CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 Weeks Alone and in Combination with Methotrexate (MTX) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are Naïve to MTX Therapy	
Sponsors:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA	
IND Number:	115,510	
EudraCT Number:	2016-000570-37	
Clinical Trials.gov Identifier:	TBD	
Indication:	Rheumatoid Arthritis	
Protocol ID:	GS-US-417-0303	
Gilead Clinical Program Manager:	Name: Telephone:	PPD PPD
Gilead Medical Monitor:	Name: Telephone: Fax: Mobile:	PPD PPD PPD PPD
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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
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Study Title:	A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 Weeks alone and in Combination with Methotrexate (MTX) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are Naïve to MTX Therapy
IND Number:	115,510
EudraCT Number:	2016-000570-37
Clinical Trials.gov Identifier:	TBD
Study Centers Planned:	Approximately 200-250 centers worldwide
Objectives:	The primary objective of this study is: • To evaluate the effects of filgotinib in combination with MTX versus MTX alone for the treatment of signs and symptoms of rheumatoid arthritis (RA) as measured by the proportion of subjects achieving an American College of Rheumatology 20% improvement response (ACR20) at Week 24 The secondary objectives of this study include: • To evaluate the effect of filgotinib in combination with MTX versus MTX alone on physical function as measured by change from Baseline in the Health Assessment Questionnaire Disability Index (HAQ-DI) score at Week 24. • To evaluate the effects of filgotinib in combination with MTX versus MTX alone for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving Disease Activity Score for 28 joint count using C-reactive protein (DAS28 [CRP]) < 2.6 at Week 24

- To evaluate the effect of filgotinib alone versus MTX alone for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving ACR20 at Week 24
- To evaluate the effect of filgotinib alone versus MTX alone on physical function as measured by change from Baseline in HAQ-DI score at Week 24
- To evaluate the effect of filgotinib alone versus MTX alone for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving DAS28(CRP) <2.6 at Week 24
- To evaluate the effects of filgotinib in combination with MTX versus MTX alone on preservation of joint structure as measured by change from Baseline in the van der Heijde modified Total Sharp Score (mTSS) at Week 24 and 52
- To evaluate the effects of filgotinib alone versus MTX alone on preservation of joint structure as measured by change from Baseline in mTSS at Week 24 and 52
- To evaluate the safety and tolerability of filgotinib alone and in combination with MTX
- To evaluate the effects of filgotinib alone and in combination with MTX on work productivity, fatigue, and general quality of life as measured by SF-36, FACIT-Fatigue, EQ-5D and WPAI-RA

The exploratory objectives of this study include:

- [redacted]
- [redacted]
- [redacted]

Study Design:

This is a randomized, double-blind, placebo- and active-controlled, Phase 3 study in adult male and female subjects with moderately to severely active RA who are naïve to MTX therapy. The study is designed to evaluate the efficacy, safety and tolerability of filgotinib alone and in combination with MTX as well as its effect on work productivity, fatigue, and quality of life.

Approximately 1200 subjects will be randomized in a 2:1:1:2 ratio to filgotinib 200 mg with MTX, filgotinib 100 mg with MTX, filgotinib 200 mg alone, or MTX alone for up to 52 weeks:

- Filgotinib 200 mg + MTX group: Filgotinib (200 mg q.d.) + PTM filgotinib 100 mg (PTM q.d.) + MTX (once weekly up to 20 mg) (N=400)
- Filgotinib 100 mg + MTX group: Filgotinib (100 mg q.d.) + PTM filgotinib 200 mg (PTM q.d.) + MTX (once weekly up to 20 mg) (N=200)
- Filgotinib 200 mg monotherapy group: Filgotinib (200 mg q.d.) + PTM filgotinib 100 mg (PTM q.d.) + PTM MTX (PTM once weekly) (N=200)
- MTX monotherapy group: PTM filgotinib 100 mg (PTM q.d.) + PTM filgotinib 200 mg (PTM q.d.) + MTX (once weekly up to 20 mg) (N=400)

Randomization will be stratified by geographic region and presence of rheumatoid factor (RF) or anti-CCP (cyclic citrullinated peptide) antibody (Ab) at Screening.

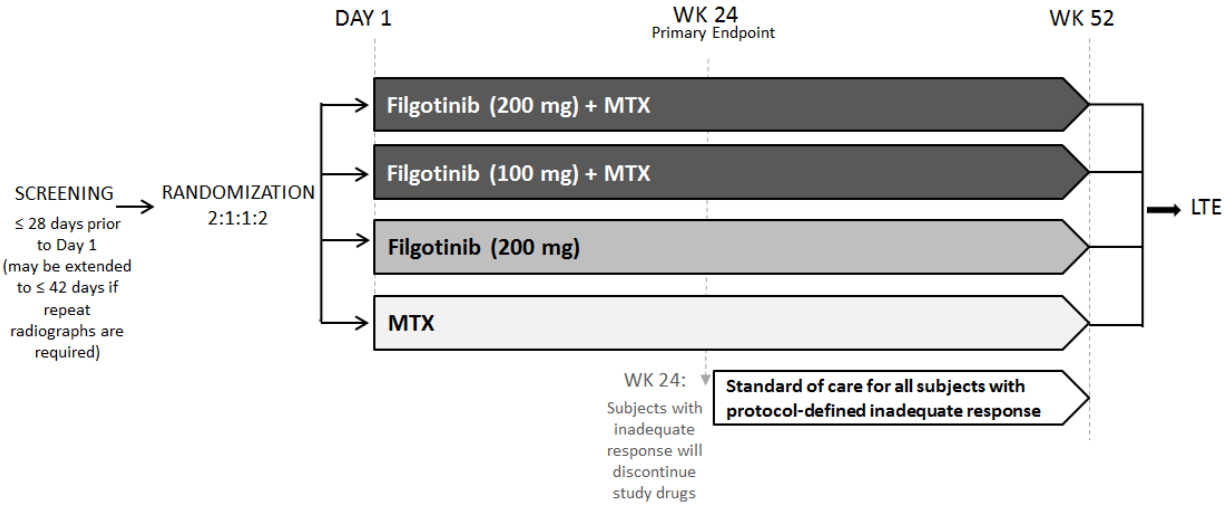
At Week 24, subjects who have not achieved at least a 20% improvement from Day 1 in both swollen joint count (SJC) and tender joint count (TJC) will discontinue investigational study drug dosing but will continue with study visits and assessments per protocol. All subjects meeting this criterion who discontinue from investigational therapy are to receive standard of care treatment for their RA as determined by the investigator. Subjects achieving at least a 20% improvement in SJC and TJC at Week 24 will continue on the dosing regimens to which they were randomized through Week 52.

All subjects who continue on study drug will be evaluated for loss of therapeutic response from Week 30 through Week 52. Subjects failing to maintain at least a 20% improvement from Day 1 in TJC and SJC, (which is confirmed at 2 consecutive visits), will discontinue from investigational study drug dosing but will continue with study visits and assessments per protocol. All subjects meeting this criterion who discontinue from investigational study drug dosing are to receive standard of care treatment for their RA as determined by the investigator.

All subjects who have received at least one dose of study drug and exit the study early will complete an early termination (ET) visit at the time of study discontinuation, with a post treatment visit four weeks after the last dose of study drug (Post Treatment Week 4) regardless of dosing duration.

At completion of the 52-week study period, subjects who have not discontinued assigned study drug dosing, will be provided the option to enroll into a separate Long Term Extension (LTE) study (GS-US-417-0304).

Study Design



Number of Subjects Planned:	Approximately 1200 subjects
Target Population:	Male or female subjects who are ≥18 years of age with a diagnosis of RA meeting the 2010 ACR/ European League Against Rheumatism (EULAR) criteria, who have active RA and had limited or no prior exposure to MTX.
Duration of Treatment:	Up to 52 weeks
Diagnosis and Main Eligibility Criteria:	For a complete list of study inclusion and exclusion criteria, please refer to Sections 4.2 and 4.3. Main Eligibility Criteria 1) Male or female subjects who are ≥18 years of age, on the day of signing informed consent 2) Have a diagnosis of RA (2010 ACR/ EULAR criteria), and are ACR functional class I-III 3) Have ≥6 swollen joints (from a SJC66) and ≥6 tender joints (from a TJC68) at Screening and Day 1

4) Must meet at least one of the following parameters at Screening:
   - positivity for either RF or anti-CCP Ab per central laboratory

     OR
   - Serum CRP ≥ 4 mg/L based on central laboratory value

     OR
   - ≥1 documented joint erosion on radiographs of the hands, wrists or feet by central reading

5) Limited or no prior treatment with MTX, ie, no more than 3 doses of MTX ≤25 mg each in their lifetime for the treatment of RA, with last dose at least 28 days prior to Day 1, and are an appropriate candidate for MTX therapy, as per investigator judgment

Study Procedures/ Frequency:

The subjects will visit the clinical study center at Screening, Day 1, Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 44, and 52 or ET.

For those subjects not entering the LTE, a follow-up visit will be planned 4 weeks after the last dose of study drug (Post Treatment Week 4). Consequently, subjects are planned to be in the study for approximately 60 weeks.

During the Screening period, the subject's radiographs (hands, wrists, and feet) will be sent for blinded central scoring. In addition, information on demographics, medical history/concomitant diseases, prior and current RA medications will be collected. A physical examination, a 12-lead electrocardiogram (ECG), and clinical laboratory assessments will be conducted to determine the subject's eligibility for study participation. The screening window may be extended to up to 42 days prior to the Day 1 visit for subjects who require repeat collection of radiographs only.

At Day 1, after the subject's eligibility for the study has been confirmed, the subject will be randomized to receive one of 4 dosing regimens: filgotinib 200 mg q.d. plus MTX up to 20 mg weekly, filgotinib 100 mg q.d. plus MTX up to 20 mg weekly, filgotinib monotherapy 200 mg q.d. or MTX monotherapy up to 20 mg weekly.

On-treatment assessments will include: adverse events (AEs), concomitant medications, review of study medication compliance through drug accountability, SJC66, TJC68, Subject's Global Assessment, Subject's Pain Assessment, HAQ-DI, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), Short-Form Health Survey (SF-36), Work Productivity and Activity Impairment- Rheumatoid Arthritis (WPAI-RA), EuroQol 5 Dimensions (EQ-5D), CCI [redacted] Treatment Satisfaction Questionnaire for Medication (TSQM), Healthcare Resource Utilization, Physician's Global Assessment, physical examination, weight, vital signs, serum CRP, blood and urine sampling for safety laboratory tests and biomarkers at selected visits, and urine pregnancy tests (females of child bearing potential only).

A resting 12-lead ECG should be performed at Screening, Weeks 12, 24, 36, and 52 or ET, and at the Post-treatment Week 4 follow-up visit. ECGs should be interpreted by the investigator (or qualified designee) for clinical significance.

For all subjects, blood samples for PK analysis should be collected at least 30 minutes post study drug dose on Week 4, prior to study drug administration on Weeks 12 and 24, and any time at the final assessment visit on Week 52 or ET.

CCI [redacted]

Blood samples for biomarker analysis should be collected at Day 1, Weeks 4, 8, 12, 24, 36, and Week 52 or ET and urine samples should be collected at Day 1, Weeks 12, 24, and Week 52 or ET.

Radiographs of the bilateral hands, wrists, and feet should be taken at Screening, Week 24, and Week 52 or ET. However, if a subject prematurely discontinues study participation and has had X-rays performed within the previous 12 weeks, then X-rays do not need to be repeated at the ET visit. Radiographs performed after enrollment may be done +/-7 days of the scheduled visit.

Post treatment follow-up assessments include AEs, concomitant medications, physical examination, 12-lead ECG, weight, vital signs, blood and urine sampling for safety laboratory tests, and urine pregnancy tests (females of child bearing potential only).

CCI	[redacted]
Test Product, Dose, and Mode of Administration:	200 mg filgotinib orally q.d. plus MTX weekly up to 20 mg 100 mg filgotinib orally q.d. plus MTX weekly up to 20 mg 200 mg filgotinib orally q.d.
Reference Therapy, Dose, and Mode of Administration:	MTX weekly up to 20 mg or PTM MTX weekly PTM filgotinib 200 mg orally q.d. PTM filgotinib 100 mg orally q.d.
Criteria for Evaluation:	
Safety:	Safety will be assessed by documentation of AEs, clinical laboratory tests, physical examinations, vital signs, and 12-lead ECGs during the study.
Efficacy:	The primary endpoint is: • The proportion of subjects who achieve an ACR20 response at Week 24. The key secondary endpoints are: • Change from Baseline in the HAQ-DI score at Week 24 • The proportion of subjects who achieve DAS28 [CRP]<2.6 at Week 24 • Change from Baseline in mTSS at Week 24
Pharmacokinetics:	Plasma concentrations of filgotinib and the active metabolite (GS-829845) will be analyzed.

Statistical Methods:

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

The primary endpoint is the proportion of subjects who achieve an ACR20 response at Week 24. The primary analysis will consist of a superiority test of filgotinib 200 mg in combination with MTX compared to MTX alone based on the ACR20 response rates at Week 24. Cochran-Mantel-Haenszel approach adjusting for the stratification factors will be used for the hypothesis testing at the 2-sided 0.05-level.

The following hypothesis testing will commence after the primary analysis reaches statistical significance, and will be tested according to the hierarchical testing principle at the 2-sided 0.05 level. If a null hypothesis is not rejected, formal sequential testing will be stopped and only nominal significance will be reported for the remaining key secondary hypotheses.

1) Superiority of filgotinib 200 mg in combination with MTX compared to MTX alone based on the change from Baseline in HAQ-DI at Week 24
2) Superiority of filgotinib 200 mg in combination with MTX compared to MTX alone based on the response rate of DAS28 (CRP)<2.6 at Week 24
3) Superiority of filgotinib 100 mg in combination with MTX compared to MTX alone based on ACR20 response rate at Week 24
4) Superiority of filgotinib 100 mg in combination with MTX compared to MTX alone based on the change from Baseline in HAQ-DI at Week 24
5) Superiority of filgotinib 100 mg in combination with MTX compared to MTX alone based on the response rate of DAS28<2.6 at Week 24
6) Superiority of filgotinib 200 mg alone compared to MTX alone based on ACR20 response rate at Week 24
7) Superiority of filgotinib 200 mg alone compared to MTX alone based on the change from Baseline in HAQ-DI atWeek 24
8) Superiority of filgotinib 200 mg alone compared to MTX alone based on the response rate of DAS28 (CRP)<2.6 at Week 24
9) Superiority of filgotinib 200 mg in combination with MTX compared to MTX alone based on the change from Baseline in mTSS at Week 24

10) Superiority of filgotinib 100 mg in combination with MTX compared to MTX alone based on the change from Baseline in mTSS at Week 24

11) Superiority of filgotinib 200 mg alone compared to MTX alone based on the change from Baseline in mTSS atWeek 24

All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum) by treatment group. All categorical endpoints will be summarized by the number and percentage of subjects who meet the endpoint definition.

Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, SD, median, Q1, Q3, minimum, maximum) for continuous data by treatment group.

Sample size is determined based on the superiority test of filgotinib 200 mg in combination with MTX compared to MTX alone based on the change from Baseline in mTSS at Week 24. When assuming a difference of 0.62 between the two groups and a common standard deviation of 2.7, 400 subjects in the filgotinib 200 mg in combination with MTX group and 400 in the MTX alone group are required to obtain 90% power at a 2-sided 0.05-level.

The total sample size will be 1200 (400 subjects for filgotinib 200 mg in combination with MTX group, 200 subjects for filgotinib 100 mg in combination with MTX group, 200 subjects for filgotinib 200 mg alone group and 400 subjects for MTX alone group). This sample size will provide over 90% power to detect an increase in ACR20 response rate of 62% to 78% between the MTX alone group and each of the filgotinib groups respectively, using a 2-sided 0.05-level test.

