A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PHASE 3 STUDY TO DEMONSTRATE NON-INFERIORITY FOR THE EFFICACY OF A ONCE DAILY DOSE OF TOFACITINIB MODIFIED RELEASE TABLET TO A TWICE DAILY DOSE OF THE IMMEDIATE RELEASE TABLET IN ADULT PATIENTS WITH RHEUMATOID ARTHRITIS ON BACKGROUND METHOTREXATE

Compound:	CP-690,550
Compound Name:	Tofacitinib citrate
United States (US) Investigational New Drug (IND) Number:	N/A
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[redacted]

Document History

Document	Version Date	Summary of Changes
Amendment 3	13-Aug-2015	Added "X" at visit 3 and 4 in Dispense Dosing Diary of the schedule of activities table and added Dispense Dosing Diary to Visits 3 and 4 in Procedures section Updated and corrected the description for mode of action of tofacitinib in section 1.1. Updated the descriptions for background information of Tofacitinib in section 1.2 Added "a history of, or current evidence for, severe gastrointestinal narrowing (pathologic or iatrogenic)" as a new exclusion criterion (#12) Added "or other methods that yield results comparable to the Westergren method" for ESR measurement in inclusion criteria #6-b Added description for washout period of other investigational drugs in exclusion criterion #23 and section 5.8.3 Corrected description of footnote in table 3 in accordance to Japan package insert of leflunomide Corrected definition of the difference between arms in primary endpoint to in section 9.2.1 and 9.2.2 Added the Gastrointestinal Perforation Review Committee (GIPRC) in list of abbreviations and section 9.6 Updated descriptions in section 8 and 15 to align with latest protocol template Corrected some typos and inadequate descriptions
Amendment 2	30-Oct-2014	Added the chest CT scan as screening procedure in schedule of activities. Added the chest CT scan as screening procedure in inclusion criterion 13. Added the chest CT scan as screening procedure in

		exclusion criterion 2. Added the subjects who have previously received other JAK3 inhibitors treatment in exclusion criterion 21. Added the chest CT scan as screening procedure in Section 6.1. Added the chest CT scan as screening procedure in Section 7.2.5. Modified the current guideline in Appendix 10.
Amendment 1	16-Sep-2014	Modified the abbreviations. Added the IWRS in Section 5.1 and 5.2. Modified the information recorded in Table 1. Modified the criteria of fasting and deleted the rule of re-screening in Section 6.1. Deleted additional biospecimens for exploratory analyses in Section 7.3.1. Modified the criteria of retesting in Section 7.5. Added the biopsy criteria in Appendix 11.
Original protocol	12-Aug-2014	Not Applicable (N/A)

ABBREVIATIONS

This is a list of abbreviations that may or may not be used in the protocol.

Abbreviation	Term
ACR	American College of Rheumatology
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AS	ankylosing spondylitis
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time profile
AUC_{inf}	area under the plasma concentration- time profile from time zero extrapolated to infinite time
BCG	Bacille Calmette Guérin
BE	bioequivalence
BID	twice daily
C_{av}	average concentration
CD	Crohn's disease
CFP	culture filtrate protein
CHD	coronary heart disease
CIs	confidence intervals
CK	creatine kinase
C_{max}	peak plasma concentration
$C_{max,adj}$	dose adjusted maximum concentration
C_{min}	trough concentration
CRF	case report form
CRP	C-reactive protein
CSA	clinical study agreement
CT	computed tomography
CV	cardiovascular
CV EAC	Cardiovascular Endpoint Adjudication Committee
CYP	cytochrome
DAS	Disease Activity Score
DMARD	Disease Modifying Antirheumatic Drug
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EBV	Epstein Barr Virus
EC	ethics committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
ELISA	Enzyme-Linked Immunosorbent Assay
EQ-5D	European Quality of Life - 5 dimensions questionnaire
EOS	end of study
ESAT	early secretory antigenic target

ESR	erythrocyte sedimentation rate
ET	early termination
EudraCT	European Clinical Trials Database
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	full analysis set
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GIPRC	Gastrointestinal Perforation Review Committee
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL	high density lipoprotein
HEENT	head, eyes, ears, nose and throat
HERC	Hepatic Event Review Committee
HIV	human immunodeficiency virus
IB	investigator's brochure
IC_{50}	concentration required to produce 50% of the maximum effect
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IFN	interferon
IL	interleukin
ILD	Interstitial Lung Disease
ILDRC	Interstitial Lung Disease Review Committee
INR	international normalized ratio
IP	interphalangeal
IR	immediate release
IRB	institutional review board
IU	international unit
IUD	intrauterine device
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
JAK	Janus Kinase
JAS	Japan Atherosclerosis Society
LCAP	leukocytapheresis

LDA	low disease activity
LDL	low density lipoprotein
LFT	liver function test
LOCF	last observation carried forward
LPD	lymphoproliferative disorder
LSLV	last subject last visit
MAC	Malignancy Adjudication Committee
MCP	metacarpophalangeal
MMRM	mixed effect model with repeated measures
MR	modified release
MTP	metatarsophalangeal
MTX	methotrexate
N/A	not applicable
NIL	spot count in the negative
NMSC	non-melanoma skin cancer
NRI	non-responder imputation
NSAID	non-steroidal anti-inflammatory drug
OI	opportunistic infection
OIRC	Opportunistic Infection Review Committee
PA	posteroanterior
PCD	primary completion date
PCP	pneumocystis pneumonia
PCR	polymerase chain reaction
PGx	pharmacogenomics
PIP	proximal interphalangeal
pIPD	potentially important protocol deviation
PK	pharmacokinetics
PPD	purified protein derivative
PRO	patient reported outcome
PsA	psoriatic arthritis
PsO	psoriasis
PT	prothrombin time
PtGA	patient's global assessment of health
QD	once daily
QFT	Quantiferon 3G/QuantiFERON®-TB
RA	rheumatoid arthritis
RANKL	receptor activator of nuclear factor kappa-β ligand
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SF-36	Short Form 36 Health Survey
SGOT	serum glutamic-oxaloacetic transferase
SGPT	serum glutamic-pyruvic transferase
SIB	suicidal ideation and behavior
SJC	swollen joint count
SOA	schedule of activities

SRSD	single reference safety document
SSID	study subject identification
TB	tuberculosis
TJC	tender joint count
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
TyK2	tyrosine kinase 2
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VZV	varicella-zoster virus
WBC	white blood cell

PROTOCOL SUMMARY

BACKGROUND AND RATIONALE

Tofacitinib is a potent, selective inhibitor of the Janus Kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome. The immediate release (IR) formulation of tofacitinib has been approved for the treatment of rheumatoid arthritis (RA) as a twice daily (BID) regimen. Tofacitinib is being developed for the treatment of psoriasis (PsO, oral and topical), spondylarthropathies (ankylosing spondylitis [AS] and psoriatic arthritis [PsA]) and inflammatory bowel disease (Crohn's disease [CD] and ulcerative colitis [UC]).

The modified release (MR) formulation of tofacitinib is being studied as a disease-modifying antirheumatic drug (DMARD) for the once daily (QD) treatment of RA. The MR QD regimen has the potential to improve drug compliance of patients, patient convenience, and to offer additional dosing options for patients.

This study will seek to compare the efficacy and safety of the MR 11 mg QD regimen to the IR 5 mg BID regimen for the treatment of RA.

OBJECTIVES AND ENDPOINTS

Objectives

Primary Objective

1. To demonstrate the non-inferiority for efficacy of tofacitinib MR 11 mg QD to IR 5 mg BID for the treatment of signs and symptoms in patients with active RA on a stable background of methotrexate (MTX), as measured by Disease Activity Score 28-4 (C-reactive protein) [DAS28-4(CRP)] change from Baseline at Week 12.

Secondary Objectives

1. To evaluate the similarity in efficacy of tofacitinib MR 11 mg QD and IR 5 mg BID for the treatment of signs and symptoms of RA, as measured by DAS28-4 erythrocyte sedimentation rate (ESR) change from Baseline, American College of Rheumatology 20% improvement (ACR20), ACR50, ACR70 responses, remission, and Low Disease Activity (LDA), at Week 12.

2. To evaluate the similarity in efficacy of tofacitinib MR 11 mg QD and IR 5 mg BID for physical function status as measured by health assessment questionnaire-disability index (HAQ-DI) change from Baseline at Week 12.

3. To evaluate the similarity in effects on patient's health outcome measures (change from Baseline in short form 36 health survey (SF-36), functional assessment of chronic illness therapy (FACIT) fatigue and euro quality of life-5 dimensions questionnaire [EQ-5D]) of tofacitinib MR 11 mg QD and IR 5 mg BID at Week 12.

4. To evaluate the safety and tolerability of tofacitinib MR 11 mg QD in comparison with IR 5 mg BID in patients.

Other Objectives

The efficacy and health outcome objectives will also be evaluated at other post-Baseline visits.

Endpoints

Efficacy Endpoints

Primary Efficacy Endpoint

- Change from Baseline in DAS28-4(CRP) at Week 12.

Secondary Efficacy Endpoints

- Change from Baseline in DAS28-4(ESR) at Week 12.
- ACR20, ACR50 and ACR70 response at Week 12.
- Remission at Week 12, as assessed by: DAS28-4(CRP) < 2.6 and DAS28-4(ESR) < 2.6.
- LDA at Week 12, as assessed by: DAS28-4(CRP) ≤ 3.2 and DAS28-4(ESR) ≤ 3.2.
- Change from Baseline in HAQ-DI at Week 12.
- HAQ-DI response (decrease of at least 0.22) at Week 12.
- Change from Baseline in the SF-36 8 domain scores and 2 component scores at Week 12.
- Change from Baseline in the FACIT-Fatigue scale at Week 12.
- Change from Baseline in the EQ-5D at Week 12.

Other Efficacy Endpoints

Primary and secondary efficacy endpoints at other selected post-baseline scheduled visits.

Safety Endpoints

All the safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations, including:

- All adverse events (AEs), including serious adverse events (SAEs).
- Clinically significant abnormal laboratory parameters.

STUDY DESIGN

This is a multicenter, randomized, double blind, parallel group, phase 3 study to evaluate efficacy and safety of tofacitinib MR 11 mg QD tablet compared to IR 5 mg BID tablet

following 12 weeks treatment in patients with moderate to severe active RA on a stable background of MTX.

Subjects will be randomized in a 1:1 ratio for the 2 treatment arms with a total sample size of approximately 200 subjects; there will be approximately 100 subjects randomized into the 11 mg MR QD group and approximately 100 patients into the 5 mg IR BID group.

STUDY TREATMENTS

All subjects will be randomly assigned to one of two active treatment arms in the study:

- Tofacitinib 11 mg MR QD
- Tofacitinib 5 mg IR BID

STATISTICAL METHOD

The primary efficacy endpoint, DAS28-4(CRP), will be expressed as a change from Baseline. The analysis will be conducted using a linear mixed effect model with repeated measures (MMRM), which will include baseline as a covariate, treatment, visit (week 4 and 12), and treatment by visit interaction as fixed effects. Subjects will be a random effect and unstructured covariance will be assumed. The estimate of treatment difference and the associated 2-sided 95% confidence interval (type-I error [alpha] of 0.025 in each tail) at the primary time point of week 12 will be made from this model. Non-inferiority of tofacitinib MR 11 mg QD to IR 5 mg BID will be concluded if the lower bound of the 2-sided 95% confidence interval is greater than the pre-specified non-inferiority margin of −0.6.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Identifier		Visits				
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
		Screening	Baseline Day 1	Week 4	Week 8	Week 12 (EOS/ET) [1]
Study Day		−27	1	29	57	85
Visit Window (Days)		+7 (i.e. −34 to 0)	0	±3	±3	±3
Informed Consent		X				
Medical History [2]		X				
Prior treatments/medications		X				
Concomitant treatments/ medications		X	→	→	→	X
Inclusion/Exclusion criteria		X	X			
Complete Physical Examination [3]		X				
Targeted Physical Examination [3]			X	X		X
Vital Signs, Temperature [4]		X	X	X		X
Whole blood interferon (IFN)-γ release assay (Quantiferon-3G/QuantiFERON®-TB Gold In-Tube or T-SPOT) [5]		X				
12-lead Electrocardiogram		X				
Chest X-ray(posteroanterior (PA) and lateral) or chest computed tomography (CT) scan [6]		X				
Blood/Urine	Rheumatoid Factor	X				
	Hematology [7], Chemistry Panel [8]	X	X	X		X
	Lipid Profile (fasting) [9]	X	X	X		X
	Serum Pregnancy Test (β -HCG) [10]	X				
	Urine Pregnancy Test (β-HCG) [11]		X	X		X
	Urinalysis [11]	X	X	X		X
	Serum β-D-glucan and KL-6	X				
	HIV Serology	X				
	HBsAg, HBcAb, HBsAb, HBV DNA testing (if necessary)[12]	X				
	HCV Ab, HCV RNA PCR (if HCV Ab positive)	X				
	Varicella-Zoster Virus (VZV)	X				
	Lymphocyte subset markers [13]		X	X		X
	Banked biospecimens (PGx sampling)		X			
ACR/ DAS	C-Reactive Protein (CRP)	X	X	X		X
	Erythrocyte Sedimentation Rate (ESR)	X	X	X		X
	Joint assessment:Tender/Painful Joint Count: (68 joints), Swollen Joint Count (66 joints)	X	X	X		X
	Patient Assessment of Arthritis Pain (VAS)		X	X		X
	Patient Global Assessment (VAS)		X	X		X
	Physician Global Assessment (VAS)		X	X		X
	Health Assessment Questionnaire - Disability Index (HAQ-DI)		X	X		X
SF-36 (Version 2, Acute)			X	X		X

Visit Identifier	Visits				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening	Baseline Day 1	Week 4	Week 8	Week 12 (EOS/ET) [1]
Study Day	−27	1	29	57	85
Visit Window (Days)	+7 (i.e. −34 to 0)	0	±3	±3	±3
FACIT- Fatigue Scale		X			X
Euro Quality of Life Questionnaire (EQ-5D)		X			X
Randomization		X			
Study Drug Dispensing-New bottles supplied		X	X	X	
Dispense Dosing Diary		X	X	X	
Drug Accountability			X	X	X
Review of subject Dosing Diary			X	X	X
Adverse Events		X	→	→	X

1. Study procedures to be performed at the End of Study (EOS) or Early Termination (ET) Visit.
2. Medical history includes previous vaccination history, smoking status, average weekly alcohol consumption, family history of premature coronary heart disease (CHD), history of any prior episodes of herpes zoster and confirmation of RA diagnosis.
3. Complete physical exam includes height, weight, general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (peripheral edema), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes.

