PHASE 3B/4 RANDOMIZED SAFETY ENDPOINT STUDY OF 2 DOSES OF TOFACITINIB IN COMPARISON TO A TUMOR NECROSIS FACTOR (TNF) INHIBITOR IN SUBJECTS WITH RHEUMATOID ARTHRITIS

Compound:	CP-690,550-10
Compound Name:	Tofacitinib citrate
US IND Number:	CCI
European Clinical Trial Database (EudraCT) Number:	2013-003177-99
Protocol Number:	A3921133
Phase:	Phase 3b/4

Document History

Document	Version Date	Summary of Changes
Original protocol	25-Apr-2013	N/A
Amendment 1	10-Jul-2013	Prior to initiation of the study and in response to US FDA comments and recommendations, the following changes were made to the study protocol: 1. Reduced the study from 8 years to 5 years. 2. Increased N from 3900 to approximately 4000. 3. Enriched the study population to include only patients ≥50 yrs with ≥6 painful/tender joints and ≥6 swollen joints and who have at least one risk factor for cardiovascular disease. 4. Eliminated the double-blind substudy (all drug supplies are open-label). 5. Changed the comparator from all adalimumab to adalimumab in US, Puerto Rico and Canada with etanercept in the rest of world. 6. Removed the need for blinded joint assessors. 7. Have all patients on background methotrexate. 8. Allow prior use of biologic DMARDs with appropriate washout, unless intolerant or unresponsive to previous use. 9. Added Section 'Immunizations' live or live-attenuated vaccines should not be given concurrently with study medication. 10. Eliminated the 2-week visit. 11. Reduced joint counts from 66/68 to 28 at every visit. 12. Aligned the contraceptive requirements with the removal of methotrexate as a comparator. 13. Removed the following PROs: MOS Sleep Scale, FACIT-Fatigue, and RA Healthcare Resource Utilization Questionnaires and reduced the frequency of SF-36, EuroQol EQ-5D, and Work Productivity and Activity Impairment (WPAI) Questionnaires.

Document	Version Date	Summary of Changes
		14. Eliminated routine urinalysis testing, except at Screening Visit. 15. Eliminated routine ECGs, except at Screening Visit and End of Study Visit. 16. Removed laboratory testing not used in safety evaluation of either tofacitinib or TNFi's; CRP will not be blinded. 17. Monitoring and discontinuation criteria is aligned with the US approved labeling. 18. There will be no interim analyses of the data, only end of study analysis. 19. The study will be stopped on recommendation of the Steering Committee and only after consultation with the US FDA. 20. The Steering Committee will maintain Performance Standards, review metrics and implement corrective actions.
Amendment 2	16-Aug-2013	1. Typographical corrections and clarifications 2. Added Japan-specific screening and monitoring requirements. 3. Added reference for endpoint definitions and clarification regarding endpoint composite for MACE. 4. Added cholestyramine or activated charcoal elimination procedure to reduce leflunomide washout to 4 weeks.
Amendment 3	20-Nov-2013	1. Typographical corrections and clarifications. 2. Changes to reporting processes for the primary safety endpoints to limit their inclusion in AE tables reviewed outside the blinded Steering Committee. 3. Addition of a washout period for rituximab as a prohibited concomitant DMARD. 4. Removed Japan-specific screening and monitoring requirements as Japan will not be participating in this study.
Amendment 4	30-Jan-2014	1. Typographical corrections. 2. Addition of voriconazole as a prohibited concomitant medication. 3. Clarification of the role of the OTIS registry in the US only and follow-up of pregnancies.

Document	Version Date	Summary of Changes
		4. Remove the requirement for adalimumab/etanercept dispensing at Visit 2, as drug supply to sites will be sufficient to supply drug at Visit 1 and then at Visit 3. 5. Clarification of the respective roles of the Steering Committee and the DMC and provision to allow the DMC to review adjudicated and non-adjudicated primary endpoint data in an unblinded manner at the explicit request of the DMC.
Amendment 5	30-Mar-2014	1. In Section 1.2 added reference to Section 7.8 of the XELJANZ Investigator Brochure as the section that contains reference safety information. 2. Added Appendix 4 with Sweden-specific text for exclusion criteria, triggered event criteria, and the addition of the Overall Risk-Benefit Assessment (ORBA) with references to the appendix in the body of the protocol at the request of the Swedish competent authority.
Amendment 6	30-May-2014	1. Added Appendix 5 with and Czech Republic, Spain and United Kingdom-specific text for exclusion criteria, triggered event criteria, and additional laboratory testing (lymphocyte subset testing) at the request of the respective competent authorities for each country.
Amendment 7	12-Jan-2015	1. Added Appendix 6 with Canada specific text regarding the use of 2 methods of contraception, one highly effective and one effective method as per the request of the competent authority.
Amendment 8		1. Reduced treatment in the tofacitinib 10 mg BID arm to 5 mg BID in response to a recommendation from the Data Safety Monitoring Board for a safety signal. 2. Added requirement for all subjects to be provided a consent addendum, which they will be required to sign agreeing to continue in the study. 3. Deep vein thrombosis, pulmonary emboli, arterial thrombosis and arterial emboli were added to the CV adjudication charter and are noted as additional events to be adjudicated.

Document	Version Date	Summary of Changes
		4. Added mandatory revised privacy text. 5. Removed Appendix 4 as no subjects were screened or randomized in Sweden and enrollment is closed.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

PROTOCOL SUMMARY

As a commitment to the United States Food and Drug Administration (US FDA), this Post Authorization Safety Study (PASS) will evaluate the safety of tofacitinib 5 mg twice daily (BID) and tofacitinib 10 mg BID compared to a tumor necrosis factor inhibitor (TNFi).

The primary objective of this endpoint study is to evaluate the safety of tofacitinib at two doses versus a TNFi; the co-primary endpoints are adjudicated major adverse cardiovascular events (MACE) and adjudicated malignancies excluding non-melanoma skin cancers during study participation.

The study will be declared complete when all of the following conditions are met:

- At least 1500 subjects have been followed for 3 years.
- The targeted number of MACE is observed.
- The targeted number of malignancies, excluding non-melanoma skin cancers, is observed.

To achieve all of these conditions, it is expected that the study will include approximately 4000 subjects, recruited over 3 years and the total duration of the study will be approximately 5 years after the first subject is randomized.

The Steering Committee will consider the ongoing accumulation of the adjudicated primary endpoint events and performance standard metrics and may determine that sufficient events have occurred to assess the primary objectives of the study or that it is not feasible to continue the trial in pursuit of these objectives. These determinations by the Steering Committee will be made in accordance with pre-specified rules documented in the Steering Committee Charter and in the Statistical Analysis Plan and following consultations with the US FDA, and could result in recommendations for changes to the study design, including changes in number of subjects studied or duration of study.

Subject population

Adult subjects who are 50 years of age or older, with moderately or severely active rheumatoid arthritis who have had an inadequate response to methotrexate alone and who have certain risk factors for cardiovascular disease will be enrolled in this study. A minimum of approximately 4000 subjects will be enrolled in the study.

Assessments

The following assessments will be used to evaluate safety:

- Changes in physical assessments, including weight and vital signs.
- AE reporting, incidence and severity.

- Incidence and severity of safety laboratory abnormalities.
- Adherence to contraceptive use.
- Adherence to protocol requirements.
- Concomitant medication review.
- Review of eligibility to continue study drug.

The following assessments will be used to evaluate efficacy:

- 28 joint counts.
- Patient Global Assessment.
- Patient Assessment of Pain.
- Physician Global Assessment.
- C-reactive Protein (CRP).
- A number of patient reported outcomes, including the Health Assessment Questionnaire – Disability Index (HAQ-DI).

Treatments

All subjects will be enrolled on their previously prescribed dose of methotrexate and will be randomly assigned to one of three active treatment arms in the study:

- Tofacitinib 5 mg BID.
- Tofacitinib 10 mg BID.*
- TNFi: adalimumab 40 mg subcutaneous (SC) injection every other week in the United States, Puerto Rico and Canada; etanercept 50 mg SC injection weekly in all other countries.

* In response to new safety information about tofacitinib that was provided to Study A3921133 investigators on 19 February 2019, investigators were notified to verbally inform subjects randomized to tofacitinib 10 mg BID to reduce the dose of tofacitinib to 5 mg BID within 7 calendar days of this notification, secure their verbal agreement to continue in the study, and if they agreed, reduce their dose of tofacitinib to 5 mg BID for the remainder of the study. Tofacitinib is supplied as 5 mg tablets, which allowed subjects to decrease from their previous dose of 2 tablets twice daily to 1 tablet twice daily.

Adjustments to methotrexate and other background medications will be allowed during the study with provisions to allow subjects who are not adequately treated with study drug to switch to standard of care while remaining in the study.

The study will be open-label and the randomization scheme for the study population (approximately 4000 subjects) will be in a ratio of 1:1:1 with approximately 1300 subjects randomized to tofacitinib 5 mg BID; approximately 1300 subjects randomized to tofacitinib 10 mg BID (subjects are switched to 5 mg BID per Amendment 8); and approximately 1300 subjects randomized to a TNFi.

Safety Analysis

The safety analysis will include all subjects in the study.

The primary statistical safety objective is the estimation of the hazard ratios relative to the TNF inhibitor control for the two tofacitinib doses combined and for each dose of tofacitinib separately for the co-primary events of major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancers. Analyses of primary safety endpoints will be based upon adjudicated events.

Both total time (ITT) and on treatment analyses of the main safety endpoints will be conducted. The on treatment analysis for MACE will censor subjects who cross over from tofacitinib or adalimumab to standard of care at 60 days after standard of care is initiated. The principal analysis for malignancies will not censor for subjects crossing to standard of care (ie, will be the total time analysis).

Secondary safety endpoints will be summarized according to treatment received at the time of the event.

For the purposes of statistical analyses, subjects who were randomized to tofacitinib 10 mg BID will be maintained in the tofacitinib 10 mg BID treatment arm after reducing the dose of tofacitinib to 5 mg BID.

SCHEDULE OF ACTIVITIES BY VISIT (SCREENING – MONTH 6)

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to 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 unplanned visits in addition to those listed on the schedule of activities, in order to conduct assessments required to protect the well-being of the subject.