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

Ab	antibody
ACPA	anti-citrullinated protein antibody
ACR X	American College of Rheumatology X% improvement
AE	adverse event
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
aPTT	activated partial thromboplastin time
ATP	adenosine triphosphate
AST	aspartate aminotransferase
$AUC_{0-\tau}$	area under the plasma drug concentration-time curve of a dosing interval
bDMARD(s)	biologic disease modifying antirheumatic drug(s)
b.i.d.	*bis in die*; twice daily
C_{τ}	trough plasma concentration (just before the next dosing ie, pre-dose sample)
CCP	cyclic citrullinated peptide
CD	Crohn's Disease
CDAI	Clinical Diagnostic Activity Index
csDMARD(s)	conventional synthetic disease modifying antirheumatic drug(s)
CES	carboxylesterases
CIA	collagen-induced arthritis
C_{max}	maximum observed plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CRO	Contract Research Organization
CRP	C-reactive protein
CV-SEAC	Cardiovascular Safety Endpoint Adjudication Committee
CYP	Cytochrome
DAS28	Disease Activity Score based on 28 joints
DBP	diastolic blood pressure
DMARD(s)	disease-modifying anti-rheumatic drugs
DMC/DSMB	data monitoring committee/data safety monitor board
dsDNA	double stranded deoxyribonucleic acid
DSS	dextran sulphate sodium
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
EU	European Union
EULAR	European League Against Rheumatism
EQ-5D	EuroQol 5 Dimensions
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	full analysis set
FDA	Food and Drug Administration

FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP	Galapagos
HAQ-DI	Health Assessment Questionnaire – Disability Index
HCV	hepatitis C virus
HCG	human chorionic gonadotropin
HCQ	hydroxychloroquine
HDL	high density lipoprotein
hERG	human ether-a-gogo related gene
HIV	human immunodeficiency virus
HR	heart rate
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Independent Review Board
ITT	Intent-to-treat
IV	intravenous
IWRS	interactive web response system
JAK	janus kinase
LCMS/MS	liquid chromatography mass spectrometry
LDL	low density lipoprotein
LH	luteinizing hormone
LTE	Long Term Extension
MAA	Marketing Authorization Application
MACE	Major adverse cardiovascular event
MCV	mean corpuscular volume
MRI	magnetic resonance imaging
MTX	methotrexate
IR	inadequate responders
mTSS	modified Total Sharp Score
NDA	New Drug Application
NSAIDs	nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
OATs	organic anion transporters
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics

PK	pharmacokinetics
PP	per-protocol
PT	prothrombin time
PTM	placebo to match
q.d.	*quaque die*; once daily
RA	rheumatoid arthritis
RAMRIS	rheumatoid arthritis magnetic resonance imaging score
RF	rheumatoid factor
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
s.c.	subcutaneous
SD	standard deviation
SDAI	Simplified Diagnostic Activity Index
SF-36	short-form health survey, 36 questions
SI	international system of units
SJC66	swollen joint count based on 66 joints
TB	tuberculosis
TEAEs	treatment emergent adverse events
TJC68	tender joint count based on 68 joints
t_{max}	the time of occurrence of maximum observed plasma concentration
TNFi	tumor necrosis factor inhibitors
TNFα	tumor necrosis factor α
TSQM	Treatment Satisfaction Questionnaire for Medication
UGTs	uridine 5'disphosphate glucuronosyltransferases
ULN	upper limit of normal
US	United States
vfPBMCs	viably frozen peripheral blood mononuclear cells
vs.	versus
WBC	white blood cell
WPAI-RA	Work Productivity and Activity Impairment for Rheumatoid Arthritis

Definition of Terms

QTcF	QT interval corrected for HR according to Fridericia's formula: QTcF = QT/(RR)^(1/3), where RR = 60/HR RR = RR interval in seconds HR = heart rate in beats per minute

1. INTRODUCTION

1.1. Background

Rheumatoid arthritis (RA) 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 ages 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.

Treatment of RA is dependent on severity, the patient's co–morbidities and initial response to therapy. Methotrexate is a conventional synthetic disease modifying anti-rheumatic drug (csDMARD) and continues to be the cornerstone of RA therapy {Singh et al 2012}. Patients with an inadequate response to csDMARD(s) are often treated with biologic therapies such as tumor necrosis factor inhibitors (TNFi) as an initial second line therapy. However, approximately 28% to 58% of RA patients with inadequate response to MTX fail TNFi as reviewed in {Redlich et al 2003}. In this setting, treatment guidelines recommend either switching to another TNFi, alternate biologic, or to a small molecule drug {Singh et al 2012}. Despite significant advances in disease management in recent years, there remains a need for new treatments, since not all patients respond adequately to current therapies, have co-morbidities and some patients experience toxicities and/or intolerance that limit the use of approved therapies.

In November 2012, tofacitinib (Xeljanz®) became the first Janus kinase (JAK) inhibitor to receive Food and Drug Administration (FDA) approval for the treatment of adult patients with RA. Tofacitinib is a small molecule, has strong binding affinity for JAK1 and JAK3, and weaker affinity for JAK2. The extensive pre-clinical and clinical development programs demonstrated its mechanisms of action via anti-inflammatory and immunosuppressive effects. The drug proved to be efficacious in treating the signs and symptoms of RA. However, the observed side-effects and risk profile of tofacitinib are similar to those of several existing anti-rheumatic agents with cytopenias, elevated levels of liver function enzymes, increased total cholesterol levels, with increases in LDL typically exceeding those for HDL, and increased risk for infections including serious and opportunistic infections. At higher doses, tofacitinib treatment was associated with anemia, which is thought to be linked to inhibition of JAK2.

While the pan JAK inhibitor tofacitinib has shown an early onset of action and long-term efficacy in RA as mono therapy 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. Filgotinib

1.2.1. General Information

Janus kinases are intracellular cytoplasmic tyrosine kinases (TYKs) that transduce cytokine signaling from membrane receptors through signal transducer and activator of transcription (STAT) to the nucleus of cells. JAK inhibitors block the signaling of various cytokines, growth factors, and hormones, including the pro-inflammatory cytokine interleukin (IL)-6. Four different types of JAKs are known, JAK1, JAK2, JAK3, and TYK2 which co-interact with different sets of membrane receptors. Inhibition of JAKs is a promising therapeutic option for a range of inflammatory conditions including RA and Crohn's Disease (CD).

Filgotinib (GS-6034, formerly GLPG0634) is a potent and selective inhibitor of JAK1. The compound has shown good preliminary efficacy in RA and CD patients in Phase 2. No typical JAK2 side effects such as anemia were observed in clinical studies of up to 24 weeks duration.

In humans, filgotinib is metabolized to form one major active metabolite, GS-829845 (formerly G254445). Though the potency of this metabolite is lower than the parent molecule, the overall exposure and peak plasma concentration in humans is higher than seen in all tested animal species. As a consequence, dedicated pharmacology and toxicology studies have been performed with GS-829845. Results from pharmacodynamics (PD) testing in healthy volunteers suggest that the clinical activity of filgotinib could result from the combination of the parent molecule and the metabolite.

For further information on filgotinib, refer to the current investigator's brochure.

1.2.2. 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.

1.2.2.1. Primary and Secondary Pharmacology

Filgotinib is an adenosine triphosphate (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 collagen-induced arthritis (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.

1.2.2.2. Safety Pharmacology

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

Filgotinib and GS-829845 had no relevant effects on cardiovascular parameters (human ether-a-gogo related gene [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 treated with 200 mg q.d. filgotinib. There were no relevant effects on electrocardiogram (ECG) and QT.

1.2.2.3. Nonclinical ADME

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

The pharmacokinetics (PK) of filgotonib 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 (h) 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 (GI) tract and urinary bladder. Filgotinib does not penetrate into central nervous system (CNS) tissues. The distribution of filgotinib indicates some affinity for melanin-containing tissues.

Excretion is nearly complete within 24 h (rat) and 48 h (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 cytochrome P450 (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 uridine 5'disphosphate glucuronosyltransferases (UGTs), and no relevant inhibition of key drug transporters, including the organic anion transporters (OATs) involved in the renal elimination of MTX, by filgotinib or GS-829845.

1.2.2.4. 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 partial reversibility, however, sperm counts remained low. 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 2.3, 1.8, and 3.4-fold when considering the mean AUC in male dogs at the no-observed-effect-levels (NOELs) in the 26 week and 39 week chronic toxicity studies, and the 39 week targeted exposure toxicity study, respectively.

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 q.d. 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.

1.2.3. Clinical Trials of Filgotinib

Comprehensive data from the Phase 1 and 2 programs are available to support development into Phase 3. As of January 2016, filgotinib has been administered to more than 150 healthy subjects, more than 1000 RA subjects, and more than 150 subjects with CD. A detailed description of all clinical studies can be found in the Investigator's Brochure (IB).

Phase 2b GLPG0634-CL-203, filgotinib with MTX in RA

In GLPG0634-CL-203, 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.

The percentage of American College of Rheumatology (ACR) 20 responders was statistically significantly higher in the 100 mg and 200 mg once daily, and 100 mg twice daily dose groups at Week 12 and in the 100 mg and 200 mg once daily, and 50 mg and 100 mg twice daily dose groups at Week 24. The percentage of ACR50 responders was statistically significantly higher compared with placebo across all filgotinib dose groups and regimens at both Weeks 12 and 24 (Table 1-1). The percentage of ACR70 responders was statistically significantly higher in the filgotinib 200 mg once daily and 100 mg twice daily dose groups compared with placebo at Week 12 and across all filgotinib dose groups and regimens at Week 24. A dose-response was observed for all three parameters. In addition, the ACR20 response appeared to plateau at Week 8 in the majority of filgotinib treatment groups and was maintained up to Week 24. At Week 24, the ACR50 response was maintained and the ACR70 response continued to increase compared with Week 12.

Starting at week 2 response was observed for ACR20 and ACR50. No statistically significant difference was found between the once and twice daily regimens.

Table 1-1. Summary and analysis of ACR20/50/70 response at Weeks 12 and 24 (NRI [ITT Population]), GLPG0634-CL-203

Parameter	Time Point	Placebo N=86	Filgotinib once daily Dose Groups			Filgotinib twice daily Dose Groups		
			50 mg N=82	100 mg N=85	200 mg N=86	25 mg N=86	50 mg N=85	100 mg N=84
		n (%)						
ACR20	W12	38 (44.2)	46 (56.1)	54 (63.5)*	59 (68.6)**	49 (57.0)	51 (60.0)	66 (78.6)***
	W24	36 (41.9)	45 (54.9)	52 (61.2)*	63 (73.3)***	48 (55.8)	51 (60.0)*	67 (79.8)***
ACR50	W12	13 (15.1)	27 (32.9)*	32 (37.6)**	37 (43.0)***	24 (27.9)*	29 (34.1)*	46 (54.8)***
	W24	14 (16.3)	29 (35.4)**	40 (47.1)***	43 (50.0)***	30 (34.9)**	30 (35.3)**	46 (54.8)***
ACR70	W12	7 (8.1)	13 (15.9)	18 (21.2)	21 (24.4)*	12 (14.0)	16 (18.8)	26 (31.0)**
	W24	8 (9.3)	18 (22.0)*	28 (32.9)**	25 (29.1)**	18 (20.9)*	20 (23.5)*	33 (39.3)***

Note 1: p-values were based on a pairwise comparisons of each group vs. the placebo group using a logistic regression model with factors treatment group, geographical region, and prior use of biologics; Hommel-corrected p-value. Note 2: The denominator for the percentage calculations = the total number of subjects per group with a response (yes or no) at that time point Note 3: Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
ACR=American College of Rheumatology; ITT=Intent-to-treat; NRI=non-responder imputation; W=week
Source: GLPG0634-CL-203

At Weeks 12 and 24 the mean decrease in DAS28(CRP) was statistically significantly greater across all filgotinib dose groups and regimens compared with placebo. A dose-response was observed. No statistically significant difference was apparent between the once and twice daily regimens. At Weeks 12 and 24, the mean decrease in Simplified Diagnostic Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) score was statistically significantly greater across all filgotinib dose groups and regimens compared with placebo (with the exception of filgotinib 50 mg once daily dose group at Week 12). In addition, the mean SDAI and CDAI scores were maintained after Week 12 in the 50 mg daily dose groups and continued to improve up to Week 24 in the 100 mg and 200 mg daily dose groups.

No unexpected safety findings were noted. Overall, no differences were observed in the incidence of treatment emergent adverse events (TEAEs) reported for subjects in any of the dosing groups, including placebo, for the duration of the study. TEAEs were reported for 51.2% of "All Placebo Exposed" subjects (ie, all subjects combined who received placebo during either the entire 24 weeks or only during the first 12 weeks) and 51.5% of "All filgotinib Exposed" subjects (ie, all subjects combined who received filgotinib during either the entire 24 weeks or only during the last 12 weeks, irrespective of dose).

A total of 15 subjects had ≥1 serious TEAE; 4 subjects in the placebo group (4.7%) and 11 subjects (2.0%) in one of the filgotinib groups. One of these subjects with ≥1 serious TEAE, who received filgotinib 100 mg twice daily with concurrent MTX, died during the second 12 weeks of the study period due to pneumonia and septic shock. Out of the 15 subjects with a serious TEAE, 11 subjects had a serious TEAE due to which the study medication was stopped and the subject discontinued the study. A total of 23 subjects had ≥1 AE leading to permanent discontinuation of the study medication and the study; 2 subjects (2.3%) in the placebo group and 21 subjects (3.9%) in one of the filgotinib groups (including a subject in the filgotinib 100 mg q.d. group who had a pre-dosing AE which was ongoing throughout the study, for which the study medication was permanently discontinued). Most of the serious TEAEs and the AEs leading to discontinuation (by preferred term) were experienced by a single subject.

For the duration of the study, the most common (≥10%) TEAEs reported by SOC in subjects from both the placebo and filgotinib dosing groups were Infections and Infestations and Gastrointestinal disorders. There were no differences between subjects who received placebo or filgotinib in the severity of TEAEs (most TEAEs were mild or moderate; severe TEAEs were observed in 1.2% of "All Placebo Exposed" subjects and in 2.2% of "All filgotinib Exposed" subjects). Treatment-related TEAEs were generally reported more often for subjects in the filgotinib dosing groups than in the placebo group (9.3% with placebo and 20.3% with filgotinib); however, within the different filgotinib dosing groups, no clear dose relationships were observed.

Six serious infections were reported (1 in placebo arm, 5 in filgotinib arm). All 6 serious and one additional non-serious infection in the filgotinib group led to dosing discontinuation. Up to Week 24, herpes zoster infections were observed in 5 subjects (1 placebo treated patient and 4 filgotinib). No cases of tuberculosis, opportunistic infections, lymphoma, or cancer were reported throughout the 24-week dosing period.

Laboratory data were consistent with prior Phase 2 studies and no new safety findings were observed from laboratory data. A summary of laboratory findings of interest, including hemoglobin, neutrophil, lymphocyte, creatinine, lipid, and hormone data are summarized below.

Up to Week 12, small increases were observed in mean hemoglobin concentrations in the filgotinib 200 mg daily dose groups (increase of 4.4 g/L from baseline in the filgotinib 100 mg b.i.d group). Thereafter, hemoglobin mean concentrations appeared to plateau and remained stable until Week 24 (increase of 4.9 g/L from baseline in the filgotinib 100 mg b.i.d group).

Up to Week 4, dose-dependent decreases were observed in mean absolute neutrophil counts in the filgotinib treatment groups. Mean absolute neutrophil counts appeared to plateau and remained stable until Week 24. No decreases in mean absolute lymphocyte counts were observed, including in lymphocyte subsets.

Up to Week 4, dose-dependent decreases were observed in mean absolute platelet counts in the filgotinib treatment groups. Mean absolute platelet counts appeared to plateau and remained stable. Dose-dependent increases in the filgotinib groups were observed in mean creatinine concentrations during the first 4 weeks of the study for most filgotinib treatment groups (up to Week 8 for the filgotinib 100 mg b.i.d group) that subsequently plateaued and remained stable up to Week 24.

Up to Week 4, dose-dependent increases were observed in mean concentrations of total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides in all filgotinib treatment groups. All these lipid parameters further increased up to Week 8 in the filgotinib 200 mg daily dose groups. Thereafter, these increases appeared to plateau and maintained at stable mean concentrations up to Week 24. At Week 24, mean increases were observed of 0.7 mmol/L in total cholesterol, 0.3 mmol/L in LDL cholesterol, 0.3 mmol/L in HDL cholesterol, and 0.1 mmol/L in triglycerides in the filgotinib 100 mg b.i.d group.

In male subjects, small non dose-dependent increases were observed in total and free testosterone during the study (at Week 24, mean increases were 3.4 nmol/L for total and 51.7 pmol/L for free testosterone in the filgotinib 100 mg b.i.d group). For FSH, inhibin B, LH, and prolactin, small changes (both increases and decreases) were observed during the study, without any trends of larger changes in male subjects of one or more of the different treatment groups.

GLPG0634-CL-204, Filgotinib administered as monotherapy in RA Subjects

The primary objective of study GLPG0634-CL-204 was to evaluate the efficacy of three doses of filgotinib q.d. compared to placebo at Week 12.

As shown in Table 1-2, the percentage of ACR20 and ACR50 responders at week 12 was statistically significantly higher across all filgotinib dose groups compared with placebo. The percentage of ACR70 responders in the filgotinib 100 mg and 200 mg once daily dose groups was statistically significantly higher compared with placebo. At Week 24, the ACR50 response was maintained and the ACR70 response showed continued improvement. An early onset of response was observed for ACR20 (from Week 1 in the filgotinib 200 mg once daily dose group and Week 4 across all other dose groups), ACR50 (from Week 2 in the filgotinib 200 mg once daily dose group and Week 4 across all other filgotinib dose groups), and ACR70 (Week 4 in the filgotinib 200 mg once daily dose group). The time to ACR20/50/70 response was shorter in all filgotinib dose groups compared with placebo.