   Targeted physical exam includes weight, examination of heart, lungs, lower extremities for peripheral edema, abdomen and lymph nodes.
4. Temperature will be collected as axillary temperature. The same method should be used throughout the study.
5. Mantoux Purified Protein Derivative (PPD) tuberculin skin test will be allowed, if there are two consecutive indeterminate results of QFT-G or T-SPOT test in subjects who have not received Bacille Calmette Guérin (BCG) vaccination during screening period.
6. Chest X-ray (PA and lateral) or chest CT scan (with or without IV contrast) must be obtained at screening or within 12 weeks prior to screening and read by a qualified radiologist or respiratologist. If necessary, a chest CT scan (with or without IV contrast) may be performed during screening following initial performance of chest radiographs (PA and lateral) at the clinical discretion of the investigator. If pulmonary signs and symptoms are observed at and after baseline visit, unscheduled imaging test (e.g. chest X-ray or chest CT scan) may be performed based on the judgment by investigator as appropriate.
7. Hematology includes hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential and platelet count.
8. Chemistry Panel includes blood urea nitrogen, creatinine, glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), albumin, creatine kinase (CK).
9. Lipid Profile includes total cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides under fasting condition.
10. Serum pregnancy test for women of childbearing potential only.
11. Dipstick in all cases; urinalysis includes specific gravity, pH, protein, glucose, ketones, blood, nitrite, leukocyte esterase and urine sediment (microscopy). Urine culture is performed if clinically indicated. Urine pregnancy test (β-HCG) is required only for women who are of childbearing potential; may be repeated more frequently if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected.
12. HBV DNA assay may be required for a subset of subjects with specified serological test results (refer to Appendix 5)
13. Lymphocyte subset markers include CD3+, CD3−CD19+, CD3+CD4+CD8−, CD3+CD4−CD8+, CD3+CD16+CD56+, CD3−CD16+CD56+, CD3−CD16+CD56−, CD3−CD16−CD56+, CD3−CD16−CD56−, CD4/CD8

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APPENDICES

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Tofacitinib, also referred to elsewhere in this protocol as tofacitinib citrate and/or CP-690,550, is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome[1]. In kinase assays, tofacitinib, inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TyK2). In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2 [2]. Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including interleukin (IL)-2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, development, homeostasis, proliferation, and function; therefore, inhibition of their signaling may result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and interferon (IFN)-γ[3,4]. At higher exposures, inhibition of erythropoietin, prolactin, and other hormones can occur via inhibition of JAK2 homodimer signaling.

The immediate release (IR) oral formulation of tofacitinib is approved in the United States (US), Japan and other countries for the treatment of rheumatoid arthritis (RA). In addition, tofacitinib is being developed for the treatment of psoriasis (PsO, oral and topical), spondylarthropathies (ankylosing spondylitis [AS] and psoriatic arthritis [PsA]) and inflammatory bowel disease (Crohn's disease [CD] and ulcerative colitis [UC]).

1.2. Background and Rationale

RA is a chronic, autoimmune disease characterized by joint inflammation and destruction, progressive disability and adverse psychological effects. RA represents significant health and socioeconomic burdens for the individual patient and society[5] and there is currently no cure for RA. The purpose of treatment is to control disease activity, alleviate signs and symptoms, maintain physical function, optimize quality of life, reduce the rate of joint damage, and, if possible, induce complete remission.

Disease-modifying antirheumatic drugs (DMARDs) partially fulfill these goals; but often fall short of adequate minimization or prevention of progressive joint damage and optimization of quality of life. In addition, these DMARDs are frequently associated with clinical tolerability and safety issues. Biologic agents, such as tumor necrosis factor (TNF) inhibitors (TNFi), are more rapidly efficacious and successfully halt or slow joint damage, especially in combination with methotrexate (MTX). However, use of these agents remains limited due to the inconvenience of the required parenteral routes of administration and apparent loss of initial efficacy with continued use in a significant proportion of patients. Thus, the need exists for additional DMARD options.

Tofacitinib (CP-690,550) is a novel, oral JAK inhibitor for the treatment of RA.

In Phase 2b dose-ranging studies that evaluated a dose range of 1-15 mg twice daily (BID), tofacitinib demonstrated sustained efficacy and manageable safety over 24 weeks in patients with active RA when used as monotherapy [6] or in combination with background MTX [7]. Tofacitinib IR 5 and 10 mg BID were selected as optimal doses for

evaluation in Phase 3, which includes a broad range of therapeutic scenarios investigating tofacitinib as monotherapy[8] or in combination with MTX [9,10] and non-MTX, nonbiologic DMARDs [11].

The Phase 3 studies demonstrated sustained efficacy and manageable safety up to 2 years in patients with active RA. Long-term extension studies have been ongoing since Phase 2 and have enrolled patients who participated in a Phase 2 or Phase 3 study; these open-label studies have demonstrated continued efficacy and a consistent safety profile as seen in the controlled clinical trials. Long-term data collected in these trials was obtained in patients on both 10 and 5 mg BID of tofacitinib.

Tofacitinib is an immunomodulator with important safety risks that include serious and other infections including tuberculosis and herpes zoster infections, and potential for malignancies including lymphoma, and potential for gastrointestinal (GI) perforations. Patients receiving tofacitinib may be at increased risk of nonmelanoma skin cancer (NMSC). Cardiovascular disease and interstitial lung disease (ILD) are findings seen in RA patients receiving tofacitinib, and are recognized comorbidities for RA as well as being associated with other RA therapies.

Changes in laboratory values have also been observed with oral tofacitinib including a dose-dependent increase in low density lipoprotein (LDL) cholesterol and dose–dependent decreases in neutrophils and hemoglobin. Other laboratory changes observed with oral tofacitinib treatment include decreases in lymphocytes and increases in transaminases, serum creatinine, and creatine kinase (CK). Laboratory changes observed with oral tofacitinib treatment are monitorable and manageable and recovery of laboratory changes upon discontinuation of oral tofacitinib treatment is characteristically observed.

Currently tofacitinib is administered as an immediate release (IR) tablet formulation twice daily (BID). A once daily (QD) formulation will enhance ease of clinical use and patient convenience. The modified release (MR) formulation administered QD has been designed to offer equivalent area under the plasma concentration-time curve (AUC), and similar maximum plasma concentration (C_{max}) and minimum plasma concentration (C_{min}) as the IR formulation administered BID; therefore, it is expected that the MR formulation will maintain comparable efficacy and consistent safety as that observed for the IR formulation.

The data from the pharmacokinetics (PK) studies conducted to date have indicated that the MR formulation of tofacitinib is similar to the IR formulation based on key exposure parameters such as area under the plasma concentration-time profile (AUC), average concentration (C_{av}), peak plasma concentration (C_{max}) and Time above JAK1/3 concentration required to produce 50% of the maximum effect (IC_{50}) in both Asian and Western healthy subjects.

Study A3921163, a randomized, 2-period crossover, single dose, fasted study (N=26, healthy Westerners), evaluated the single dose bioequivalence (BE) of the MR 11 mg tablet and the IR 10 mg (5 mg tablet ×2). Results from A3921163 demonstrated that ratio of the geometric means (MR 11 mg/IR 10 mg [5 mg tablet ×2]) for AUC_{inf} was 103.89% and the 90% confidence intervals (CIs) for AUC_{inf} were (100.46%, 107.44%); the 90% CIs were completely contained within the 80-125% BE acceptance limits indicating that

the MR 11 mg tablet and the IR 10 mg (5 mg tablet ×2) are equivalent. The ratio of geometric means (MR 11 mg/IR 10 mg [5 mg tablet ×2]) for dose adjusted maximam concentration ($C_{max, adj}$), comparing the observed peak exposure for MR 11 mg to the expected peak exposure for a single IR 5 mg dose (half of the observed C_{max} for IR 10 mg), was 92.44% and the 90% CIs were (85.03%, 100.50%); the 90% CIs for $C_{max, adj}$ were also contained within the 80% to 125% interval. A single dose of the MR tablet was found to be safe and well tolerated in this study.

A consistent daily coverage for inhibition of JAK1/3 may be required to preserve the effectiveness of tofacitinib. As a result of simulation utilizing the single dose PK data from Study A3921163, Time above JAK1/3 IC_{50} for the MR 11 mg tablet administered QD was predicted to be similar compared to the IR 5 mg tablet administered BID, suggesting the possibility of similar efficacy and safety between the MR tablet QD and IR tablet BID. Additionally, AUC, C_{av}, C_{max} and trough concentration (C_{min}) were predicted to be similar to the IR tablet BID.

Study A3921215 is a Phase 3, three month, randomized, double blind, parallel group, multicenter study that seeks to demonstrate non inferiority for the efficacy of tofacitinib MR 11 mg QD compared to IR 5 mg BID in adult Japanese patients with RA on stable background methotrexate.

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the investigators brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary objective

1. To demonstrate the non-inferiority for efficacy of tofacitinib MR 11 mg QD to IR 5 mg BID for the treatment of signs and symptoms in patients with active RA on a stable background of MTX, as measured by DAS28-4(CRP) change from Baseline at Week 12.

2.1.2. Secondary objectives

1. To evaluate the similarity in efficacy of tofacitinib MR 11 mg QD and IR 5 mg BID for the treatment of signs and symptoms of RA, as measured by DAS28-4(ESR) change from Baseline, ACR20, ACR50, ACR70 responses, remission, and LDA, at Week 12.

2. To evaluate the similarity in efficacy of tofacitinib MR 11 mg QD and IR 5 mg BID for physical function status as measured by HAQ-DI change from Baseline at Week 12.

3. To evaluate the similarity in effects on patient's health outcome measures (change from Baseline in SF-36, FACIT Fatigue and EQ-5D) of tofacitinib MR 11 mg QD and IR 5 mg BID at Week 12.

4. To evaluate the safety and tolerability of tofacitinib MR 11 mg QD in comparison with IR 5 mg BID in patients.

2.1.3. Other Objectives

The efficacy and health outcome objectives will also be evaluated at other post-Baseline visits.

2.2. Endpoints

2.2.1. Efficacy Endpoints

2.2.1.1. Primary Efficacy Endpoint

- Change from Baseline in DAS28-4(CRP) at Week 12.

2.2.1.2. Secondary Efficacy Endpoints

- Change from Baseline in DAS28-4(ESR) at Week 12.
- ACR20, ACR50 and ACR70 response at Week 12.
- Remission at Week 12, as assessed by: DAS28-4(CRP) < 2.6 and DAS28-4(ESR) < 2.6.
- LDA at Week 12, as assessed by: DAS28-4(CRP) ≤ 3.2 and DAS28-4(ESR) ≤ 3.2.
- Change from Baseline in HAQ-DI at Week 12.
- HAQ-DI response (decrease of at least 0.22) at Week 12.
- Change from Baseline in the SF-36 8 domain scores and 2 component scores at Week 12.
- Change from Baseline in the FACIT-Fatigue scale at Week 12.
- Change from Baseline in the EQ-5D at Week 12.

2.2.1.3. Other Efficacy Endpoints

Primary and secondary efficacy endpoints at other selected post-baseline scheduled visits.

2.2.2. Safety Endpoints

All the safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations, including:

- All adverse events (AEs), including serious adverse events (SAEs).
- Clinically significant abnormal laboratory parameters.

3. STUDY DESIGN

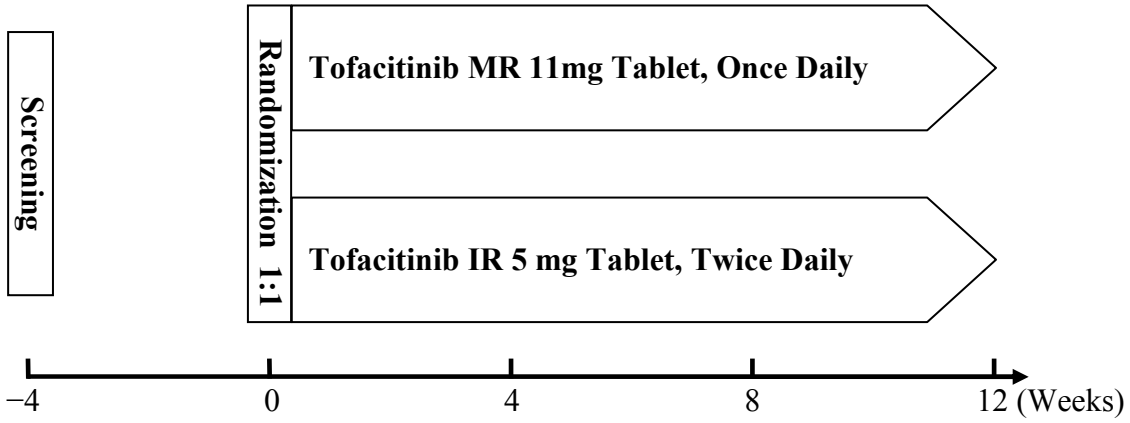
This is a multicenter, randomized, double blind, parallel group, phase 3 study to evaluate efficacy and safety of tofacitinib MR 11 mg QD tablet compared to IR 5 mg BID tablet at 12 weeks treatment in patients with active RA on a stable background MTX.