Protocol Activities – Screening to Month 6	**Screen**	**Visit 1** Day 1	**Visit 2** Month[f] 2	**Visit 3** Month[f] 3	**Visit 4** Month[f] 6
Visit Windows (see Section 6.2.1 for further detail)	NA	See 6.2.1	±2 weeks	±1.5 months	±1.5 months
Informed Consent	X				
Medical History and Confirm Diagnosis	X				
Physical Examination, including height	X				
Assessment of New Physical Findings		X	X	X	X
Weight, Vital Signs	X	X	X	X	X
Inclusion/Exclusion criteria	X	X			
Blood Chemistry[a], Hematology[a]	X	X	X	X	X
C-reactive Protein (CRP)	X	X	X	X	X
Banked Biospecimens		X			
HIV Serology, HBsAg, HBcAb, HBsAb[b]	X				
HCV Ab, HCV RNA[c]	X				
Lipid Profile (fasting)	X	X	X		
Pregnancy test[d]	X	X	X	X	X
QuantiFERON Gold®™ In-Tube Test	X				
Rheumatoid Factor	X				
Anti-cyclic citrullinated peptide (anti-CCP)	X				
Urinalysis	X				
Chest X-ray	X				
ECG	X				
Randomization		X			
Study Medication Dispensing		X		X	X
Contraceptive Use Documentation	X	X	X	X	X
Joint Count (28)	X	X	X	X	X
Patient Assessment of Arthritis Pain		X	X	X	X
Patient Global Assessment of Arthritis		X	X	X	X
Physician Global Assessment of Arthritis		X	X	X	X
HAQ-DI		X	X	X	X
SF-36 (Version 2, Acute)		X		X	X
EuroQol EQ-5D		X		X	X
Work Productivity and Activity Impairment (WPAI)		X		X	X
Safety Assessment/ AE Reporting		X	X	X	X
Concomitant Medication Review	X	X	X	X	X
End of Study Assessment					

a. Re-testing of abnormal laboratories may be required (see Section 7.15).
b. See Exclusion Criteria 4e and 4f for details.
c. See Exclusion Criteria 4g for details.
d. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.
e. History of concomitant medications at Screening includes a history of prior DMARD treatment.
f. Calendar months.

SCHEDULE OF ACTIVITIES BY VISIT (MONTH 9 – END OF STUDY)

Visits are outlined through Month 60, but will continue sequentially until the end of study is declared, at which time all subjects will be required to return for an End of Study Visit.

Protocol Activities – Months 9 to 60 and End of Study Follow-up Visit	**Visits 5, 9, 13, 17, 21** [Months[f] 9, 21, 33,45, 57]	**Visit 6, 10, 14, 18, 22** [Months[f] 12, 24, 36, 48, 60]	**Visits 7, 11, 15, 19** [Months[f] 15, 27, 39, 51]	**Visits 8, 12, 16, 20** [Months[f] 18, 30, 42, 54]	**End of Study Visit**	**End of Study Follow Up[g]**
Visit Windows (see Section 6.2.1)	±1.5 months	±1.5 months	±1.5 months	±1.5 months	±1.0 months	+0.5 months
Assessment of New Physical Findings	X	X	X	X	X	X
Weight, Vital Signs	X	X	X	X	X	X
Blood Chemistry[a], Hematology[a]	X	X	X	X	X	
C-reactive Protein (CRP)	X	X	X	X	X	
Banked Biospecimens		X[b]			X	
Lipid Profile (fasting)		X			X	
Pregnancy test[c]	X	X	X	X	X	X
QuantiFERON Gold®™ In-Tube Test		X[d]				
Chest X-ray		X[e]			X[e]	
ECG					X	
Study Medication Dispensing	X	X	X	X		
Contraceptive Use Documentation	X	X	X	X	X	X
Joint Count (28)	X	X	X	X	X	
Patient Assessment of Arthritis Pain	X	X	X	X	X	
Patient Global Assessment of Arthritis	X	X	X	X	X	
Physician Global Assessment of Arthritis	X	X	X	X	X	
HAQ-DI	X	X	X	X	X	
SF-36 (Version 2, Acute)		X			X	
EuroQol EQ-5D		X			X	
Work Productivity and Activity Impairment (WPAI) Questionnaire		X			X	
Safety Assessment/ AE Reporting	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X
End of Study Assessment					X	

a. Re-testing of abnormal laboratories may be required (see Section 7.15).
b. Month 12 visit only.
c. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.
d. QFT is not performed in subjects who had a positive test previously and were adequately treated for latent TB, subjects newly testing positive for latent TB with negative CXR and no evidence of active disease are required to start a 9 month treatment course of isoniazid to continue in the study.
e. Only for subjects testing positive to QFT at annual visit.
f. Calendar Months.
g. Occurs 28 days after End of Study visit.

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1. INTRODUCTION

1.1. Indication

Tofacitinib (CP-690,550) is a novel, oral Janus kinase (JAK) inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy in Rheumatoid Arthritis (RA).[1,7]

1.2. 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.[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 heterodimers containing JAK1 or JAK3 (JAK1/3) with functional selectivity over JAK2 homodimer signaling.[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. Tofacitinib is efficacious in rodent models of arthritis as assessed by clinical and histological measures of disease progression in the mouse collagen-induced arthritis (CIA) and rat adjuvant-induced arthritis (AIA) models. Tofacitinib is also efficacious in delayed type hypersensitivity models[5] and rodent and primate transplant models.[5, 6] Thus, tofacitinib shows promise in multiple models of autoimmunity and immune dysregulation. The broad immunosuppressive, immunomodulatory mechanisms of JAK3 inhibition is expected to block cytokine signaling which plays a key role in the pathogenesis of psoriasis, and dampen innate and adaptive immune responses which plays a role in ulcerative colitis. The anti-inflammatory properties of JAK are expected to inhibit the effect of the infiltrating lymphocytes in the ocular surface and lacrimal gland.

RA is a chronic and debilitating autoimmune disease characterized by inflammation and destruction of the joints, substantial disability, and a significant impact on health status and quality of life; this results in a substantial economic burden to patients and society.[8] In kinase assays, tofacitinib inhibits JAK1, JAK2, and JAK3, and to a lesser extent tyrosine kinase 2; in cellular settings, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over JAK2-paired receptors. 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,[7,9] which are integral to lymphocyte function, and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response.

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[10] or in combination with background methotrexate (MTX).[11] Tofacitinib 5 and 10 mg BID were selected as optimal doses for

evaluation in Phase 3, which included a broad range of therapeutic scenarios investigating tofacitinib as monotherapy[12] or in combination with MTX[13,14] and non-MTX nonbiologic disease modifying antirheumatic drugs (DMARDs).[15]

Phase 3 studies were initiated with two doses of tofacitinib, 5 mg BID and 10 mg BID, administered as monotherapy or concurrently on a background of non-biologic DMARDs. These 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 similar safety profile as seen in the controlled clinical trials. The preponderance of long-term data collected in these trials was obtained in patients on 5 mg BID of tofacitinib.

This Post-Authorization Safety Study (PASS) was developed in response to the requirements of the US Food and Drug Administration to further define the safety profile of tofacitinib 5 mg BID and 10 mg BID, especially with respect to major adverse cardiovascular events (MACE) and malignancies, and to provide comparative safety analyses to a TNF inhibitor in an open-label manner.

The subcutaneously self-administered TNFi's, adalimumab and etanercept, will be included in this study. Subjects randomized to receive TNFi in the United States (US), Puerto Rico and Canada will receive adalimumab; in all other countries, subjects randomized to receive TNFi will receive etanercept.

Based on the totality of the non-clinical and clinical data generated thus far, identified risks associated with tofacitinib include infection, lipid elevations, anemia, neutropenia and malignancies. The identified risks for the completed studies with tofacitinib in RA are presented in the XELJANZ™ (tofacitinib citrate) Investigator Brochure.

New safety information about tofacitinib was provided to Study A3921133 investigators on 19 February 2019. That information stated that Pfizer received communication from the Tofacitinib Rheumatology Data Safety Monitoring Board (DSMB) stating that on the basis of the data reviewed thus far in Study A3921133, there is a statistically and clinically important difference in the occurrence of pulmonary embolism within the tofacitinib 10 mg BID treatment arm compared to the TNFi control arm, and the overall incidence per person year in the tofacitinib 10 mg BID arm is substantially higher than the TNFi control arm and substantially higher than observed in other studies across the tofacitinib program. Additionally, the DSMB noted an increase in all-cause mortality in the 10 mg BID arm compared to the tofacitinib 5 mg BID and TNFi treatment arms.

Based on the totality of evidence including a review of selected efficacy parameters and a finding of only minor increments in efficacy with tofacitinib 10 mg BID beyond the efficacy seen in the 5 mg BID group, the DSMB further stated that continued treatment with tofacitinib 10 mg BID in Study A3921133 entails a risk that is not sufficiently balanced.

The DSMB stated they also believe that the risk-benefit profile of tofacitinib 5 mg BID in comparison to TNFi control remains appropriately balanced, and that the scientific question of evaluating the safety of tofacitinib 5 mg BID versus TNFi with respect to the co-primary and secondary safety endpoints in Study A3921133 is worthwhile and important.

For this reason, the DSMB has recommended modifying Study A3921133 to discontinue treatment with tofacitinib 10 mg BID. They further recommended that patients in the tofacitinib 5 mg BID and TNFi control treatment arms should continue to receive their assigned treatments.

Pfizer has accepted this recommendation and with Amendment 8 is modifying the tofacitinib 10 mg BID treatment arm accordingly. Investigators were instructed to contact all subjects taking tofacitinib 10 mg BID within 7 calendar days and verbally inform them of this information, secure their verbal agreement to continue in the study and if they agreed, reduce their dose of tofacitinib to 5 mg BID. This amendment documents these changes and requires all subjects to sign the Addendum to the Informed Consent Document at their next study visit, explaining the safety information and secure their agreement to continue in the study.

The comparator TNFi, adalimumab, is reported to be associated with risks of infection, malignancy, anaphylaxis or serious allergic reactions, demyelinating disease, cytopenias, pancytopenia, heart failure, and Lupus-like syndrome. The identified risks for adalimumab in RA are presented in the Humira® (adalimumab) United States Package Insert (USPI), content revised January 2019.

The comparator TNFi, etanercept, is reported to be associated with risks of infection, malignancy, demyelinating disease, lymphoma, congestive heart failure, pancytopenia or aplastic anemia, anaphylaxis or serious allergic reactions, Lupus-like syndrome or autoimmune hepatitis. The identified risks for etanercept in RA are presented in the Enbrel® (etanercept) EU SmPC, revised October 2017.

Complete information for tofacitinib may be found in the Single Reference Safety Document (SRSD), which for this study is the XELJANZ™ (tofacitinib citrate) Investigator Brochure, Section 7.8 Undesirable Effects (All indications); the Single Reference Safety Document for the comparator agent, adalimumab, is the USPI, revised January 2019; the Single Reference Safety Document for etanercept is the EU SmPC, revised October 2017.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Safety

The primary objective of this endpoint study is to evaluate the safety of tofacitinib at two doses versus TNFi; the co-primary endpoints are adjudicated major adverse cardiovascular events (MACE) and adjudicated malignancies excluding non-melanoma skin cancers during study participation.

The following assessments will be used to evaluate safety in the entire study population:

- Changes in physical assessments, including weight and vital signs.
- AE reporting, incidence and severity.
- Incidence and severity of safety laboratory abnormalities.
- Adherence to contraceptive use.
- Adherence to protocol requirements.
- Concomitant medication review.
- Review of eligibility to continue study drug

2.1.2. Efficacy

The following assessments will be used to evaluate efficacy in the study population:

- 28 joint counts.
- Patient Global Assessment.
- Patient Assessment of Pain.
- Physician Global Assessment.
- C-reactive Protein (CRP).
- A number of patient reported outcomes, including the Health Assessment Questionnaire – Disability Index (HAQ-DI).

2.2. Endpoints

This study will use independent endpoint adjudication committees for the adjudication of events of interest (EoI), including the co-primary endpoints. For those events meeting the co-primary endpoint pre-defined criteria, the Steering Committee will be responsible for reviewing the aggregate accumulation of these events and for informing the Sponsor of recommendations made (eg, to continue the study or to stop the study). All other adjudicated events (eg, opportunistic infections, hepatic events, non-primary CV or malignancy events) will be reported in the usual fashion (See Section 8 Adverse Event Reporting).