Table 1-2. Summary and analysis of ACR20/50/70 response at Weeks 12 and 24 (NRI [ITT Population]); GLPG0634-0204

Parameter	Time Point	Placebo	Filgotinib once daily Dose Groups		
		N=72	50 mg N=72	100 mg N=70	200 mg N=69
		n (%)			
ACR20	W12	21 (29.2)	48 (66.7)***	46 (65.7)***	50 (72.5)***
	W24	Not applicable	41 (56.9)	55 (78.6)	46 (66.7)
ACR50	W12	8 (11.1)	25 (34.7)***	26 (37.1)***	30 (43.5)***
	W24	Not applicable	24 (33.3)	27 (38.6)	31 (44.9)
ACR70	W12	2 (2.8)	6 (8.3)	13 (18.6)**	9 (13.0)*
	W24	Not applicable	14 (19.4)	18 (25.7)	17 (24.6)

Note 1: p-values were based on a pairwise comparisons of each group vs. the placebo group using a logistic regression model with factors treatment group, geographical region, and prior use of biologics; Hommel-corrected p-value.
Note 2: The denominator for the percentage calculations = the total number of subjects per group with a response (yes or no) at that time point
Note 3: Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
ITT=Intent-to-treat; NRI=non-responder imputation; W=week
Source: GLPG0634-CL-204

At Week 12, the mean decrease in DAS28(CRP) was statistically significantly greater across all filgotinib dose groups compared with placebo. At Week 24, the mean decrease in DAS28(CRP) was maintained in the 50 mg once daily dose group and showed a small improvement in the highest dose groups. In addition, at Week 12 the percentage of subjects with DAS28(CRP) remission was higher across all filgotinib dose groups compared with placebo. Differences vs. placebo were not statistically significant for any of the filgotinib dose groups. The numbers of subjects with DAS28(CRP) < 2.6 and < 3.2 were higher across all filgotinib dose groups compared with placebo at Week 12; differences vs. placebo were statistically significant for the filgotinib 200 mg once daily dose group.

Safety data revealed no differences in the incidence of TEAEs reported for subjects in any of the treatment groups, including placebo, during both the first 12 weeks of treatment and the full 24 weeks of treatment. TEAEs were reported for 38.9% of "All Placebo Exposed" subjects (ie, all subjects combined who received placebo during the first 12 weeks) and 41.3% of "All filgotinib Exposed" subjects (i.e., all subjects combined who received filgotinib during either the entire 24 weeks or only during the last 12 weeks, irrespective of dose).

No deaths were reported and a total of 9 subjects had a serious TEAE; 1 subject (1.4%) during placebo dosing and 8 subjects (2.9%) during filgotinib dosing. No serious TEAE (by preferred term) was experienced by more than 1 subject, and all subjects recovered from their serious TEAEs. Out of the 9 subjects with a serious TEAE, 3 subjects had a serious TEAE for which the study medication was stopped and the subject discontinued the study. There were no differences in incidences of AEs leading to discontinuation among all the different dosing groups, including placebo. A total of 11 subjects had ≥1 TEAE leading to discontinuation of the study medication; 4 subjects (5.6%) during placebo dosing and 7 subjects (2.5%) during filgotinib dosing.

During the whole study, the most common TEAEs reported by System Organ Class in subjects from both the placebo and filgotinib treatment groups, were 'Infections and Infestations' and 'Gastrointestinal disorders'. There were no differences between subjects who received placebo or filgotinib in the severity of TEAEs (most TEAEs were mild or moderate; severe TEAEs were observed in 1.4% of "All Placebo Exposed" subjects and in 1.1% of "All filgotinib Exposed" subjects). Treatment-related TEAEs were generally reported more often for subjects in the filgotinib treatment groups than in the placebo group (9.7% with placebo and 16.7% with filgotinib); however, within the different filgotinib treatment group, no clear dose relationships were observed.

Low numbers of infections were reported as serious (4 subjects with filgotinib) or led to discontinuation of the study medication (2 serious infections; ie, cellulitis and pneumonia). Up to Week 24, 1 subject (filgotinib 50 mg q.d. group) had a herpes zoster infection. No cases of tuberculosis, opportunistic infections, lymphoma, or cancer were reported throughout the 24-week dosing period.

Laboratory data were consistent with prior studies and no new safety findings were observed.

Please refer to the IB for additional data regarding efficacy and safety.

1.3. Rationale for This 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 biologic DMARDs may be ineffective or produce only partial responses in some subjects and may be associated with significant safety and tolerability concerns. There is a 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. MTX-naïve patients with RA have several medications to choose from, however, it is clear that as patients progress through the available therapies, they may be left with active disease and a need for additional options. Development of another drug for these patients is appropriate, since participation in this study will not preclude the use of approved RA therapies for these subjects in the future. Moreover, all subjects in this study will receive active drug: MTX, filgotinib, or a combination of the two, as well as frequent monitoring of their health and RA status. Any subjects considered to be non-responders at Week 24 and those with loss of response at 2 consecutive visits after week 30, will discontinue study drug and take standard of care medications.

Filgotinib is an orally administered, small molecule inhibitor of JAK1, an intracellular tyrosine kinase that is 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.

1.3.1. Rationale for Study Design

The current study (GS-US-417-0303) is a Phase 3, randomized, double-blind, placebo and active-controlled study designed to evaluate the efficacy and safety of filgotinib in subjects with active RA who have limited or no prior exposure to MTX therapy. Study drugs will be administered for up to 52 weeks. The objectives of the study are to evaluate the efficacy of filgotinib as monotherapy, and in combination with MTX on the signs and symptoms of RA, to evaluate effects on physical function and radiographic progression, and to assess work productivity, fatigue, and quality of life. In addition, the safety, tolerability and pharmacokinetics (PK) of filgotinib will be assessed.

The active comparator in this study is oral MTX. Methotrexate is the most commonly prescribed first line csDMARD in the treatment of moderately to severely active RA and has been shown to reduce the signs and symptoms of disease as well as to inhibit radiographic progression {Lopez-Olivo et al 2014}. The inclusion of MTX will allow comparison of the efficacy and safety of filgotinib to an approved and frequently prescribed product indicated for use in treatment-naïve patients {Lopez-Olivo et al 2014}. In this study, MTX will be titrated up to the maximal tolerated dose over a period of 8 weeks. Non-responders at Week 24 (as defined in Section 3.2) will discontinue investigational therapy but will continue with study visits and assessments per protocol. All subjects who discontinue from investigational therapy will receive standard of care treatment for their RA as determined by the investigator.

Given that all subjects will receive at least one active drug in this study, determining non-responder status at 24 weeks is considered both clinically and ethically appropriate and allows an acceptable time to assess initial response to therapy, especially since MTX will be titrated upward over an 8 week period. The study eligibility criteria are consistent with those of recent clinical trials evaluating novel investigational treatments for RA. Subjects should meet the 2010 ACR/European League Against Rheumatism (EULAR) criteria for RA, and are required to have active disease, defined as ≥6 swollen and ≥6 tender joints at both Screening and Day 1, as well as one of the following: the presence of at least 1 joint erosion on radiographs of the hands, wrists, or feet, or a positive test for anti-citrullinated peptide antibody (anti-CCP Ab) or rheumatoid factor (RF), or an elevated CRP level. The study duration of up to 52 weeks allows sufficient time to evaluate safety, reduction in disease activity, and confirmation that clinical benefit is sustained over time.

1.3.2. Rationale for the Outcome Measures

Safety and tolerability will be assessed by the evaluation of adverse events (AEs), selected clinical laboratory parameters, vital signs, physical examinations, and electrocardiograms (ECGs), all of which are standard safety evaluations in clinical trials of RA.

The ACR20, ACR50, and ACR70 responses and the DAS28 (CRP) are considered reliable measures of response to treatment and disease activity, respectively, in subjects with RA. Comparison between the treatment arms of the proportions of subjects achieving an ACR20 response at Week 12 and the proportions of subjects achieving low disease activity in DAS28 (CRP) allows for interpretation of a clinically meaningful response and these measures have been shown to achieve high discriminatory capacity.

Evaluation of continuous outcome measures of DAS28 (CRP) and American College of Rheumatology N (ACR-N) as secondary endpoints enables the demonstration of improvement and magnitude of benefit. The EULAR/ACR remission response criteria classify subjects as non, moderate-, or good responders depending on the extent of change and the level of disease activity reached. These response criteria are useful when describing clinically meaningful therapeutic results. The CDAI and the SDAI have been widely used in clinical studies to demonstrate the impact of a study drug on controlling disease activity in patients with RA.

Assessing quality of life (measured by the Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-Fatigue], 36-item short form health survey [SF-36], and EuroQol 5-Dimension [EQ-5D]) at Day 1 and during the course of study treatment provides insight into the effects on modifying RA disease course and the impact on daily living. Treatment satification will be assessed by using the Treatment Satisfaction Questionnaire for Medication (TSQM) at Day 1 and during the course of the study. Assessing the change in economic impact (Work Productivity and Activity Impairment [WPAI] and Healthcare Resource Utilization) of RA over the course of the study provides insight into the subject's ability to work and other daily activities as well as the impact on the burden of healthcare resources.

Radiographs have been widely used in assessing structural joint damage associated with RA and are therefore essential in evaluating the efficacy of a study drug. Reduction in radiographic evidence of structural damage progression is an important predictor of long-term benefits in delaying or preventing the progression to disability related to RA. While X-ray remains the widely accepted method for assessing progression of structural joint damage, evaluation by MRI may provide specific advantages CCI [redacted] Radiographic data using validated scoring methods will be used to demonstrate efficacy in this domain.

1.3.3. Rationale for the Choice of Dose and Dosing Interval

Enrolled subjects will be randomized to receive filgotinib or active comparator MTX, or a combination thereof. The 100 mg and 200 mg q.d. dose regimens of filgotinib have been selected for Phase 3 evaluation based on non-clinical data and information concerning efficacy, tolerability, and safety data derived from the Phase 1 and Phase 2 studies, and are supported by non-clinical safety studies.

In seven Phase 1 studies conducted in healthy subjects (GPLG0634-CL-101, -102, −103, - 104, -105, -107, and -110), filgotinib administered at doses up to 450 mg q.d. for up to 10 days was safe and well tolerated.

In the 2 Phase 2a studies in subjects with RA (Study GLPG0634-CL-201 and -202), dosing with filgotinib was well tolerated and achieved a high level of efficacy at a 200 mg daily dose (ACR20 response of 75-92% at Week 4). Administration of a higher filgotinib dose (300 mg) did not demonstrate greater efficacy, therefore, the highest dose to be tested in this study will be 200 mg q.d.

In two Phase 2b studies, filgotinib at doses of 50 mg, 100 mg, or 200 mg daily, administered in addition to a background therapy with MTX (GLPG0634-CL-203) or as monotherapy (GLPG0634-CL-204) was shown to be safe and efficacious in subjects with moderately to severely active RA who had an inadequate response to MTX alone (Section 1.2.3).

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/above the 200 mg total daily dose on the dose-response curve. Additionally, in Study GLPG0634-CL-203, no statistically significant difference in efficacy was observed at 200 mg daily dose, administered as 200 mg q.d. or 100 mg b.i.d. 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 and intermediate inhibition (~47%) at 100 mg {Namour et al 2015}.

Overall, the 100 mg and 200 mg once-daily dose regimens have been proposed based on the safety and efficacy data from the Phase 2 studies in RA and the observed plateau in the pSTAT1 response which indicates doses above 200 mg are unlikely to add additional benefit. Inclusion of two doses in the proposed Phase 3 trials will enable establishment of an appropriate nominal dose for the treatment of RA and determine the regimen with the most favorable risk:benefit profile in these populations.

Safety data collected across Phase 2 clinical studies showed no dose-dependent trends in the incidence of AEs or SAEs, including infections, or laboratory abnormalities with the exception of a numerical increase in select gastrointestinal AEs (eg, nausea, vomiting, abdominal pain, and upper abdominal pain). This numerical increase was observed in the 200 mg compared to the 100 mg dose. However, the overall frequency was low and clinical relevance is unknown. Filgotinib, administered at a dose of 100 mg or 200 mg daily was found to be safe and well tolerated. The safety profile was consistent with that observed for an immunomodulatory compound administered to subjects with RA.

Overall, the 100 mg and 200 mg once-daily dose regimens have been proposed based on the safety and efficacy data from the Phase 2 studies in RA and the observed plateau in the pSTAT1 response which indicates doses above 200 mg are unlikely to add additional benefit. Inclusion of two doses in the proposed Phase 3 trials will enable establishment of an appropriate nominal dose for the treatment of RA and determine the regimen with the most favorable risk:benefit profile in these populations.

1.4. Risk/Benefit Assessment for the Study

As of January 2016, Filgotinib has been administered to more than 150 healthy subjects as single doses ranging from 1 to 200 mg, and as multiple doses at 25 to 100 mg twice daily, and 200, 300, and 450 mg daily for 10 days. In addition, filgotinib has been administered to more than 1000 RA subjects and more than 150 subjects with Crohn's Disease at daily doses ranging from 50-200 mg. In general, filgotinib has been safe and well tolerated in all populations studied.

Nonclinical studies in rats and dogs identified the testes and lymphoid tissue as target organs for filgotinib in long term repeat-dose toxicity studies. In both species, histopathological changes in the testes included germ cell depletion and degeneration, with reduced sperm content and increased cell debris in the epididymis and reduction in fertility in rats. The dog was determined to be the most sensitive species. 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 2.3, 1.8, and 3.4-fold when considering the mean AUC in male dogs at the no-observed-effect-levels (NOELs) in the 26 week and 39 week chronic toxicity studies, and the 39 week targeted exposure toxicity study, respectively. Decreased lymphocytes observed in nonclinical studies have not been shown in clinical studies.

Filgotinib has shown an increased risk of embryofetal malformations at exposures similar to human doses; the use of highly effective contraception in the subject population will be implemented in the study to mitigate this risk.

No clinically relevant impact on cardiovascular parameters (including vital signs and ECG), respiratory or neurologic function has been observed in Phase 1 and 2 trials of filgotinib. Across the phase 2 trials in RA, filgotinib was well-tolerated. In the RA studies (including the open label extension Darwin 3), infections were reported more commonly in the filgotinib groups, including serious infections leading to hospitalization, and even death. The most common system organ classes (SOC) with AEs were infections and infestations, and gastrointestional disorders. Dose dependent decreases in the phase 2b studies were observed in mean neutrophil counts and platelet counts (but mean changes in both remained within normal laboratory reference ranges), and there were no decreases in lymphocytes or lymphocyte subsets. Hemoglobin levels slightly improved (increased) with filgotinib treatment, confirming that no anemia was induced. Mild and clinically insignificant serum creatinine increases were noted in both Phase 2b studies, with stabilization by Week 24. Neutrophil decreases (in the RA population) and a potential increased risk of infection may be considered risks consistent with the mechanism of JAK inhibition.

Overall clinical findings and laboratory changes are consistent with selective JAK inhibition and based on Phase 2 data the expected benefit of using filgotinib as proposed in this study is considered to outweigh any associated risks.

An independent data monitoring committee (DMC) appointed to monitor the study (with an interim safety analysis after approximately 100 subjects complete Week 12) will provide an additional level of risk mitigation.

The overall risk:benefit balance of this study is considered favorable. For additional information about the risks of filgotinib, reference is made to the IB.

1.5. Compliance

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

2. OBJECTIVES

The primary objective of this study is as follows:

- To evaluate the effects of filgotinib in combination with MTX versus MTX alone for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving ACR20 at Week 24

The secondary objectives of this study are as follows:

- To evaluate the effect of filgotinib in combination with MTX versus MTX alone on physical function as measured by change from Baseline in the Health Assessment Questionnaire Disability Index (HAQ-DI) score at Week 24
- To evaluate the effects of filgotinib in combination with MTX versus MTX alone for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving Disease Activity Score for 28 joint count using CRP (DAS28 [CRP])<2.6 at Week 24
- To evaluate the effects of filgotinib alone versus MTX alone for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving ACR20 at Week 24
- To evaluate the effect of filgotinib alone versus MTX alone on physical function as measured by change from Baseline in HAQ-DI score at Week 24
- To evaluate the effects of filgotinib alone versus MTX alone for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving DAS28 (CRP)<2.6 at Week 24
- To evaluate the effects of filgotinib in combination with MTX versus MTX alone on preservation of joint structure as measured by change from Baseline in the mTSS at Week 24 and 52
- To evaluate the effects of filgotinib alone versus MTX alone on preservation of joint structure as measured by change from Baseline in mTSS at Week 24 and 52
- To evaluate the safety and tolerability of filgotinib alone and in combination with MTX
- To evaluate the effects of filgotinib alone and in combination with MTX on work productivity, fatigue, and general quality of life as measured by SF-36, FACIT-Fatigue, EQ-5D and WPAI-RA

The exploratory objectives of this study are as follows:

[redacted]

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint is the proportion of subjects who achieve an ACR20 response at Week 24.

