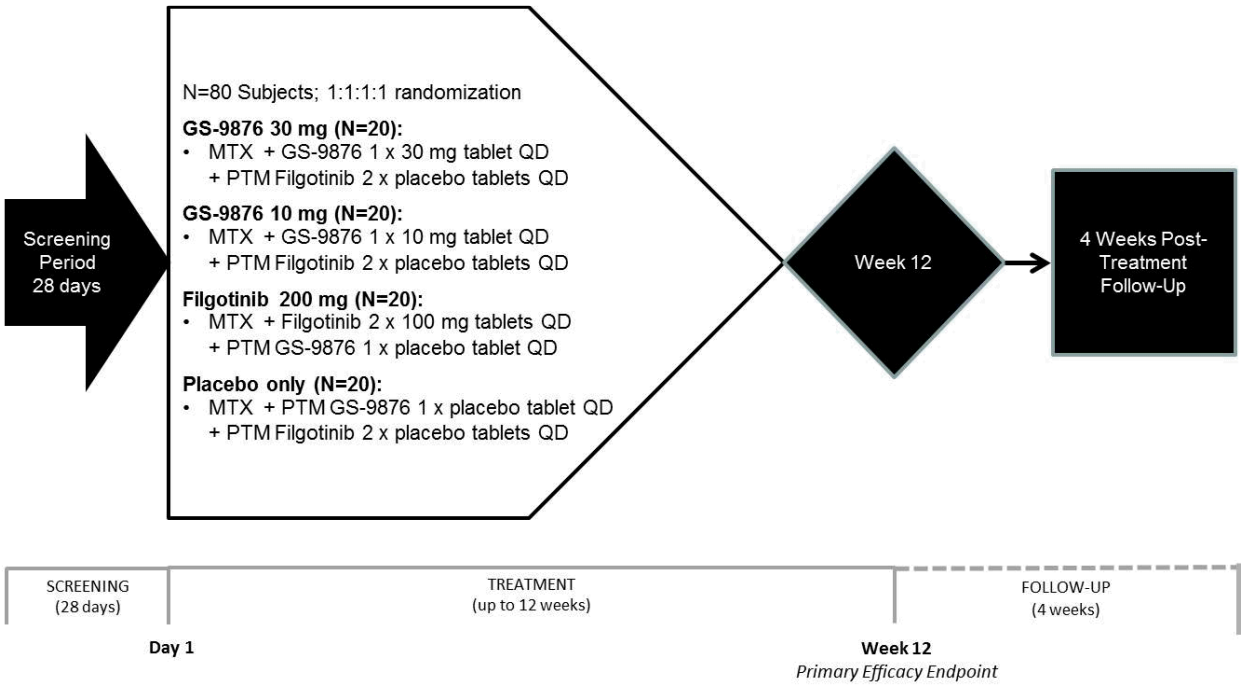


3.2. Study Design

This is a randomized, double-blind, placebo-controlled, Phase 2 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). In addition, the effect of GS-9876 and filgotinib on disease and/or pathway markers relevant to RA and/or the SYK and JAK pathways will be assessed.

A total of approximately 80 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 1:1:1:1 ratio as follows (all groups will continue to take MTX):

- **GS-9876 30 mg:** GS-9876 (1 x 30 mg tablet QD) + PTM filgotinib (2 x placebo tablets QD) (N=20)
- **GS-9876 10 mg:** GS-9876 (1 x 10 mg tablet QD) + PTM filgotinib (2 x placebo tablets QD) (N=20)
- **Filgotinib 200 mg:** Filgotinib (2 x100 mg tablets QD) + PTM GS-9876 (1 x placebo tablets QD) (N=20)
- **Placebo only:** PTM GS-9876 (1 x placebo tablet QD) + PTM filgotinib (2 x placebo tablets 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 dosed for up to 12 weeks and then followed for 4 weeks after their last dose of study drug.

3.5. Criteria for Interruption and Discontinuation Criteria

3.5.1. Study drug interruption considerations

The Gilead Medical Monitor should be consulted prior to study drug interruption when medically feasible.

Study drug interruption should be considered in the following circumstances; *prior to resumption of study drug, the investigator should discuss the case with the Gilead medical monitor*:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Subject is scheduled for emergency surgery (excluding minor skin procedures under local or no anesthesia); timing of study drug pausing should be determined in consultation with the Gilead medical monitor. Elective surgery should not be planned during the 12 week study period.
- If the subject has any signs or symptoms suggestive of infection (regardless of severity), study drug dosing should be immediately interrupted, and the medical monitor notified. Any subject who develops a new infection during the study should undergo prompt and complete diagnostic testing appropriate for an immuncompromised individual, and the subject should be closely monitored. Study drug should continue to be paused until the subject's event has resolved, per judgment of the investigator. Prior to resuming study drug dosing, the investigator should discuss these cases with the sponsor or its designee
- *NOTE: During the time of study drug interruption for any of the above, the subject may continue to have study visits and to take part in procedures and assessments, if deemed medically appropriate by the investigator.*

3.5.2. Study drug discontinuation considerations

The Gilead Medical Monitor should be consulted prior to study drug discontinuation when medically feasible.