The investigator for the site of incidence will be notified of any malignancy or cardiovascular event reported as an EoI that is adjudicated by the Endpoint Adjudication Committee as NOT meeting endpoint criteria; the investigator at the study site must re-evaluate the EoI and report the event to Pfizer. SAEs must be reported in accordance with the timeframes described in the Serious Adverse Event Reporting Requirements section of this protocol (See 8.13). The investigator's SAE awareness date in this instance is identified as the date that the investigator site of incidence receives the notification that an EoI does not meet endpoint

criteria. Handling SAEs in this manner will allow Pfizer to meet its Sponsor reporting obligations to regulatory authorities upon receipt of such SAEs. Any EoI that are pending adjudication at the annual safety report cutoff date will not be included in the safety tables of the annual report.

2.2.1. Safety Endpoints

The safety endpoints will be collected and analyzed for all subjects in the study, through the end of the study.

2.2.1.1. Co-Primary Safety Endpoints

The following co-primary safety endpoints will be analyzed to provide comparative rates for tofacitinib vs. the combined TNFi:

- Malignancies, excluding non-melanoma skin cancers (adjudicated).
- Major adverse cardiovascular events (MACE) (adjudicated).

The definitions of MACE used in this study are consistent with those outlined in the Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials[22] with the exclusion of cardiovascular death due to pulmonary embolism. The following events are included, as defined:

- Cardiovascular death.
    - Death due to acute myocardial infarction (MI).
    - Sudden cardiac death.
    - Death due to heart failure.
    - Death due to stroke.
    - Death due to cardiovascular procedures.
    - Death due to cardiovascular hemorrhage.
    - Death due to other cardiovascular causes: peripheral artery disease.
- Non-fatal myocardial infarction (MI).
- Non-fatal stroke of any classification, including reversible focal neurologic defects with imaging evidence of a new cerebral lesion consistent with ischemia or hemorrhage.

2.2.1.2. Secondary Safety Endpoints

The secondary safety endpoints will include an evaluation of the following events:

- Opportunistic infection events including tuberculosis (adjudicated).
- Hepatic events (adjudicated).
- Cardiovascular events other than MACE (adjudicated).
- All adverse events (AEs), including serious adverse events (SAEs).
- Clinically significant abnormal laboratory parameters.
- All cause mortality (adjudicated).
- Reasons for permanent or temporary discontinuation of study medication.

2.2.2. Efficacy Endpoints

Efficacy endpoints will include:

- Change from baseline to each post-baseline scheduled visit in DAS28-4 (CRP). Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI).
- Rate of remission at each post-baseline scheduled visit including:
  - ACR-EULAR Boolean remission (defined as the subject satisfying all of the following: tender joint count ≤1, swollen joint count ≤1, C-reactive protein ≤1 mg/dL, patient global assessment ≤1 on a 0-10 scale).
  - SDAI ≤3.3.
  - CDAI ≤2.8.
- Rate of low disease activity (LDA) at each post-baseline scheduled visit including:
  - SDAI ≤11.
  - CDAI ≤10.
  - DAS28-4(CRP) ≤3.2.
- ACR20, ACR50, and ACR70 response rate of at each post-baseline scheduled visit.
- Change from baseline to each post-baseline scheduled visit in the HAQ-DI.

3. STUDY DESIGN

This is a Phase 3b/4 randomized, parallel arm, open-label safety endpoint study. All subjects will be randomized in a 1:1:1 ratio to one of the three treatment arms with approximately 1300 subjects in each treatment arm:

1. Tofacitinib 5 mg BID (oral).

2. Tofacitinib 10 mg BID (oral).*

3. TNFi: In the US, Puerto Rico and Canada, subjects randomized to TNFi will receive adalimumab 40 mg every other week (QOW) by subcutaneous injection (SC); in all other countries, subjects randomized to TNFi will receive etanercept 50 mg once weekly by SC injection.

* In response to new safety information about tofacitinib that was provided to Study A3921133 investigators on 19 February 2019, investigators were notified to verbally inform subjects randomized to tofacitinib 10 mg BID to reduce the dose of tofacitinib to 5 mg BID within 7 calendar days of this notification, secure their verbal agreement to continue in the study, and if they agreed, reduce their dose of tofacitinib to 5 mg BID for the remainder of the study. Tofacitinib is supplied as 5 mg tablets, which allowed subjects to decrease from their previous dose of 2 tablets twice daily to 1 tablet twice daily.

During the study, subjects may require alternate therapies in addition to, or instead of, their randomized drug assignment. All subjects, regardless of their treatment regimen will participate in the study until study completion. (See Sections 5.6.1 and 6.5).

Study completion will be declared when all 3 of the following conditions are met:

1. At least 1500 subjects have been followed for at least 3 years.

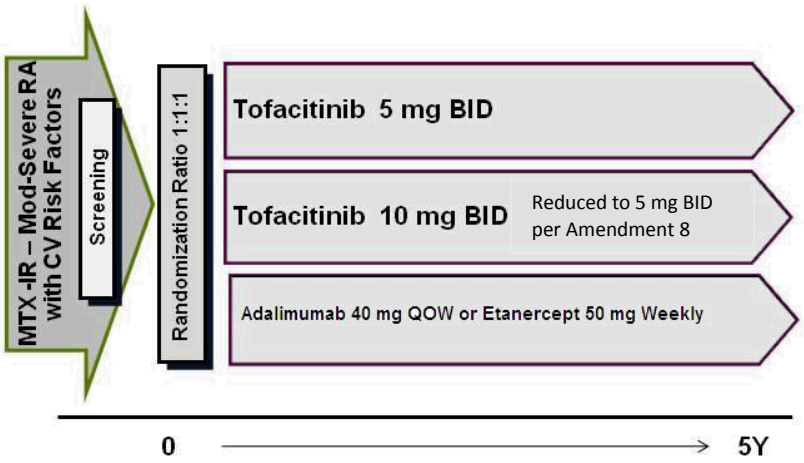
2. The targeted number of MACE are observed (See Section 9.2.1).

3. The targeted number of malignancies excluding non-melanoma skin cancers are observed (See Section 9.2.1).

It is expected that approximately 4000 subjects will participate in the study and the expected duration of the study is approximately 5 years following randomization of the first subject. The exact number of subjects and duration of the study will be determined by the pre-specified rules outlined in the charter of the blinded Steering Committee. (See Section 9.6)

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

Figure 1. Study Design (Minimum 1300 Per Arm, Total N=4000)



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 non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

All subjects are required to meet the inclusion and exclusion criteria defined below.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified 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 legal representative) has been informed of all pertinent aspects of the study.

2. Must be at least 50 years of age or older.

3. Has moderate to severe rheumatoid arthritis inadequately controlled with methotrexate alone with a score of 6 or greater on the 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis (Appendix 1).

4. Has ≥6 tender/painful joints on motion and ≥6 swollen joints (28 joint count).

5. Has a C-reactive protein measured by a high sensitivity assay (hs-CRP) ≥0.3 mg/dL in the central laboratory.

6. Meets Class I, II or III of the American College of Rheumatology (ACR) 1991 Revised Criteria for Global Functional Status in RA where usual self-care activities including dressing, feeding, bathing, grooming, and toileting; avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are subject-desired and age- and sex-specific.

    - 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.

7. Has taken methotrexate continuously for at least 4 months prior to the Screening visit and has taken a stable weekly dose of methotrexate with supplemental folic or folinic acid for at least 6 weeks prior to the Baseline visit.

    - Methotrexate doses less than 15 mg/week are allowed only in the presence of documented intolerance or toxicity from higher doses.

    - Doses higher than 25 mg/week are not permitted under any circumstances.

    - Folic acid doses should be at least 5 mg per week; folinic acid doses should be at least 2.5 mg per week.

8. Have at least one of the following cardiovascular risk factors at screening:

    - Current cigarette smoker.

    - Diagnosis of hypertension.

    - High density lipoprotein (HDL) <40 mg/dL.

    - Diabetes mellitus.

    - Family history of premature coronary heart disease (CHD); the family history should be considered positive for premature CHD if clinical CHD or sudden death can be documented in a first degree male relative younger than 55 years of age or in a first degree female relative younger than 65 years of age.

    - Presence of extra-articular disease associated with rheumatoid arthritis, which may include nodules, Sjögren's syndrome, anemia of chronic disease and pulmonary manifestations.

- History of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina, acute coronary syndrome.

9. Subjects must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

10. Male and female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active. (For Canada, please refer to Appendix 6 for specific contraception requirements).

11. Female subjects of childbearing potential must test negative for pregnancy.

12. Female subjects who are not of childbearing potential must meet at least one of the following criteria:

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure or;
    - Achieved postmenopausal status, defined as: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulation hormone (FSH) level within the laboratory's reference range for postmenopausal females.

13. Subjects must screen negative for active tuberculosis or inadequately treated tuberculosis infection (active or latent) as evidenced by the following:

    a. Negative QuantiFERON Gold®™ In-Tube test performed at screening:

        - This is required unless the subject has been adequately treated for active or latent tuberculosis or a negative QuantiFERON Gold®™ In-Tube test was previously performed and documented within the 3 months prior to screening.
        - A negative tuberculin skin test (TST) is one that is <5 mm induration and it can be substituted for the QuantiFERON Gold ® ™ In-Tube test only if the central laboratory is unable to perform the test or the test is reported as indeterminate after at least 2 successive attempts.
        - It is strongly recommended that subjects with a history of Bacille Calmette Guérin (BCG) vaccination be tested with the QuantiFERON Gold®™ In-Tube test.

    b. Chest radiograph taken at screening without changes suggestive of active tuberculosis (TB) infection, unless previously performed and documented within 3 months prior to screening (see Section 7.3).

c. No history of tuberculosis infection unless one of the following is documented:

- Subject with prior or current latent tuberculosis has no evidence of active tuberculosis and must be taking or have completed an adequate course of therapy for latent tuberculosis (9 months of isoniazid in a locale where rates of primary multi-drug resistant TB infection are <5% or an alternative regimen recognized by the World Health Organization) and a chest radiograph is negative for active disease; the chest radiograph must be obtained at screening or, if previously performed and documented, within 3 months prior to screening (see Section 7.3).

- Subject with prior active tuberculosis has no current evidence of active disease and has completed an adequate course of therapy for active tuberculosis (a multi-drug regimen recognized by the World Health Organization) and a chest radiograph is negative for active disease; the chest radiograph must be obtained at screening or, if previously performed and documented, within 3 months prior to screening (see Section 7.3).

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study and the reason for exclusion from the study will be documented:

1. Subjects who are investigational site staff members directly involved in the conduct of the trial 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 trial.

2. Subjects who are classified Class IV of the ACR 1991 Revised Criteria for Global Functional Status in RA (ie, are limited in their ability to perform usual self-care, vocational, and avocational activities).

3. Pregnant females; breastfeeding females; sexually active males and females 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 last dose of investigational product (for Canada, please refer to Appendix 6 for specific contraception requirements).