Subjects will be randomized in a 1:1 ratio for the 2 treatment arms with a total sample size of approximately 200 subjects; there will be approximately 100 subjects randomized into the 11 mg MR QD group and approximately 100 patients into the 5 mg IR BID group.

The study design schematic for the study is represented in Figure 1.

Figure 1. Study Design

Approximately 100 per arm, N=200



4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Subjects must be 20 years of age or older at time of informed consent.

4. Subjects must meet the American Rheumatism Association 1987 revised criteria for classification of RA at least 6 months prior to screening (refer to Appendix 1). This information must be documented in the subject's source documents.

5. Subjects must have active disease **at both screening and baseline,** as defined by having both:

    a. ≥6 tender/painful joints on motion (from 68 joints assessed); ***and;***

    b. ≥6 swollen joints (from 66 joints assessed).

6. Subjects must also have active disease, as defined by one of the following criteria at screening:

    a. CRP >0.7 mg/dL in the central laboratory; ***or;***

    b. ESR (Westergren method or other methods that yield results comparable to the Westergren method) >28 mm/hr.

7. Subjects must meet Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA at screening (refer to Appendix 2).

8. Subjects must be receiving ongoing treatment with MTX and folic acid as described below.

    - Subjects must have taken oral MTX continuously for at least 4 months prior to the first dose of study medication (baseline visit) and be on a stable dose of 6.0 mg to 16 mg weekly, for at least 6 weeks prior to baseline visit.

    - Subjects should be on an adequate and stable dose of folic acid or folinic acid for at least 4 weeks prior to baseline visit. The doses of folic acid or folinic acid are according to local standard of care.

9. Subjects must have discontinued all prohibited concomitant medications for the required time prior to baseline visit (refer to section 5.8.3 and Appendix 3).

10. Subjects receiving non-prohibited concomitant medications for any reason must be on a stable regimen, which is defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever is longer) prior to baseline visit, or as defined in Concomitant Medications (refer to section 5.8.1 and 5.8.2).

11. Female subjects of childbearing potential must have negative pregnancy test results at screening and baseline visit.

12. Female subjects who are not of childbearing potential (ie, meet at least 1 of the following criteria):

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    - Have medically confirmed ovarian failure; or

    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or

physiological cause; a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

13. No evidence of active or latent or inadequately treated infection with *mycobacterium tuberculosis* (TB) as defined by meeting both criteria "a" and "b" below:

    a. Chest radiographs (PA and lateral) or chest CT scan (with or without IV contrast), taken at or within 12 weeks prior to screening visit, without changes suggestive of active TB infection as determined by a qualified radiologist or a respirologist. If necessary, a chest CT scan (with or without IV contrast) may be performed during screening following initial performance of chest radiographs (PA and lateral) at the clinical discretion of the investigator.

    b. Subjects who correspond to any of the following

        1) A negative test for blood IFN-γrelease assay, i.e. Quantiferon-3G/QuantiFERON® TB Gold In-tube (QFT-G) or T-SPOT test, performed at or within 12 weeks prior to screening visit.

            Note 1)
            Subjects with a history of *Bacille Calmette Guérin* (BCG) vaccination **MUST** be tested with the blood IFN-γ release assay.

            Note 2)
            In subjects who didn't receive BCG vaccination, if there are two consecutive indeterminate results of QFT-G or T-SPOT test, a Mantoux/ Purified Protein Derivative (PPD) tuberculin skin test will be allowed during screening period. A negative Mantoux/PPD tuberculin skin test result is required to meet the inclusion criterion.

            Note 3)
            In subjects who have previously received an adequate course of therapy for either latent (6-9 months of isoniazid or an acceptable alternative regimen) or active (acceptable multi drug regimen) TB infection, neither a QFT-G or T-SPOT test nor a PPD test need be obtained. Documentation of adequate treatment for active and/or latent TB will be obtained prior to baseline visit.

        2) Subjects who are currently being treated for latent TB infection can only be enrolled with documentation of an adequate treatment regimen and with prior approval by the sponsor.

            Note 1)
            In this study, latent TB is defined to meet all following conditions:

            - A positive result of blood IFN-γ release assay or PPD skin test performed at or within 12 weeks prior to screening visit, AND

- Without any changes suggestive of active TB or old TB infection on the chest radiograph or chest CT scan evaluated by a qualified radiologist or a respirologist, AND
- Without clinical signs or symptoms suggestive of active TB, AND
- Without history of previously treated active or latent TB

Note 2)
Adequate treatment regimens for latent TB is defined to meet following conditions.

- At least 4 weeks of treatment with isoniazid or an acceptable alternative regimen must be completed prior to randomization, and the treatment with isoniazid or an acceptable alternative regimen for latent TB must continue for 9 months or appropriate period.

If at least 4 weeks of treatment with isoniazid or an acceptable alternative regimen for latent TB is not completed prior to randomization, the subject is to be a screening failure. If the subject is still willing to participate to this study, the screening procedures must be repeated (and meet the eligibility criteria) after taking separate informed consent.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Subjects with any of the following laboratory abnormalities:
   a. Hemoglobin < 9 g/dL;
   b. Absolute white blood cell (WBC) count of < 3.0×10^9/L (< 3000/mm^3);
   c. Absolute neutrophil count of < 1.2×10^9/L (< 1200/mm^3);
   d. Absolute lymphocyte count of < 0.75×10^9/L (< 750/mm^3);
   e. Platelet count < 100×10^9/L (< 100,000/mm^3);
   f. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 times the upper limit of normal (× ULN);
   g. Estimated glomerular filtration rate (GFR) <40 mL/min using the Cockcroft-Gault formula (refer to Appendix 4).
2. Current or recent history of uncontrolled clinically significant renal, hepatic, hematological, gastrointestinal, endocrine, metabolic (including uncontrolled clinically significant hypercholesterolemia), pulmonary, cardiac, or neurological disease. Investigators should carefully evaluate patients who exhibit symptoms, especially fever or cough. If clinical laboratory findings (serum β-D glucan, KL-6)

or findings on the chest radiograph or chest CT scan (taken within 12 weeks prior to screening) are suggestive of serious lung disease, such as interstitial pneumonia, the patient will be excluded from enrollment in this study.

3. History of any other autoimmune rheumatic disease, other than rheumatoid arthritis and Sjogren's syndrome.

4. History of an infected joint prosthesis at any time, with the prosthesis still in situ.

5. History of any lymphoproliferative disorder (LPD), such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.

6. History of recurrent (more than one episode) herpes zoster or disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.

7. History of infection requiring hospitalization, history of infection requiring parenteral antimicrobial therapy, or infection otherwise judged clinically significant by the investigator, within the 6 months prior to baseline visit.

8. History of infection requiring antimicrobial therapy within 2 weeks prior to baseline visit.

9. Any prior treatment with non B cell-specific lymphocyte depleting agents/therapies [e.g., rituximab, alkylating agents (e.g., cyclophosphamide or chlorambucil), total lymphoid irradiation, etc] and leukocytapheresis (LCAP).

10. Subjects who have been vaccinated with live or attenuated vaccines within the 6 weeks prior to baseline visit or are to be vaccinated with these vaccines at any time during treatment and within 6 weeks after the last dose of investigational product.

11. Subjects with any condition possibly affecting oral drug absorption, e.g., gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass. Procedures such as gastric banding, that simply divide the stomach into separate chambers, are NOT exclusionary.

12. Subjects with a history of, or current evidence for, severe gastrointestinal narrowing (pathologic or iatrogenic).

13. Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant; male and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.

14. History of alcohol or drug abuse, unless in full remission for greater than 6 months of abstinence prior to baseline visit.

15. Screening 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities which may affect subject safety or interpretation of study results.

16. Subjects with a first degree relative with a hereditary immunodeficiency.

17. Subjects with a malignancy or with a history of malignancy, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin, cervical carcinoma in situ.

18. Significant trauma or major surgery procedure within 4 weeks prior to baseline visit.

19. Subjects requiring prohibited concomitant medications including prohibited dietary supplements (Refer to Appendix 3).

20. Subjects infected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) (Please refer the detail of HBV screening in Appendix 5).

21. Subjects infected with hepatitis C virus (HCV). Subjects with positive HCV antibodies (HCV Ab) must have further testing for HCV RNA by polymerase chain reaction (PCR). Subjects with detectable HCV RNA will be excluded from the study.

22. Subjects who have previously received tofacitinib or other JAK3 inhibitors treatment including clinical study.

23. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

24. Participation in other clinical studies involving investigational drug(s) (Phases 1-4) within 12 weeks or 5 half-life (whichever is longer), or device(s) within 12 weeks, prior to baseline visit and/or during study participation.

25. Subjects who have an allergy/hypersensitivity to MTX, or previous serious toxicity when administered methotrexate.

26. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4.3. Randomization Criteria

Subjects must complete all screening tests and procedures without evidence of exclusionary conditions and the investigator must attest to the suitability of the subject for inclusion in the study prior to randomizing the subject.

4.4. Lifestyle Guidelines

In order to participate in the study, subjects must be made aware of the following life style guidelines and restrictions that apply during and after the study period. Details of these life style guidelines are provided in sections as noted.

- On study visit days, comply with fasting requirement for at least 9 hours prior to the visit.

- On study visit days, do not smoke or ingest caffeine (e.g., tea, coffee, some soft drinks/ colas and energy drinks) during the 30 minutes prior to blood pressure, pulse rate and ECG measurements.

4.4.1. Non-Pharmacologic Interventions

The subject may continue non-pharmacologic therapies, such as physical therapy, as indicated and deemed appropriate for physical condition. The subject should not initiate new non-pharmacologic therapies or change the currently on-going non-pharmacologic therapies throughout the study period.

4.4.2. Vaccination

4.4.2.1. Household Contact with Others Vaccinated

During the study and for 6 weeks following the last dose of study drug, subjects should avoid routine household contact with children or adults who have been vaccinated with live or attenuated live vaccines in the previous 6 weeks.

Due to these vaccine guidelines, it is recommended that study investigators advise potential subjects to be current with vaccinations before being randomized into the study (note time window per exclusion criteria #10). Subjects may still be vaccinated with killed or inactivated vaccines at any time during the study; however, the adequacy of the immune response to vaccination for subjects taking tofacitinib has not been studied and is not known.The data on the adequacy of the immune response to vaccination for subjects taking tofacitinib are limited.

4.4.3. Diet and Dietary Supplements

It is recommended that subjects avoid consumption of grapefruit or grapefruit juice while in the study.

For the purposes of this protocol, dietary supplements are defined as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties.

Vitamins, minerals and purified food substances are allowed in amounts not known to be associated with adverse effects (such as hypervitaminosis). Herbals with pharmaceutical properties are allowed only if there is acceptable evidence of no potent CYP3A inhibition or induction. Otherwise, herbals with pharmaceutical properties should not be given concurrently with investigational product.

4.4.4. Reproductive Status of Women Subjects and Partners of Male Subjects

All male and female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his/her designee, in consultation with the subject, will confirm the subject has selected the most appropriate method of contraception for the individual subject from the permitted list of contraception methods (refer to below) and instruct the

subject in its consistent and correct use. Subjects need to affirm that they meet at least one of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities (SOA) and document such conversation in the subject's chart. In addition, the investigator or his/her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, or implanted hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

4.5. Surgery

During the course of this study, no elective surgery should be scheduled without first consulting with sponsor. Investigators should contact sponsor regarding subjects who undergo non-elective surgery to discuss their suitability to remain in the study.

4.6. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the coordinator's manual.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems

that may arise during the study. The help desk number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

Study treatments include tofacitinib MR 11 mg QD and IR 5 mg BID, administered orally. All subjects will be randomized to one of the two treatment arms.

5.1. Allocation to Treatment

Subjects will be allocated in accordance with the randomization schedule.

Randomization will be accomplished using interactive web response system (IWRS) /interactive voice response system (IVRS) (an automated web/telephone randomization system provided by the sponsor). The IWRS/IVRS contains the randomization schedule. At the Screening Visit, the investigative site will contact the IWRS/IVRS (online or by telephone call). The site will enroll the subject into the IWRS/IVRS by indicating minimal information sufficient to distinguish one subject from another (e.g., date of birth) and receive the subject identification (ID) number. At the baseline visit, the system will associate that subject with the next available treatment on the randomization schedule and provide the randomization number.

The system will then give the investigative site a code which corresponds to study medication that has been previously shipped to the site and is in the site's inventory ready to be dispensed. This code corresponds to study medication of that treatment group to which the subject has just been randomized.

The site will call the system on visits when study medication is to be dispensed. The randomization schedule allows for overage as such enrollment will be controlled by the IWRS/IVRS and when a sufficient number of subjects have enrolled, the randomization part of the system will be stopped. The part of the system that supplies codes will continue until the last subject randomized has been dispensed the last supply of study medication.

All study medication will be dispensed as appropriate for self-administration by study subjects.

5.2. Breaking the Blind

The study will be subject, investigator, and sponsor-blinded and the process for breaking the blind is outlined below. At the initiation of the study at sites participating in this study, the study site will be instructed on using IWRS/IVRS for breaking the blind. Blinding should only be broken in emergency situations for reasons of subject safety. The investigator should contact the Pfizer study team before breaking the blind. When the blind for a subject has been broken, the reason must be fully documented and entered on the case report form (CRF). At all other times, treatment and randomization information will be kept confidential and will not be released to the investigator/study staff until the conclusion of the study.

5.3. Subject Compliance

Study medication accountability and compliance will be assessed by the site at each clinic visit starting at the visit after the baseline visit (Visit 2) up to Week 12 (Visit 5). Non-compliance is defined as taking less than 80% or more than 120% of study drug products during the double-blind study treatment period and as directed by the dosing instructions. Subjects will record their study drug dosing information in a Subject Dosing Diary.