The key secondary endpoints are:

- Change from Baseline in the HAQ-DI score at Week 24
- The proportion of subjects who achieve DAS28 (CRP)<2.6 at Week 24
- Change from Baseline in mTSS at Week 24

Other secondary endpoints include:

- Change from Baseline in the mTSS at Week 52
- The proportion of subjects who achieve ACR50 and ACR70 at Weeks 4, 12, 24 and 52, ACR20 at Weeks 4, 12, and 52, and ACR20/50/70 over time from Day 1 through Week 52
- Change from Baseline in individual components of the ACR response at Weeks 4, 12, 24, and 52 and over time from Day 1 through Week 52
- The proportion of subjects who achieve improvement in HAQ-DI of ≥0.22 at Weeks 4, 12, 24, and 52, and over time from Day 1 through Week 52
- Change from Baseline in DAS28 (CRP) at Weeks 4, 12, 24, and 52, and over time from Day 1 through Week 52
- The proportion of subjects who achieve DAS28 (CRP)≤3.2 at Weeks 4, 12, 24, and 52, and over time from Day 1 through Week 52
- The proportion of subjects who achieve DAS28 (CRP)<2.6 at Weeks 4, 12, and 52, and over time from Day 1 through Week 52
- ACR-N and EULAR response at Weeks 4, 12, 24, and 52, and over time from Day 1 through Week 52
- Change from Baseline in CDAI at Weeks 4, 12, 24, and 52, and over time from Day 1 through Week 52
- Change from Baseline in SDAI at Weeks 4, 12, 24, and 52, and over time from Day 1 through Week 24

- The proportion of subjects who had no radiographic progression from Baseline at Week 24 and 52

- Absolute value and change from Baseline in SF-36, FACIT-Fatigue, and the EQ-5D over time at Weeks 4, 12, 24 and 52, and over time from Day 1 through Week 52

- Absolute value and change from Baseline in WPAI-RA at Weeks 4, 12, 24, and 52, and over time from Day 1 through Week 52

3.2. Study Design

This is a randomized, double-blind, placebo- and active-controlled, Phase 3 study in adult male and female subjects with moderately to severely active RA who have limited or no prior exposure to MTX therapy. The study is designed to evaluate the efficacy, safety and tolerability of filgotinib as well as its effect on patient-reported outcomes, including work productivity, fatigue, and quality of life. In addition, PK will be assessed.

Adult male and female subjects with active RA will be screened to determine eligibility as per the inclusion and exclusion criteria (see Section 4.2 and 4.3, respectively). The Screening period will be up to 28 days. The screening window may be extended to up to 42 days prior to the Day 1 visit for subjects who require repeat collection of radiographs.

Written informed consent must be obtained before any study-related procedures take place. During the Screening period, following signing of the informed consent form (ICF), the subject's radiographs (hands, wrists, and feet) will be sent to central review for confirmation of joint erosion (see inclusion criterion 5; Section 4.2). Note that the subject's radiographs need to be sent to central review as soon as possible after completion and prior to Day 1 to allow for central reading and confirmation of one or more joint erosion in subjects that are seronegative.

Subjects will be randomized in a 2:1:1:2 ratio to filgotinib 200 mg plus MTX, filgotinib 100 mg plus MTX, filgotinib 200 mg alone, or MTX alone for up to 52 weeks in a double-blind fashion.

At Week 24, subjects who have not achieved a 20% improvement from Day 1 in both SJC and TJC will discontinue investigational therapy but will continue with study visits and assessments per protocol. All subjects who discontinue from investigational therapy are to receive standard of care treatment for their RA as determined by the investigator.

Responders at Week 24 will continue on the treatment regimens to which they were randomized through Week 52.

All subjects will be evaluated for loss of therapeutic response from Week 30 through the Week 52 study visit. Subjects failing to maintain at least a 20% improvement from Day 1 in TJC and SJC (as confirmed at 2 consecutive visits) will discontinue investigational therapy but will continue with study visits and assessments. All subjects who discontinue from investigational therapy are to receive standard of care treatment for their RA as determined by the investigator.

Subjects who have received at least one dose of study drug and choose to prematurely terminate study participation for any reason should complete an ET visit at the time of study discontinuation, as well as a post dosing visit four weeks after the last dose of study drug (post treatment Week 4) regardless of dosing duration.

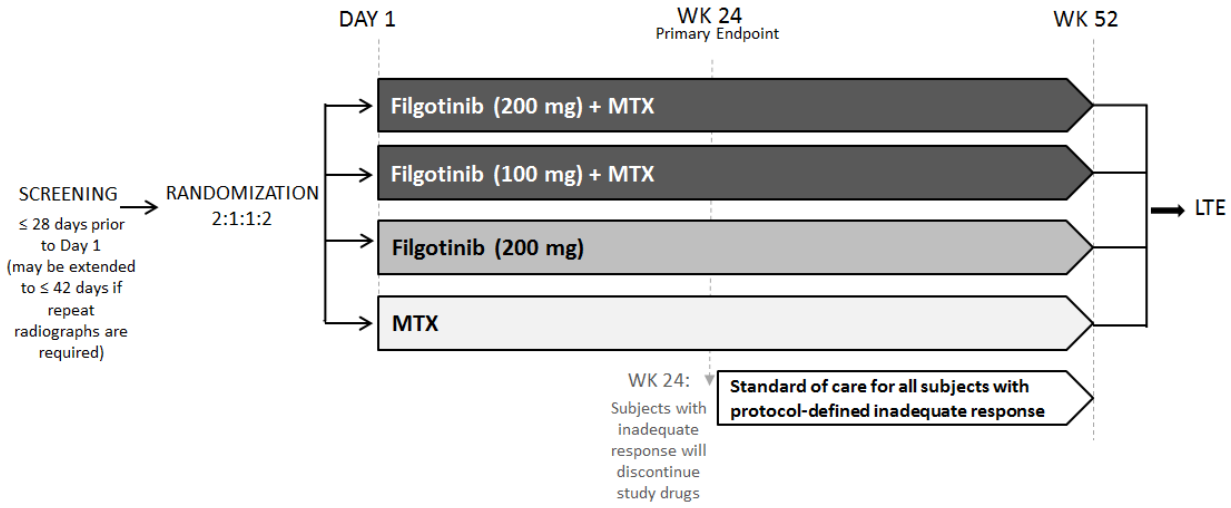
At completion of the 52-week treatment period, subjects (who did not discontinue assigned study drug or have not met criteria for loss of therapeutic response) will be provided the option to enter a Long Term Extension (LTE) study (GS-US-417-0304).

For those subjects not entering the LTE, a follow-up visit will be planned at Post Treatment Week 4.

To enhance the safety monitoring during the study, a DMC consisting of independent experts will be convened to periodically review the accumulating safety data for the study. In addition, a cardiovascular safety endpoint adjudication committee (CV-SEAC) will be convened to periodically review and adjudicate all possible major cardiovascular events (MACE).

The assessments planned to be performed at each visit are detailed in the study procedures table (Appendix 2). A schedule of the study design is provided below.

Figure 3-1. Study Design



3.3. Study Treatments

Approximately 1200 subjects with active RA will be randomized in a 2:1:1:2 ratio to filgotinib 200 mg plus MTX, filgotinib 100 mg plus MTX, filgotinib 200 mg alone, or MTX alone, for up to 52 weeks:

- Filgotinib 200 mg + MTX group: Filgotinib (200 mg q.d.) + PTM filgotinib 100 mg (PTM q.d.) + MTX (once weekly up to 20 mg) (N=400)

- Filgotinib 100 mg + MTX group: Filgotinib (100 mg q.d.) + PTM filgotinib 200 mg (PTM q.d.) + MTX (once weekly up to 20 mg) (N=200)

- Filgotinib 200 mg monotherapy group: Filgotinib (200 mg q.d.) + PTM filgotinib 100 mg (PTM q.d.) + PTM MTX (PTM once weekly) (N=200)

- MTX monotherapy group: PTM filgotinib 100 mg (PTM q.d.) + PTM filgotinib 200 mg (PTM q.d.) + MTX (once weekly up to 20 mg) (N=400)

NOTE: on study visit days, subjects should wait to take their regularly scheduled dose of study drug until instructed by site personnel, in case there are pre-dose blood draws or other pre-dose procedures required on that day.

3.4. Duration of Treatment

Subjects are planned to participate in the study for approximately 60 weeks (from the Screening visit to Follow-up visit or entry into the LTE); the duration of dosing is up to 52 weeks.

3.5. Criteria for Interruption or Discontinuation of Study Treatment

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 elective or 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.

- 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.

  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)
- Evidence of active HCV during the study, as evidenced by HCV RNA positivity
- Evidence of active HBV during the study, as evidenced by HBV DNA positivity
- 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
- Non-responder at Week 14 OR at 2 consecutive visits after Week 30 as outlined in Section 3.2
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study (Section 7.7.2.1 and Appendix 5)
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)
- Subject use of prohibited concurrent therapy *may* trigger study drug discontinuation; consultation should be made with the Gilead medical monitor.
- Laboratory criteria:

After becoming aware of any of the below described abnormal laboratory changes occurring at any one time, an unscheduled visit (ie sequential visit) should occur to retest within 3 to 7 days (except creatinine, which should be retested 7-14 days apart).

— 2 sequential neutrophil counts <750 neutrophils/mm^3 (SI: <$0.75x10^9$ cells/L) after dose adjustment of MTX/PTM (Section 5.3.4)

- 2 sequential platelet counts <75,000 platelets/mm^3 (SI: <75.0x10^9 cells/L) after dose adjustment of MTX/PTM (Section 5.3.4)
- 2 sequential AST or ALT elevations >3xULN and ≥1 total bilirubin value >2xULN or accompanied by symptoms consistent with hepatic injury[1] after dose adjustment of MTX/PTM (Section 5.3.4)
- 2 sequential AST or ALT elevations >5xULN after dose adjustment of MTX/PTM (Section 5.3.4)
- 2 sequential values for estimated creatinine clearance <35 mL/min based on the Cockroft Gault formula

Subjects who permanently discontinue study medication for any reason are to receive standard of care treatment for their RA as determined by the investigator, and those subjects should be encouraged to continue study visits and procedures, if deemed medically appropriate by the investigator. Subjects who permanently discontinue study medication for pregnancy should not continue in the study; if there are any questions regarding permanent discontinuation, these should be discussed with the Sponsor.

Subjects withdrawing from the study should complete ET and Post Treatment Week 4 visits. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without 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. These 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 52 weeks of dosing plus the 4 week post treatment visit or has entered the LTE.

[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

3.7. Post Study Care

All subjects who meet criteria for clinical response (per protocol), and who complete 52 weeks of study assessments will be offered an opportunity to participate in a LTE study (GS-US-417-0304). Subjects who discontinue early from the main study, or switch to standard of care treatment during the study, are not eligible for the LTE. The long term care of subjects who do not qualify for the LTE or choose not to participate in the LTE will remain the responsibility of their primary treating physician.

3.8. Biomarker Samples

3.8.1. Biomarker Samples to Address the Study Objectives:

The following biological specimens will be collected in this study which may be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response, including efficacy and/or adverse events, and help inform the mechanism of action and mechanism of intrinsic and acquired resistance to filgotinib in RA. The specific samples to be collected from all subjects (unless otherwise stated) include the following:

- Plasma, serum, and urine samples for potential analysis of circulating factors including but not limited to cytokines, metabolome, biomarkers of joint damage, and miRNA
- Paxgene blood samples for potential gene expression analyses
- [redacted]
- Whole blood sample for potential B-/T-cell receptor sequencing
- Viably frozen PBMCs (vfPBMCs) and Leukocyte subsets to profile immune cell subsets and inflammatory signaling pathways

The biomarker sample collection schedule is described in Study Procedures Table (Appendix 2). Since biomarker science is a rapidly evolving area of investigation, it is not possible to specify prospectively all tests that may be performed on the specimens collected. The testing outlined above 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 parameters based upon the growing state of art knowledge. Any future testing of new tests not described above must be approved by local authorities as applicable according to specific local regulations.

The biomarker samples will be destroyed no later than 15 years after the end of study unless the subject gives specific consent for the remainder of the samples to be stored for optional future research.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

3.8.2. Biomarker Samples for Optional Future Research

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4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A sufficient number of subjects will be screened to ensure that approximately 1200 subjects with moderately to severely active RA will be randomized to one of 4 dosing groups.

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 ≥18 years of age, on the day of signing informed consent.

2) Have a diagnosis of RA (2010 ACR/EULAR criteria) (Appendix 8), and are ACR functional class I-III

3) Have ≥6 swollen joints (from a SJC66) and ≥6 tender joints (from a TJC68) at both Screening and Day 1 (need not be the same joints) (Appendix 7)

4) Must meet at least one of the following parameters at Screening:

   - ≥1 documented joint erosion on radiographs of the hands, wrists or feet by central reading

     OR

   - positivity for either RF or anti-CCP Ab (based on central laboratory)

     OR

   - Serum CRP ≥ 4 mg/L (based on central laboratory)

5) Have limited or no prior treatment with MTX, ie, no more than 3 doses of MTX ≤25 mg each in the subject's lifetime for the treatment of RA, with the last dose at least 28 daysprior to Day 1, and are an appropriate candidate for MTX therapy, as per investigator judgment

6) Females of childbearing potential (as defined in Appendix 5) must have a negative pregnancy test at Screening and Day 1

7) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5

8) Lactating female subjects must agree to discontinue nursing from Screening through the end of their study participation.

9) Meet one of the following tuberculosis (TB) Screening criteria:

   a) No evidence of active or latent TB:

      - A negative QuantiFERON® TB-Gold In-Tube test at Screening and
      - A chest radiograph (views as per local guidelines) taken at Screening or within the 3 months prior to Screening (with the report or films available for investigator review) without evidence of active or latent TB infection and
      - No history of either untreated or inadequately treated latent or active TB infection

   b) Previously treated for TB: ie, if a subject has previously received an adequate course of therapy as per local standard of care for either latent TB (9 months of isoniazid in a location where rates of primary multi-drug resistant TB infections are <5% or an acceptable alternative regimen) or active TB (acceptable multi-drug regimen). In these cases, no QuantiFERON® TB-Gold In-Tube test (or equivalent assay) need be obtained, but a chest radiograph must be obtained if not done so within 3 months prior to Screening (with the report or films available for investigator review). It is the responsibility of the investigator to verify the adequacy of previous anti-tuberculosis treatment and provide appropriate documentation.

   c) Newly identified latent TB during Screening: ie, a subject who has a newly identified positive diagnostic TB test result (defined as a positive QuantiFERON® TB Gold in Tube test [or equivalent assay]) in which active TB has been ruled out and for which appropriate, ongoing, prophylactic treatment for latent tuberculosis has been initiated prior to the first administration of study medication. Adequate treatment for latent TB is defined according to local country guidelines for immunocompromised subjects.

      Cases falling under category “b” and “c” need to be approved by the Sponsor prior to enrollment in the study. No subject with currently ACTIVE TB may be enrolled in the study, regardless of past or present anti-TB medication use.

10) Able and willing to sign the informed consent as approved by the IEC/IRB. 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 trial, and must be willing to comply with all trial visits and assessments; subjects who cannot read or understand the ICF may not be enrolled by a guardian or any other individual.

11) Subjects receiving non-prohibited medication for any reason should be be on a stable dose (defined as no change in prescription) within 7 days or 5 half-lives (whichever is longer) prior to the first administration of study drug on Day 1.

4.3. Exclusion Criteria

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

1) Prior treatments for RA as follows:

   a) Alkylating agents, eg, chlorambucil or cyclophosphamide, at any time

   b) Previous treatment with any JAK inhibitor

   c) Previous therapy with csDMARDs other than MTX or hydroxychloroquine (eg, gold salts, cyclosporine, leflunomide, azathioprine, sulfasalazine or any other immunosuppressive).

      NOTE: Subjects with prior exposure to csDMARD may be enrolled if the subject had limited exposure (less than 3 months of total exposure). Washout periods need to be satisfied per protocol (section 5.4).

   d) Use of any licensed or investigational biologic DMARDs (eg, B-cell depleting agents, tumor necrosis factor (TNF) alpha inhibitors, and/or interleukin (IL)-1, IL-6, IL-17, IL-12/23 inhibitors, including but not limited to abatacept, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, secukinumab, ustekinumab or tocilizumab

2) Known hypersensitivity or allergy to study drug, its metabolites, or formulation excipients.