4. Subjects with infections or history of infections:

   a. Any infection requiring treatment within 2 weeks prior to the Baseline visit.

   b. Any infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the past 6 months.

   c. Infected joint prosthesis at any time with the prosthesis still in situ.

   d. Recurrent (more than one episode) herpes zoster or disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.

e. Subjects will be screened for human immunodeficiency virus (HIV). Subjects who test positive for HIV will be excluded from the study.

f. Subjects will be screened for hepatitis B virus infection. Subjects with hepatitis B surface antigen (HBsAg) negative testing but who test positive for hepatitis B core antibody (HBcAb) must have further testing for hepatitis B surface antibody (HBsAb). If HBsAb is negative, the subject will be excluded from the study.

g. Subjects will be screened for hepatitis C virus antibodies (HCV Ab). Subjects with positive HCV Ab tests will be reflex tested for hepatitis C virus ribonucleic acid (HCV RNA). Only subjects with negative HCV Ab or HCV RNA will be allowed to enroll in the study.

h. Subjects are excluded for current active tuberculosis infection or prior active or latent tuberculosis that was inadequately treated or cannot be documented (See Section 4.1 Inclusion Criteria #13).

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

6. Subjects with any uncontrolled clinically significant laboratory abnormality or any of the following laboratory abnormalities (For additional Sweden-specific laboratory criteria, see Appendix 4 and Czech Republic, Spain and United Kingdom-specific laboratory criteria, see Appendix 5):

   a. Evidence of hematopoietic disorder or hemoglobin <9 g/dL.

   b. White blood cell count $<3.0 \times 10^9$/L ($<3000/mm^3$).

   c. Absolute lymphocyte count $<0.5 \times 10^9$/L ($<500/mm^3$).

   d. Absolute neutrophil count $<1.0 \times 10^9$/L ($<1000/mm^3$).

   e. Platelet count $<100 \times 10^9$/L ($<100,000/mm^3$).

   f. Alanine aminotransferase (ALT), or aspartate aminotransferase (AST) >1.5 times the upper limit of normal (x ULN).

   g. Estimated glomerular filtration rate (GFR) <60 mL/min using the Cockcroft-Gault formula (Appendix 3).

7. Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks or 5 half-lives (whichever is longer) after discontinuation of the investigational compound before the current study begins and/or during study participation, unless further restrictions to class of compound are specified in Section 4.2 Exclusion Criteria and Section 5.5 Concomitant Medication(s).

8. Subjects requiring or have received any prohibited concomitant medication as outlined in Appendix 2, including:

    a. Subjects who have received live or live attenuated vaccines within 6 weeks prior to the first dose of study drug or at any time during treatment or within 6 weeks following discontinuation of study drug (See Section 4.4.2).

    b. Subjects who have been previously treated with tofacitinib.

    c. Subjects who are being treated with biologic or non-biologic DMARDs other than MTX or antimalarials within their specified washout window at study entry (see Table 1).

    d. Subjects who previously experienced inadequate response, intolerance, allergy or hypersensitivity to adalimumab (US, Puerto Rico and Canada) or to etanercept (all other countries) or for whom adalimumab (US, Puerto Rico and Canada) or etanercept (all other countries) are contraindicated.

    e. Subjects who are being treated with corticosteroids, other than low dose oral corticosteroids in doses equivalent to ≤10 mg prednisone per day at study entry.

    f. Subjects who require concomitant treatment with medications that are potent inhibitors of cytochrome P450 3A4 (CYP3A4), both moderate inhibitors of CYP3A4 and potent inhibitors of CYP2C19, or potent CYP inducers.

9. Subjects who have Class III or Class IV heart failure according to the New York Heart Association (NYHA) functional classification system.

10. Subjects with a screening 12-lead electrocardiogram that demonstrates clinically significant abnormalities requiring urgent treatment (eg, acute myocardial infarction, serious tachy- or bradyarrhythmias) or that is indicative of serious underlying heart disease (eg, cardiomyopathy, major congenital heart disease, low voltage in all leads).

11. Subjects who had significant trauma or surgical procedure within 1 month prior to the Baseline visit.

12. Subjects with any rheumatic autoimmune disease, other than RA and Sjogren's syndrome.

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

14. Subjects with lymphoproliferative disorders (eg, Epstein Barr Virus (EBV) related lymphoproliferative disorder), a history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.

15. Alcohol or substance abuse unless in full remission for greater than 6 months prior to first dose of study drug.

16. 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. Study treatments include orally administered tofacitinib and subcutaneously injected adalimumab in the US, Puerto Rico and Canada or subcutaneously injected etanercept in all other countries.

4.4. Life Style Guidelines

4.4.1. Non-Pharmacologic Interventions

The subject may continue or initiate all non-pharmacologic therapies, such as physical therapy, as indicated and deemed appropriate for his/her physical condition.

4.4.2. Vaccine Guidelines

It is recommended that subjects be up to date on all recommended vaccinations prior to enrollment in the study, including pneumococcal vaccine, herpes zoster vaccine, and flu vaccine.

Vaccination with live components should not be given concurrently with study medication. In addition, current routine household contact with children and others who have been vaccinated with live vaccine components may pose a risk during treatment and for 6 weeks following completion of the study. Some of these vaccines include adenovirus Type 4 & Type 7, BCG, Dengue Fever, herpes zoster ("shingles"), measles, mumps, rubella, varicella, oral polio vaccine, rotavirus, Yellow Fever, and the intranasal flu vaccine.

Subjects should avoid household contact with individuals receiving live or attenuated vaccinations; some examples include: varicella, attenuated typhoid fever, oral polio, attenuated rotavirus, FluMist® (inhaled flu vaccine).

4.4.3. Dietary Supplements

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 moderate or potent CYP3A inhibition or induction. Otherwise, herbals with pharmaceutical properties should not be given concurrently with study drug.

4.4.4. Surgery

It is recommended that subjects who require major surgery temporarily discontinue study medication approximately 2 weeks prior to the surgical procedure, unless there are other safety concerns that require earlier discontinuation; if discontinued, study medication can be resumed following the surgical procedure when the sutures/staples are removed. If absorbing sutures or chemical closure methods are utilized, study medication can be resumed when the operative site is sufficiently healed and risk of infection is minimal.

If a biopsy is performed during the course of the study, histopathology slides should be sent to the central laboratory for processing and over-read by the central pathology laboratory. Subjects should be treated based on the local pathology results.

4.4.5. 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, in consultation with the subject, will select the most appropriate method of contraception for the individual subject from the permitted list of contraception methods, and instruct the subject in its consistent and correct use. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the subject to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected (for Canada, please refer to Appendix 6 for specific contraception requirements).

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:

1. Established use of oral, inserted, injected or implanted hormonal methods of contraception are allowed provided the subject remains 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, suppository).

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

5. Bilateral tubal ligation or bilateral salpingectomy.

4.5. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial 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, subject study number, 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 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 they will be directed back to the investigational site.

4.6. Rater Qualifications

This study will use a Joint Count Assessor to assess the number of swollen and tender/painful joints, as part of the assessment of RA activity. The Joint Count Assessor should be a health care provider who has been trained in rheumatology and specializes in the treatment of patients with rheumatoid arthritis or has experience in conducting at least 20 joint count assessments in clinical trials or has been trained by a health care professional and conducted over 20 supervised joint count assessments.

5. STUDY TREATMENTS

Study treatments include tofacitinib 5 mg BID or 10 mg BID (10 mg BID reduced to 5 mg BID with Amendment 8), administered orally, as the citrate salt tablet formulation or TNFi (adalimumab 40 mg administered every other week in solution for subcutaneous injection in the US, Puerto Rico and Canada or etanercept 50 mg administered weekly in solution for subcutaneous injection in all other countries). Subjects will be randomized to one of the three treatment arms.

5.1. Allocation to Treatment

Subjects will be allocated to receive open-label drug supplies in accordance with the randomization schedule.

Randomization will be accomplished using IVRS (an automated web/telephone randomization system provided by the sponsor). The IVRS contains the randomization schedule. At the Screening Visit, the investigative site will contact the IVRS (online or by telephone call). The site will enroll the subject into the IVRS by indicating minimal information sufficient to distinguish one subject from another (eg, date of birth and initials) 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 is 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; enrollment will be controlled by the 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 subjects will be provided open-label study medication through the end of the study.

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

With Amendment 8, those subjects previously randomized to tofacitinib 10 mg BID will only receive 1 bottle of 5 mg tablets instead of 2 bottles at each visit.

5.2. Breaking the Blind

All drug supplies will be open-label supplies and labeled appropriately to include drug substance, dose, and dosing instructions. There will be no need to "break the blind" as drug will not be blinded.

5.3. Drug Supplies

5.3.1. Formulation and Packaging

Each bottle of tofacitinib and prefilled syringe of either adalimumab or etanercept will be labeled appropriately as per the regulatory label requirement. Refer to investigational product manual for details on clinical packaging.

5.3.1.1. Open-Label Study Medication

5.3.1.1.1. Tofacitinib Supplies

Tofacitinib will be provided as 5 mg tablets for oral administration by the Sponsor. Tablets will be supplied in bottles as appropriate for the dosing regimen.

5.3.1.1.2. Comparator Study Medication: Adalimumab Supplies

The comparator adalimumab will be provided as 40 mg prefilled syringes for injection in cartons by Sponsor or sourced locally by the study sites.

5.3.1.1.3. Comparator Study Medication: Etanercept Supplies

The comparator etanercept will be provided as 50 mg prefilled syringes for injection in cartons by the Sponsor.

5.3.2. Preparation and Dispensing

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

5.3.3. Administration

All subjects must continue using their personal supply of methotrexate. The pre-study stable dose of methotrexate will be continued in all subjects throughout the study, unless modification is clinically indicated.

Subjects will be trained prior to receiving their study medication supplies in the proper techniques for study medication administration, including proper self-injection, if required. 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. The amount of trial medication dispensed at each visit must be recorded. At each drug dispensing study visit the subject must return the trial medication containers and any unused medication and unused syringes for accountability and the amount of drug returned will be recorded to account for all dispensed trial medication.

Dosage of adalimumab used in this study (subcutaneous injections of 40 mg every other week) is as approved in the Single Reference Safety Document (SRSD) for adalimumab in patients with RA, as identified in Section 1 of this protocol.

Dosage of etanercept used in this study (subcutaneous injections of 50 mg every week) is as approved in the Single Reference Safety Document (SRSD) for etanercept in patients with RA, as identified in Section 1 of this protocol.

5.3.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong drug, 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 adverse event (AE) page of the case report forms (CRFs) 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 and, if applicable, any associated adverse event(s) is

captured on an adverse event (AE) CRF page (refer to Adverse Event Reporting section for further details).

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 sections provide examples of overdosage for each study medication.

5.3.4.1. Tofacitinib Overdosage

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 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.

Please note, that concomitant treatment with a prohibited potent CYP3A inhibitor (Appendix 2) is assumed to result in a doubling of exposure. Thus, the doses noted above should be reduced by one half for each of the time intervals if the subject is taking a prohibited potent CYP3A inhibitor. For further details, please refer to the XELJANZ™ (tofacitinib) Investigator Brochure.