Study medication should be permanently discontinued in the following instances:

- Any opportunistic infection
- Any **serious** infection that requires antimicrobial therapy or hospitalization, or any infection that meets SAE reporting criteria.
- Complicated herpes zoster infection (with multi-dermatomal, disseminated, ophthalmic, or CNS involvement)
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest

- Subject request to discontinue for any reason
- Subject noncompliance
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)
- Subjects use of non-permitted concurrent therapy
- Pregnancy during the study; refer to Appendix 5
- Investigator discretion

After becoming aware of any of the below described abnormal laboratory changes at any one time, an unscheduled visit (ie, second sequential) to retest must occur within 3 to 5 days. If the laboratory abnormality is confirmed by the retest, study medication should be discontinued.

- 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]
- 2 sequential AST or ALT elevations >5xULN, regardless of total bilirubin or accompanying symptoms[1]
- 2 sequential values for estimated creatinine clearance <40 mL/min based on the Cockroft Gault formula

Subjects who stop study medication for any reason will not be replaced. Subjects withdrawing from the study should complete the ET and Post-Treatment Week 4 visits. Subjects may withdraw from the study at any time without providing reason(s) for withdrawal and without

[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.

prejudice to further treatment. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF).

Reasonable efforts will be made to contact subjects who are lost to follow-up. All contacts and contact attempts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of safety concerns or if special circumstances concerning the study medication or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) and relevant authorities will be informed of the reason for study termination.

3.6. End of Study

End of Study is defined as when the last subject 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 study 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, filgotinib and the metabolite of filgotinib (GS-829845) 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 or filgotinib, but prior to the next dose of GS-9876 or filgotinib. At Week 4, PK sampling will occur at approximately 2 hours postdose. The samples will be used to evaluate PK of GS-9876 or filgotinib and may also be used to measure protein binding of GS-9876 or filgotinib. Plasma concentrations of GS-9876 metabolites, other filgotinib metabolite(s), and/or MTX may be determined.

PPD

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 and JAK pathways) may be performed at Day 1, Week 4, and Week 12 or ET. Blood and urine samples will also be collected for assessments of immunoglobulins (Day 1 and Week 12 or ET), B and T cell panels (Day 1, Week 4, and Week 12), whole blood samples for MoA studies (Day 1, Week 4 and Week 12), and bone markers (Day 1 [fasting], Week 4, and Week 12 [fasting]). 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. Biomarker Samples for Optional Future Research

PPD

3.9.2. Optional Genomic Research

PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 80 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), an SJC of ≥ 6 (out of 66) at Screening and Day 1

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 (defined as no change in prescription) 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 (defined as no change in prescription) 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 (defined as no change in prescription) for at least 14 days prior to the first dose of study drug; PRN use for other indications is allowed.

8) No evidence of active or latent TB as demonstrated by a negative QuantiFERON® TB-Gold In-Tube test at Screening. Tests with inconclusive results may be repeated one time. If an inconclusive test is repeated and is returned with inconclusive results a second time, the subject will be excluded from the study. Any prior history of active or latent TB (regardless of treatment) is exclusionary.

9) 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.

10) A negative serum pregnancy test is required for female subjects of childbearing potential, as defined in Appendix 5

11) Lactating females must agree to discontinue nursing before the study drug is administered and for the duration of the study.

12) 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.

13) Male subject agrees to refrain from sperm donation throughout the study period and for at least 90 days following their last dose of study drug.

14) Female subject agrees to refrain from egg donation/harvest throughout the study period and for at least 35 days after their last dose of study drug.

4.3. Exclusion Criteria

1) Prior treatment with B-cell depleting agents (eg, rituximab), unless more than 6 months prior to the first dose of study drug and documented return of CD19+ cells at Screening

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

3) Concurrent treatment at Screening with any other csDMARD other than MTX and/or HCQ (prior csDMARD treatment allowed if appropriate wash out as defined in Section 5.7)

4) Concurrent treatment at Screening with any bDMARD (prior bDMARD treatment allowed if appropriate wash out as defined in Section 5.7). Prior failure to treatment with bDMARDs is not an exclusion criterion.

5) QT interval corrected for heart rate using the Fridericia 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 the modified CTCAE 4.03[Appendix 4]) within the last year or personal or family history of bleeding disorder

   OR

   current use of chronic anticoagulant, not including daily aspirin for cardiac prophylaxis

7) Treatment with moderate or strong CYP3A inducers or inhibitors within 2 weeks prior to the first dose of study drug (examples are provided in Section 5.6)

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

9) Known hypersensitivity or allergy to GS-9876, filgotinib or MTX, and their metabolites, or their formulation excipients

10) Administration of a live or attenuated vaccine within 30 days of Screening or planned for during the study.

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 that would interfere with study procedures or assessments per the discretion of the investigator (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 arthropathies, systemic lupus erythematosus, scleroderma, inflammatory myopathy, mixed connective tissue disease, an 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 prior to Screening: 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 participating in the study.