Subjects are to bring the Subject Dosing Diary and the two bottles of investigational product with any remaining study drug to each visit for review. Upon completion of each visit, the Subject Dosing Diary shall be collected from the subject at the site and stored in the site master file only.

The investigator has the discretion to withdraw any subject from the study for reasons of non-compliance with the dosing regimen. Investigators should indicate on the appropriate CRF page noncompliance with study treatment and provide an explanation.

Inventory control of all study medications must be rigorously maintained throughout the duration of the study until all medication has been accounted for and/or returned to the sponsor. Any discrepancies noted between drug dispensing records and the drug inventory must be reported to Pfizer.

5.4. Drug Supplies

Tofacitinib tablets and matching placebo tablets will be provided by the sponsor and dispensed for oral administration. Sufficient study medication will be dispensed at baseline visit (Visit 2), week 4 visit (Visit 3) and week 8 visit (Visit 4) to complete dosing for the entire study treatment period.

5.4.1. Dosage Form(s) and Packaging

Subjects will be randomized to receive either tofacitinib MR 11 mg QD or tofacitinib IR 5 mg BID. The following medication will be provided by the sponsor and dispensed for oral administration:

- Tofacitinib MR 11 mg tablets
- Placebo tablets to match tofacitinib MR 11 mg tablets
- Tofacitinib IR 5 mg tablets
- Placebo tablets to match tofacitinib IR 5 mg tablets

The IR 5 mg and the matching placebo tablets are identical in appearance. The MR 11 mg and the matching placebo tablets are identical in appearance.

Study medication will be packaged in two bottles. Each bottle will be labeled appropriately. Refer to investigational product manual for details on clinical packaging.

5.4.2. Preparation and Dispensing

All study medication will be dispensed in bottles. At each dispensing visit, subjects will receive a sufficient quantity of study medication to last until their next scheduled visit plus an additional amount to accommodate visits scheduled within the allowed visit range. Subjects will also receive written dosing instructions and a dosing diary.

The investigational product should be dispensed using a drug management system at each visit from baseline visit (Visit 2) to week 8 visit (Visit 4). Dispensing will be performed by a qualified staff member according to unique container numbers on the bottles provided, in quantities appropriate for the study visit schedule. The subject/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing and return the bottle to the site at the next study visit.

Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

5.5. Administration

Subjects will be provided with medication instructions relevant to their study treatment arm. Study medication will be taken according to the instructions provided to the subject.

Subjects should be instructed to take one tablet from each bottle in the morning and one tablet from bottle of IR in the evening, approximately 12 hours apart. Subjects will therefore be taking three tablets per day. Subjects must record drug compliance on the subject dosing diary.

If a tofacitinib dose is missed and the interval to the next scheduled dose is less than 6 hours, the missed dose of tofacitinib IR should not be administered. Subjects will swallow the study medication whole, and will not manipulate or chew the medication prior to swallowing.

5.6. Drug Storage

The investigator, or an approved representative, e.g., pharmacist, will ensure that all investigational products, including any comparative agents and/or marketed products are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the drug label. Storage conditions stated in the single reference safety document (SRSD) (ie, investigator's brochure [IB] or Japan package insert) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be available. The operation of the temperature

monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct subjects on the storage requirements for take home medications including how to report temperature excursions.

5.7. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies by using patient dosing diary. To ensure adequate records, all drug supplies will be accounted for in the drug accountability inventory forms as instructed by sponsor and will be monitored by counting of unused medications from individual bottles returned by the subject at each visit from week 4 (Visit 3) to week 12 (Visit 5).

All bottles must be returned to the investigator or designee by the subject and the investigator or designee will return the bottles to sponsor unless sponsor authorizes destruction at the study site. In the event of destruction at the site, the investigator or designee must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by sponsor. Destruction must be adequately documented. The sponsor or designee will provide guidance on the destruction of unused investigational product (e.g., at the site).

5.8. Prior and Concomitant Treatment(s)

All prior and concomitant treatments will be recorded with generic name of the medication (or treatment name), reason for usage, dose and frequency, route of administration and start and stop dates in the subject's case report form (CRF) from the first day of the screening period until the end of the study. A subject who is receiving a permitted concomitant medication for any reason should be on a locally approved medication and a dose that is considered standard of care for the treated indication.

5.8.1. Prior treatment(s)

The information for prior treatment therapies and medications received within the specified time periods prior to signing the informed consent form (ICF) are to be recorded as identified in Table 1.

Table 1. Prior Treatment(s)

Treatment type	Information Recorded	Recording Period
For RA biologics, non-biologic DMARDs including MTX, folic acid or folinic acid, corticosteroids, NSAIDs and others	Dose, unit, frequency, route, start and stop dates and reason for discontinuation (biologics and non-biologic DMARDs excluding MTX only)	From 4 months prior to signing ICF to the first day of screening visit
Lipid lowering agents	Dose, unit, frequency, route, start and stop dates	From 4 weeks prior to signing ICF to the first day of screening visit
All other treatments	Indication, start and stop dates	From 4 weeks prior to signing ICF to the first day of screening visit

Abbreviations:
RA= Rheumatoid Arthritis; DMARDs= Disease Modifying Antirheumatic Drugs; ICF= Infromed Consent form; MTX=Methotrexate; NSAIDs=Non-Steroidal Anti-Inflammatory Drugs

All prior biologics and DMARDs are excluded at entry into the study, except MTX.

5.8.2. Permitted Concomitant treatment(s)

All concomitant treatments taken during the study will be recorded from the first day of the screening period until the end of the study as identified in Table 2.

Table 2. Concomitant Treatment(s)

Treatment type	Information Recorded	Recording Period
For RA* background MTX, folic acid or folinic acid, corticosteroids, NSAIDs and others	Dose, unit, frequency, route, start and stop dates	From the first day of screening visit to last visit date
Lipid lowering agents	Dose, unit, frequency, route, start and stop dates	From the first day of screening visit to last visit date
All other treatments**	Indication, start and stop dates	From the first day of screening visit to last visit date

Table 2. Concomitant Treatment(s)

Treatment type	Information Recorded	Recording Period

*: Concomitant treatment for RA must remain at a stable dose (no increase or decrease) during the study treatment period. Concomitant treatment should not be started during the study treatment period.
**: Includes nonprescription drugs, vitamins, and dietary supplements.
Abbreviations:
RA= Rheumatoid Arthritis; MTX = Methotrexate; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs

Please note that all concomitant DMARDs are excluded at entry into the study, except MTX. The following treatments of RA are allowed providing they are stable for the specified period of time prior to the first dose of study medication and are not permitted to change (dose reduction or increase) during the study treatment period.

5.8.2.1. Methotrexate

All subjects entering the study must have taken MTX continuously for at least 4 months prior to the first dose of study medication (baseline visit) and have been taking a stable dose of 6.0 mg to 16 mg weekly, for at least 6 weeks prior to the baseline visit and continue taking that dose throughout the study, unless modification is clinically indicated.

5.8.2.2. Folate Supplementation

Subjects must receive either folic acid or folinic acid as folate supplementation according to MTX labeling, practice guidelines and standard of care.

5.8.2.3. Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Other Analgesics

Subjects may continue taking stable daily doses of NSAIDs and other analgesics provided that the dose is stable for at least 4 weeks prior to the baseline visit and for the duration of the study.

Subjects who require intermittent therapy for symptom relief, may use short-acting analgesics including NSAIDs and acetaminophen. However, these medications are not permitted within 24 hours of the scheduled joint assessments. Topical NSAIDs and other topical analgesics are allowed at any time during the study.

5.8.2.4. Corticosteroid

Oral corticosteroids are allowed during the study up to the dose of 10 mg/day of oral prednisone or equivalent providing that the dose is stable for at least 4 weeks prior to the baseline visit; dose should also remain stable for the duration of study treatment. Reductions in oral corticosteroid dose are only allowed as needed to protect a subject's safety.

5.8.3. Prohibited Concomitant Treatment(s)

The following treatments are prohibited throughout the double-blind study treatment period. Prohibited concomitant treatments include, but not limited to, the following:

- DMARDs excepting of MTX

- Other investigational or marketed immunosuppressants or biologics with immunomodulatory properties
- Moderate to potent cytochrome (CYP)3A and CYP2C19 inhibitors and CYP3A inducers (Refer to Appendix 3)
- Herbal medicines
- Parenteral injections of corticosteroids and hyaluronic acid (e.g. intravenous, intra-articular, soft tissue, intra-muscle), articular drainage, articular local anesthetic and nerve block
- Cytotoxic (immunosuppressive) drugs (e.g., cyclophosphamide)
- Plasma exchange therapy
- Surgery which affects the efficacy assessments, such as Synovectomy, Artificial joint replacement, etc.
- Any live (attenuated) vaccines
- LCAP

Specific medications and required discontinuation times are listed below. A list of prohibited concomitant medications is provided in Appendix 3.

Any investigational treatment must be discontinued a minimum of 12 weeks or 5 half-life (whichever is longer) prior to the baseline visit.

For investigational drugs which half-life is unknown or pharmacological effect possibly persist beyond 5 half-life (e.g. receptor activator of nuclear factor kappa-β ligand [RANKL] inhibitors), investigator should consult with sponsor to determine the washout period.

5.8.3.1. Disease Modifying Antirheumatic Drugs (DMARDs)

Subjects who have received biologic or non-biologic DMARDs excepting MTX are eligible to participate in the study, providing the following discontinuation periods are observed prior to baseline visit (Table 3).

Table 3. DMARDs - Required Washout Period Prior to Baseline Visit

Washout period	Drugs
20 weeks	oral gold and injectable gold
12 weeks	abatacept, certolizumab pegol, leflunomide*, tocilizumab
10 weeks	golimumab
8 weeks	infliximab (including biosimilar)
6 weeks	adalimumab (including biosimilar)
4 weeks	azathioprine, cyclosporine, etanercept (including biosimilar), minocycline, penicillamine, sulfasalazine, tacrolimus, other DMARDs (e.g., bucillamine, mizoribin,etc.)

12 weeks or 5 half-life (whichever is longer)	Other investigational drugs (excluding drugs listed above)

* Leflunomide may be discontinued 4 weeks prior to baseline visit when discontinued using an elimination procedure (i.e., 4 grams cholestyramine, 3 times daily, for approximately 17 days). Administration duration of cholestyramine may be adjusted based on the patient's condition and findings of clinical testing.

5.8.3.2. Immune-Modulating Biologic Products

While receiving study drug, no immune-modulating biologic products are allowed to be administered concomitantly, including other biologic DMARDs (refer to Appendix 3).

5.8.3.3. CYP3A and CYP2C19 Inhibitors and CYP3A Inducers

Tofacitinib exposure is increased when co-administered with medications that are potent inhibitors of CYP 3A (e.g., ketoconazole) and medications that result in both moderate inhibition of CYP3A and potent inhibition of CYP2C19 (e.g., fluconazole).

Tofacitinib exposure is decreased when co-administered with potent CYP3A inducers (e.g., rifampicin).

All prohibited drugs that are CYP3A/CYP2C19 inhibitors require at least a 7 day or 5 half-lives (whichever is longer) washout prior to the first dose of study drug. Note: Amiodarone requires discontinuation at least 290 days (~5 half-lives, half-life averages ~58 days) prior to the first dose of study drug.

All prohibited drugs that are CYP3A inducers require at least a 28 day or 5 half-lives (whichever is longer) washout prior to the first dose of study drug.

If a medication that is a potent CYP3A inhibitor or is both a moderate inhibitor of CYP3A4 and potent inhibitor of CYP2C19 needs to be administered during the study for any reason, including the treatment of an adverse event, all study medication should be interrupted during treatment.

6. STUDY PROCEDURES

6.1. Screening (Week −4: Day −34 to Day 0)

Subjects must complete the screening procedures and have test results available prior to the baseline visit to confirm that they meet the entrance criteria for the study. All screening procedures must be completed within a 4 weeks window, unless otherwise noted.

Subjects who do not have all tests completed within the 4 weeks screening period or who temporarily do not meet study entry criteria (e.g., treatment with antibiotics during the screening period or for administrative reasons) may re-screen; the subject's prior study subject identification (SSID) number and reason for re-screening must be documented.

Subjects should be fasting for at least 9 hours prior to the visit.

Subjects who do not meet screening criteria or do not re-screen, must be discontinued and the reason for screening-failure must be documented in the CRF.

Procedures to be performed during the screening period (day −34 to day 0) include:

- Informed consent
- Confirmation of RA diagnosis: subject must meet the American Rheumatism Association 1987 revised criteria for classification of RA at least 6 months prior to screening (refer to Appendix 1).
- Medical history: include previous vaccination (including zoster vaccine) history, smoking status, average weekly alcohol consumption, family history of premature coronary heart disease (CHD), and history of any prior episodes of herpes zoster.
- Prior treatments/medications (refer to Section 5.8.1): This includes start dates and stop dates with reason for discontinuation (if appropriate), dosage and frequency of administration, and indication treated (make sure all indications are listed in the medical history) for all current medications, any medications taken within the 4 weeks prior to screening procedures, and a complete history of all DMARDs ever taken including the dates of administration and the reasons for discontinuation.
- Review of Inclusion/Exclusion criteria.
- Complete physical examination: height, weight, general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (peripheral edema), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes.
- Vital signs (blood pressure and pulse rate) and body temperature (axilla).
- Whole blood IFN-γ release assay: Quantiferon-3G/QuantiFERON®-TB Gold In Tube test or T-SPOT unless the subject has previously received an adequate course of therapy for either latent or active TB infection.
- 12-lead ECG.
- Chest X-ray (PA and lateral) or chest CT scan must show no evidence of active tuberculosis or other finding that would exclude the subject from the study (refer to Section 7.2.5).
- Laboratory tests: Rheumatoid factor, hematology, chemistry panel (including fasting lipid profile), serum pregnancy tests (β-human chorionic gonadotropin [HCG], female subjects who have child-bearing potential only), urinalysis, serum β-D-glucan, KL-6, serology (HIV, HBV, HCV), varicella-zoster virus (VZV) titer, CRP and ESR (refer to Section 7.2.6).
  All required laboratory testing must be complete and reported; any invalid specimens must be retested and reported prior to the baseline visit.
- RA Activity: 68/66 tender/painful and swollen joint counts performed and the number of swollen joints and the number of tender/painful joints meet the criteria for inclusion.