5.3.4.2. Adalimumab Overdosage

Doses up to 10 mg/kg have been administered to subjects in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the subject be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately as described in the locally approved labeling for adalimumab.

5.3.4.3. Etanercept Overdosage

Toxicology studies have been performed in monkeys at doses up to 30 times the human dose with no evidence of dose-limiting toxicities. No dose-limiting toxicities have been observed

during clinical trials of etanercept. Single intravenous doses up to 60 mg/m^2 (approximately twice the recommended dose) have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities.

5.3.5. Compliance

Compliance with expected consumption of dispensed medication will be assessed by determining the expected number of doses to be taken during any given time period and comparing that to the number of doses returned, keeping in mind that subjects may have their study drug temporarily withheld due to abnormal laboratory tests, adverse events, or the need to take a short course of a prohibited concomitant medication. Doses not taken during these events do not constitute protocol deviations and should not be considered dosing errors, but should be noted in the dosing log with the reason for reduced drug consumption.

Subjects, who are less than 80% compliant with the orally administered dosage regimen or have not used 2 or more injectable syringes expected to be used in the interval, will be counseled and the site will implement appropriate measures to secure subject compliance, including instituting interim visits to evaluate and encourage compliance, as appropriate to the site and reason for non-compliance.

When compliance of less than 70% of the expected number of doses for any one of the orally administered study medications or the subject has not used 3 or more injectable syringes that were expected to be used in the interval is suspected, the reason for non-compliance (more than or less than expected consumption) with the dosing regimen should be documented in the dosing log of the subject's case report form, and should be reported as a protocol deviation and unless there is a protocol stipulated reason for non-compliance with the dosing regimen, this should be recorded as a dosing error.

When compliance of more than 120% of the expected number of doses for the orally administered dosage regimen or have used 2 or more injectable syringes than was expected to be used in the interval, the reason for non-compliance (more than expected consumption) with the dosing regimen should be documented in the dosing log of the subject's case report form with the reason for non-compliance, reported as a protocol deviation, and recorded as a dosing error.

5.4. Drug Storage and Drug Accountability

The investigational drug product should be stored in accordance with the drug label. Storage conditions stated in the SRSD (ie, Investigator Brochure (IB) for tofacitinib, United States Package Insert (USPI) for adalimumab, EU SmPC for etanercept, or Local Product Document (LPD)) will be superseded by the drug label storage requirements.

Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

Investigators and site staff are reminded to check temperatures daily (ie, manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for both the room storage and refrigerator storage. Any temperature excursions should be reported to the sponsor in accordance with Drug Administration Information (DAI) sheets provided to the site.

To ensure adequate records, all drug supplies will be accounted for in the drug accountability inventory forms and will be monitored by the accounting of unused study medication returned by the patients. At the end of the clinical trial, all drug supplies unallocated or unused by the patients must be returned to Pfizer or its appointed agent, or destroyed in an approved manner unless otherwise authorized by Pfizer. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a subject by subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug.

5.5. Concomitant Medication(s)

All concomitant medication taken during the study must be recorded with generic name of the medication, reason for administration, dose and frequency, route of administration and start and stop dates in the subject's case report form. A subject who is receiving an allowed 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.

5.5.1. Allowed Concomitant Medications

Please note that all concomitant DMARDs are excluded at entry into the study, except methotrexate and antimalarial DMARDs (ie, chloroquine, hydroxychloroquine). During the study, if a subject is not adequately treated with their assigned study treatment, non-biologic DMARDs (ie, chloroquine, hydroxychloroquine, sulfasalazine, leflunomide) may be added to their treatment regimen; methotrexate dosage may be modified if clinically indicated (see Section 5.6).

5.5.1.1. Methotrexate

All subjects entering the study must have taken MTX continuously for at least 4 months prior to the Screening visit and have been taking a stable, weekly dose of MTX for at least 6 weeks prior to the Baseline visit and continue taking that dose throughout the study, unless modification is clinically indicated.

MTX doses less than 15 mg/week are allowed only in the presence of documented intolerance to or toxicity from higher doses. Doses higher than 25 mg/week are not permitted under any circumstances.

5.5.1.2. Folate Supplementation

Subjects must receive either folic acid (at least 5 mg weekly) or folinic acid (at least 2.5 mg weekly) as folate supplementation according to local MTX label guidelines and standard of care.

5.5.1.3. Treatment for Latent Tuberculosis

Subjects who are diagnosed as having latent tuberculosis (ie, positive tuberculosis test, chest x-ray negative for active tuberculosis, and no evidence of active disease) at Screening or during the course of the study must have either been previously treated with an adequate course of treatment or be currently taking isoniazid. Subjects that the investigator considers

to be at high-risk to develop tuberculosis (eg, residing in high-risk areas or travel to high-risk areas) may be started on isoniazid treatment at the discretion of the investigator. When indicated, isoniazid treatment is required to be administered orally at 300 mg/day for a total of 9 months of treatment and the treatment must be recorded in the subject's case report form. If an alternate treatment regimen is implemented, the reason for this must be documented and a copy of the local standard of care guideline identifying such treatment must be provided to the study team. Within approximately one month of initiating treatment with isoniazid, the subject should have transaminase levels checked.

PLEASE NOTE: although commonly used in the treatment of tuberculosis, rifampin, rifampicin, rifabutin and rifapentene are prohibited concomitant medications in this study.

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

Subjects may continue taking stable daily doses of NSAIDs. Subjects, who require intermittent therapy for symptom relief, may use short-acting analgesics including NSAIDs, acetaminophen/paracetamol, and opioids. Topical NSAIDs are allowed at any time during the study.

5.5.1.5. Corticosteroid Use

Daily dosages of oral corticosteroids should remain at doses ≤10 mg prednisone or equivalent per day. Reductions in oral corticosteroid dose are allowed as needed to protect a subject's safety.

Intra-articular corticosteroids, intramuscular corticosteroids (eg, DepoMedrol®) and short-term oral corticosteroid use (eg, Medrol Pak) will be allowed during the study.

5.5.2. Disallowed Concomitant Medications

All prohibited concomitant medications should be discontinued at least 4 weeks or 5 half lives (whichever is longer) prior to the Baseline visit; specific medications and required discontinuation times are listed below. A list of prohibited concomitant medications is provided in Appendix 2.

Any investigational treatment must be discontinued prior to the Baseline visit for 4 weeks or 5 half lives, whichever is longer.

5.5.2.1. Disease Modifying Antirheumatic Drugs (DMARDs)

5.5.2.1.1. Methotrexate

All subjects should be maintained on their stable dose of MTX, unless modification of dose is clinically indicated.

5.5.2.1.2. Other DMARDs

Subjects who have received biologic or non-biologic DMARDs are eligible to participate in the study, providing the following discontinuation periods are observed prior to the first dose of study drug (Table 1).

Table 1. DMARDs - Required Washout Period Prior to Randomization Visit

52 weeks	Rituximab (subject must have normal CD 19/20+ counts by FACS analysis)
20 weeks	Gold compounds, including auranofin (Ridaura),and injectable gold (aurothioglucose or aurothiomalate)
12 weeks	Abatacept, certolizumab pegol, leflunomide*, tocilizumab
10 weeks	Golimumab
8 weeks	Infliximab
6 weeks	Adalimumab
4 weeks	Anakinra, azathioprine, cyclosporine, etanercept, minocycline, penicillamine, sulfasalazine, tacrolimus

* Alternately, leflunomide may be discontinued 4 weeks prior to Randomization Visit when discontinued using an elimination procedure (ie, 8 grams cholestyramine 3 times daily for at least 24 hours or 50 grams activated charcoal 4 times daily for at least 24 hours), as described in the leflunomide package labeling to significantly lower leflunomide drug levels.

5.5.2.2. Immune-Modulating Biologic Products

While receiving study drug, no immune-modulating biologic products are allowed to be administered concomitantly, including other biologic DMARDs (Appendix 2).

5.5.2.3. CYP3A4 and CYP2C19 Inhibitors and CYP3A4 Inducers

Tofacitinib exposure is increased when co-administered with medications that are potent inhibitors of cytochrome P450 (CYP) 3A4 (eg, ketoconazole) and medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (eg, fluconazole).

Tofacitinib exposure is decreased when co-administered with potent CYP3A4 inducers (eg, rifampin).

During treatment with adalimumab, the formation of CYP450 enzymes may be suppressed by increased levels of cytokines (eg, TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of adalimumab in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (eg, warfarin) or drug concentration (eg, cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

To ensure sufficient washout of these effects on safety and efficacy endpoints, drugs that are potent CYP3A4 and CYP2C19 inhibitors and drugs that are potent CYP3A4 inducers must be discontinued for at least 7 days or 5 half lives (whichever is longer) prior to the Baseline visit. Only systemically administered drugs listed in Appendix 2 require discontinuation; other routes of administration (eg, topical, vaginal, ophthalmic) are not prohibited.

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

If a medication that is a potent CYP3A inducer is administered during the study for any reason, including the treatment of an adverse event, study medication may be continued, but the concomitant administration of the medication should be noted as a protocol deviation.

5.5.2.4. Immunizations

Live or live-attenuated vaccines should not be given concurrently with study medication. If immunization with a live or live-attenuated vaccine is required during the study, study drug should be temporarily discontinued prior to vaccination.

5.6. Rescue Therapy

All subjects enrolled in this study should remain on their randomized, assigned treatment for the length of the study. However, it is understood that some subjects may need adjustments to their therapy during the study. If adjustment in RA therapy is being considered, it is recommended that the first modification to a subject's therapy be the addition or optimization of treatment with short-acting analgesics, corticosteroids and methotrexate.

5.6.1. Changes in Assigned Drug

The investigator should consider the need for adjustment in treatment for the individual subject based on 1) disease duration, 2) disease activity, and 3) current medication regimen. It is recommended that subjects who have Clinical Disease Activity Index (CDAI) >10 and have not had at least a 10 point decrease in CDAI compared to Baseline at Month 3 may be considered for modification of treatment. Subjects who in the investigator's opinion require treatment should be treated appropriately.

Changes in the randomized dose of study drug (ie, tofacitinib 5 mg BID, tofacitinib 10 mg BID, adalimumab 40 mg every other week, etanercept 50 mg weekly) are not allowed prior to Amendment 8, at which time subjects in the tofacitinib 10 mg BID treatment arm had their dose of tofacitinib decreased to 5 mg BID. If modification of analgesic, corticosteroid or methotrexate is not sufficient, consider adding a nonbiologic DMARD (eg, chloroquine, hydroxychloroquine, sulfasalazine, leflunomide) in addition to the study treatment. It is recommended that if modifications are made to the subject's treatment regimen, the investigator should wait 3-6 months before further modifications are made. If such modifications do not provide adequate treatment, and it is in the subject's best interest to discontinue study assigned treatment (tofacitinib or adalimumab or etanercept), standard of care therapy should be initiated. It should be noted that standard of care treatment will not be provided by the study.

It is important to note that investigators will be required to document all treatments, time on treatment regimens and the rationale for decisions in escalating or changing therapies.

Subjects on alternate therapies will remain in the study and continue to be followed, performing all study procedures according to the protocol until the end of the study.