14) History of malignancy within the past 5 years prior to Screening (except for adequately treated 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 organ or bone marrow transplant.

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

18) History of opportunistic infection or immunodeficiency syndrome which would put the subject at risk, as per investigator judgment.

19) Known active infection of any kind (excluding fungal infections of nail beds) or any major episode of infection requiring hospitalization or treatment with intravenous (IV) or oral anti-infectives within 4 weeks of Screening.

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

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

22) History within the previous 2 years prior to Screening or current drug or alcohol abuse, or heavy tobacco use, per the investigator judgment.

23) Any condition or circumstances (such as fibromyalgia or others) 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.

24) Have any chronic, uncontrolled medical condition, which would put the subject at increased risk during study participation, such as uncontrolled: diabetes, hypertension, morbid obesity, thyroid, adrenal, pulmonary, hepatic, renal, neurologic or psychiatric disease, or other disease of concern, as per investigator judgment

25) Significant blood loss (>450 mL) or transfusion of any blood product within 12 weeks prior to the first dose of study drug

26) Subject has donated blood within 56 days of the first dose of study drug or plasma within 7 days of the first dose of study drug or does not agree to refrain from blood donation throughout the study period and for at least 30 days following the last dose of study drug.

27) The results of the following laboratory tests performed at the central laboratory at Screening meet any of the criteria below (out of range lab values may be rechecked one time, per investigator judgment, before subject is considered a screen-failure):

    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 (estimated GFR) < 60 mL/min based on the Cockcroft-Gault (CG) formula

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 eCRF, along with the date on which the treatment assignment was obtained. The investigator is advised 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 must discontinue study drug. 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 of GS-9876 and PTM GS-9876

5.2.1. Formulation of GS-9876 and PTM GS-9876

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 and 30 mg GS-9876 tablets and contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, 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 of GS-9876 and PTM GS-9876

GS-9876 tablets, 10 mg or 30 mg, and PTM GS-9876 tablets are packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

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

5.3. Description of Filgotinib and PTM Filgotinib

5.3.1. Formulation of Filgotinib and PTM Filgotinib

Filgotinib will be provided as 100 mg tablets that are capsule-shaped, biconvex, and film-coated beige tablets debossed with “GSI” on one side and “100” on the other. Each tablet contains the equivalent of 100 mg filgotinib free base in the form of filgotinib maleate. In addition to the active ingredient, filgotinib tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, fumaric acid, pregelatinized starch, silicon dioxide, magnesium stearate, macrogol/PEG 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red.

Placebo-to-match filgotinib tablets are identical in appearance to the active filgotinib tablets. Placebo-to-match filgotinib tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, macrogol/PEG 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red.

5.3.2. Packaging and Labeling of Filgotinib and PTM Filgotinib

Filgotinib 100 mg tablets and PTM filgotinib tablets are packaged in white, 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 fitted with an induction-sealed, aluminum-faced liner.

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

5.4. Storage and Handling of Study Drugs

GS-9876 tablets, PTM GS-9876 tablets, filgotinib tables, and PTM filgotinib 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 drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drugs and to ensure proper product identification, the drug products should not be stored in a container other than the containers in which they are supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.5. Dosage and Administration of Study Drugs

Subjects will receive study drugs according to their randomization assignment to one of the following 4 arms:

- **GS-9876 30 mg:** GS-9876 (1 x 30 mg tablet QD) + PTM filgotinib (2 x placebo tablets QD) (N=20)
- **GS-9876 10 mg:** GS-9876 (1 x 10 mg tablet QD) + PTM filgotinib (2 x placebo tablets QD) (N=20)
- **Filgotinib 200 mg:** Filgotinib (2 x100 mg tablets QD) + PTM GS-9876 (1 x placebo tablet QD) (N=20)
- **Placebo only:** PTM GS-9876 (1 x placebo tablet QD) + PTM filgotinib (2 x placebo tablets QD) (N=20)

The study drugs should be administered orally once daily with water, with or without food. The study drugs should be swallowed whole and administered together. 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, subjects should be instructed to take the missed dose(s) of study medication as soon as possible during the **same day**. If more than 12 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. In those cases, the missed dose should be returned to the study drug bottle.

5.6. Other Medication Administered

Methotrexate should be administered weekly at a dose of 7.5 to 25 mg, orally or parenterally. Subjects must also receive folic acid supplementation.

5.7. Prior and Concomitant Medications

At Screening, all medication taken up to 30 days prior to the Screening visit and all prior and current RA medication 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 (defined as no change in prescription) 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 HCQ, with at least 8 weeks of stable dose (defined as no change in prescription) prior to first study dose and maintained at a stable dose throughout the study.

- Oral steroids ≤10 mg/day prednisone or equivalent, with at least 28 days of stable dose (defined as no change in prescription) prior to the first dose of study drug and maintained at a stable dose throughout the study.

- NSAIDs or other analgesics (including aspirin ≤ 100 mg) are allowed if doses are stable (defined as no change in prescription) for at least 14 days prior to first study dose and maintained at a stable dose throughout the study. Pro re nata use for other indications is allowed.