3) Known hypersensitivity or allergy to the MTX, its metabolites, or formulation excipients.

4) Oral steroids at a dose >10 mg/day of prednisone (or equivalent) or a prescription for oral steroids which has changed within 4 weeks of Day 1.

5) Receipt of an intra-articular or other injectable corticosteroid within 4 weeks prior to Day 1.

6) Use of nonsteroidal anti-inflammatory drugs (NSAIDs) which have not been at a stable dose (defined as no change in prescription) for at least 2 weeks prior to Day 1. NOTE: subjects are permitted to take acetylsalicylic acid at a dose of ≤325mg daily for cardiac prophylaxis, or occasional NSAIDs for non-RA indications (eg, headache).

7) Administration of a live/attenuated vaccine within 30 days from Day 1, or planned during the study.

8) Participation in any clinical study of an investigational drug/device within 4 weeks or 5 half-lives prior to Screening, whichever is longer. Exposure to investigational biologics are excluded as outlined in 1d.

9) Have undergone surgical treatments for RA, including synovectomy or arthroplasty in >4 joints

10) 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 judgment of investigator.

11) Have a history of major surgery (requiring regional block or general anesthesia) within the last 3 months prior to Screening or planned major surgery during the study.

12) Have a moderately to severely active, generalized musculoskeletal disorder that would interfere with assessment of study parameters or increase risk to the subject by participating in the study, eg, generalized osteoarthritis, systemic inflammatory condition other than RA such as, but not limited to: ankylosing spondylitis, reactive arthritis, psoriatic arthritis, inflammatory bowel disease associated arthropathies, systemic lupus erythematosus, scleroderma, inflammatory myopathy, mixed connective tissue disease, overlap syndrome, or gout. Subjects with any history of Felty's syndrome or juvenile idiopathic arthritis are excluded, regardless of the disease activity level at Screening. (NOTE: subjects with concurrent Sjogren's syndrome or limited cutaneous vasculitis associated with RA are not excluded, and may be enrolled, based on investigator judgment).

13) Active autoimmune disease other than those listed above, that would interfere with assessment of study parameters or increase risk to the subject by participating in the study, eg, inflammatory bowel disease, uncontrolled thyroiditis, systemic vasculitis, transverse myelitis or uveitis.

14) Any known condition or contraindication as addressed in the local labeling or local clinical practice for MTX that would preclude the subject from participating in this study.

15) History of or current moderate to severe congestive heart failure (NYHA class III or IV), or within the last 6 months, a cerebrovascular accident, myocardial infarction, unstable angina, unstable arrhythmia new or significant ECG finding at Screening, or any other cardiovascular condition which, in the opinion of the Investigator, would put the subject at risk by participation in the protocol.

16) 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).

17) History of lymphoproliferative disease or current lymphoproliferative disease.

18) History of gastrointestinal perforation.

19) History of organ or bone marrow transplant.

20) Positive serology for human immunodeficiency virus (HIV) 1 or 2.

21) Evidence of active Hepatitis C Virus (HCV) infection. Subjects with positive HCVAb at screening, require reflex testing for HCV RNA. Subjects with positive Hep C RNA viral load (VL) at screening will be excluded. Subjects with positive HCV Ab, but negative HCV RNA VL are eligible per investigator judgment, but require ongoing monitoring as outlined in the schedule of assessments. Subject with active HCV during the study, as evidenced by RNA positivity will be discontinued from study drug as outlined in the protocol.

22) Evidence of active Hepatitis B Virus (HBV) infection. Subjects with positive HBV surface antigen (HBsAg) at screening are excluded from the study. Subjects with positive HBV core Ab and negative HBsAg, require reflex testing for HBV DNA. Subjects with positive HBV DNA at screening will be excluded. Subjects with positive HBV core Ab, and negative HBV DNA are eligible per investigator judgment, but may require prophylactic treatment in accordance with HBV treatment guidelines/local standard of care and require ongoing monitoring with blood tests for HBV DNA every 3 months, as outlined in the schedule of assessments. Subject with evidence of active Hepatitis B during the study, as evidenced by DNA positivity, will be discontinued from study drug as outlined in the protocol.

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

24) Active infection that is clinically significant, as per judgment of the investigator, or any infection requiring hospitalization or treatment with intravenous anti-infectives within 60 days of Screening; or any infection requiring oral anti-infective therapy within 30 days of Screening.

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

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

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

28) Current drug, tobacco or alcohol abuse, per investigator judgment.

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

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

31) Use of prohibited medication as outlined in section 5.4

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

33) Tests performed at the central laboratory at Screening that meet any of the criteria below (out of range lab values may be rechecked one time, after consultation with the sponsor or it's designee, 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 x 10^3 cells/mm^3 (SI: <3.0 x 10^9 cells/L);

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

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

e) Platelets <100 x 10^3 cells/mm^3 (SI: <100 x 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) Estimated creatinine clearance <40 mL/min based on the Cockroft-Gault formula.

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5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

An Interactive Web Response System (IWRS) 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 may obtain individual subject treatment assignment directly from the IWRS system. 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 emergency medical care for the subject. The rationale for unblinding must be clearly explained in source documentation and on the electronic case report form (eCRF), along with the date on which the treatment assignment was unblinded. The investigator is requested to contact the Gilead Medical Monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this Phase 3 clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study drug discontinued.

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

5.2. Description and Handling of Filgotinib and PTM Filgotinib

5.2.1. Formulation of Filgotinib and PTM Filgotinib

Filgotinib is provided as 100 mg and 200 mg strength tablets. Filgotinib tablets, 100 mg and 200 mg tablets, are beige, capsule-shaped, debossed with "GSI" on one side and "100" or "200" on the other, biconvex, film-coated tablets for clinical use. Each tablet contains the equivalent of 100 mg or 200 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, 100 mg and 200 mg, will be identical in appearance to the respective active 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.

5.2.2. Packaging and Labeling for Filgotinib and PTM Filgotinib

Filgotinib tablets, 100 mg and 200 mg, and PTM filgotinib tablets, 100 mg and 200 mg, 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 fitted with an induction-sealed, aluminum-faced liner.

Study drugs to be distributed to participating centers, shall 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.

Sufficient quantities of filgotinib tablets, 100 mg and 200mg, and PTM filgotinib tablets to complete the entire study will be shipped to the investigator or qualified designee from the Gilead Supply Management Team (or its designee).

5.2.3. Storage and Handling for Filgotinib and PTM Filgotinib

Filgotinib tablets, 100 mg and 200 mg, PTM filgotinib tablets should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F).

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 drug and to ensure proper product identification, the drug product should not be stored in a container other than the container 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.

5.2.4. Dosage and Administration of Filgotinib

Filgotinib tablets, 100 mg and 200 mg, and PTM filgotinib will be administered once daily with or without food. Each subject should be given instructions to maintain approximately the same daily time of administration to ensure a similar dosing interval between study drug doses.

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 the missed dose is not taken on the original day, subjects should be cautioned not to double the next dose with the missed dose of study drug under any circumstances. In those cases, the missed dose should be returned to the study drug bottle.

5.3. Description and Handling of Methotrexate (MTX) and PTM MTX

5.3.1. Formulation for MTX and PTM MTX

MTX is available as 2.5-mg strength capsules. MTX capsules are white opaque capsules. Each capsule contains one commercially sourced MTX tablet, 2.5 mg, and microcrystalline cellulose. Information regarding the formulation can be found in the current prescribing information.

Placebo to match MTX capsules is visually identical to the MTX capsule. Each PTM MTX capsule contains a placebo tablet and microcrystalline cellulose. The placebo tablet contains the inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and iron oxide yellow.

5.3.2. Packaging and Labeling for MTX and PTM MTX

Methotrexate and PTM methotrexate capsules are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 100 capsules and 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 centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products) and/or other local regulations, as applicable.

5.3.3. Storage and Handling for MTX and PTM MTX

Methotrexate and PTM methotrexate capsules should be stored at 25°C (77°F), until required for administration; excursions are permitted between 15 – 30°C (59 – 86°F).

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 drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3.4. Dosage and Administration of MTX

The titration period for MTX will be 8 weeks. Subjects will be started on 10 mg (4 capsules) of either MTX or PTM, in a blinded fashion. In the absence of any lack of tolerance as specified below, subjects will be advanced to 15 mg (6 capsules) of MTX or PTM at their 4 week visit and advanced to 20 mg (8 capsules) of MTX or PTM at their 8 week visit. Subjects should be on an adequate dose of folic acid (as per local practice) which should be confirmed or initiated at Day 1, and continued throughout the study.

All local standard-of-care practices for the administration of MTX, including follow-up care and contraindications should be performed according to local standards of care throughout the study.

Events that might indicate a lack of tolerance *may include, but are not limited to*:

- Moderate to severe headaches not responding to simple medical management;
- Moderate to severe nausea not responding to simple medical management;
- Moderate to severe fatigue;
- Mucocutaneous problems: oral ulcers or stomatitis not responding to simple medical management;
- Alopecia not responding to simple medical management;
- Elevated transaminases, confirmed by two consecutive blood tests (3-7 days apart);
- Cytopenia, on blood samples taken 3-7 days apart:
  - Thrombocytopenia, defined as two sequential platelet counts<100,000 platelets/mm3;
  - Neutropenia, defined as two sequential neutrophil counts <1.0 x 10^9/L;
  - Leukopenia, defined as two sequential white blood cell count <3.0 x 10^9/L;

Simple medical management of adverse events typical of suspected intolerance to MTX may include allowed concomitant medications (e.g., anti-emetic medication), or replacing folic acid with up to 5 mg dose of leucovorin (folic acid) dosed 8 to 24 hours after the MTX weekly dose.

Single Dose Reduction of Methotrexate

After the first 4 weeks, a single dose reduction of MTX/PTM by 5 mg (2 capsules weekly) is allowed during the study, as long the patient remains on a dose of at least 4 capsules of MTX/PTM weekly. Lack of tolerance and dose reductions are to be documented by the investigator. Should significant laboratory abnormalities or symptoms persist after dose adjustment, please refer to the discontinuation guidelines as outlined in Section 3.5. If the subject cannot tolerate the MTX/PTM tablets within the first 4 weeks of the study, consideration should be given to discontinuing the subject from study drug dosing, as no dose reduction is permitted within the first 4 weeks.

5.4. Prior and Concomitant Medications

Concomitant therapies taken for the treatment of pre-existing conditions can continue during the study provided they are in accordance with the inclusion and exclusion criteria (see Section 4.2 and 4.3). It is preferred that these medications be continued without variation of

dose or regimen during the study, as much as possible. All non-RA medication used within 30 days of consent (including any changes) is to be documented in the eCRF. All prior medication used in the treatment for RA, are to be documented in 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.

In case new (non-prohibited) therapies need to be administered during the study, the risk/benefit to the subject should be carefully assessed and consideration given to the timing of any necessary introduction of new medications.

Permitted concomitant medications should be kept stable for the study duration, as much as possible, and include:

- NSAIDs, at a stable dose and regimen, as much as possible; NSAID doses should be held starting 12 hours before a study visit until after all scheduled assessments have taken place, as much as possible

- Anti-malarial DMARDs (hydroxychloroquine ≤400mg/day or chloroquine ≤250mg/day) provided that the prescription has been stable for at least 4 weeks prior to Day 1

- Oral prednisone ≤10 mg/day or equivalent, provided that the prescription has been stable for at least 28 days prior to Day 1. After Week 24, subject's steroid dose can be reduced or tapered based on investigator judgment (and may also be adjusted back up as needed), but should NOT exceed the stable dose identified at Baseline

- Analgesics, including opioids and other non-NSAID based therapies, at a stable dose and regimen, as much as possible; analgesic doses should be held starting 12 hours before a study visit until after all scheduled assessments have taken place, as much as possible

- 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

Female subjects of childbearing potential must agree to use highly effective birth-control methods as outlined in Appendix 5 and must agree to continue their use during the study and for at least 35 days after the last dose of study medication. The use of hormonal contraceptives will be recorded in the Concomitant Therapy section of the eCRF. Applicable procedures and treatment guidance based on package inserts will be respected.

Hormone replacement therapy, thyroid replacement and other chronic therapies (such as those for well-controlled diabetes or hypertension) are permitted during the study, and should be kept at a stable dose and regimen, as much as possible.

Vitamin, mineral or herbal supplementations are permitted during the study per judgment of investigator, and should be kept at a stable dose and regimen, as much as possible.

Prohibited concomitant medications (and their wash out period as applicable) while on study drugs include:

- Use of csDMARDs (other than the study-provided MTX/PTM or ongoing hydroxychloroquine ≤400 mg/day or chloroquine ≤250 mg/day)
- Use of any biologic DMARD
- Any cytotoxic agent, including chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents.
- Use of any other JAK inhibitor or other small molecule immunomodulator
- Any injectable corticosteroids and receipt of an intra-articular or parenteral corticosteroid injection within 4 weeks prior to Day 1 is prohibited.
- Potent Pg-p inducers (e.g. rifampin, phenytoin, carbamazepine, and St. John's wort) within 3 weeks prior to Day 1

Subjects with prior exposure to csDMARD other than HCQ or MTX may be enrolled if there is documented evidence of limited exposure (less than 3 months). Washout period of ≥ 8 weeks for leflunomide, or ≥4 weeks for all other csDMARD(s) prior to Day 1 need to be satisfied.

Any prior use of biologic DMARDs for RA is prohibited

Previous treatment at any time with a cytotoxic agent is prohibited.

Previous use of JAK inhibitors is prohibited. For subjects who are treated with isoniazid, consideration should be given to supplementation with vitamin B6 (pyridoxine) to reduce the risk of peripheral neuropathy.

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 filgotinib and its impact on immune responses following vaccination.

5.5. Accountability for Study Drugs

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.

Filgotinib and MTX accountability records will be provided to each study site to:

- Record the date received and quantity of study drugs
- Record the date, subject number, subject initials, the study drug number dispensed
- Record the date, quantity of used and unused study drugs returned, along with the initials of the person recording the information.
- Dispensing records will include the initials of the person dispensing the study drug or supplies.

5.5.1. Investigational Medicinal Product Return or Disposal

At study initiation, the monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with Gilead's requirements. Study drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to these procedures. If the site cannot meet Gilead's requirements for disposal, arrangements will be made between the site and Gilead's or its representative for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

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 in the study are presented in tabular form in Appendix 2 and described in the text that follows. Additional information is provided in the study procedures manual.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

The study assessments as described below will be performed at the time points specified in the Study Procedures Table (Appendix 2). Visits are to be scheduled within a window as specified in the schedule of assessment and in such a way that the total study duration from Day 1 to last dosing does not exceed 52 weeks, as much as possible.

6.1. Subject Enrollment and Treatment Assignment

Subject eligibility will be established at the conclusion of the screening evaluations. The screening number and subject ID will be assigned for each subject by IWRS.

It is the responsibility of the investigator to ensure that each subject is eligible for the study before randomization. A subject will be considered enrolled once randomized.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened before randomization to determine eligibility for participation in the study. The screening window may be extended to up to 42 days prior to the Day 1 visit for subjects who require repeat collection of radiographs. Subject-reported outcomes, including Global Assessment, HAQ-DI and Pain Scale are recommended to be done before any other study procedures. Invasive study procedures such as blood draws should be done at the end of a study visit, as much as possible. The following will be performed and documented at screening:

- Obtain written informed consent
- Obtain demographics and medical history (including onset of RA, disease characteristics, smoking habits, average weekly alcohol consumption, and family history of coronary heart disease)
- Complete physical examination including height
- Weight
- Vital Signs

- Perform 66 swollen and 68 tender joint count assessment (SJC66/TJC68)
- Physician's global assessment
- Subject's global assessment
- HAQ-DI and Pain Scale
- Radiographs of hands, wrists, and feet to be sent to central review for confirmation of joint erosion(s)
- 12-Lead ECG
- TB test and Chest X-ray (if applicable)
- Obtain blood samples for:
  - Serology
  - Hematology and Chemistry
  - Serum CRP
  - Serum Pregnancy Test (if applicable)
  - Rheumatoid factor, anti-CCP Ab
  - Quantitative immunoglobulin (Ig)
  - FSH (for females only), TSH, Hemoglobin A1c
- Urinalysis (including pregnancy test, if applicable)
- Review of concomitant medications
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form.

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

Subjects who do not meet the eligibility criteria will be excluded from randomization; subjects 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 investigational medicinal product, the investigative site is to record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Day 1 Assessments

At Day 1, after the subject's eligibility for the study has been confirmed, the subject will be randomized into the study to receive one of four study dosing regimens.