6. STUDY PROCEDURES

6.1. Screening Visit

The study investigator or a sub-investigator will discuss, with each subject, the nature of the study, its requirements, and its restrictions. Written informed consent must be obtained prior to performance of any protocol specific procedures.

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 1 month window, unless otherwise noted.

Subjects, who are on prohibited medications and are deriving a beneficial response from them, should not be entered into this study. However, there may be subjects taking a prohibited medication who have experienced an ineffectual/suboptimal response or side effects and wish to enter the study. These subjects may require a washout period that extends beyond the screening duration (See Section 5.5 Concomitant Medication(s)). Additionally, screening procedures may need to be repeated to provide valid data (eg, laboratory testing) and turnaround time may extend beyond the screening duration. For these subjects, written informed consent and a Study Subject Identification (SSID) number must be obtained prior to initiation of the washout period. In no instance should the screening window exceed 3 months.

Subjects who do not have all tests completed within the 1 month screening period or who temporarily do not meet study entry criteria (eg, treatment with antibiotics during the screening period or for administrative reasons) may re-screen one time; the subject's prior SSID number and reason for re-screening must be documented.

Subjects should be fasting for at least 6 hours prior to laboratory testing. No subject who is disqualified by laboratory testing will be permitted to re-screen (ie, positive hepatitis or HIV screen, positive QuantiFERON Gold®™ In-Tube Test without adequate treatment, confirmed hemoglobin<9 g/dL, confirmed transaminases >1.5 x ULN).

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

Procedures to be performed during the screening period include:

- Informed Consent.
- Confirmation of RA diagnosis and Classification of RA: subject must have a score of 6 or greater on the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis (Appendix 1).
- Medical History: include previous vaccination history, smoking status, average weekly alcohol consumption, family history of premature coronary heart disease (CHD), and history of any prior episodes of herpes zoster.

- Complete Physical Examination: height, weight, vital signs, 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.

- Fasting laboratory testing (Blood Chemistry, Hematology, CRP, HIV Serology, HBsAg, HBcAb, HBsAb, HCV Ab, HCV RNA, Rheumatoid Factor, anti-cyclic citrullinated peptide antibodies (anti-CCP), Urinalysis, Lipid Profile): All required laboratory testing must be complete and reported; any invalid specimens must be retested and reported prior to the Baseline visit.

- Pregnancy testing must be completed for all women of child-bearing potential: all subjects must test negative; confirmation and documentation of the use of a highly effective method of contraception by sexually active subjects of child-bearing potential must be done (for Canada, please refer to Appendix 6 for specific contraception requirements).

- QuantiFERON Gold®™ In-Tube Test: unless the subject has previously received an adequate course of therapy for either latent or active TB infection (Section 5.5.1.3 Treatment for Latent Tuberculosis).

- Chest x-ray must show no evidence of active tuberculosis or other finding that would exclude the subject from the study (see Section 7.3 Chest Radiograph).

- 12-lead electrocardiogram.

- RA Activity: 28 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.

- History of Prior and Concomitant Medications: 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.

6.2. Study Period

It is expected that a minimum of approximately 4000 subjects will be enrolled in the study and the study will continue until at least 1500 subjects complete 3 years in the study and the estimated number of malignancy events and MACE are observed. Screening to enroll a total of approximately 4000 subjects is expected to be completed in approximately 3 years and the endpoints achieved in approximately 5 years from first subject randomized. Thus, each subject's individual participation will vary, depending on when the subject is randomized into the study.

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

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 product(s), request the subject to return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

6.2.1. Visit Windows

The screening period is expected to be no longer than 4 weeks in duration, unless exceptions noted in Section 6.1 are documented, with the Baseline visit (Day 1) occurring within the 28 days following the day that the subject signs the informed consent.

All other visits (Visits 2-22) should be conducted as close to the scheduled visit day as possible. Exceptions may be made to accommodate holidays and unexpected events, such as weather-related site closures or illnesses requiring hospitalization. In these cases, the visit should be scheduled or re-scheduled as close to the original visit schedule as possible.

All visits will contribute to the dataset. The visit window for Visit 2 (Month 2) is ±2 weeks; all other visit windows are ±1.5 months to ensure capture of all data.

Partial visits (ie, those that do not include all required procedures) must be noted clearly and the reason documented in the subject's case report form.

6.3. Visit 1, Baseline Visit (Day 1)

Subjects are required to fast for at least 6 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:

- Physical assessment including assessment of new physical findings, weight and vital signs.
- Review of inclusion/exclusion criteria.
- Fasting laboratory testing including blood chemistry, hematology, CRP, lipid profile.
- Pregnancy testing must be completed for all women of child-bearing potential: all subjects must test negative; confirmation and documentation of the use of a highly effective method of contraception by sexually active subjects of child-bearing potential must be done (for Canada, please refer to Appendix 6 for specific contraception requirements).

- Banked biospecimen sample.
- 28 tender /painful and swollen joint counts.
- Completion of the following assessments:
  - Patient assessment of arthritis pain.
  - Patient global assessment of arthritis.
  - Physician global assessment of arthritis.
  - HAQ-DI.
  - SF-36 (Version 2, Acute).
  - EuroQol EQ-5D.
  - Work Productivity and Activity Impairment (WPAI) Questionnaire.
- Safety Assessment and AE Reporting.
- Concomitant Medication Review.
- Confirm that all screening procedures have been completed and the subject is eligible for randomization.
- Randomize and dispense study medication as identified by the randomization/drug dispensing system.
- Schedule the subject to return for Visit 2 (Month 2).

6.4. Follow-up Visits

6.4.1. Visit 2 (Month 2)

Subjects are required to fast for at least 6 hours prior to the visit. Procedures that will be performed on Visit 2, Month 2 include:

- Assessment of new physical findings, weight and vital signs.
- Fasting laboratory testing including blood chemistry, hematology, CRP, lipid profile.
- Pregnancy testing must be completed for all women of child-bearing potential: all subjects must test negative; confirmation and documentation of the use of a highly effective method of contraception by sexually active subjects of child-bearing potential must be done (for Canada, please refer to Appendix 6 for specific contraception requirements).

- 28 tender /painful and swollen joint counts.
- Completion of the following assessments:
  - Patient assessment of arthritis pain.
  - Patient global assessment of arthritis.
  - Physician global assessment of arthritis.
  - HAQ-DI.
- Safety Assessment and AE Reporting.
- Concomitant Medication Review.
- Schedule the subject to return for Visit 3 (Month 3).

6.4.2. Visit 3 (Month 3)

Subjects are not required to fast for this visit. Procedures that will be performed on Visit 3, Month 3 include:

- Assessment of new physical findings, weight and vital signs.
- Non-fasting laboratory testing including blood chemistry, hematology, CRP.
- Pregnancy testing must be completed for all women of child-bearing potential: all subjects must test negative; confirmation and documentation of the use of a highly effective method of contraception by sexually active subjects of child-bearing potential must be done (for Canada, please refer to Appendix 6 for specific contraception requirements).
- 28 tender /painful and swollen joint counts.
- Completion of the following assessments:
  - Patient assessment of arthritis pain.
  - Patient global assessment of arthritis.
  - Physician global assessment of arthritis.
  - HAQ-DI.
  - SF-36 (Version 2, Acute).
  - EuroQol EQ-5D.

- Work Productivity and Activity Impairment (WPAI) Questionnaire.

- Safety Assessment and AE Reporting.
- Concomitant Medication Review.
- Dispense study medication.
- Schedule the subject to return for Visit 4 (Month 6).

6.4.3. Visit 4 (Month 6)

Subjects are not required to fast for this visit. Procedures that will be performed on Visit 4, Month 6 include:

- Assessment of new physical findings, weight and vital signs.
- Non-fasting laboratory testing including blood chemistry, hematology, CRP.
- Pregnancy testing must be completed for all women of child-bearing potential: all subjects must test negative; confirmation and documentation of the use of a highly effective method of contraception by sexually active subjects of child-bearing potential must be done (for Canada, please refer to Appendix 6 for specific contraception requirements).
- 28 tender /painful and swollen joint counts.
- Completion of the following assessments:
  - Patient assessment of arthritis pain.
  - Patient global assessment of arthritis.
  - Physician global assessment of arthritis.
  - HAQ-DI.
  - SF-36 (Version 2, Acute).
  - EuroQol EQ-5D.
  - Work Productivity and Activity Impairment (WPAI) Questionnaire.
- Safety Assessment and AE Reporting.
- Concomitant Medication Review.
- Dispense study medication.
- Schedule the subject to return for Visit 5 (Month 9).

6.4.4. Visits 5, 7, 9, 11, 13, 15, 17, 19, 21, etc, as Required Through the End of the Study (Calendar Months 9, 15, 21, 27, 33, 39, 45, 51, 57, etc)

Subjects are not required to fast for this visit. Procedures that will be performed at Visits 5, 7, 9, 11, 13, 15, 17, 19 and 21 (Months 9, 15, 21, 27, 33, 39, 45, 51 and 57, respectively) include:

- Assessment of new physical findings, weight and vital signs.
- Non-fasting laboratory testing including blood chemistry, hematology, CRP.
- Pregnancy testing must be completed for all women of child-bearing potential: all subjects must test negative; confirmation and documentation of the use of a highly effective method of contraception by sexually active subjects of child-bearing potential must be done (for Canada, please refer to Appendix 6 for specific contraception requirements).
- 28 tender /painful and swollen joint counts.
- Completion of the following assessments:
    - Patient assessment of arthritis pain.
    - Patient global assessment of arthritis.
    - Physician global assessment of arthritis.
    - HAQ-DI.
- Safety Assessment and AE Reporting.
- Concomitant Medication Review
- Dispense study medication.
- Schedule the subject to return for next visit.

6.4.5. Visits 6, 10, 14, 18, 22, etc, as Required Through the End of the Study (Months 12, 24, 36, 48, 60, etc.) – Annual Study Visits

Subjects are required to fast for 6 hours prior to the visit and withhold their study medication on the day of the visit. Procedures that will be performed at Visits 6, 10, 14, 18 and 22 (Months 12, 24, 36, 48 and 60, etc.) include:

- Assessment of new physical findings, weight and vital signs.
- Fasting laboratory testing including blood chemistry, hematology, CRP, lipid profile.

- Banked biospecimen sample (Visit 6 only).
- QuantiFERON Gold®™ In-Tube Test (QFT) only for subjects who tested negative at their last QFT; subjects newly testing positive must have chest x-ray performed. Please note: subjects with a new positive QFT, a chest x-ray that does not show active disease and no other evidence of active disease are required to be treated for latent tuberculosis infection, as described in Section 5.5.1.3 Treatment for Latent Tuberculosis. QFT is not performed in subjects who had prior positive testing (screening visit or prior annual visits) and/or previously received adequate treatment for tuberculosis.
- Pregnancy testing must be completed for all women of child-bearing potential: all subjects must test negative; confirmation and documentation of the use of a highly effective method of contraception by sexually active subjects of child-bearing potential must be done (for Canada, please refer to Appendix 6 for specific contraception requirements).
- 28 tender /painful and swollen joint counts.
- Completion of the following assessments:
  - Patient assessment of arthritis pain.
  - Patient global assessment of arthritis.
  - Physician global assessment of arthritis.
  - HAQ-DI.
  - SF-36 (Version 2, Acute).
  - EuroQol EQ-5D.
  - Work Productivity and Activity Impairment (WPAI) Questionnaire.
- Safety Assessment and AE Reporting.
- Concomitant Medication Review.
- Dispense study medication.
- Schedule the subject to return for next visit.