- Concomitant treatments/medication (refer Section 5.8.2 and 5.8.3).

6.2. Study Period

Eligible subjects will be randomized and treated in a double-blind fashion. Refer to SCHEDULE OF ACTIVITIES for the detail overview of the procedures.

Subjects who discontinue assigned investigational drug are required to continue in the study and perform all study tests and procedures until the study is complete.

6.2.1. Visit 2, Baseline Visit (Day 1)

Subjects are required to fast for at least 9 hours prior to the visit. Subjects who have met all the inclusion criteria and have no exclusion criteria present may participate in the study.

Procedures that will be performed prior to the first dose of study drug include:

- Review of inclusion/exclusion criteria.
- Targeted physical examination: weight, examination of heart, lungs, lower extremities for peripheral edema, abdomen and lymph nodes.
- Vital signs/temperature.
- Laboratory tests: Hematology, chemistry panel (including fasting lipid profile), urine pregnancy tests (β-HCG, female subjects who have child-bearing potential only), urinalysis, lymphocyte subset markers, CRP and ESR (refer to Section 7.2.6).
- Banked biospecimens (refer to section 7.3) .
- Joint assessment: tender/painful joint count (68 joints) and swollen joint count (66 joints).
- Completion of the following assessments:
    - Patient assessment of arthritis pain
    - Patient global assessment of arthritis
    - Physician global assessment of arthritis
- Patient reported outcome (PRO):
    - HAQ-DI
    - SF-36 (ver.2, acute)
    - FACIT-Fatigue
    - EQ-5D

- Concomitant treatments/medications review.
- Randomize: Investigators have to confirm that all screening procedures have been completed and the subject is eligible for randomization.
- Dispense of investigational product and dosing diary
- Safety assessment and AE reporting
- Schedule the subject to return for Visit 3 (Week 4)

6.2.2. Visit 3 (Week 4: Day 29 ±3 days)

Subjects are required to fast for at least 9 hours prior to the visit. Procedures that will be performed on Visit 3 include:

- Targeted physical examination: weight, examination of heart, lungs, lower extremities for peripheral edema, abdomen and lymph nodes.
- Vital signs/temperature.
- Laboratory tests: Hematology, chemistry panel (including fasting lipid profile), urine pregnancy tests (β-HCG, female subjects who have child-bearing potential only), urinalysis, lymphocyte subset markers, CRP and ESR (refer to Section 7.2.6).
- Joint assessment: tender/painful joint count (68 joints) and swollen joint count (66 joints).
- Completion of the following assessments:
  - Patient assessment of arthritis pain
  - Patient global assessment of arthritis
  - Physician global assessment of arthritis
- Patient reported outcome (PRO):
  - HAQ-DI
  - SF-36 (ver.2, acute)
- Drug accountability (include review of dosing diary) and dispense of new investigational product and dispense dosing diary
- Concomitant treatments/medications review
- Safety assessment and AE reporting
- Schedule the subject to return for Visit 4 (Week 8)

6.2.3. Visit 4 (Week 8: Day 57 ±3 days)

Procedures that will be performed on Visit 4 include:

- Drug accountability (include review of dosing diary) and dispense of new investigational product and dispense dosing diary
- Concomitant treatments/medication review
- Safety assessment and AE reporting
- Schedule the subject to return for Visit 5 (Week 12)

6.2.4. Visit 5 (Week 12: Day 85 ±3 days) End of Study or Early Termination

Subjects are required to fast for at least 9 hours prior to the visit. Procedures that will be performed on Visit 5 include:

- Targeted physical examination: weight, examination of heart, lungs, lower extremities for peripheral edema, abdomen and lymph nodes. Assessment of new physical findings.
- Vital signs/temperature.
- Laboratory tests: Hematology, chemistry panel (including fasting lipid profile), urine pregnancy tests (β-HCG, female subjects who have child-bearing potential only), urinalysis, lymphocyte subset markers, CRP and ESR (refer to Section 7.2.6).
- Joint assessment: tender/painful joint count (68 joints) and swollen joint count (66 joints).
- Completion of the following assessments:
  - Patient assessment of arthritis pain
  - Patient global assessment of arthritis
  - Physician global assessment of arthritis
- Patient reported outcome (PRO):
  - HAQ-DI
  - SF-36 (ver.2, acute)
  - FACIT-Fatigue
  - EQ-5D
- Drug accountability (include review of dosing daily)

- Concomitant treatments/medications review
- Safety assessment and AE reporting

6.3. Follow-up Visit

A follow-up visit is not planned in this study. However, when a follow-up visit is necessary due to an adverse event or abnormal test finding, the investigator may arrange follow-up at investigator's discretion for subjects.

6.4. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

If subjects withdraw prior to Week 12 (Visit 5), the subject should complete the procedures for Week 12 (Visit 5) (refer to section 6.2.4).

It is important to continue all subjects in the study and perform all tests and procedures until the study is completed to enable collection of safety data, even if a subject withdraws from the study assigned treatment, unless the subject withdraws their consent to continue participation.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject and document their current status. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational products, request the subject to return for a final visit, if applicable, and follow up with the subject regarding any unresolved Adverse Events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Efficacy

7.1.1. Assessments of Disease Activity

Individual components for the following indicators of disease activity will be collected throughout the study as described in Table 4.

Table 4. Disease Activity Indicators

Indicator	Definition/Calculation
DAS28-4(CRP)	0.56*√(TJC28) + 0.28*√(SJC28) + 0.36*ln(CRP in mg/L +1) + 0.014*PtGA in mm+ 0.96
DAS28-4(ESR)	0.56*√(TJC28) + 0.28*√(SJC28) + 0.70*In(ESR in mm/hour) + 0.014*PtGA in mm
ACR Response Rates	The ACR's definition for calculating a 20% improvement in RA (ACR20) is as follows: a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant (e.g., CRP). Similarly, ACR50 and 70 are calculated with the respective percent improvements.

DAS = Disease Activity Score; CRP = C-reactive protein in mg/L; TJC = tender joint count; SJC = swollen joint count; ESR = erythrocyte sedimentation rate in mm/first hour, PtGA = patient's global assessment of health; ACR = American College of Rheumatology

7.1.2. DAS Assessments

The Disease Activity Score (DAS) assessment is a derived measurement with differential weighting given to each component[12]. The DAS 28-4(CRP) and the DAS28-4(ESR) will be calculated.

The components of the DAS 28 arthritis assessment are:

1. Tender/Painful Joint Count (28 joints);
2. Swollen Joint Count (28 joints);
3. CRP or ESR;
4. Patient Global Assessment of Arthritis.

7.1.2.1. Tender/Painful Joint Count (28 joints)

Twenty-eight (28) joints will be assessed by investigator to determine the number of joints that are considered tender or painful. The response to pressure/motion on each joint will be assessed using the following scale:

- Present/Absent/Not Done/Not Applicable (to be used for artificial joints).

The 28 joints to be assessed are the shoulders, elbows, wrists, metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, and knees. Artificial joints will not be assessed. As a general rule, the same investigator should perform these assessments throughout the term of study.

7.1.2.2. Swollen Joint Count (28 joints)

The investigator will also assess these joints for swelling using the following scale:

- Present/Absent/Not Done/Not Applicable (to be used for artificial joints).

The 28 swollen joint count includes the following joints: shoulders, elbows, wrists, MCP joints, PIP joints and knees. Artificial joints will not be assessed. As a general rule, the same investigator should perform these assessments throughout the term of study.

7.1.2.3. C-Reactive Protein (CRP)

The CRP will be analyzed by a central laboratory. It will be used in the calculation of several efficacy parameters. CRP results will not be blinded and will be provided to the investigator for all visits.

7.1.2.4. Erythrocyte Sedimentation Rate (ESR) (At Participating Sites)

The ESR will be analyzed by a local laboratory using the Westergren method or other methods that yield results comparable to the Westergren method (the same ESR assessment method should be used consistently for a subject throughout the study). ESR results will be used in the calculation of several efficacy parameters. ESR results will not be blinded.

7.1.3. ACR Assessments

The American College of Rheumatology's definition for calculating improvement in RA (ACR20) is calculated as a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant. Similarly, ACR50 and 70 are calculated with the respective percent improvements.

The specific components of the ACR Assessments that will be used in this study are:

1. Tender/Painful Joint count (68 joints);
2. Swollen Joint Count (66 joints);
3. Patient Assessment of Arthritis Pain;
4. Patient Global Assessment of Arthritis;
5. Physician Global Assessment of Arthritis;
6. CRP;
7. HAQ-DI.

7.1.3.1. Tender/Painful Joint Count (68 joints)

Sixty-eight (68) joints will be assessed by investigator to determine the number of joints that are considered tender/painful. The response to pressure/motion on each joint will be assessed using the following scale:

- Present/Absent/Not Done/Not Applicable (to be used for artificial joints).

As a general rule, the same investigator performed these assessments throughout the term of study.

The 68 joints to be assessed are the following (Artificial joints will not be assessed):

- Upper Body: temporomandibular, sternoclavicular, acromioclavicular;
- Upper Extremity: shoulder, elbow, wrist (includes radiocarpal, carpal and carpometacarpal considered as one unit), metacarpophalangeals (MCP I, II, III, IV, V), thumb interphalangeal (IP), proximal interphalangeals (PIP II, III, IV, V), distal interphalangeals (DIP II, III, IV, V);
- Lower Extremity: hip, knee, ankle, tarsus (includes subtalar, transverse tarsal and tarsometatarsal considered as one unit), metatarsophalangeals (MTP I, II, III, IV, V), great toe interphalangeal (IP), proximal and distal interphalangeals combined (PIP II, III, IV, V).

7.1.3.2. Swollen Joint Count (66 joints)

Investigator will also assess these joints for swelling using the following scale:

- Present/ Absent/Not Done/Not Applicable (to be used for artificial joints).

Sixty-six (66) joints will be assessed for swelling, the same as those listed above for tenderness/pain, except that the right and left hip joints are not included in the swollen joint count. Artificial joints will not be assessed. As a general rule, the same investigator should perform these assessments throughout the term of study.

7.1.3.3. Patient Assessment of Arthritis Pain

Subjects will assess the severity of their arthritis pain using a 100 mm visual analog scale (VAS) placing a mark on the scale between 0 (no pain) and 100 (most severe pain), which corresponds to the magnitude of their pain.

7.1.3.4. Patient Global Assessment of Arthritis

Subjects will answer the following question, “Considering all the ways your arthritis affects you, how are you feeling today?” The subject’s response will be recorded using a 100 mm VAS.

7.1.3.5. Physician Global Assessment of Arthritis

The investigator will assess how the subject’s overall arthritis appears at the time of the visit. This is an evaluation based on the subject’s disease signs, functional capacity and physical examination, and should be independent of the Patient Global Assessment of Arthritis. The investigator’s response will be recorded using a 100 mm VAS.

7.1.4. Patient Reported Outcomes

7.1.4.1. Health Assessment Questionnaire-Disability Index (HAQ-DI)

The HAQ-DI assesses the degree of difficulty a subject has experienced during the past week in 8 domains of daily living activities: dressing and grooming, arising, eating,

walking, hygiene, reach, grip, and other activities[13]. Each activity category consists of 2-3 items. For each question in the questionnaire, the level of difficulty is scored from 0 to 3 with 0 representing "no difficulty," 1 as "some difficulty," 2 as "much difficulty," and 3 as "unable to do". Any activity that requires assistance from another individual or requires the use of an assistive device adjusts to a minimum score of 2 to represent a more limited functional status. The form should then be checked by the site staff for completeness (refer to Appendix 6).

7.1.4.2. SF-36 Health Survey (Version 2, Acute)

The SF-36 is a widely used general health status questionnaire that assesses 8 domains of functional health and well-being: Physical Functioning, Role Limitations due to Physical Health Problems, Bodily Pain, Social Functioning, Mental Health, Role Limitations due to Emotional Problems, Vitality, and General Health Perceptions[14]. A Physical health component summary score and Mental health component summary score are calculated from the 8 domain scores. The acute form uses a recall period of one week. The SF-36 is a psychometrically valid and reliable instrument that has been translated into many languages, and the scores have been shown to be responsive to change. Higher scores indicate a better health-related quality of life. On the specified study visit days, subjects should complete the SF-36. The SF-36 should be checked for completeness by the study site staff (refer to Appendix 7).

7.1.4.3. Functional assessment of chronic illness therapy (FACIT)-Fatigue

The FACIT-Fatigue Scale is a subject completed questionnaire consisting of 13 items that assess fatigue[15]. Instrument scoring yields a range from 0 to 52, with higher scores representing better subject status (less fatigue). This questionnaire should be completed by the subject prior to any procedures being performed at the visit, if possible. The form should then be checked by site staff for completeness (refer to Appendix 8).

7.1.4.4. Euro Quality of Life Questionnaire (EQ-5D)

The EQ-5D is a patient completed instrument designed to assess impact on quality of life in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[16]. Additionally, scores from the five domains may be used to calculate a single index value. The instrument provides a simple descriptive profile and a single index value for health status, and is applicable to a wide range of health conditions and treatments. On the specified study visit days, subjects should complete the EQ-5D at the clinic. The EQ-5D should be checked for completeness by the study site staff (refer to Appendix 9).