Subject's Global Assessment, HAQ-DI and Pain Scale, FACIT- Fatigue, and SF-36 are recommended to be done before any other study procedures. Invasive study procedures such as blood draws should be done at the end of a study visit. The following will be performed and documented at Day 1 prior to dosing:

- Subject's global assessment
- HAQ-DI and Pain Scale FACIT-Fatigue and SF-36
- WPAI-RA and EQ-5D, where available
- [redacted]
- TSQM , when and where available
- Healthcare resource utilization questionnaire
- Symptom-driven physical examination
- Weight
- Vital signs
- SJC66/TJC68
- Physician's global assessment
- Obtain blood samples for:
  - Hematology and Serum Chemistry
  - Lipid profile (fasting)
  - Serum CRP

— Biomarker blood samples

— Pre-dose vfPBMC and leukocyte subsets samples (US and Canada only)

CCI [redacted]

- Urinalysis (including pregnancy test, if applicable)
- Urine stored for biomarker analysis
- Review of concomitant medications
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form

CCI [redacted]

6.3. Randomization

Subjects will be randomly allocated to a dosing group according to a pre-specified randomization scheme prepared by an independent statistician. Upon qualification for the study, subjects will be randomized using a computerized IWRS system. Randomization will be stratified by geographic region and presence of RF or anti-CCP Ab at Screening.

For each subject at each visit, the clinic will contact the IWRS system and for the appropriate kit number to be dispensed. The kit will contain the relevant study drugs for the period until the next dispensation visit.

CCI [redacted]

6.4. Week 2 through Week 44 Assessments

The following assessments will be completed at each visit or as specified. All assessments are summarized in the Study Procedures Table (Appendix 2).

Subject's Global Assessment, HAQ-DI and Pain Scale, FACIT- Fatigue, and SF-36 are recommended to be done before any other study procedures. Invasive study procedures such as blood draws should be done at the end of a study visit.

- Subject's global assessment
- HAQ-DI and Pain Scale
- FACIT-Fatigue and SF-36 at Weeks 4, 12, and 24

- WPAI-RA and EQ-5D at Weeks 4, 12, and 24, where available
- [redacted]
- TSQM at Weeks 12, 24 and 36, when and where available
- Healthcare resource utilization questionnaire at Weeks 12, 24 and 36
- SJC66/TJC68
- Vital signs
- Weight
- Complete physical examination at Week 24 (symptom-driven PE conducted at all other visits)
- Physician's global assessment
- 12-lead ECG at Weeks 12, 24, and 36
- Assessment of serious AE(s), (S)AE(s) and concomitant medication
- Obtain blood samples for:
  - Hematology and Serum Chemistry
  - Serum CRP
  - Pre-dose vfPBMC and leukocyte subset samples samples at Weeks 4, 8, 12, 24, and 36 (US and Canada only)
  - Blood sampling for PK at Weeks 4, 12 and 24
  - Biomarker samples at Weeks 4, 8, 12, 24, and 36
  - Lipid profile (fasting) at Weeks 12 and 24
  - Quantitative Ig at Week 24
- Radiographs of hands, wrists, and feet at Week 24
- Urinalysis at Week 24
- Urine stored for biomarker analysis at Week 12 and Week 24

- Urine pregnancy test (for women of childbearing potential, as defined per protocol). During the periods where study visits are every 6-8 weeks, women should continue to have pregnancy tests every 4 weeks, using home pregnancy urine tests, that will be provided to them. The site will call the subject every 4 weeks to obtain results of these pregnancy tests and will record the information in the source documents and CRF.

[redacted]

6.5. Week 52/Early Termination (ET)

If a subject discontinues the study, every attempt should be made to perform the required study-related ET and Post Treatment Week 4 visits and procedures.

Subject's Global Assessment, HAQ-DI and Pain Scale, FACIT- Fatigue, and SF-36 are recommended to be done before any other study procedures. Invasive study procedures such as blood draws should be done at the end of a study visit.

- Subject's global assessment
- HAQ-DI and Pain Scale
- FACIT-Fatigue and SF-36,
- WPAI-RA and EQ-5D, where available

[redacted]

- TSQM, when and where available
- Healthcare resource utilization questionnaire
- Complete physical examination
- Weight
- Vital signs
- SJC66/TJC68
- Physician's global assessment
- 12-Lead ECG
- Radiographs of hands, wrists, and feet

- Obtain blood samples for:
  - Hematology and Serum Chemistry
  - Lipid profile (fasting)
  - Serum CRP
  - Pregnancy test (serum required if subject is entering into LTE)
  - Blood sampling for PK
  - Biomarker blood samples
  - Quantitative Ig
  - vfPBMC and leukocyte subset samples (US and Canada only)
- Urinalysis (including pregnancy test if applicable)
- Urine stored for biomarker analysis
- Assessment of AE(s)/serious (S)AE(s) and concomitant medication
- Review Entry criteria for LTE (if applicable)

6.6. Post Treatment Week 4

The following procedures will be completed 4 weeks after the subject's last dose of study treatment. This visit is not applicable if the subject is continuing onto the LTE study.

- Symptom-driven physical examination
- Weight
- Vital signs
- Urinalysis (including pregnancy test if applicable)
- 12-lead ECG
- Obtain blood samples for:
  - Hematology and Serum Chemistry
- Urinalysis
- Assessment of AE(s)/SAE(s) and concomitant medication

6.7. Study Assessments

6.7.1. Efficacy

Efficacy assessments will be carried out at Day 1 and at Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 44, and 52, or at ET (if applicable).

Assessments of RA will include the derived ACR (ACR20, 50, 70 as well as ACR-N and EULAR response criteria, DAS28 [CRP], CDAI, and SDAI as well as the individual components of the ACR response criteria [TJC68, SJC66], HAQ-DI, Physician's Global assessment, Subject's Global Assessment, Subject's Assessment of Arthritis Pain and CRP]) and radiographs of hands, wrists and feet (mTSS and mTSS components of erosion score and joint space narrowing).

Additionally, subjects will be asked to complete questionnaires, including the FACIT-Fatigue scale, SF-36, EQ-5D, TSQM, WPAI-RA at Day 1 and at Weeks 4, 12, 24, 36, and 52, or at ET (if applicable). Healthcare resource utilization will be assessed at the Day 1 and at Weeks 12, 24, 36 and 52, or at ET (if applicable).

6.7.1.1. Evaluation of Disease Activity: Tender and Swollen Joint Counts

Assessment of tender and swollen joints will take place at the time points indicated in the study procedures table (Appendix 2) and according to the assessments described in Section 6.4.

Each of 68 joints will be evaluated for tenderness and each of 66 joints will be evaluated for swelling (a list of joints to be evaluated is provided in Appendix 7).

An independent joint assessor with adequate training and experience in performing joint assessments will be designated at each study site to perform all joint assessments, and should be blinded to the other study assessments performed on that day. The joint assessor should preferably be a rheumatologist; however, if a rheumatologist is not available, it should be a health care worker with experience in performing joint assessments. The assessor should remain the same throughout the study per subject, as much as possible. It is required that the designated joint assessor identify an appropriate back up assessor to provide coverage if the designated joint assessor is absent.

6.7.1.2. Subject's Global Assessment of Disease Activity

The Subject's Global assessment of Disease Activity will be performed at the time points indicated in the study procedures table (Appendix 2). The Subject's Global assessment of Disease Activity should be completed before any other study procedures.

The Subject's Global Assessment of Disease Activity will be recorded on a 0-100 mm visual analog scale (VAS), with 0 indicating "no arthritis" and 100 indicating "severe arthritis".

6.7.1.3. Physician's Global Assessment of Disease Activity

The Physician's Global assessment of Disease Activity will be performed at the time points indicated in the study procedures table (Appendix 2).

The Physician's Global Assessment of Disease Activity will be recorded on a 0-100 mm VAS, with 0 indicating "no disease activity" and 100 indicating "maximum disease activity". The evaluating physician and the subject should complete the global assessments independently of each other.

6.7.1.4. Serum CRP

The subject's serum CRP will be measured at the time points indicated in the study procedures table (Appendix 2).

6.7.1.5. Health Assessment Questionnaire – Disability Index and Pain Scale

The functional status of the subject will be assessed using the HAQ-DI at the time points indicated in the study procedures table (Appendix 2) and should be completed before any other study procedures. The HAQ-DI is a 20-question instrument that assesses the degree of difficulty a person has in accomplishing tasks in 8 domains (dressing, arising, eating, walking, hygiene, reaching, gripping and errands/chores). Responses are scored on a 4-point Likert scale from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area. The need for aids or help from another person will also be recorded. The HAQ-DI total score ranges from 0 to 3 with higher scores indicating greater dysfunction.

As part of the HAQ-DI, subjects will be asked to assess their average pain during the last week on a 0-100 mm VAS, with 0 indicating "no pain" and 100 indicating "severe pain". This assessment should be completed before the joint examination. This pain score will be used to drive the ACR20/50/70.

6.7.1.6. FACIT - Fatigue Scale

The FACIT-Fatigue scale (version 4) will be completed at the time points indicated in the study procedures table (Appendix 2) and should be completed before any other study procedures where local language questionnaires are available.

The FACIT-Fatigue scale measures an individual's level of fatigue during their usual daily activities over the past week. It consists of 13 questions with a 7-day recall period on a 5-point Likert scale, with 0 indicating "not at all" and 4 indicating "very much". The total score ranges from 0 to 52. Higher scores indicate a better the quality of life.

6.7.1.7. 36-Item Short-form Health Survey

The SF-36 (version 2) will be completed at the time points indicated in the study procedures table (Appendix 2) and should be done before any other study procedures.

The SF-36 is a health related quality of life instrument consisting of 36 questions belonging to 8 domains in 2 components and covers a 4-week recall period:

- physical well-being: 4 domains: physical functioning (10 items), role physical (4 items), bodily pain (2 items), and general health perceptions (5 items)

- mental well-being: 4 domains: vitality (4 items), social functioning (2 items), role emotional (3 items), and mental health (5 items).

The remaining item (health transition) is not part of the above domains but is kept separately. These scales will be rescaled from 0 to 100 (converting the lowest possible score to 0 and the highest possible score to 100), with higher scores indicating a better quality of life.

6.7.1.8. EuroQol 5 Dimensions

The EQ-5D questionnaire will be completed at the time points indicated in the study procedures table (Appendix 2) and should be completed before any other study procedures where local language questionnaires are available.

The EQ-5D is a standard measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economical appraisal {The EuroQol Group 1990}. The EQ-5D is not disease specific and has been validated in numerous health states.

The tool consists of the EQ-5D descriptive system and the EQ VAS. The descriptive part comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each of these 5 dimensions has 3 levels (no problem, some problems, and severe problems). Results for each of the 5 dimensions are combined into a 5-digit number to describe the subject's health state. The VAS records the subject's health on a 0-100 mm VAS scale, with 0 indicating "the worst health you can imagine" and 100 indicating "the best health you can imagine".

6.7.1.9. Work Productivity and Activity Impairment

The WPAI-RA is a questionnaire developed to measure impairments in work activities in subjects with RA {Zhang et al 2010} and will be completed at the time points indicated in the study procedures table (Appendix 2) and should be done before any other study procedures where local language questionnaires are available.

The questionnaire consists of 6 questions (currently employed, work time missed due to RA, Work time missed due to other reasons, hours actually worked, degree RA affected productivity while working [0-10 VAS; with 0 indicating no effect and 10 indicating RA completely prevented the subject from working], and degree RA affected productivity in regular unpaid activities [0-10 VAS; with 0 indicating no effect and 10 indicating RA completely prevented the subject's daily activities]). The recall period for questions 2 to 6 is 7 days.

Four main outcomes (expressed in percentages) can be obtained from the WPAI-RA: percentage of work time missed due to RA, percentage of impairment due to RA, percentage of overall work impairment due to RA, percentage of activity impairment due to RA. Note that for subjects who did not work during the 7 days covered by the WPAI-RA, the percent overall work impairment will be equal to the percent of work time missed due to RA.

6.7.1.10. Healthcare Resource Utilization

The Healthcare Resource Utilization Questionnaire is designed to assess healthcare usage during the previous three months across a number of direct medical cost domains.

This questionnaire should be completed by the patient prior to any procedures being performed at the visit, if possible where local language questionnaires are available.

6.7.1.11. Hands, Wrists, and Feet Radiographs

Hands, wrists, and feet radiographs will be taken at the time points indicated in the study procedures table (Appendix 2). Note that if a subject discontinues the study early and has had X-rays performed in the <12 weeks prior to discontinuation, these do not need to be repeated at ET. Radiographs performed after enrollment may be done +/-7 days of the scheduled visit.

All subjects who discontinue from investigational therapy but continue study visits and procedures, should continue to have radiographs performed as outlined in the study procedure table (Appendix 2).

The radiographs will be evaluated through central review by 2 independent blinded assessors using the mTSS.

6.7.1.12. Exploratory Patient Reported Outcomes

CCI [redacted]

6.7.1.13 Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM will assess the overall level of satisfaction or dissatisfaction with medication subjects are taking. Subjects will be asked to rate their treatment satisfaction at the time points indicated in the study procedures table (Appendix 2). The TSQM will implemented when and where local language TSQM are available.

6.7.2. Safety and Tolerability

Adverse events, physical examinations, vital signs, ECG and laboratory assessments (standard hematology, serum/plasma chemistry, and urinalysis) will be collected.

6.7.3. Clinical Laboratory Evaluations

The hematology and serum chemistry laboratory analyses will be performed at a central laboratory. Reference ranges will be supplied by the central laboratory and will be used by the investigator to assess the laboratory data for clinical significance and pathological changes.

Blood samples will be collected by venipuncture [redacted] in the arm at the time points indicated in the study procedures table (Appendix 2) In addition, urine samples for the clinical laboratory assessments will be collected. Subjects only need to be fasted at days were lipid profiling is scheduled.

Please refer to Appendix 6 for table of Clinical laboratory tests.

The laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. More frequent sampling as well as additional tests may be performed as deemed necessary by the investigator as indicated.

Note that in the case where clinically significant laboratory test results are a potential reason for discontinuation from the study drug and withdrawal from the study, retesting of the affected parameter(s) should be prompt (within 3 to 7 days) after the investigator has consulted with the medical monitor. A decision regarding subject discontinuation should be made after the results from the retest are available (see Section 3.5 for additional information).

The details of sample handling and shipment instructions will be provided in a separate laboratory manual.

6.7.4. Vital Signs

Vital signs will be measured at the time points indicated in the study procedures table (Appendix 2).

Vital signs should be taken after the subject has been resting for 5 min and will include heart rate, respiratory rate, SBP, DBP, and body temperature.

6.7.5. Physical Examination

A physical examination should be performed at the time points indicated in the study procedures table (Appendix 2).

Any changes from the Day 1 will be recorded. Height should be measured at Screening only.

At Screening, Week 24 and Week 52 (or at ET), a complete physical examination should be performed. Symptom-driven physical exams should be performed at all other visits. Weight is measured at all visits.

6.7.6. Other Safety Assessments

6.7.6.1. 12-lead Electrocardiogram

A resting 12-lead ECG will be performed at the time points indicated in the study procedures table (Appendix 2).

The ECG should be obtained after the subject has been resting in the supine position for 5 min and will include heart rate (HR), R-R interval, QRS, uncorrected QT, morphology, and rhythm analysis. QT interval corrected for HR according to Fridericia (QTcF) will be derived during the statistical analysis. ECGs will be interpreted by the investigator for clinical significance and results will be entered into the eCRF.

6.8. Pharmacokinetics Assessments

For all subjects, blood samples for PK analysis will be collected at least 30 minutes post study drug dosing at Week 4, prior to study drug dose at Week 12 and Week 24, and at Week 52 or ET.

CCI [redacted]

Plasma concentrations of filgotinib and GS-829845 will be analyzed.

Additional analyses (e.g., for MTX and its metabolites) may be performed.

6.9. Biomarker Assessments

Blood and urine samples for biomarker analysis will be collected at Day 1, Weeks 4, 8, 12, 24, 36, and Week 52 or ET for assessment of markers including but not limited to inflammation, immune status, joint damage, and the JAK-STAT pathway. CCI [redacted] Specific information regarding the collection and processing of biomarker samples (if applicable) will be provide to each site in a separate laboratory manual.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An adverse event (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 7.7.1)
- 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. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (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 to be recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., 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 (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

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

The relationship to study procedures (e.g., invasive procedures such as venepuncture or biopsy) should be assessed using the following considerations:

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

7.2.2. Assessment of Severity

The severity of AEs will be graded using the modified CTCAE, version 4.03. For each episode, the highest grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the adverse event. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7-1 and Appendix 4.