6.4.6. Visits 8, 12, 16, 20, etc, as Required Through the End of the Study (Months 18, 30, 42, 54, etc)

Subjects are not required to fast for this visit. Procedures that will be performed at Visits 8, 12, 16 and 20 (Months 18, 30, 42 and 54, etc.) include:

- Assessment of new physical findings, weight and vital signs.

- Non-fasting laboratory testing including blood chemistry, hematology, CRP.
- Pregnancy testing must be completed for all women of child-bearing potential: all subjects must test negative; confirmation and documentation of the use of a highly effective method of contraception by sexually active subjects of child-bearing potential must be done (for Canada, please refer to Appendix 6 for specific contraception requirements).
- 28 tender /painful and swollen joint counts.
- Completion of the following assessments:
  - Patient assessment of arthritis pain.
  - Patient global assessment of arthritis.
  - Physician global assessment of arthritis.
  - HAQ-DI.
- Safety Assessment and AE Reporting.
- Concomitant Medication Review.
- Dispense study medication.
- Schedule the subject to return for next visit.

6.5. End of Study Visit

Within one month following the official end of study, subjects are to return for an End of Study Visit. Subjects are required to fast for 6 hours prior to the visit. Procedures that will be performed at the end of the study include:

- Complete physical examination, including height.
- Assessment of new physical findings, weight and vital signs.
- Fasting laboratory testing including blood chemistry, hematology, CRP, lipid profile.
- 12-lead electrocardiogram.
- Banked biospecimen sample.
- Pregnancy testing must be completed for all women of child-bearing potential: all subjects must test negative; confirmation and documentation of the use of a highly effective method of contraception by sexually active subjects of child-bearing potential must be done (for Canada, please refer to Appendix 6 for specific contraception requirements).

- 28 tender /painful and swollen joint counts.
- Completion of the following assessments:
  - Patient assessment of arthritis pain.
  - Patient global assessment of arthritis.
  - Physician global assessment of arthritis.
  - HAQ-DI.
  - SF-36 (Version 2, Acute).
  - EuroQol EQ-5D.
  - Work Productivity and Activity Impairment (WPAI) Questionnaire.
- Safety Assessment and AE Reporting.
- Concomitant Medication Review.
- End of study assessment, including a discussion and plans for future care.
- Schedule the subject to return after 28 days for End of Study Follow-up visit.

6.6. End of Study Follow-up Visit

One month (28 days) after the last dose of study medication is taken, the subject will attend an end of study follow-up visit. The following procedures will be performed:

- Assessment of new physical findings, weight and vital signs.
- Pregnancy testing must be completed for all women of child-bearing potential; confirmation and documentation of the use of a highly effective method of contraception by sexually active subjects of child-bearing potential must be done (for Canada, please refer to Appendix 6 for specific contraception requirements).
- Safety Assessment and AE Reporting, including follow-up of any ongoing AEs.
- Concomitant Medication Review.

6.7. Subject Withdrawal

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.

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 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 product(s), 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, this should be documented and 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 which he/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. 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. Assessment of New Physical Findings and Safety Assessments

At all visits after the Screening visit, an abbreviated physical examination will be performed assessing the following: weight, vital signs, 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 adverse events (AEs); ongoing AEs should be updated, as appropriate.

7.3. Chest Radiograph

A chest radiograph will be obtained at the Screening Visit in all subjects, unless it has been taken and documented within the 3 months prior to the Screening visit. To be considered eligible for the study, the radiograph must be negative for active tuberculosis infection.

During the course of this study, annual screening for latent and/or active TB will be conducted using the QuantiFERON®-TB Gold In-Tube test. All subjects with positive results must have a chest radiograph performed and the radiograph must be negative for active tuberculosis infection. Subjects identified as having latent TB should be treated appropriately (Section 5.5.1.3 Treatment for Latent Tuberculosis).

Chest computed tomography (CT) scans will not be performed as part of the study procedures. However, if a chest CT scan has been performed for other reasons within the 3 months prior to a scheduled chest radiograph; subjects do not have to perform a chest radiograph, but rather, the results of the chest CT scan may be used to confirm the absence of active tuberculosis infection.

7.4. Electrocardiogram

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

End of Study ECGs will be compared to the Screening ECG and any clinically significant changes will be recorded as adverse events, submitted for adjudication and evaluated further, as clinically warranted.

7.5. Assessments of Disease Activity

Individual components for the following indicators of disease activity will be collected throughout the study as described in Table 2.

Table 2. Disease Activity Indicators

Indicator	Definition/Calculation
DAS28-4 (CRP)	DAS28-CRP(4) = 0.56*√(TJC28) + 0.28*√(SJC28) + 0.36*ln(CRP+1) + 0.014*PtGA + 0.96
Simplified Disease Activity Index (SDAI)	(28TJC) + (28SJC) + PhyGA + PtGA + CRP
Clinical Disease Activity Index (CDAI)	(28TJC) + (28SJC) + MDGA + PtGA
American College of Rheumatology (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 (eg, CRP). Similarly, ACR50, 70 and 90 are calculated with the respective percent improvements.
ACR/EULAR Boolean-based definition of remission	At any time point, a subject must satisfy all of the following: tender joint count ≤1, swollen joint count ≤1, CRP ≤1 mg/dL, patient's global assessment of health ≤1 on a 0-10 scale

TJC = tender joint count; SJC = swollen joint count; CRP = C-reactive protein in mg/L; PtGA = patient's global assessment of health; PhyGA = physician's global assessment of health

7.6. Joint Counts

7.6.1. Tender/Painful Joint Count (28 Joint Count)

Twenty-eight (28) joints will be assessed by a joint assessor 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 joints (MCP), proximal interphalangeal joints (PIP), and knees. Artificial joints will not be assessed.

7.6.2. Swollen Joint Count (28 Joint Count)

The joint assessor 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, metacarpophalangeal joints (MCP), proximal interphalangeal joints (PIP), and knees. Artificial joints will not be assessed.

7.7. 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.

7.8. 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 visual analog scale (VAS).

7.9. 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's Global Assessment of Arthritis. The investigator's response will be recorded using a 100 mm visual analog scale (VAS).

7.9.1. 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.[17] 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.

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

The SF-36 v.2 (Acute)[18] is a 36-item generic health status measure. It measures 8 general health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. These domains can also be summarized as physical and mental component scores. The form should be checked for completeness by the site staff.

7.9.3. EuroQol EQ-5D Health State Profile (Health-related Quality of Life)

The EuroQol EQ-5D Health State Profile is a copyrighted, subject completed instrument designed to assess impact on health-related quality of life in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Additionally, scores from the five domains may be used to calculate a single index value, also known as a utility score. The validity and reliability of the EuroQol EQ-5D has been established in a number of disease states, including rheumatoid arthritis.[19] The form should then be checked by site staff for completeness.

7.9.4. Work Productivity and Activity Impairment (WPAI) Questionnaire

The Work Productivity & Activity Impairment Questionnaire (WPAI): Rheumatoid Arthritis is a 6-item questionnaire that is specific for rheumatoid arthritis and yields four types of scores: absenteeism, presenteeism (impairment at work/reduced job effectiveness), work productivity loss and activity impairment. WPAI outcomes are expressed as impairment percentages with higher numbers indicating greater impairment and less productivity.

7.9.5. C-reactive Protein (CRP)

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

7.10. Clinical Laboratory Tests

Blood and urine samples will be collected at the time points identified in Table 3. Unscheduled clinical laboratory tests may be obtained at any time during the study to assess any perceived safety concerns. For Czech Republic, Spain and United Kingdom, see Appendix 5 for additional testing required.

Table 3. Clinical Laboratory Tests

Tests	Visits	Comments
Chemistry Total Bilirubin Direct Bilirubin Indirect Bilirubin ALT (SGPT) AST (SGOT) Creatinine	Screening Visit and every visit thereafter including the End of Study Visit	Creatinine clearance is calculated by the central laboratory according to the Cockcroft-Gault Formula at Screening Visit (Appendix 3) See Section 7.15 for retesting requirements for ALT and AST elevated ≥3 X ULN
Hematology Hemoglobin Hematocrit RBC with morphology WBC Neutrophils (%, abs) Lymphocytes (%, abs) Monocytes (%, abs) Eosinophils (%, abs) Basophils (%, abs) Platelets	Screening Visit and every visit thereafter including the End of Study Visit	See Section 7.15 for monitoring requirements related to hemoglobin, neutrophil and lymphocyte counts
C-reactive Protein	Screening visit and every study visit including the End of Study Visit	Refer to Section 7.9.5
Banked Biospecimens	Visit 1, Visit 6 and End of Study Visit	Refer to Section 7.13
Rheumatoid Factor Anticyclic citrullinated peptide antibodies (ACPA)	Screening visit	
HIV Serology	Screening visit	
Hepatitis B Surface antigen (HBsAg) Hepatitis B Core Antibody (HBcAb) Hepatitis B Surface Antibody (HBsAb)	Screening Visit	Subjects with hepatitis B surface antigen (HBsAg) negative testing but who test positive for hepatitis B core antibody (HBcAb) must have further testing for hepatitis B surface antibody (HBsAb). If HBsAb is negative, the subject will be excluded from the study (see Section 4.2)

Table 3. Clinical Laboratory Tests

Tests	Visits	Comments
Hepatitis C virus antibody (HCV Ab) Hepatitis C RNA (HCV RNA)	Screening Visit	Subjects with positive HCV Ab tests will be reflex tested for hepatitis C virus ribonucleic acid (HCV RNA). Only subjects with negative HCV Ab or HCV RNA will be allowed to enroll in the study.
Lipids Triglycerides Total Cholesterol HDL (direct) LDL (Friedwald)	Screening Visit, Visit 1, Visit 2, Visit 6 and annually thereafter, End of Study Visit	Subjects should be fasting for at least 6 hours prior to obtaining specimen.
Serum Pregnancy Testing	Screening Visit and every study visit thereafter, including End of Study Follow-up Visit May be repeated if pregnancy is suspected or at the request of the IRB/IEC or local regulations.	All female subjects of childbearing potential, regardless of whether or not they are sexually active. All pregnancy tests used in this study must have sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. (See Section 7.11)
Quantiferon TB Gold	Screening Visit, Visit 6 and annually thereafter.	Subjects should withhold study medication on the day of the visit. See Section 5.5.1.3 and 7.3 for further details on management of positive tests.
Urinalysis Specific Gravity pH Protein Glucose Ketones Blood Leukocyte Esterase	Screening Visit	
Tests to include when repeat AST and/or ALT are required: Albumin Creatine kinase (CK) Total bilirubin Direct bilirubin Indirect bilirubin, GGT PT/INR Alkaline phosphatase	At same time as AST and/or ALT are repeated for elevations as noted in Section 7.15	See Section 8.6.2 for further details on management of elevations.

ALT = alanine aminotransferase (SGPT); AST = aspartate transaminase (SGOT); 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; X ULN = times the upper limit of normal;

7.11. Pregnancy Testing

Pregnancy testing must be conducted on all female subjects of childbearing potential, regardless of whether or not they are sexually active at least at every scheduled visit of the study. Serum pregnancy testing will be performed by the central laboratory for all visits.