7.2. Safety

7.2.1. Complete Physical Examination

A standard physical examination will be performed at the screening visit. The following parameters and body systems will be examined and any abnormalities described: height, weight, general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (peripheral edema), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes.

7.2.2. Targeted Physical Examinations

At Visit 2, 3 and 5, a targeted physical examination will be performed assessing the following: weight, lungs, heart, lower extremities for peripheral edema, abdomen and lymph nodes. Any clinically significant changes from the last complete physical examination should be recorded as AEs; ongoing AEs should be updated, as appropriate.

7.2.3. Vital signs and body temperature

Blood pressure should be measured in the subject's dominant arm and recorded to the nearest mmHg. The same arm will be used throughout the study. All blood pressure in this study will be measured with the subject in the sitting position after resting for at least 5 minutes. The use of automated devices for measuring blood pressure and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained first. Temperature will be collected as axillary temperature.

7.2.4. 12-lead electrocardiogram

A 12-lead ECG will be obtained on all subjects at the screening visit. All ECGs should be performed after the subject has rested quietly for at least 10 minutes. ECGs will be read locally. Screening ECG results will be used as a screening tool and should be maintained in the subject's source documentation. Subjects with a screening 12-lead electrocardiogram that demonstrates clinically significant abnormalities requiring urgent treatment (e.g., acute myocardial infarction, serious tachy- or bradyarrhythmias) or that is indicative of serious underlying heart disease (e.g., cardiomyopathy, major congenital heart disease, low voltage in all leads) should not be enrolled in the study.

7.2.5. Chest Radiograph or chest CT scan

Subject must have a chest radiograph (PA and lateral views) or chest CT scan with no evidence of current, active TB or previous inactive TB, general infections, heart failure or malignancy taken at screening or within 12 weeks prior to screening and read by a qualified radiologist or respiratologist. Documentation of the official reading must be located and available in the source documentation.

If necessary, a chest CT scan (with or without IV contrast) may be performed during screening following initial performance of chest radiographs (PA and lateral) at the clinical discretion of the investigator. If pulmonary signs and symptoms are observed at and after baseline visit, unscheduled imaging tests (e.g. chest X-ray or chest CT scan) may be performed based on the judgment by investigator as appropriate.

7.2.6. Clinical Laboratory Tests

Blood and urine samples will be collected at the time points identified in Table 5. Unscheduled clinical laboratory tests may be obtained at any time during the study to assess any perceived safety concerns.

Table 5. Clinical Laboratory Tests

Tests	Visits	Comments
Chemistry blood urea nitrogen, creatinine, glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, ALP, gamma-glutamyl transferase (GGT), albumin, creatine kinase (CK)	Visit 1, Visit 2, Visit 3 and Visit 5	Creatinine clearance is calculated by the central laboratory according to the Cockcroft-Gault Formula at screening Visit (Appendix 4). Refer to Section 7.5 for retesting requirements for ALT and AST elevated ≥3 × ULN.
Hematology Hemoglobin Hematocrit RBC WBC Neutrophils (%, abs) Lymphocytes (%, abs) Monocytes (%, abs) Eosinophils (%, abs) Basophils (%, abs) Platelets	Visit 1, Visit 2, Visit 3 and Visit 5	Refer to Section 7.5 for monitoring requirements related to hemoglobin, neutrophil and lymphocyte counts.
C-reactive Protein (CRP)	Visit 1, Visit 2, Visit 3 and Visit 5	Refer to Section 7.1.2.3.
Erythrocyte sedimentation ratio (ESR)	Visit 1, Visit 2, Visit 3 and Visit 5	Refer to Section 7.1.2.4.
Rheumatoid Factor	Visit 1	
Banked Biospecimens	Visit 2	Refer to Section 7.3.
Serum β-D-glucan and KL-6	Visit 1	
HIV Serology	Visit 1	
Hepatitis B Surface antigen (HBsAg) Hepatitis B Core Antibody (HBcAb) Hepatitis B Surface Antibody (HBsAb)	Visit 1	Refer to Section 7.2.6.2 and Appendix 5.
Hepatitis B virus DNA (HBV DNA)	Visit 1, recommended every 4 weeks	Refer to Section 7.2.6.2 and Appendix 5 to determine when necessary.
Hepatitis C virus antibody (HCV Ab) Hepatitis C RNA (HCV RNA)	Visit 1	HCV RNA assay will be performed, if HCV Ab is positive.
Lipids (fasting) Triglycerides Total Cholesterol HDL Cholesterol LDL Cholesterol	Visit 1, Visit 2, Visit 3 and Visit 5	Subjects should be fasting for at least 9 hours prior to each visit. Refer to Section 7.2.6.4.
Serum Pregnancy Testing	Visit 1	All female subjects of childbearing potential, regardless of whether or not they are sexually active. Refer to Section 7.2.6.1 .
Whole blood IFN-γ release assay (Quantiferon-3G/QuantiFERON® -TB Gold In-Tube or T-SPOT)	Visit 1	If there are two consective indeterminate results of QFT-G/QuantiFERON® -TB Gold In-Tube or T-SPOT test, a Mantoux Purified Protein Derivative (PPD) tuberculin skin test can be performed during screening period. Refer to Section 7.2.6.3.1.

Table 5. Clinical Laboratory Tests

Tests	Visits	Comments
Varicella-Zoster Virus (VZV)	Visit 1	
Lymphocyte subset markers	Visit 2, Visit 3 and Visit 5	Lymphocyte subset markers include: CD3+, CD3−CD19+, CD3+CD4+CD8−, CD3+CD4−CD8+, CD3+CD16+CD56+, CD3−CD16+CD56+, CD3−CD16+CD56−, CD3−CD16−CD56+, CD3−CD16−CD56−, CD4/CD8
Urinalysis Specific Gravity pH Protein Glucose Ketones Blood Nitrite Leukocyte Esterase Pregnancy test (excluding visit 1) Urine sediment (microscopy) Urine culture (if clinically indicated)	Visit 1, Visit 2, Visit 3 and Visit 5	
Tests to include when repeat AST and/or ALT are required: Albumin Creatine kinase (CK) Total bilirubin Direct bilirubin Indirect bilirubin, GGT PT/INR ALP	At same time as AST and/or ALT are repeated for elevations as noted in Section 7.5	Refer to Section 8.7.2 for further details on management of elevations.

ALT = alanine aminotransferase (SGPT); AST = aspartate aminotransferase (SGOT) ; ALP = alkaline phosphatase; HDL = high density lipoprotein; HIV = human immunodeficiency virus; LDL = low density lipoprotein; SGOT = serum glutamic-oxaloacetic transaminase (AST); SGPT = serum glutamic pyruvate transaminase (ALT); TB = tuberculosis;
× ULN = times the upper limit of normal;

7.2.6.1. Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test will be performed at the screening visit. For female subjects of childbearing potential, urine pregnancy test with sensitivity of at least 25 mIU/mL will be performed prior to starting study therapy (before investigational product administration at the baseline visit), visit 3 (week 4) and visit 5 (week 12). A negative pregnancy result is required before the subject may receive the investigational product. Urine pregnancy test may be repeated more frequently if a menstrual cycle is missed or if potential pregnancy is otherwise suspected.

7.2.6.2. Hepatitis B virus screening

All subjects must undergo testing for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) and hepatitis B surface antibody (HBsAb). Subjects who have

negative HBsAg, negative HBcAb and positive HBsAb without documentation of prior HBV vaccination, and subjects who have negative HBsAg, positive HBcAb and positive HBsAb are required to undergo HBV DNA testing at the screening visit. Refer to Appendix 5 for the detail of HBV screening.

7.2.6.3. Tuberculosis Screening

During the screening period, it must be determined and documented that a subject does not have evidence of active or latent or inadequately treated infection with TB per the inclusion criteria. The results of TB screening conducted in 12 weeks prior to Screening or during the screening period must be documented in study records prior to Baseline/Day 1.

7.2.6.3.1. Whole blood IFN-γ release assay

QFT-G is an *in vitro* diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10 and TB 7.7 proteins to stimulate cells in heparinized whole blood. Detection of IFN-γ performed by Enzyme-Linked Immunosorbent Assay (ELISA) is used to identify in vitro responses to these peptide antigens that are associated with *Mycobacterium tuberculosis* infection. QFT-G is an indirect test for *M. tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

The T-SPOT® TB test is an IFN-γ release assay, and enumerates the response of effector T cells that have been sensitized to *Mycobacterium tuberculosis*. IFN-γ is captured and presented as spots from T cells sensitized to *Mycobacterium tuberculosis* antigens. The results are interpreted by subtracting the spot count in the negative (NIL) control from the spot count in Panels A (ESAT-6) and B (CFP-10).

A negative QFT-G and/or T-SPOT test result is required to meet the inclusion criterion. QFT-G and T-SPOT test results will be reported as positive, negative or indeterminate. In the case of an indeterminate result, repeat tests should be permitted for the purpose of determining eligibility of subjects to enroll in this study. Mantoux/PPD testing will be allowed, if there are two consecutive indeterminate results in subjects who have been received BCG vaccination. Subjects with a history of BCG vaccination will be tested with the QFT-G and/or T-SPOT test.

7.2.6.3.2. Mantoux/Purified Protein Derivative (PPD) Tuberculin Skin Test

Mantoux Purified Protein Derivative (PPD) tuberculin skin test will be allowed during screening period, if there are two consecutive indeterminate results of QFT-G or T-SPOT test in subjects who have not received BCG vaccination. Subjects must have a Mantoux/PPD tuberculin skin test administered and then evaluated by a health care professional 48 to 72 hours later. If performed, a negative Mantoux/PPD tuberculin skin test result is required to meet the inclusion criterion.

The Tuberculin Test consists of intracutaneous injection of PPD in 0.1 mL of solution on the volar aspect of the forearm, using a short beveled 26-or 27-gauge needle (Mantoux test). The test is positive if the diameter of the erythema is over 10 mm in 48 to 72 hours after injection.

7.2.6.4. Serum Lipid Profile

Total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides will be measured during the study requiring subjects to be fasting at least 9 hours prior to Visit 1, Visit 2, Visit 3 and Visit 5. Refer to Appendix 10 for recommended clinical management of cholesterol.

7.2.6.5. Creatinine Clearance

A commonly used surrogate marker for actual creatinine clearance is the Cockcroft-Gault formula (refer to Appendix 4), which employs creatinine measurements and a subject's weight to predict the clearance. For subjects to be eligible for the study, GFR needs to be >40 mL/min based on Cockcroft-Gault calculation. Cockcroft-Gault GFR calculation will be done as part of clinical laboratory tests in Visit 1.

7.2.7. Adjudicated Adverse Events

Specific safety events such as cardiovascular (CV) events, malignancies, opportunistic infections (OI), hepatic events and interstitial lung disease (ILD) in this study will be adjudicated by external or internal committees to harmonize and to standardize selected safety event assessments (Refer to Section 9.6).

Subjects will be monitored for development of any CV events, malignancies, infections (viral, bacterial, and fungal), liver disease and lung disease during the study.

The study site has responsibility to obtain and submit the event documentation to related committee. Event documentation will vary with the event requiring adjudication and may include (but not be limited to): hospital discharge summaries, operative reports, clinic notes, ECGs, diagnostic tests, pathology reports, autopsy reports and death certificate information, as applicable. Criteria for defining specific events will be provided to investigators in a separate study document.

Refer to Appendix 11 for the steps to take in the event of potentially malignant tumors, lymphadenopathy or possible extra-nodal lymphoproliferative disorder (LPD) which might arise in the course of this study.

7.3. Banked Biospecimens

7.3.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited as such by local regulations or ethics committee (EC) decision.

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study identification (ID) number. Samples will be kept in a facility accessible only by badge-swipe. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will only be used for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also postmarketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians, nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical study.

A 4 mL blood biospecimen, **Prep D1 (K_2 edetic acid (ethylenediaminetetraacetic acid) (EDTA) whole blood collection optimized for DNA analysis)**, will be collected at the baseline visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or EC decision. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The Banked Biospecimens will be collected from all subjects **unless prohibited by local regulations or ethics committee decision**. Detailed collection, processing, storage and shipment instructions are provided in the central laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

7.3.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, subjects will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical study, and related conditions;

- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the

natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimen specified in the Markers of Drug Response section will be used. Subjects may still participate in the clinical study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.4. Assessment of Suicidal Ideation and Behavior (SIB)

There are no current medically significant suicidality concerns for the study drug (ie, tofacitinib) in this study or their respective mechanisms of action. Ongoing and aggregate cumulative safety reviews and pharmacovigilance activities will be conducted; if any concerns are identified that would warrant changes to these assessments, surveillance tools will be implemented, as appropriate.

7.5. Triggered Requirements

The following laboratory abnormalities require re-testing ideally within 3-5 days, prompt retesting, withdrawal of study treatment or withdrawal from this study.

Condition	Action
Neutrophil counts <1000 cells/mm^3	The subject should return to the study site for prompt retesting, ideally within 3-5 days.
Platelet counts <100,000 platelets/mm^3	The subject should return to the study site for prompt retesting, ideally within 3-5 days.
Lymphocyte counts <500 lymphocytes/mm^3	The subject should return to the study site for prompt retesting, ideally within 3-5 days.
Any single AST and/or ALT elevation ≥3 × ULN *	The subject should return to the study site for prompt retesting, ideally within 3-5 days.
Any single hemoglobin value <8.0 g/dL or one that drops ≥2 gm/dL below baseline.	The subject should return to the study site for prompt retesting, ideally within 3-5 days.
Any serum creatinine increase >50% over the average of screening (most recent value prior to baseline) and baseline values OR an absolute increase in serum creatinine >0.5 mg/dL (>44.2 μmol/L) over the average of screening (most recent value prior to baseline) and baseline values	The subject should return to the study site for prompt retesting, ideally within 3-5 days.
* The subject must return to the study site for prompt retesting and include the following tests: albumin, creatine kinase (CK), total bilirubin, direct and indirect bilirubin, GGT, PT/INR, and ALP. Additional investigations include a detailed history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, work exposure, history of ethanol, recreational drug and dietary supplement consumption. Testing for acute hepatitis A, B or C infection and biliary tract imaging may be considered.	