- For pain while on study, the subject may take acetaminophen or other non-NSAID pain medications as directed by the treating physician. Any scheduled or PRN pain medications, including chronic NSAIDs, should be held on study visit days until after the visit procedures have been completed.

- Dose adjustments for management of toxicity of the above medications are allowed and should be documented, along with documentation of the AE which led to the change in the medication.

Prohibited Medications:

- Any herbal/natural supplements, unless approved by the investigator

- 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 (except for adverse events and toxicities per the discretion of the investigator)

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

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

  — minocycline, penicillamine, sulfasalazine, anakinra, etanercept, azathioprine, cyclosporine, tacrolimus, sirolimus, everolimus, mycophenolate mofetil, tofacitinib or biosimilar versions of these drugs, where applicable

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

  — infliximab, golimumab, certolizumab pegol, abatacept, tocilizumab, adalimumab or biosimilar versions of these drugs, where applicable

- Treatment with IV antibiotics for a clinical infection or other medical condition within 30 days prior to first dose of study drug and throughout the study. If subject acquires an infection during the course of the study that requires antibiotic treatment, study drug should be paused until discontinuation of the antibiotic treatment, clearance of the infection and discussion of the case with the medical monitor.

- Treatment with B-cell depleting agents (ie, rituximab) within 6 months prior to the first dose of study drug and throughout the study

- Treatment with any other investigational study drug within 4 weeks or 5 half-lives prior to Screening (whichever is longer) and throughout the study

- Prior treatment with any commercially available or investigational SYK inhibitor and throughout the study

- Joint injections within 4 weeks prior to the first dose of study drug and throughout the study. If a joint injection has been administered within 6 weeks of the first dose of study drug, 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:

- Prior to study participation, it is recommended that the subject's vaccinations be brought up to date according to local vaccination standards.

- Live or attenuated vaccines (including, but not limited to varicella and inhaled flu vaccine) are prohibited within 30 days of Day 1, throughout the study, and for 6 weeks after the last dose of study drug.

- Subjects should be advised to avoid routine household contact with persons vaccinated with live/attenuated vaccine components. General guidelines suggest that a study subject's exposure to household contacts should be avoided for the below stated time periods:

  — Varicella or attenuated typhoid fever vaccination – avoid contact for 4 weeks following vaccination

  — Oral polio vaccination -- avoid contact for 6 weeks following vaccination

  — Attenuated rotavirus vaccine -- avoid contact for 10 days following vaccination

  — Inhaled flu vaccine -- avoid contact for 1 week following vaccination

- Inactivated vaccines (such as inactivated flu vaccines) should be administered according to local vaccination standards whenever medically appropriate; however, there are no available data on the concurrent use of GS-9876 or filgotinib and their respective 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[c]	adenosine diphosphate (ADP) receptor inhibitors, phosphodiesterase inhibitors, PAR-1 antagonists, Glycoprotein 2b/3a inhibitors
Anti-coagulant	warfarin, any Vitamin K antagonist, any novel oral anticoagulant, any heparin or low molecular heparins, inhibitors of factor Xa

a In vitro data indicate GS-9876 is a substrate of CYP3A4. Co-administration of CYP3A4 inhibitors may increase GS-9876 exposure. These agents are prohibited while subject is on study drug and 2 weeks prior to study drug administration.
b In vitro data indicate GS-9876 is a substrate of CYP3A4. Co-administration of CYP3A4 inducers may decrease GS-9876 exposure. These agents are prohibited while subject is on study drug and 2 weeks prior to study drug administration.
c ≤ 100 mg aspirin and NSAIDs are permitted
d Herbal/Natural supplements not listed require investigator review and approval.

5.8. Investigational Medicinal Product Accountability and Disposal or Return

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

Accountability records will be maintained by each study site to:

- Record the date received and quantity of study drugs;
- Record the date, subject number, subject initials, and the study drugs number dispensed; and
- Record the date, quantity of used and unused study drugs 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 (first dose of study drug) 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 enroll approximately 80 subjects.

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 and cardiovascular disease
- Perform complete physical examination (refer to Appendix 9)
- Obtain vital signs (refer to Appendix 9)
- Obtain height and weight (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
  - Lipid Panel
  - CRP
  - TSH
  - HbA1c
  - Serology (HIV, HCV, and HBV)
  - Serum pregnancy test for females of childbearing potential only
  - QuantiFERON® TB-Gold
  - CD19 count, as applicable (refer to exclusion criteria)
- Obtain urine for urinalysis and urine drug screen (refer to Appendix 3)
- 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 may return to the clinic after Screening for randomization into the study.

Subjects who do not meet the eligibility criteria will be considered screen failures and excluded from randomization. Screen failures may be considered for rescreening one time for the study in consultation with the Sponsor or its designee.