Table 7-1. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Death	Death related AE

* Activities of Daily Living (ADL) Instrumental ADL refer to opening preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

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

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

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

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

Serious Adverse Events

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

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

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

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

Electronic Serious Adverse Event (eSAE) Reporting Process

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

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

  Gilead DSPH: Fax: PPD
  E-mail: PPD

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

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

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

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

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

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

7.4. Gilead Reporting Requirements

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

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

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

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

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity should be recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, which can be found at:

http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

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.

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3 and as outlined below.

7.5.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.5.2. Grades 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinically significant laboratory abnormality or clinical event, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.

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

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

7.5.3. Grades 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to investigational medicinal product, investigational medicinal product should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Investigational medicinal product 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 investigational medicinal product.

7.6. Toxicity Management

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead Sciences medical monitor, who will have a discussion with the investigator and decide the appropriate course of action. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Grade 3 or 4 clinically significant laboratory abnormalities should be managed as outlined in Appendix 3 and Sections 7.5.2 and 7.5.3.

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

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 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 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 Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows:
Email: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to 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 PPD or email PPD

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 or Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

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

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

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoint

8.1.1. Analysis Objectives

The primary objective of this study is as follows:

- To evaluate the effects of filgotinib in combination with MTX versus MTX alone for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving ACR20 at Week 24

The secondary objectives of this study are as follows:

- To evaluate the effect of filgotinib in combination with MTX versus MTX alone on physical function as measured by change from Baseline in the HAQ-DI score at Week 24
- To evaluate the effects of filgotinib in combination with MTX versus MTX alone for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving Disease Activity Score for 28 joint count using CRP (DAS28 [CRP])<2.6 at Week 24
- To evaluate the effect of filgotinib alone versus MTX alone for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving ACR20 at Week 24
- To evaluate the effect of filgotinib in dose of 200 mg q.d. alone versus MTX alone on physical function as measured by change from Baseline in HAQ-DI score at Week 24
- To evaluate the effect of filgotinib alone versus MTX alone for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving DAS28 (CRP)<2.6 at Week 24
- To evaluate the effects of filgotinib in combination with MTX versus MTX alone on preservation of joint structure as measured by change from Baseline in the mTSS at Week 24 and 52
- To evaluate the effects of filgotinib versus MTX alone on preservation of joint structure as measured by change from Baseline in mTSS at Week 24 and 52
- To evaluate the safety and tolerability of filgotinib alone and in combination with MTX
- To evaluate the effects of filgotinib alone and in combination with MTX on work productivity, fatigue, and general quality of life as measured by SF-36, FACIT-Fatigue, EQ-5D and WPAI-RA

The exploratory objectives of this study are as follows:

[redacted]

8.1.2. Primary Endpoint

The primary endpoint is the proportion of subjects who achieve an ACR20 response at Week 24.

8.1.3. Secondary Endpoints

The key secondary endpoints are:

- Change from Baseline in the HAQ-DI score at Week 24
- Proportion of subjects who achieve DAS28 (CRP)<2.6 at Week 24
- Change from Baseline in the mTSS at Week 24

Other secondary endpoints include:

- Change from Baseline in the mTSS at Week 52
- The proportion of subjects who achieve ACR50 and ACR70 at Weeks 4, 12, 24 and 52, ACR20 at Weeks 4, 12, and 52, and ACR20/50/70 over time from Day 1 through Week 52
- Change from Baseline in individual components of the ACR response at Weeks 4, 12, 24, and 52 and over time from Day 1 through Week 52
- The proportion of subjects who achieve change in HAQ-DI of ≥0.22 at Weeks 4, 12, 24, and 52, and over time from Day 1 through Week 52
- Change from Baseline in DAS28 (CRP) at Weeks 4, 12, 24, and 52, and over time from Day 1 through Week 52
- The proportion of subjects who achieve DAS28 (CRP)≤3.2 at Weeks 4, 12, 24, and 52, and over time from Day 1 through Week 52
- The proportion of subjects who achieve DAS28 (CRP)<2.6 at Weeks 4, 12, and 52, and over time from Day 1 through Week 52

- ACR-N and EULAR response at Weeks 4, 12, 24, and 52, and over time from Day 1 through Week 52
- Change from Baseline in CDAI at Weeks 4, 12, 24, and 52, and over time from Day 1 through Week 52
- Change from Baseline in SDAI at Weeks 4, 12, 24, and 52, and over time from Day 1 through Week 24
- The proportion of subjects who had no radiographic progression from Baseline at Week 24 and 52
- Absolute value and change from Baseline in SF-36, FACIT-Fatigue, and the EQ-5D over time at Weeks 4, 12, 24 and 52, and over time from Day 1 through Week 52
- Absolute value and change from Baseline in WPAI-RA at Weeks 4, 12, 24, and 52, and over time from Day 1 through Week 52

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

8.2.1.2.1. Full Analysis Set (FAS)

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

8.2.1.2.2. Per-Protocol (PP) Analysis Set

The secondary analysis set for efficacy analyses will be the Per-Protocol (PP) Analysis set, which includes all subjects in the Full Analysis Set who have not committed any major protocol violation, including the violation of key entry criteria.

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 one dose of study drug.

8.2.1.4. Pharmacokinetic

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8.2.1.4.2. Pharmacokinetic (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 nonmissing concentration data for filgotinib and/or its metabolite GS-829845.

8.3. Data Handling Conventions

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

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

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group using standard descriptive statistics including sample size, mean, SD, median, Q1, Q3, minimum, and maximum for continuous variables and number and percentages of subjects for categorical variables.

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

Baseline characteristics may include prior exposure to MTX (yes/no), RF status, anti-CCP Ab status, DAS28 (CRP), HAQ-DI, mTSS, SDAI, CDAI, and other variables of interest.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary endpoint for the study is the proportion of subjects who achieve an ACR20 response at Week 24. The primary hypothesis will consist of a superiority test of filgotinib 200 mg in combination with MTX compared to MTX alone based on the ACR20 response rate at Week 24. Cochran-Mantel-Haenszel (CMH) approach adjusting for the randomization stratification factors

will be used for the hypothesis testing at the 2-sided 0.05-level. Subjects who do not have sufficient measurements to establish efficacy at Week 24 will be considered as failures (i.e. non-responder imputation [NRI]). Sensitivity analyses will be conducted and described in the statistical analysis plan (SAP).

8.5.2. Secondary Analyses

The following hypothesis testing will commence after the primary analysis reaches statistical significance, and will be tested according to the hierarchical testing principle at the 2-sided 0.05 level. If a null hypothesis is not rejected, formal sequential testing will be stopped and only nominal significance will be reported for the remaining hypotheses.

1) Superiority of filgotinib 200 mg in combination with MTX compared to MTX alone based on the change from Baseline in HAQ-DI at Week 24.

2) Superiority of filgotinib 200 mg in combination with MTX compared to MTX alone based on the response rate of DAS28 (CRP)<2.6 at Week 24.

3) Superiority of filgotinib 100 mg in combination with MTX compared to MTX alone based on ACR20 response rate at Week 24.

4) Superiority of filgotinib 100 mg in combination with MTX compared to MTX alone based on the change from Baseline in HAQ-DI at Week 24.

5) Superiority of filgotinib 100 mg in combination with MTX compared to MTX alone based on the response rate of DAS28 (CRP)<2.6 at Week 24.

6) Superiority of filgotinib 200 mg alone compared to MTX alone based on ACR20 response rate at Week 24.

7) Superiority of filgotinib 200 mg alone compared to MTX alone based on the change from Baseline in HAQ-DI to Week 24.

8) Superiority of filgotinib 200 mg alone compared to MTX alone based on the response rate of DAS28 (CRP)<2.6 at Week 24.

9) Superiority of filgotinib 200 mg in combination with MTX compared to MTX alone based on the change from Baseline in mTSS at Week 24.

10) Superiority of filgotinib 100 mg in combination with MTX compared to MTX alone based on the change from Baseline in mTSS at Week 24.

11) Superiority of filgotinib 200 mg alone compared to MTX alone based on the change from Baseline in mTSS at Week24.

For categorical endpoints (the response rate of DAS28 [CRP]<2.6), the same CMH approach with NRI as in the primary analysis will be adopted. For continuous endpoints (HAQ-DI and mTSS), mixed-effects model for repeated measures (MMRM) will be used to evaluate treatment effect on change from Baseline, with treatment, visit, stratification factors and baseline value included as fixed effects and subject being the random effect. Missing change scores in HAQ-DI and mTSS due to early withdrawal or treatment reassignment will not be otherwise imputed using the MMRM approach. Sensitivity analyses will be conducted by imputing missing data via, for example, last observation carried forward (LOCF) and multiple imputation (MI) methods. More details will be specified in the SAP.

For other secondary endpoints listed under Section 8.1.3, summary statistics will be provided by treatment group. Differences across treatment groups will be summarized and treatment comparisons may be performed. Details on efficacy analyses will be described in the SAP.

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:

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

Summaries (number and percentage of subjects) of TEAEs by SOC and PT will be provided by treatment group. TEAEs will also be summarized by relationship to study drug and severity. In addition, TEAEs leading to premature discontinuation of study drug 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 and study visit along with corresponding change from Baseline. The incidence of treatment-emergent graded laboratory abnormalities will be summarized similarly.

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

8.7. Pharmacokinetic Analysis

Plasma concentrations of filgotinib and its metabolite (GS-829845) will be listed and summarized for all subjects by treatment using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum).

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Exposure-response analysis may be performed.

8.8. Biomarker Analysis

Exploratory analyses may be performed to evaluate the association of each biomarker or combination of biomarkers with clinical outcomes, the modulation of biomarkers related to mechanism of action and disease progression, and biomarker or combination of biomarkers predictive of treatment response.

Exploratory biomarkers analyses that may enhance the understanding of the biological effects, the mechanism of action, or safety, may be performed. Biomarker objectives may be further described and updated based on evolving scientific knowledge of filgotinib. If an exploratory biomarker analysis is to be performed, biomarker analysis plan, with details on objectives and analysis methods, will be issued prior to the actual data analysis.

8.9. Sample Size

Sample size is determined based on the superiority test of filgotinib 200 mg in combination with MTX compared to MTX alone based on the change from Baseline in mTSS at Week 24. When assuming a difference of 0.62 between the two groups and a common standard deviation of 2.7, 400 subjects in the filgotinib 200 mg in combination with MTX group and 400 in the MTX alone group are required to obtain 90% power at a 2-sided 0.05-level.

The total sample size will be 1200 (400 subjects for filgotinib 200 mg in combination with MTX group, 200 subjects for filgotinib 100 mg in combination with MTX, 200 subjects for filgotinib 200 mg alone group and 400 subjects for MTX alone group). This sample size will provide over 90% power to detect an increase in ACR20 response rate of 62% to 78% between the MTX alone group and each of the filgotinib groups respectively, using a 2-sided 0.05-level test.

8.10. Data Monitoring Committee

An external multidisciplinary DMC will review the progress of the study and perform interim reviews of safety data and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.

The initial reviews will be conducted after approximately 100 subjects enrolled complete 12 weeks treatment. The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

8.11. Cardiovascular Endpoint Adjudication Committee

A Cardiovascular Endpoint Adjudication Committee (CV-SEAC) consisting of at least 2 cardiologists and governed by a Charter will be set up to perform adjudication of Major Adverse Cardiovascular Events occurring during the study. The adjudication of these events will be performed in a blinded fashion for the purposes of data analysis, and not for monitoring of subject safety.

8.12. Analysis Schedule

The primary and secondary analyses will be conducted after all subjects either complete their Week 24 visit or prematurely discontinue from the study. The final analysis will be performed when all subjects complete the study or prematurely discontinue from the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators 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 subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (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. The investigator will not begin any study subject activities until approval from 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 and the person conducting the consent discussion, and also by an impartial witness if required by local requirements. The consent form will inform subjects about genomic testing and sample retention, and their right to receive clinically relevant genomic analysis results.

9.1.4. Confidentiality

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

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, eCRF, the 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, CRF 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, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);

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

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (i.e., 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. eCRF 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 EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her 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 (e.g., data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Where possible, IMP should be destroyed at the site. At the start of the study, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for disposal or return of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead Sciences, the site may destroy used (empty or partially empty) and unused IMP supplies as long as performed in accordance with the site's SOP. This can occur only after the study monitor has performed drug accountability during an on-site monitoring visit.

A copy of the site's IMP Disposal SOP or written procedure (signed and dated by the PI or designee) will be obtained for Gilead site files. If the site does not have acceptable procedures in place, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies.

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

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

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRB/IEC, 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 the regulatory agency. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

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, e.g., 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

Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62 (9):2569-81.

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

Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38 (6):727-35.

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

Lopez-Olivo MA, Siddhanamatha HR, Shea B, Tugwell P, Wells GA, Suarez-Almazor ME. Methotrexate for treating rheumatoid arthritis. Cochrane Database Syst Rev 2014;6:CD000957.

Namour F, Diderichsen PM, Cox E, Vayssiere B, Van der Aa A, Tasset C, et al. Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Modeling of Filgotinib (GLPG0634), a Selective JAK1 Inhibitor, in Support of Phase IIB Dose Selection. Clin Pharmacokinet 2015;54 (8):859-74.

Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38 (1):44-8.

Redlich K, Schett G, Steiner G, Hayer S, Wagner EF, Smolen JS. Rheumatoid arthritis therapy after tumor necrosis factor and interleukin-1 blockade. Arthritis Rheum 2003;48 (12):3308-19.

Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis care & research 2012;64 (5):625-39.

The EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. . Health Policy 1990;16 (3):199-208.

Zhang W, Bansback N, Boonen A, Young A, Singh A, Anis AH. Validity of the work productivity and activity impairment questionnaire--general health version in patients with rheumatoid arthritis. Arthritis research & therapy 2010;12 (5):R177.

11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 Weeks Alone and in Combination with Methotrexate (MTX) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are Naïve to MTX Therapy

GS-US-417-0303, Amendment 1 Protocol, 05 July 2016

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

PPD

Name (Printed)
Author

PPD

Signature

6 July, 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 Table

EVENT			Treatment Period												Follow-Up[d]
Visits			Day 1[b]	W2	W4	W8	W12	W16	W20	W24	W30	W36	W44	W52/ ET[c]	Post Treatment Week 4
Visit window (Days)		Screening[a]		(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±7 days)	(±7 days)	(±7 days)	(±7 days)	(±7 days)
Screening Assessments	Informed Consent	X													
	Inclusion/Exclusion Criteria	X	X[e]												
	Demographics and Baseline Disease Characteristics	X													
	RA diagnosis and Prior RA Treatment, Medical History [f]	X													
	Complete Physical Examination [g]	X								X				X	
	TB test and Chest X-Ray [h]	X													
	RF/anti-CCP Ab	X													

EVENT			Treatment Period												Follow-Up[d]
Visits			Day 1[b]	W2	W4	W8	W12	W16	W20	W24	W30	W36	W44	W52/ ET[c]	Post Treatment Week 4
Visit window (Days)		Screening[a]		(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±7 days)	(±7 days)	(±7 days)	(±7 days)	(±7 days)
Patient Questionnaires	Subject's global assessment [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	
	HAQ-DI and Pain Scale [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	
	FACIT-Fatigue, SF-36, WPAI-RA, EQ-5D [i]		X		X		X			X		X		X	
	Healthcare Resource Utilization Questionnaire and TSQM [i]		X				X			X		X		X	
	CCI														
Physical Exam and Provider Assessments	Physician's global assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	
	Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Symptom-driven physical examination		X	X	X	X	X	X	X		X	X	X		X
	12-Lead ECG	X					X			X		X		X	X
	SJC66/TJC68	X	X	X	X	X	X	X	X	X	X	X	X	X	
	Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X

EVENT			Treatment Period												Follow-Up[d]
Visits			Day 1[b]	W2	W4	W8	W12	W16	W20	W24	W30	W36	W44	W52/ ET[c]	Post Treatment Week 4
Visit window (Days)		Screening[a]		(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±7 days)	(±7 days)	(±7 days)	(±7 days)	(±7 days)
Laboratory Assessments	Pregnancy test [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Hematology and Chemistry [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Serum CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	
	Urinalysis and urine for biomarkers [m]	X	X				X			X				X	X
	Quantitative IG	X								X				X	
	Endocrine: FSH, TSH, and HbA1c	X													
	Lipid profile (fasting) [l]		X				X			X				X	
	CCI														
	PK blood samples [o]				X		X			X				X	
	Biomarker Blood Samples: Plasma biomarker, serum biomarker, transcriptome, TCR/BCR repertoire [p]		X		X	X	X			X		X		X	
	vfPBMC and Leukocyte subset [q]		X		X	X	X			X		X		X	
	Serology	X[r]													
	Viral Monitoring [s]						X			X		X		X	