Condition	Action
2 sequential AST or ALT elevations ≥3 × ULN with a total bilirubin value ≥2 × ULN	Treatment with all study drugs will be discontinued and the subject withdrawn from this study. Follow-up to resolution
2 sequential AST or ALT elevations ≥3 × ULN with an elevated INR	Treatment with all study drugs will be discontinued and the subject withdrawn from this study. Follow-up to resolution
2 sequential AST or ALT elevations ≥3 × ULN accompanied by symptoms consistent with hepatic injury	Treatment with all study drugs will be discontinued and the subject withdrawn from this study. Follow-up to resolution
2 sequential AST or ALT elevations ≥5 × ULN, regardless of Total Bilirubin or accompanying symptoms	Treatment with all study drugs will be discontinued and the subject withdrawn from this study. Follow-up to resolution
2 sequential hemoglobins <8.0 g/dL or a decrease of more than 30% from baseline value	Treatment with all study drugs will be discontinued and the subject withdrawn from this study. Follow-up to resolution
2 sequential platelet counts <75,000 platelets/mm^3	Treatment with all study drugs will be discontinued and the subject withdrawn from this study. Follow-up to resolution
2 sequential neutrophil counts <1000 cells/mm^3	Treatment with all study drugs will be discontinued and the subject withdrawn from this study. Follow-up to resolution
2 sequential lymphocyte counts <500 lymphocytes/mm^3	Treatment with all study drugs will be discontinued and the subject withdrawn from this study. Follow-up to resolution
Confirmed increases in serum creatinine >50% over the average of screening and baseline values.	Treatment with all study drugs will be discontinued and the subject withdrawn from this study. Retesting should occur until the serum creatinine is within 10% of the pretreatment value.
Serious infections defined as any infection (viral, bacterial, or fungal) requiring parenteral antimicrobial therapy or hospitalization for treatment, or meeting other criteria that require the infection to be classified as a serious adverse event.	Treatment with all study drugs will be discontinued and the subject withdrawn from this study.
Opportunistic infection judged significant by investigator	Treatment with all study drugs will be discontinued and the subject withdrawn from this study.
Malignancies excluding adequately treated non- melanoma skin cancer (NMSC) and cervical carcinoma in situ	Treatment with all study drugs will be discontinued and the subject withdrawn from this study.

Condition	Action
Increase lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)	Monitor and treat according to local guidance (eg, diet and behavior modification, statin therapy).
Pregnancy or refusal to use appropriate contraception	Permanently withdraw the subject from the study drug and follow any pregnancy to resolution.
Anaphylactic or other serious allergic reaction	Immediately discontinue study drug and institute appropriate therapy.
Symptoms suggestive of a lupus-like syndrome	Discontinue study drug and institute appropriate therapy.
Detection of HBV-DNA by the two sequential quantitative tests (for subjects who have HBV-DNA assay at screening)	Immediately discontinue study drug and institute appropriate therapy.
Other serious or severe AEs, after consultation with the sponsor.	Treatment with all study drugs will be discontinued and the subject withdrawn from this study.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; DNA = deoxyribonucleic acid; g/dL = grams per deciliter; GGT = gamma-glutamyl transferase; HBV = hepatitis B virus; PT/INR = Prothrombin Time/International Normalized Ratio; mm = millimeter; × ULN = times the upper limit of normal	

Additional individual subject safety monitoring in above actions is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled laboratory testing through the central laboratory may be obtained at any time during the study to assess such concerns, and a subject may be withdrawn at any time at the discretion of the investigator.

Because of the potential higher risk of interstitial pneumonia in Japanese patients than in Western patients, investigators should carefully evaluate all patients who exhibit symptoms, especially fever and cough.

If a patient develops fever, cough, or dyspnea, temporary discontinuation of study drug should be considered. The differential diagnosis should include assessment for pneumonia, TB, pneumocystis pneumonia (PCP), and invasive fungal infection.

Additionally, if a patient's absolute lymphocyte count is decreased to <1000/mm^3, please consider appropriate action based on the patient's condition, such as retest of lymphocyte counts, as warranted. If the absolute lymphocyte count is decreased to <500/mm^3, prompt retesting, ideally within 3-5 days from the awareness, is required and please consider temporary discontinuation of study drug while the patient is under evaluation for the cause of the abnormality (ies), e.g., pneumonia, TB or PCP.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the sponsor.

AEs (serious and nonserious) should be recorded on the Case Report Form (CRF) from the time the subject has taken at least 1 dose of study treatment through the subject's last visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (AE) page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the adverse event (AE) page and, if applicable, any associated AE(s) are captured on an AE CRF page.

All overdoses are medication errors. For the purpose of this study, medication errors will be reported as protocol deviations if the subject reported taking 2-fold or more of their prescribed dose for one or more days or were identified as consuming more than 120% of their prescribed dose over the visit interval.

The following is an example of tofacitinib overdose:

8.4.1. Tofacitinib Overdose

There is no experience with overdose of tofacitinib. Pharmacokinetic data up to and including a single dose of 100 mg in healthy volunteers indicate that more than 95% of the administered dose is expected to be eliminated within 24 hours. There is no specific antidote for overdose with tofacitinib. In case of an overdose, it is recommended that the subject be monitored for signs and symptoms of adverse reactions. Subjects who develop adverse reactions should receive appropriate treatment.

Overdoses of tofacitinib are defined by doses and duration of dosing not administered in the tofacitinib development program. The following doses and duration of dosing have been administered in tofacitinib rheumatoid arthritis clinical trials without evidence of dose-limiting symptoms and are not considered overdoses:

- ≤100 mg tofacitinib daily for up to 2 weeks
- ≤60 mg tofacitinib daily for up to 6 weeks
- ≤30 mg tofacitinib daily for up to 6 months

8.5. Infections

All treated infections occurring during the study, including, but not limited to, respiratory infections, cutaneous infections, urinary tract infections and episodes of suspicious or febrile diarrhea, should be cultured if possible and any identified organisms noted in the CRF.

Infections should be classified as either serious infections or treated infections, as defined below.

8.5.1. Treated Infections

A treated infection is any infection that requires antimicrobial therapy by any route of administration or any surgical intervention (eg, incision and drainage). Subjects who experience infections that require treatment can have their study drug temporarily discontinued during antimicrobial therapy. This information should be noted in the CRF.

8.5.2. Serious Infections

A serious infection is any treated infection that requires hospitalization for treatment or requires parenteral antimicrobial therapy or meets other criteria that require it to be classified as a serious adverse event. A patient who experiences a serious infection should be discontinued from the study and the serious adverse event should be listed as the reason for discontinuation in the eCRF. Appropriate laboratory investigations, including but not limited to cultures should be performed to establish the etiology of any serious infection. All adverse events, including serious adverse events, should be reported as described in Section 8.2 on Adverse Event Reporting.

8.6. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (e.g., temporary discontinuation of study drug) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.7. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.7.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (refer to section on Serious Adverse Event Reporting Requirements).

8.7.2. Potential Cases of Drug-Induced Liver Injury

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to run LFTs because of clinical sign/symptom presentation in a subject, such LFT results should be handled and followed up as described below.

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an ALP value ≤2 × ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

    Concurrent with

    - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and ALP. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.8. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for workup of persistent pre-treatment laboratory abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical examination);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.9. Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.10. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (refer to section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.11. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (e.g., because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (e.g., because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on a Serious Adverse Event (SAE) Report Form and Exposure During Pregnancy (EDP) supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (refer to below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.12. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to the drug safety unit within 24 hours of the Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE Report form is maintained in the investigator site file.

8.13. Withdrawal Due to Adverse Events (Refer to Also the Section on Subject Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.14. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

8.15. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.15.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of

the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.15.2. Non-serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.15.3. Sponsor Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The primary objective of the study is to demonstrate the non-inferiority in efficacy of tofacitinib 11 mg MR QD to 5 mg IR BID for the treatment of signs and symptoms in patients with active RA on a stable background of MTX, as measured by DAS28-4(CRP) change from baseline at Week 12.

The following assumptions in treatment comparison for the primary endpoint have been applied: (1) one-sided type-I error (alpha) of 0.025, (2) subjects assigned to tofacitinib MR 11 mg QD and IR 5 mg BID groups in a 1:1 ratio, (3) difference of treatment means is zero, (4) a common standard deviation of 1.3 based on the previous tofacitinib studies. Based on the forgoing assumptions, a total of at least 200 evaluable subjects (100 in each treatment arm) will be required to demonstrate non-inferiority with a power of 90% and a non-inferiority margin of 0.6, which is equal to the minimum improvement in disease activity by DAS consistent with a “moderate response” by the European League Against Rheumatism (EULAR) criteria.[17]

It is anticipated that the sample size of 100 subjects in each formulation group will provide 0.36 half-width of 2-sided 95% confidence interval for the difference on the change from baseline in DAS28-4(CRP) at Week 12 assuming a common standard deviation of 1.3.

9.2. Efficacy Analysis

9.2.1. Statistical Hypothesis

The primary hypothesis associated with the statistical objective is to demonstrate non-inferiority of tofacitinib MR 11 mg QD to IR 5 mg BID as measured by DAS28-4(CRP) change from baseline at Week 12. The null hypothesis is that the treatment difference (tofacitinib MR 11 mg QD – IR 5 mg BID) is 0.6 or more, and the alternative hypothesis is that the treatment difference is less than 0.6.

9.2.2. Statistical Decision Rule

If the lower bound of the 2-sided 95% confidence interval (type-I error [alpha] of 0.025 in each tail) for the difference in change from baseline in DAS28-4(CRP) between the two arms (MR 11 mg QD – IR 5 mg BID) is less than 0.6, then the treatment of tofacitinib MR 11 mg QD will be declared to be non-inferior to that of tofacitinib IR 5 mg BID.

9.2.3. Analysis of Primary Efficacy Endpoint

The primary efficacy variable of DAS28-4(CRP) will be expressed as a change from baseline. The analysis will be conducted using a linear mixed effect model with repeated measures (MMRM), which will include baseline as a covariate, treatment, visit (week 4 and 12), and treatment by visit interaction as fixed effects. Subjects will be a random effect and unstructured covariance will be assumed. The estimate of treatment difference and the associated 2-sided 95% confidence interval (type-I error [alpha] of 0.025 in each tail) at the primary time point of week 12 will be constructed based on the model. The statistical decision rule is described in Section 9.2.2.

The primary efficacy analysis will use the full analysis set (FAS) which will include all subjects who were randomized and received at least one dose of the randomized investigational drug.

9.2.4. Robustness Analysis

To support the interpretation of the primary analysis, robustness analyses will be performed for the primary endpoint. However, the conclusions will be purely based on the results of the primary analysis.

The robustness analyses will be conducted using the ‘Per Protocol’ analysis set rather than the FAS.

The ‘Per Protocol’ analysis set will include all randomized subjects who completed the 12 week study with no important protocol deviations that could impact the efficacy analysis. The list of potentially important protocol deviations (pIPDs) and the subjects to be excluded from the ‘Per Protocol’ analysis set will be identified, reviewed, and finalized prior to the release of the database.

9.2.5. Analysis of Secondary and Other Efficacy Endpoints

For each endpoint, treatment comparisons are performed at Week 12 and other time points when assessed. There is no non-inferiority testing in these analyses. The point estimate of the treatment difference and the associated 2-sided 95% confidence intervals (CIs) will be calculated, for descriptive purposes.

All the secondary and other efficacy analyses are based on FAS.

The continuous data, i.e., change from baseline in DAS28-4(ESR) and HAQ-DI will be analyzed in a similar manner as described for change from baseline in DAS28-4(CRP) in the primary analysis.

Dichotomized data will be summarized and compared between two treatment groups using the normal approximation to the difference in proportions. The 2 sided 95% confidence interval of the treatment difference will be constructed. Examples of the secondary and other efficacy endpoints for each scheduled post-baseline measurement are:

- ACR20, ACR50 and ACR70 response.
- Remission, as assessed by: DAS28-4(CRP) < 2.6 and DAS28-4(ESR) < 2.6.
- LDA, as assessed by: DAS28-4(CRP) ≤ 3.2 and DAS28-4(ESR) ≤ 3.2.
- HAQ-DI response (decrease of at least 0.22).

Subjects who drop-out for any reason will be considered as a non-responder (non-responder imputation [NRI]). For the composite endpoint, the last observation carried forward (LOCF) mixed components method will be used to impute any missing components before drop-out. Only post-baseline values will be carried forward in the latter case.

Descriptive statistics of the patient-reported outcome instruments for baseline and for each scheduled post-baseline measurement will be provided.

Remaining secondary and other efficacy analyses will be detailed in the analysis plan.

9.3. Safety Analysis

All the safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations, including:

- All AEs, including SAEs.
- Clinically significant abnormal laboratory parameters.

The safety analysis will be conducted on the safety analysis set (SAFETY), which is defined as all subjects who were randomized and received at least one dose of the investigational drug. By definition, it is identical to the full analysis set defined above.

9.4. Interim Analysis

No interim analysis of the study data will be performed for use outside the data monitoring committee (DMC).