From the time of obtaining informed consent through the first administration of study drug, 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 4 treatments as described in Section 3.3. The 66 swollen and 68 tender joint count assessments must be performed prior to all other study procedures on Day 1 and prior to randomization to confirm subject eligibility. 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 66 swollen and 68 tender joint count assessments must be performed prior to all other study procedures on Day 1 and prior to randomization to confirm subject eligibility. The HAQ-DI including Patient's Assessment of Pain, and Patient's Global Assessment of Disease Activity are recommended to be done prior to any invasive study procedures. Blood draws should be the last study assessment prior to dosing and dosing should be the last study procedure on Day 1.

The following will be performed and documented on Day 1:

- Confirm study eligibility
- Perform symptom driven physical examination
- Obtain vital signs
- Obtain weight
- Perform 12-lead ECG (predose)
- Assess AEs and concomitant medications
- Subject completes disease specific questionnaires and activity scales (refer to Appendix 9):
  - HAQ-DI including 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
  - Lipid Panel (Fasting)
  - CRP
  - RF/CCP
  - Inflammation and Pathway Biomarkers
  - RNA
  - Immunoglobulins
  - Whole Blood Sample for MoA Studies
  - B and T Cell Panels
- Obtain urine sample for urine pregnancy test for females of childbearing potential only
- Obtain urine sample for bone marker (fasting)
- PPD .
- Drug Administration
  - Dispense study drugs as directed by the IXRS.
  - Instruct the subject on the packaging, storage and administration of all study drugs.
  - Instruct the subject to document their daily dose administration.
  - 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 the subject to bring their study drug to all study visits and not to take study drug until after predose assessments at Week 2, Week 8, and Week 12 visits. Instruct the subject 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
- Obtain weight
- Perform 12-lead ECG
- Assess AEs and concomitant medications
- Subject completes disease specific questionnaires and activity scales:
  - HAQ-DI including 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
  - Lipid Panel
  - CRP
- Obtain urine sample for urine pregnancy test for females of childbearing potential only (obtain blood for serum pregnancy test if urine pregnancy test is positive)
- 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
- Obtain weight
- Perform 12-lead ECG
- Assess AEs and concomitant medications
- Subject completes disease specific questionnaires and activity scales:
  - HAQ-DI including 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
  - Lipid Panel
  - CRP
  - Inflammation and Pathway Biomarkers
  - RNA
  - Whole Blood Sample for MoA Studies
  - B and T Cell Panels
- Obtain urine sample for urine pregnancy test for females of childbearing potential only (obtain blood for serum pregnancy test if urine pregnancy test is positive)
- Obtain urine sample for bone marker
- 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
- Obtain weight
- Perform 12-lead ECG
- Assess AEs and concomitant medications
- Subject completes disease specific questionnaires and activity scales:
  - HAQ-DI including 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
  - Lipid Panel
  - CRP
- Obtain urine sample for urine pregnancy test for females of childbearing potential only (obtain blood for serum pregnancy test if urine pregnancy test is positive)
- 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 including 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
- Obtain weight
- Perform 12-lead ECG
- Assess AEs and concomitant medications
- Subject completes disease specific questionnaires and activity scales:
  - HAQ-DI including 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
  - Lipid Panel (Fasting)
  - CRP
  - RF/CCP
  - Inflammation and Pathway Biomarkers
  - RNA
  - Immunoglobulins
  - Whole Blood Sample for MoA Studies
  - B and T Cell Panels
- Obtain urine sample for urine pregnancy test for females of childbearing potential only (obtain blood for serum pregnancy test if urine pregnancy test is positive)

- Obtain urine sample for bone marker (fasting)
- 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.

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 dosing 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, including 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
  - Lipid Panel
  - CRP
  - RF/CCP
  - Inflammation and Pathway Biomarkers
  - RNA
  - Immunoglobulins
- Obtain urine sample for urine pregnancy test for females of childbearing potential only (obtain blood for serum pregnancy test if urine pregnancy test is positive)
- Collect PK sample
- All study drug must be returned by subject. Study drug not previously returned by the subject should also be collected.
- Complete medication pill count.

6.6. Post-Treatment Assessments (± 5 days)

Study procedures and assessments are outlined in Appendix 2. The Post-Treatment Week 4 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
- Obtain weight
- Perform 12-lead ECG
- Assess AEs and concomitant medications
- Obtain blood samples for:
  - Hematology, Chemistry, and Coagulation
  - Lipid Panel
  - CRP
- Obtain urine sample for urine pregnancy test for females of childbearing potential only (obtain blood for serum pregnancy test if urine pregnancy test is positive)

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, PK samples may be retained in storage by Gilead at its research partner facility for a period of up to 2 years. Other 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 study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

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

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified 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 study drug therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than study drug. 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 study drug.

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

Any SAEs and deaths that occur after the post treatment follow-up visit but within 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 study drug, he/she should promptly document and report the event to Gilead DSPH.

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

7.3.1.3. Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the CRF/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 CRF/eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the CRF/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 CRF/eCRF Database according to instructions in the CRF/eCRF completion guidelines.

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

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

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

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

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

7.4. Gilead Reporting Requirements

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

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

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB/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 study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2, respectively. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (i.e., anemia) not the laboratory result (i.e., decreased hemoglobin).