EVENT		Treatment Period												Follow-Up[d]
Visits		Day 1[b]	W2	W4	W8	W12	W16	W20	W24	W30	W36	W44	W52/ ET[c]	Post Treatment Week 4
Visit window (Days)	Screening[a]		(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±7 days)	(±7 days)	(±7 days)	(±7 days)	(±7 days)
Imaging — Hand, Wrist and Feet Radiographs [t]	X								X				X	
CCI														
Assessment of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization/reassignment		X							X[v]		X[w]	X[w]	X[w]	
Study Drugs Dispensation [x]		X		X	X	X	X	X	X	X	X	X		
Review entry criteria for LTE (if applicable)													X	

Footnotes

a Screening window is 28 days prior to Day 1, the window may be extended to up to 42 days prior to the Day 1 visit for subjects who require repeat collection of radiographs
b Subject will begin study drugs on Day 1, following baseline assessments and randomization.
c Early Termination Visit to be performed if subject discontinues before Week 52
d The follow-up visit will be performed only for subjects discontinuing prematurely from the study and for those completing Week 52 but not entering the LTE.
e Eligibility criteria check based on the laboratory results from the Screening visit, TJC/SJC at screening and Day 1 and for female subjects of childbearing potential, the urine pregnancy test at Day 1.
f Medical History includes smoking status, average weekly alcohol consumption, family history of coronary heart disease and any other chronic medical conditions or prior surgeries
g At Screening, Week 24 and Week 52 (or at ET), a complete physical should be performed. Symptom driven exams should be performed at all other visits. Height will be measured at Screening only.
h Chest X-ray for TB assessment should be performed unless performed in the previous 3 months, with results available at the site.
i Subject reported outcomes are recommended to be performed first at each visit prior to any other visit-related procedures (other than signing of informed consent), as much as possible. Questionnaire translations will be provided to subjects when and where available.
j Vital signs are defined as heart rate, respiratory rate, blood pressure (systolic and diastolic) and body temperature.

k For female subjects of childbearing potential only. To be performed on serum sample at Screening and on urine samples for other visits. For female subjects entering the LTE, at the Week 52 visit pregnancy test should be performed on serum. During the periods where visits are every 6-8 weeks, women should continue to have monthly home pregnancy tests performed at home. The site will call the subject every 4 weeks to obtain results of these pregnancy tests. If any pregnancy test is positive, study drug should be immediately interrupted and subject should come to the site for serum pregnancy test.

l Refer to list provided in Laboratory assessment table (Appendix 6).

m Urine samples for biomarker analysis should be collected at Day 1, Weeks 12, 24, and Week 52 or ET

[redacted]

o The PK sample at Week 4 should be collected at least 30 minutes post study drug dose in the clinic. PK samples at Week 12 and Week 24 should be collected prior to study drug dose (within 2 hours prior to dosing). The PK sample at Week 52 or ET can be collected at any time during the visit. CCI [redacted]

p Details of biomarker collection are outlined in lab manual

q Only for subjects in United States and Canada

r Hepatitis B surface Ag and core Ab, reflex Hep B DNA, Hepatitis C Ab, reflex HCV RNA, HIV 1 and 2 at Screening.

s Viral monitoring for HBV or HCV as applicable (see Exclusion criteria, Section 4.3).

t Radiographs performed after enrollment may be done +/- 7 days of the scheduled visit. If subject discontinues study early and has had x-rays in the <12 weeks prior, x-rays do not need to be repeated at the ET visit.

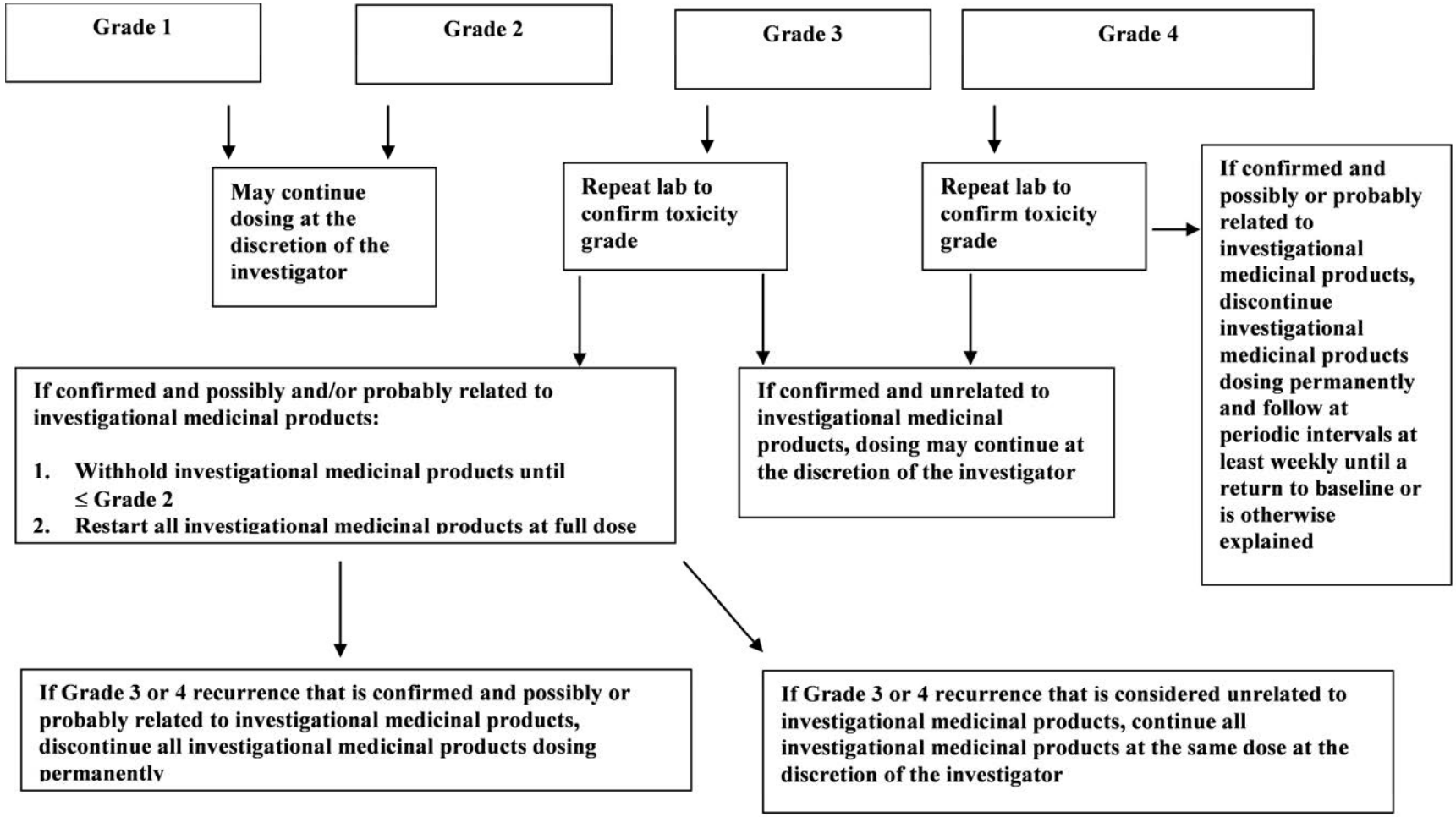
[redacted]

v Subjects failing to achieve at least a 20% improvement from Day 1 in TJC and SJC will discontinue study drugs, but will continue with study visits and assessments

w Subjects failing to maintain at least a 20% improvement from Day 1 in TJC and SJC (confirmed at 2 consecutive visits) will discontinue study drugs, but will continue with study visits and assessments

x Dispensation of study drugs according to IWRS manual.

Appendix 3. Management of Clinical and Laboratory Adverse Events



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

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

http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.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 Methods

The administration of filgotinib in embryo-fetal animal development studies resulted in decreased numbers of viable rat fetuses, increased resorptions, and visceral and skeletal malformations. Similar effects were noted in the rabbit. A safety margin relative to human exposure has not been identified. Pregnancy is contraindicated during use of filgotininb.

For participation in this study, all subjects of childbearing potential must agree to the use of *highly effective* contraception as outlined below.

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 $\geq$ 54 years of age with cessation of previously occurring menses for $\geq$ 12 months without an alternative cause. In addition, women of any age with amenorrhea $\geq$ 12 months may also be considered postmenopausal if their FSH level is in the postmenopausal range at Screening and they are not using hormonal contraception or hormonal replacement therapy. `

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

b) Definition of Male Fertility

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

2) Contraception for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

Filgotinib is contraindicated in pregnancy as there is a possibility of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data. 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, clinically relevant drug-drug interactions between hormonally-based contraceptives and filgotinib or its active metabolite GS-829845 are not expected. In vitro studies in HepaRG cells using reference substrates indicate that filgotinib and GS-829845 do not induce CYP1A2, CYP2B6, or CYP3A4, enzymes involved in metabolism of common hormonal contraceptives. Preliminary results using primary human hepatocytes also confirmed that filgotinib and GS-829845 did not induce mRNA expression of CYP1A2, CYP2B6, or CYP3A4. The lack of induction potential of filgotinib and GS-829845 on CYP3A4 was further confirmed in a clinical drug-drug interaction study, where multiple dose administration of 200 mg filgotinib did not affect the pharmacokinetics of midazolam (a prototypical in vivo probe CYP3A4 substrate). Additionally, clinically relevant inhibition of CYPs or UGTs during filgotinib treatment is unlikely, based on in vitro data.

Based on the totality of the in vitro and clinical data, clinically relevant drug interactions between filgotinib or GS-829845 with hormonal contraceptives are not expected. For female subjects, hormonal contraceptives will be permitted as a form of contraception when used in conjunction with a barrier method (preferably male condom). For male subjects, male condom should be used; for their female partners of childbearing potential, an accepted contraceptive method should also be considered. Details are outlined below.

Please refer to the latest version of the filgotinib investigator's brochure for additional information.

b) Contraception for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. Women must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on the Baseline/Day 1 visit prior to randomization. Pregnancy tests will be performed at monthly intervals thereafter. In the event of a delayed menstrual period (> one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is true even for women of childbearing potential with infrequent or irregular periods. Female subjects must agree to use one of the following methods 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, with documentation of sperm-free ejaculate)

These above described methods are considered *preferred methods* of highly effective contraception in this protocol.

Female subjects who wish to use a hormonally based method must agree to use it in conjunction with a barrier method (used either by the female subject or by her male partner). Female subjects who utilize a hormonal contraceptive as one of their birth control methods must have consistently used the same method for at least three months prior to study dosing. Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (subject must agree to use with a barrier method, preferably, with a male condom)
  - — Oral contraceptives (either combined estrogen/progestin or progesterone only)
  - — Injectable progesterone
  - — Implants of levonorgestrel
  - — Transdermal contraceptive patch
  - — Contraceptive vaginal ring
- Barrier methods (subject must agree to use with a hormonal method)
  - — Male or female condom, with or without spermicide
  - — Diaphragm with spermicide
  - — Cervical cap with spermicide
  - — Sponge with spermicide

All female subjects must also agree to refrain from egg donation and in vitro fertilization during study participation and for at least 35 days after the last study drug dose.

3) Contraception for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure to the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must agree to use condoms during study participation and for 90 days after the last study drug dose. Female partners of male study subjects should consider using one of the above methods of contraception as well. Male subjects must also agree to refrain from sperm donation during treatment and until at least 90 days after the end of dosing.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator 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 are to report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the dosing period through 35 days after their last dose of study drug. During the dosing period when study visits are every 6-8 weeks, the subject will be provided with home urine pregnancy tests, and will be contacted every 4 weeks to report results of the urine pregnancy tests. If a positive urine pregnancy test is reported, the subject will be asked to return to the clinic for a confirmatory serum pregnancy test.

Appendix 6. Laboratory Assessment Table

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count Red blood cell indices White blood cell (WBC) count Differentials (absolute and percentage), including: Leukocytes Monocytes Neutrophils Eosinophils Basophils Mean corpuscular volume (MCV)	Alkaline phosphatase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyl transpeptidase (GGT) Total bilirubin Direct and indirect bilirubin Total protein Albumin Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride CPK Serum creatinine Glucose Phosphorus Magnesium Potassium Sodium Amylase Lipase Uric Acid (screening) <u>Lipid profile (fasting)</u>: Triglycerides Cholesterol and its subfractions (high-density lipoprotein [HDL] and low-density lipoprotein [LDL])	Appearance Blood Color Glucose Leukocyte esterase Nitrites pH Protein Specific gravity Urobilinogen Reflex to microscopic urinalysis if dipstick result is abnormal.	Urine drug screen for: Amphetamines Cocaine Methadone Opiates vfPBMC* Leucocyte subsets* C-reactive protein (hsCRP) Rheumatoid factor and anti-cyclic citrullinated peptide (RF/ Anti-CCP) QuantiFERON- TB GOLD Quantitative Ig subclasses at Screening, Week 24 and Week 52
Endocrine (At Screening Only)		**Serology**	**Pregnancy**
Hemoglobin A1c TSH FSH (for women only)		Hepatitis BsAg and core Ab (if positive core Ab, then reflex Hep B DNA) Hepatitis C Ab (if positive then reflex HCV RNA) HIV	*In females of childbearing potential:* Serum β-hCG (Screening and if positive urine β-hCG) Urine β-hCG (all other visits)†

* vfPBMC and Leukocyte subsets US and Canada only.

† During the periods where visits are every 6-8 weeks, women should continue to have monthly home pregnancy tests performed at home. The site will call the subject every 4 weeks to obtain results of these pregnancy tests.

Appendix 7. List of Joints to be Evaluated (66/68 Joint Count)

An overview of the joints assessed is provided below (left and right):

- Temporomandibular
- Sternoclavicular
- Acromioclavicular
- Shoulder
- Elbow
- Wrist
- Metacarpophalangeal: first, second, third, fourth, fifth
- Proximal interphalangeal: first, second, third, fourth, fifth
- Distal interphalangeal: second, third, fourth, fifth
- Hip[2]
- Knee
- Ankle
- Tarsus
- Metatarsophalangeal: first, second, third, fourth, fifth
- Proximal interphalangeal (toe) : first, second, third, fourth, fifth

Replaced (or otherwise not assessable) joints should be documented at screening and omitted from further evaluation during the study.

[2] Assessed for tenderness only

Appendix 8. 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 upper limit of normal (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 (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Appendix 9. American College of Rheumatology Response Evaluations/ Preliminary Definition of Improvement in Rheumatoid Arthritis {Felson et al 1995}

ACR 20 Required

≥20% improvement in tender joint count, AND
≥ 20% improvement in swollen joint count, AND

≥ 20% improvement in at least 3 of the following 5 items:

- Patient pain assessment
- Patient global assessment of disease activity
- Physician global assessment of disease activity
- Patient's assessment of physical function (HAQ-DI)
- Acute-phase reactant (CRP)

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

1. Tender joint count

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

2. Swollen joint count

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

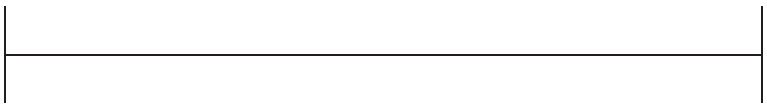
3. Patient's assessment of pain

The pain score from the HAQ-DI will be used to calculate ACR response.

4. Patient's global assessment of disease activity

A horizontal, visual analog scale will be used to provide the patient's overall assessment of how the arthritis is doing.

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



No arthritis **Severe arthritis**

5. Physician's global assessment of disease activity

A horizontal visual analog scale 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 patient's self-assessment of physical function.

7. Acute-phase reactant value

C-reactive protein level as measured at the central laboratory

Appendix 10. Disease Activity Score (DAS28) {Prevoo et al 1995}

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

- DAS28-CRP = $0.56\sqrt{TJC28} + 0.28\sqrt{SJC28} + 0.36\ln(CRP + 1) + 0.014(\textit{patients global VAS}) + 0.96$
- TJC28 = number of joints tender out of 28
- SJC28 = number of joints swollen out of 28
- CRP = C-reactive protein
- Patient global VAS as defined in Appendix 9

Appendix 11. Procedures and Specifications

Complete Physical Examination

A complete physical examination should 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; and neurological. .

Blood Pressure

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 be resting 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.

Creatinine Clearance

Creatinine clearance is calculated by the Cockcroft-Gault equation {Cockcroft et al 1976} using actual body weight (BW).

Male: $$CL_{cr}\ (mL/min) = \frac{[140 - age\ (years)] \times BW(kg)}{72 \times S_{cr}}$$

Female: $$CL_{cr}\ (mL/min) = \frac{[140 - age\ (years)] \times BW(kg) \times 0.85}{72 \times S_{cr}}$$

S_{cr} = serum creatinine (mg/dL)

12-Lead ECG

Subjects should be resting 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 Screening as part of routine safety monitoring.