9.5. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

9.6. Safety Event Adjudication/Review Committees

To help assess specific safety events in this study adjudication committees have been established to harmonize and standardize selected safety event assessment. Members of these safety event adjudication committees will be blinded to treatment assignment in order to allow for unbiased assessments. These committees include a Cardiovascular Endpoint Adjudication Committee (CV EAC), Malignancy Adjudication Committee (MAC), Opportunistic Infection Review Committee (OIRC), Hepatic Event Review Committee (HERC) and Gastrointestinal Perforation Review Committee (GIPRC). In addition to these external committees, an internal committee of medically qualified Pfizer personnel with expertise in the assessment and diagnosis of respiratory disease will review and categorize potential events of interstitial lung disease (Interstitial Lung Disease Review Committee [ILDRC]).
Further information about these committees can be found in the respective charters, including specific descriptions of the scope of their responsibilities and the processes and definitions used to review and assess specific safety events.

Additional safety event adjudication committees may be established to harmonize and standardize selected safety event assessments. As described above, individual committee charters will provide specific descriptions of the scope of responsibilities and the processes and definitions used to review and assess specific safety events.

In addition to the event adjudication or review committees described above, all biopsies of potentially malignant tumors, suspicious lymphadenopathy, or possible extranodal lymphoproliferative disorder (LPD) should be submitted to the central laboratory for review by central laboratory pathologists. In some instances, additional expert pathology review of submitted samples may be performed. Description of the scope of review and the processes used to obtain and assess biopsies is described in the Histopathology Review for Potential Malignancy charter.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data is compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject’s actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

Whenever consent is obtained from a subject's legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, then the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his/her own consent, the source documents must record why the subject did not provide consent (e.g., minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (e.g., parent, spouse) and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

12.4. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of Trial in all participating countries is defined as Last Subject Last Visit (LSLV) for the last subject.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of tofacitinib at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects

and the hospital pharmacy (if applicable) within one week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer has no objection to publication by an investigator of any information collected or generated by the investigator, whether or not the results are favorable to the investigational drug. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information (other than the study results themselves) before disclosure.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

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Appendix 1. American College of Rheumatology (ACR) 1987 Revised Classification Criteria[18]

Patients must have a diagnosis of rheumatoid arthritis (RA) according to the American College of Rheumatology (ACR) 1987 Revised Criteria. These criteria require that patients fulfill at least four (4) of the seven (7) criteria; criteria 1 through 4 must have been present for at least 6 weeks.

1. Morning Stiffness.
   Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.

2. Arthritis of three or more joint areas.
   At least three joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.

3. Arthritis of hand joints.
   At least one area swollen (as defined above) in a wrist, MCP, or PIP joint.

4. Symmetric arthritis.
   Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).

5. Rheumatoid nodules.
   Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician.

6. Serum rheumatoid factor.
   Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects.

7. Radiographic changes.
   Radiographic changes typical of rheumatoid arthritis on PA hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

Appendix 2. Criteria for Classification of Functional Status in Rheumatoid Arthritis[19]

Class I: Completely able to perform usual activities of daily living (self-care, vocational, and avocational).

Class II: Able to perform usual self-care and vocational activities, but limited in avocational activities.

Class III: Able to perform usual self-care activities, but limited in vocational and avocational activities.

Class IV: Limited in ability to perform usual self-care, vocational, and avocational activities.

Usual self-care activities including dressing, feeding, bathing, grooming, and toileting.
Avocational (recreational and/or leisure) and vocational (work, school, homemaking)

Appendix 3. Prohibited Concomitant Medications

Moderate or potent CYP3A/CYP2C19 inhibitors and moderate or potent CYP3A inducers may include, but are not limited to, those listed below. Only systemically administered drugs listed below are prohibited; topical, ophthalmic, or intra vaginal administration is allowed. This listing of prohibited concomitant treatments is not considered all inclusive.

Prohibited Concomitant Medications	
Moderate or Potent CYP3A/CYP2C19 Inhibitors*	**Moderate or Potent CYP3A Inducers****
Protease inhibitors: indinavir nelfinavir ritonavir delavirdine saquinavir atazanavir	Protease inhibitors: efavirenz nevirapine Anticonvulsants: barbiturates phenobarbital phenytoin carbamazepine
Macrolide antibiotics: clarithromycin telithromycin erythromycin,	Antibiotics: rifampicin rifabutin
Other antibiotics: chloramphenicol norfloxacin	Antidepressants: St. John's Wort
Antifungals: fluconazole ketoconazole itraconazole clotrimazole voriconazole	Other compounds: modafinil troglitazone
Antidepressants: fluvoxamine nefazodone	
Other compounds: amiodarone, cimetidine, diethyl-dithiocarbamate, diltiazem, imatinib, mifepristone (RU-486) , verapamil	
Prohibited Concomitant DMARDs***	
Biologic DMARDs	**Nonbiologic DMARDs**
etanercept, adalimumab, infliximab, abatacept, tocilizumab (including	oral gold, injectable gold, sulfasalazine, D-penicillamine, bucillamine, mizoribin,

biosimilar), etc.	azathioprine, leflunomide, cyclosporine, tacrolimus, etc.

* All prohibited drugs that are CYP3A/CYP2C19 inhibitors require at least a 7 day or 5 half-lives (whichever is longer) washout prior to the first dose of study drug. Note: Amiodarone requires discontinuation at least 290 days (~5 half-lives, half-life averages ~58 days) prior to the first dose of study drug.

** All prohibited drugs that are CYP3A inducers require at least a 28 day or 5 half-lives (whichever is longer) washout prior to the first dose of study drug.

*** Refer to Section 5.8.3 for specific washout requirements.

Appendix 4. Cockcroft-Gault Formula for Estimating GFR

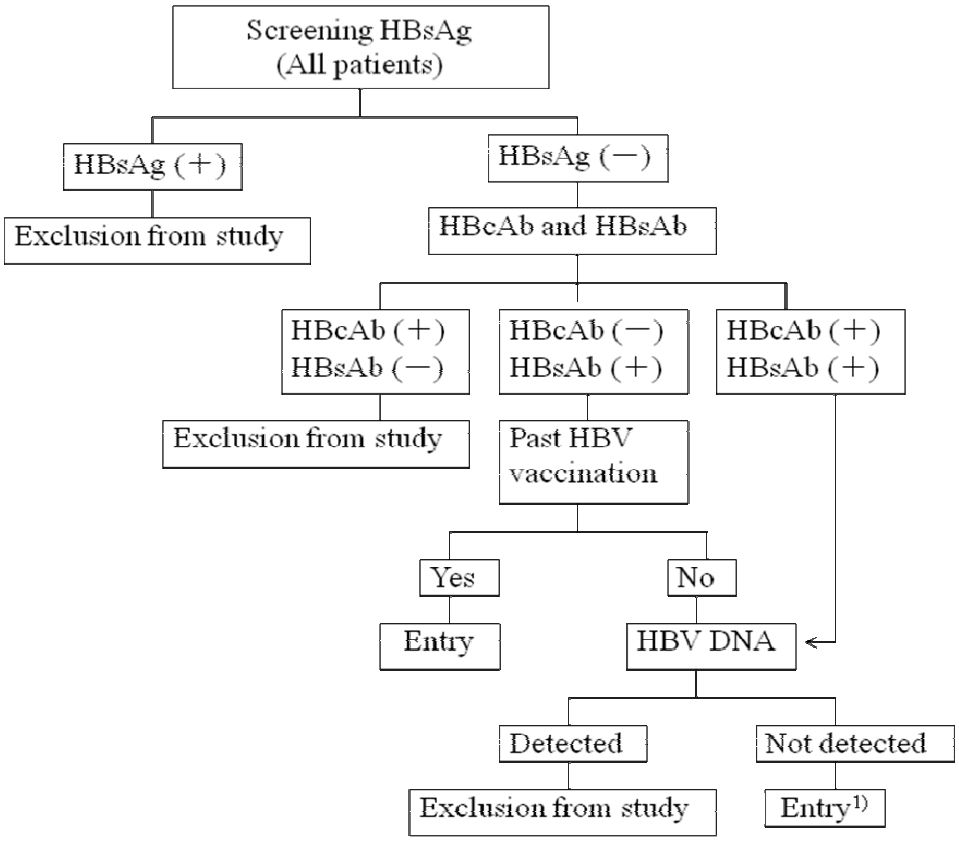
Creatinine Clearance (estimated) / Conventional mL/min =

((140 - Age (years)) × Weight (kg) × Factor[a]) / (72 × Serum Creatinine (mg/dL))

[a] Factor is equal to 0.85 in females and 1.00 in males.

Appendix 5. Screening Procedure of Hepatitis B virus Infection

A subject will be screened for HBV infection. All patients must undergo testing for hepatitis B surface antigen (HBsAg), hepatitis B core antbody (HBcAb) and hepatitis B surface antibody (HBsAb). Refer to the following figure for the detail of screening procedure of HBV infection[20].



1) HBV DNA assay is recommended to perform every 4 weeks.

Appendix 6. Health Assessment Questionnaire-Disability Index (HAQ-DI)

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
DRESSING & GROOMING				
Are you able to:				
- Dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____
- Shampoo your hair?	_____	_____	_____	_____
ARISING				
Are you able to:				
- Stand up from a straight chair?	_____	_____	_____	_____
- Get in and out of bed?	_____	_____	_____	_____
EATING				
Are you able to:				
- Cut your meat?	_____	_____	_____	_____
- Lift a full cup or glass to your mouth?	_____	_____	_____	_____
- Open a new milk carton?	_____	_____	_____	_____
WALKING				
Are you able to:				
- Walk outdoors on flat ground?	_____	_____	_____	_____
- Climb up five steps?	_____	_____	_____	_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____ Cane

_____ Walker

_____ Crutches

_____ Wheelchair

_____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)

_____ Built up or special utensils

_____ Special or built up chair

_____ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Dressing and Grooming

_____ Eating

_____ Arising _____ Walking

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
HYGIENE				
Are you able to:				
- Wash and dry your body?	_____	_____	_____	_____
- Take a tub bath?	_____	_____	_____	_____
- Get on and off the toilet?	_____	_____	_____	_____
REACH				
Are you able to:				
- Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	_____	_____	_____	_____
- Bend down to pick up clothing from the floor?	_____	_____	_____	_____
GRIP				
Are you able to:				
- Open car doors?	_____	_____	_____	_____
- Open jars which have been previously opened?	_____	_____	_____	_____
- Turn faucets on and off?	_____	_____	_____	_____
ACTIVITIES				
Are you able to:				
- Run errands and shop?	_____	_____	_____	_____
- Get in and out of a car?	_____	_____	_____	_____
- Do chores such as vacuuming or yardwork?	_____	_____	_____	_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____ Raised toilet seat _____ Bathtub bar

_____ Bathtub seat _____ Long-handled appliances for reach

_____ Jar opener (for jars previously opened) _____ Long-handled appliances in bathroom

_____ Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Hygiene _____ Gripping and opening things

_____ Reach _____ Errands and chores

Appendix 7. Short Form -36, version 2, acute (SF-36)

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h. Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i. Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past week</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 8. FACIT-Fatigue

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 9. EQ-5D

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*eg, work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

Appendix 10. Recommended Clinical Management of Cholesterol

Safety monitoring of a subject's lipid panel results is recommended to include an assessment of individual subject risk for cardiovascular disease. Management of lipid levels should be determined on an individual subject level due to the individualized nature of cholesterol treatment recommendations. The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III, National Cholesterol Education Program 2002) [21] provides guiding principles for the intensity of lipid lowering therapy based on an individual's absolute risk for coronary heart disease (CHD). ATP III guidelines and/or Japan Atherosclerosis Society(JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2014 [22] should be used to determine if any lipid lowering intervention is required for a subject. Such assessments should occur throughout the study, including during the screening period and prior to randomization into the study, in light of the known co-morbidities associated with RA (e.g., metabolic syndrome, cardiovascular morbidity and mortality) and the observed increases in lipid levels in previous clinical trials with CP-690,550. Subject management of lipid elevations may be referred to the primary care physician at the discretion of the investigator.

A copy of the ATP III guidelines At-A-Glance Quick Desk Reference[23] will be provided to each study site for reference.

Appendix 11. Evaluation of Potentially Malignant Tumors, Suspicious Lymphadenopathy or Possible Extra-nodal Lymphoproliferative Disorder (LPD)

In the event of potentially malignant tumors, lymphadenopathy or possible extra-nodal lymphoproliferative disorder (LPD), which might arise in the course of this study, the following steps are to be taken.

When there is a decision to biopsy a potentially malignant tumor, lymph node, or other tissue, the investigator and/or consultants should contact the sponsor to discuss the issue and any decisions as soon as possible. It is recommended that specialists with experience in the evaluation of immunosuppressed patients be consulted.

If a biopsy for lymphadenopathy or lymphoma is to be performed, the investigator or consultant should refer to the study biopsy procedures instructions and review the following points with the surgeon and pathologist:

- Fine needle aspiration and core needle biopsy are strongly discouraged; excisional biopsy is required for accurate diagnosis;
- Tissue must be sent fresh to the pathology laboratory; the pathologist must be consulted before the procedure;
- Archive multiple frozen tissue samples, if possible;
- Include flow cytometry and cytogenetics as part of the pathologic evaluation;
- Culture for mycobacterium and fungi, if indicated;
- Collect and snap freeze peripheral blood lymphocytes for germ line evaluation (DNA);
- Archive multiple aliquots of serum samples.

For <u>all biopsies</u> of potentially malignant tumors, suspicious lymphadenopathy, or possible extranodal lymphoproliferative disorder (LPD), please request the pathologist to send the original slides used to make the definitive diagnosis, ancillary study reports, and the pathologist's report to the central laboratory for a blinded review by a central pathologist, to be paid for by Pfizer. Should the central pathologist make a diagnosis that is not essentially similar to the local pathologist's diagnosis, the site and the local pathologist will be notified and provided with an opportunity to consult with the central pathologist (paid for by Pfizer). Translation during this consultation, if needed, will be provided by the staff of the Pfizer Clinical Country Office or designee.

Both the local pathologist's diagnosis and the central pathologist's diagnosis will be reported in the study database.