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

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

7.5.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.5.2. Grade 3 Laboratory Abnormality or Clinical Event

For Grade 3 clinically significant laboratory abnormality or clinical event, study drug may be continued if the event is considered to be unrelated to study drug.

For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to study drug, study drug should be withheld until the toxicity returns to ≤ Grade 2.

If a laboratory abnormality recurs to ≥ Grade 3 following re-challenge with study drug and is considered related to study drug, then study drug should be permanently discontinued and the subject managed according to local clinical practice. Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation.

7.5.3. Grade 4 Laboratory Abnormality or Clinical Event

For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing, study drug should be permanently discontinued and the subject managed according to local clinical 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 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Study drug may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 CK after strenuous exercise or triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to study drug.

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 should 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 Sections 7.5.2 and 7.5.3.

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, occupational exposure with an AE, pregnancy reports regardless of an associated AE, and an AE in an infant following exposure from breastfeeding.

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

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

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

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively 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.

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

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study 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 CRF/eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead 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 drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

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

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

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

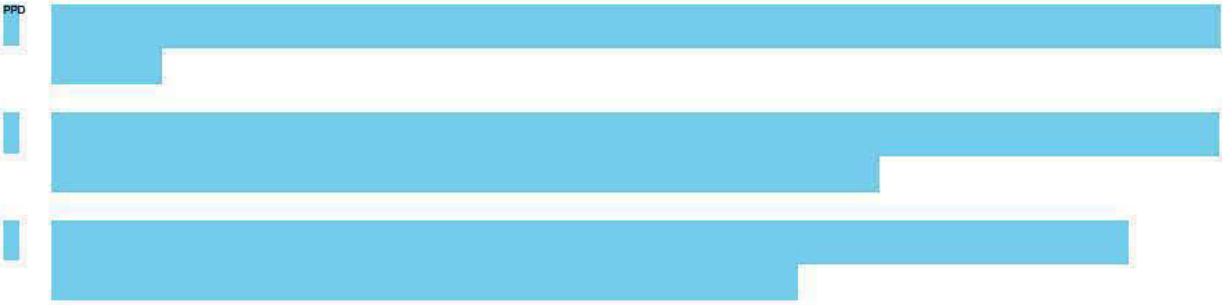
The primary objective is:

- 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:



8.1.2. Primary Endpoint

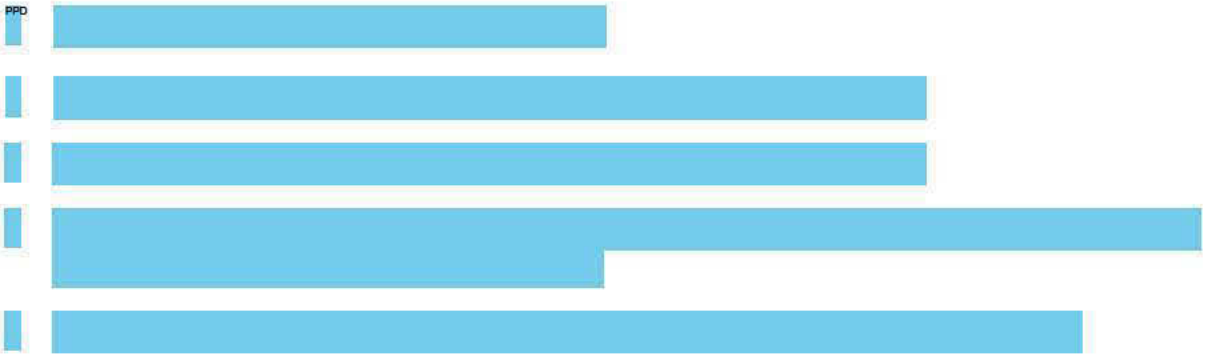
The primary endpoint is change from baseline in DAS28 (CRP) at Week 12.

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



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, filgotinib and/or their metabolite(s).

8.3. Data Handling Conventions

Pharmacokinetic concentration values and PK parameter values below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listings. The 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. 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, 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 ACR 20/50/70 at Week 12 and change from baseline in HAQ-DI score at Week 12. The ACR 20/50/70 response rates between each of the 2 GS-9876 dosed 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 each of the 2 GS-9876 dosed groups and the placebo group 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 and filgotinib and the active metabolite of filgotinib (GS-829845) 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), other filgotinib metabolite(s) and/or MTX may also be determined and analyzed.

8.8. Biomarker Analysis

PPD

8.9. Sample Size

Sample sizes for GS-9876 and placebo groups are 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. PPD . Therefore, the total sample size will be 80 (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 (legally authorized representatives are not allowed for this study) 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 optional genomic testing and sample retention.

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

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 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 study drug, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

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

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

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

9.1.6. Case Report Forms

For each subject consented, an 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, study drug should be destroyed at the site. At the start of the study, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for disposal or return of unused study drug 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 study drug 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 study drug 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 study drug is destroyed on site, the investigator must maintain accurate records for all study drugs destroyed. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

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

9.1.8. Inspections

The investigator will make available all source documents and other records for this 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

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Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.

STUDY ACKNOWLEDGEMENT

A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 2 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, Amendment 1 Protocol, 27 June 2016

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

PPD

Franziska Matzkies, MD

Medical Monitor Name (Printed)

28- June -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]	Post-Treatment Week 4[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, Height, and Weight [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 [i, j, k]	X	X	X	X	X	X	X	X
Lipid Panel [i, j, k, l]	X	X	X	X	X	X	X	X
CRP [i, j, k]	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Test [i, j, k, m]	X	X	X	X	X	X	X	X
Serology [j]	X							
Urinalysis and Urine Drug Screen [j]	X							
TSH [j]	X							
HbA1c [j]	X							
QuantiFERON® TB-Gold [j]	X							
CD19 Count [j, n]	X							
Randomization after Confirmation of Eligibility [h]		X						
Disease-Specific Questionnaires and Activity Scales [i, o]		X	X	X	X	X	X	
RF/CCP [i, j, k]		X				X	X	

Visit	Screening[a]	Day 1	Week 2	Week 4	Week 8	Week 12	ET[b]	Post-Treatment Week 4[c]
Window in Days	**-28**		**±3**	**±3**	**±3**	**±3**	**±3**	**±5**
Inflammation and Pathway Biomarkers [i, j, k, p]		X		X		X	X	
RNA Sample [i, j, k]		X		X		X	X	
Immunoglobulins [i, j, k]		X				X	X	
Whole Blood Sample for MoA Studies [i, j, k]		X		X		X		
Bone Marker (Urine) [i, j, k, l]		X		X		X		
B and T Cell Panels [i, j, k]		X		X		X		
[redacted] PPD		X						
PK Samples [r]			X	X	X	X	X	
[redacted] PP					X			
Study Drug Dispensation		X		X	X			
Study Drug Administration (In-Clinic) [t]		X	X	X	X	X		
Study Drug Bottle Return [u]				X	X	X	X	
Adverse Events [v]	Continuous							
Concomitant Medications [w]	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 subject discontinuation.
c Twenty-eight (±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 and cardiovascular disease
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, height and weight. Weight will be collected at all study visits. Height will be collected at Screening only.
g Conduct Day 1 ECG predose (prior to study drug administration).
h The 66 swollen and 68 tender joint count assessments must be performed prior to all other study procedures on Day 1 and prior to randomization to confirm subject eligibility.

i At Day 1, the subject questionnaires (ie, HAQ-DI including Patient's Assessment of Pain, and Patient's Global Assessment of Disease Activity) are recommended to be done prior to any invasive study procedures. At Week 12, the subject questionnaires are recommended to be done prior to the 66 swollen and 68 tender joint count assessments and before any invasive study procedures. At both Day 1 and Week 12, blood draws should be the last study assessment prior to study dosing.
j Refer to Appendix 3 for complete laboratory assessments.
k Samples to be collected prior to dosing, except at Week 4 visit.
l Lipid panel and bone marker (urine) samples should be fasting at Day 1 and Week 12.
m 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.
n As needed per exclusion criteria (refer to Section 4.3)
o Disease-specific questionnaires and activity scales include the HAQ-DI including the Patient's Assessment of Pain, Patient's Global Assessment of Disease Activity, and Physician's Global Assessment of Disease Activity.
p Samples will be collected at Day 1, Week 4, and Week 12 or ET visits for PPD 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.
q PPD
r 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.
s PPD
t 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.
u Subject should bring their study drug to all study visits. At Week 4, Week 8, and Week 12 or ET, site should collect any previously dispensed study drug bottles.
v 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.
w 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

<table>
<tr><th>Hematology</th><th>Chemistry</th><th>Urinalysis</th><th>Other</th></tr>
<tr><td>Hematocrit
Hemoglobin
Platelet count
Red blood cell (RBC) count
White blood cell (WBC) count
Differentials (absolute and percentage), including:
Leukocytes
Monocytes
Neutrophils
Eosinophils
Basophils
Reticulocyte count
Mean corpuscular volume (MCV)</td><td rowspan="3">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
Creatine phosphokinase (CPK)</td><td>Clarity
Blood
Color
Glucose
Leukocyte esterase
pH
Protein
Urobilinogen
Reflex to microscopic urinalysis if dipstick result is abnormal.</td><td rowspan="2">Urine drug screen for:
Amphetamines
Cocaine
Methadone
Opiates
Inflammation and pathway biomarkers
B and T cell panels
Immunoglobulins: IgA, IgE, IgG, IgM
Whole blood sample for MoA studies
Bone marker (urine)
C-reactive protein (CRP)
Rheumatoid factor and cyclic citrullinated peptide (RF/CCP)
QuantiFERON® TB-Gold
CD19 (if required per exclusion criteria)
RNA
TSH
HbA1c</td></tr>
<tr><td></td><th>Lipid Panel</th></tr>
<tr><td></td><td>Total cholesterol
Low-density lipoprotein (LDL)
High-density lipoprotein (HDL)
Triglycerides</td><td></td></tr>
<tr><th>Coagulation</th><td></td><th>Serology</th><th>Pregnancy</th></tr>
<tr><td>Activated partial thromboplastin time (aPTT)
Prothrombin time (PT)
International normalized ratio (INR)</td><td></td><td>Hepatitis BsAg and core Ab
Hepatitis C Ab
HIV</td><td>In females of childbearing potential:
Serum β-hCG (Screening and if positive urine β-hCG)
Urine β-hCG (all study visits other than Screening)</td></tr>
</table>

Ab = antibody
β-hCG = beta-human chorionic gonadotropin
BsAg = B surface antigen
IgA, IgE, IgG, IgM = immunoglobulins A, E, 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. Filgotinib is contraindicated in pregnancy as there is a possibility of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data.

GS-9876 has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. A dedicated study assessing the impact of filgotinib on the efficacy of hormonally-based contraceptives (with ovulation inhibition as mechanism of action) has not yet been performed to fully verify the absence of any clinically significant interaction between filgotinib and oral contraceptives. However, based on the totality of the available in vitro and clinical data, clinically relevant drug interactions between filgotinib or GS-829845 with hormonal contraceptives are not expected. In this study, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Subjects may remain on their hormonal contraception if they prefer to do so, but will still be required to choose from contraceptive methods delineated below as the efficacy of their hormonal contraception during study dosing is unknown.

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

b) Contraceptive Methods Permitted for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of *highly effective* contraceptive measures. Women must agree to also not rely on hormone-containing contraceptives as a form of birth control during the study, though they may continue hormonal contraception if they prefer to do so. Women must have a negative serum pregnancy test at

Screening and a negative pregnancy test on the Day 1 visit prior to first dose of study drug. Pregnancy tests will be performed as defined by the schedule of assessments (Appendix 2).

Female subjects of childbearing potential must agree to one of the following from Screening until 35 days following the last dose of study drug.

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

Or

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

- Intrauterine device (IUD) with a failure rate of <1% per year
- Tubal sterilization
- Essure micro-insert system (provided confirmation of success 3 months after procedure)
- Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success at least 3 months after procedure)

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 35 days after the last dose of study drug.

Contraception Requirements for Male Subjects

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

Male subjects must also refrain from sperm donation during treatment and until at least 90 days after the last dose of study drug.

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.

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 35 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 TJC 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.

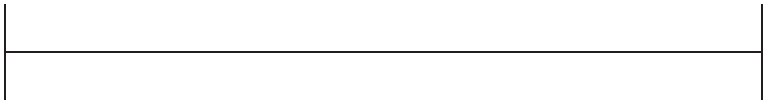
2. Swollen joint count

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

3. Patient's Assessment of Pain

The Patient's Assessment of Pain, part of the HAQ-DI assessment, is a horizontal (0 – 100) visual analog scale (VAS) that will be used to assess the subject's current level of pain.[2]

How much pain have you had because of your illness in the past week? Place a vertical (|) mark on the line to indicate the severity of the pain:



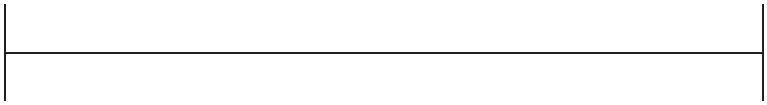
No Pain **Severe Pain**
0 **100**

[2] 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 (0 – 100) VAS will be used to collect the subject's overall assessment of how their arthritis is doing.

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

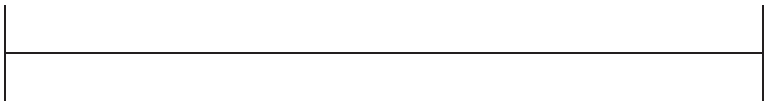


No Arthritis **Severe Arthritis**

5. Physician's Global Assessment of Disease Activity

A horizontal (0 – 100) 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 RA 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 subject's self-assessment of physical function. The HAQ-DI includes the Patient's Assessment of Pain VAS.

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 subjects 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 subject

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.

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.

Height and Weight

The subject's standing height will be collected at Screening only. The subject's weight will be collected at all study visits.

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.

Fridericia Formula (QTcF)

QTcF = QT/(RR)^(1/3), where RR = 60/HR

RR = RR interval in seconds
HR = heart rate in beats per minute

Creatinine Clearance (estimated GFR) Formula

Creatinine clearance (estimated GFR) (mL/min) = [(140 – age (yrs)) x weight (kg) x (0.85 if female)] / [serum creatinine (mg/dL) x 72], where weight is total body mass in kilograms

Health Assessment Questionnaire – Disability Index including the Patient's Assessment of Pain

The HAQ-DI is a subject 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. It includes the Patient's Assessment of Pain horizontal VAS that ranges from "No Pain" (0) to "Severe Pain" (100).

Patient's Global Assessment of Disease Activity

The Patient's Global Assessment of Disease Activity is a horizontal (0 – 100) VAS that ranges from "No Arthritis" to "Severe Arthritis".

Physician's Global Assessment of Disease Activity

The Physician's Global Assessment of Disease Activity is a horizontal (0 – 100) VAS that ranges from "No Disease Activity" to "Maximum Disease Activity".

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.