For female subjects of childbearing potential, a serum pregnancy test, with sensitivity of ≥ 25 mIU/mL, will be performed at screening, before investigational product administration at the baseline visit, and at the end of treatment visit. A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), repeated at every study visits and at the end of the study to confirm the subject has not become pregnant during the study. In the case of a positive human chorionic gonadotropin (hCG) test, the subject will be withdrawn from study medication but may remain in the study. Pregnancy tests may also be repeated as per request of an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or if required by local regulations.

7.12. Pregnancies Occurring During Study

If an unplanned pregnancy occurs in a female subject or the partner of a male subject while the man or woman is enrolled in this study, regardless of therapy at the time of pregnancy, the pregnancy will be followed to termination and outcome will be documented.

In addition, for those pregnancies occurring in the United States, the pregnancy will be followed through an existing Pfizer-sponsored pregnancy registry (ie, Tofacitinib Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy Project, A3921203). The registry will collect exposure and outcome information for those pregnancies and all live born infants followed in this registry will be examined by one of a team of study-dedicated dysmorphologists within the first year of life.

7.13. Banked Biospecimens

7.13.1. Markers of Drug Response

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), 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 decision.

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study 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 post-marketing 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 trial.

A 4 mL blood biospecimen, **Prep D1 (K_2 EDTA whole blood collection optimized for DNA analysis)**, will be collected at the Visit 1, Visit 6, and the End of Study Visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee 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. Additional biospecimens to be retained for exploratory analyses in this study include:

- **Prep B1 (K2 EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis)**: a 10 mL blood biospecimen will be collected at the Visit 1, Visit 6 and the End of Study Visit.

- **Prep B2 (serum collection optimized for biomarker/ proteomics/metabonomic analysis)**: a 10 mL blood biospecimen will be collected at the Visit 1, Visit 6 and the End of Study Visit.

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.

7.13.2. Additional Research

Unless prohibited by local regulations, 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 trial, 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 Markers of Drug Response Section will be used. Subjects may still participate in the clinical trial if they elect not to allow their Banked Biospecimens to be used for the additional purposes described in this section.

7.14. Suicidality Assessment

There are no current medically significant suicidality concerns for any of the study drugs (ie, tofacitinib, adalimumab or etanercept) 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.

7.15. Triggered Requirements for Monitoring

For additional Czech Republic, Spain and United Kingdom-specific laboratory criteria, see Appendix 5.

Condition	Action
Neutrophil counts <1000 cells/mm^3	The subject should return to the study site for prompt retesting.
Persistent neutrophil counts of 500-1000 cells/mm^3	Interrupt study drug until neutrophil count is greater than or equal to 1000 cells/mm^3
Confirmed neutrophil counts <500 cells/mm^3 by repeat testing	Discontinue study drug and follow to resolution.
Lymphocyte counts <1000 cells/mm^3	The subject should return to the study site for prompt retesting.
Confirmed lymphocyte counts <500 lymphocytes/mm^3 by repeat testing	Discontinue study drug and follow to resolution.
Any single AST and/or ALT elevation ≥3 x ULN	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 alkaline phosphatase.
2 sequential AST or ALT elevations ≥3 x ULN with a total bilirubin value ≥2 x ULN	• If drug-induced liver injury is suspected, interrupt study drug until the diagnosis is excluded. • 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 alkaline phosphatase. • 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. • Conduct study visits until end of study.
2 sequential AST or ALT elevations ≥3 x ULN with an abnormal INR	• Permanently withdraw the subject from the study drug and follow to resolution. • 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 alkaline phosphatase. • 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. • Conduct study visits until end of study.

Condition	Action
2 sequential AST or ALT elevations ≥3 x ULN accompanied by symptoms consistent with hepatic injury	• Permanently withdraw the subject from the study drug and follow to resolution. • 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 alkaline phosphatase. • 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. • Conduct study visits until end of study.
2 sequential AST or ALT elevations ≥5 x ULN, regardless of Total Bilirubin or accompanying symptoms	• Permanently withdraw the subject from the study drug and follow to resolution. • 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 alkaline phosphatase. • 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. • Conduct study visits until end of study.
Increased lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)	Monitor and treat according to local guidance (eg, diet and behavior modification, statin therapy).
Hemoglobin <8.0 g/dL or a decrease of ≥2 g/dL compared to baseline, confirmed by repeat testing	Interrupt the administration of study drug until hemoglobin values have normalized.
Serious infections (those requiring hospitalization and/or those requiring parenteral antimicrobials)	Interrupt study drug until the infection is controlled.
Surgery	Interrupt study drug 2 weeks prior to a scheduled surgical procedure and may resume when operative site is sufficiently healed and risk of infection is minimal.
Subjects who cannot be adequately treated for RA within study guidelines	Provide alternate treatment and continue the subject in the study.
Pregnancy or refusal to use appropriate contraception	Permanently withdraw the subject from the study drug and follow any pregnancy to resolution conducting study visits until end of study.
Use of prohibited concomitant medications	See Section 5.5 Concomitant Medication(s) of the protocol for specific actions.

Condition	Action
Anaphylactic or other serious allergic reaction	Immediately discontinue study drug and institute appropriate therapy. Continue subject in study on standard of care treatment and conduct study visits until the end of the study
Symptoms suggestive of a lupus-like syndrome	Discontinue study drug and institute appropriate therapy. Continue subject in study on standard of care treatment and conduct study visits until the end of the study
Vomiting, diarrhea, or if stomatitis occurs, all of which may result in dehydration	Interrupt study drug until recovery occurs.
Interruption of study assigned drug for ≥2 months	Must be switched to standard of care treatment

ALT = alanine aminotransferase; AST = aspartate aminotransferase; g/dL = grams per deciliter; GGT = gamma-glutamyl transpeptidase, PT/INR = Prothrombin Time International Normalized Ratio; mm = millimeter; x ULN = times the upper limit of normal

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 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 non-serious adverse event 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 trial.

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. Serious adverse events 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 serious adverse events 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 non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject 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;
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. 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 and any identified organisms noted in the CRF.

All potential opportunistic infections will be adjudicated by an external review committee (see Section 9.7.2 Opportunistic Infection Review Committee).

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

8.4.1. 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.

8.4.2. 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 subject who experiences a serious infection should have study drug interrupted until the subject recovers. 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 on Adverse Event Reporting. All serious infections will be reviewed by the Opportunistic Infection Review Committee to determine whether they are potential opportunistic infections (Section 9.7.2).

8.5. 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 (eg, 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.

8.6. 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.

Lack of efficacy should be reported as an AE when it is associated with an SAE.

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 if the event 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.

8.6.1. Protocol-Specified Serious Adverse Events

All lymphomas and lymphoproliferative disorders, regardless of causality must be reported as SAEs and as potential safety endpoints.

For all other potential safety endpoint events, unless the investigator believes that there is a causal relationship between study drug and an event specified below, these events should not be reported by the investigator as SAEs as described in Section 8.13.1. These events are anticipated to occur in a population with rheumatoid arthritis. However, these events should still be captured as adverse events in the potential safety endpoint case report form.

Protocol-specified events that will not be reported in an expedited manner:

1. Malignancies, excluding non-melanoma skin cancers.
2. Major adverse cardiovascular events (MACE).

The definitions of MACE used in this study include the following events:

- Cardiovascular death.
    - Death due to acute myocardial infarction (MI).

- Sudden cardiac death.
- Death due to heart failure.
- Death due to stroke.
- Death due to cardiovascular procedures.
- Death due to cardiovascular hemorrhage.
- Death due to other cardiovascular causes: peripheral artery disease.

- Non-fatal myocardial infarction (MI).
- Non-fatal stroke of any classification, including reversible focal neurologic defects with imaging evidence of a new cerebral lesion consistent with ischemia or hemorrhage.

Should the Data Monitoring Committee (DMC) determine that these pre-specified events occur more frequently in a drug treatment group, these events will be submitted and reported in accordance with Pfizer's safety reporting requirements as described in Section 2.2.

Except for the co-primary endpoints identified above, all EoIs, including EoIs that require adjudication (eg, hepatic events, NMSC, non-cardiovascular deaths, opportunistic infections) will be reported as described in Section 8.13. EoIs that are adjudicated as not meeting the pre-specified endpoint criteria will be returned to the investigator for re-evaluation and submission as an AE or SAE, as appropriate. For all EoIs returned to the investigator, the awareness date of the event becomes the date the EoI is received back from adjudication.

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin 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.

Reported transaminase elevations from both AEs and laboratory reports will be reviewed by the study team to identify any potential cases of drug-induced liver injury that occur during the course of the study; all potential cases of drug-induced liver injury will be adjudicated by an external review committee, which may request additional data surrounding the event to assist in the classification of such events (see Section 9.7.1 Hepatic Event Review Committee). The investigator should refer to the following guidance when evaluating subjects with transaminase elevations.

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 ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 X ULN or not available;

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

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

Concurrent with

    - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal **or** ≥3 times the upper limit of normal (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 AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase. 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 subject, 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 (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for 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 and study drug should be interrupted at least until the event is resolved.

All potential cases of drug-induced liver injury will be reviewed by the Hepatic Event Review Committee (Section 9.7.1).

8.7. Hospitalization

AEs reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- 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 (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive 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.

8.8. Severity Assessment

If required on the AE case report forms (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 subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse 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 (see 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 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.

8.10. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as exposure in-utero (EIU) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or being exposed (eg, due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the investigational product;

2. A male has been exposed (eg, due to treatment or environmental exposure) to the investigational product prior to or around the time of conception 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 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 (eg, 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 (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information 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 pre-procedure 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 serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to 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 (eg, 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 on the EDP Supplemental Form that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Withdrawal Due to Adverse Events (See Also Section on Subject Withdrawal)

Please note: Subjects should not be withdrawn from the study due to adverse events. However, the assigned study drug may be withdrawn and is considered a withdrawal from the assigned treatment group. Withdrawal as described in this section refers to withdrawal from the assigned treatment group, as subjects should continue in the study until the study is completed.

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page. Insufficient response to study medication should only be reported as an AE only when associated with an SAE (See Section 8.6 Serious Adverse Events).

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

8.12. 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.

8.13. 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.

8.13.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. If an SAE occurs, Pfizer is to be notified within 24 hours of the site's notification that an SAE has been deemed a non-endpoint and has been sent back to the site. The investigator's SAE awareness date in this instance is identified as the date that the investigator receives the non-endpoint SAE back from the endpoint adjudication committee. As noted in the Endpoints section, when the investigator has judged the SAE to have a causal relationship with the investigational product, the investigator must report the event to the sponsor within 24 hours of investigator awareness, even if that event is a component of the endpoint.

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 timeframe 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 and exposure via breastfeeding cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, 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/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes 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 and 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.

8.13.2. 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.

8.13.3. Sponsor Reporting Requirements to Regulatory Authorities

Adverse event 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, 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 statistical objectives with respect to the primary safety endpoints, that is, malignancy (excluding non-melanoma skin cancer), and MACE, include drawing inferences with 95% (two-sided) confidence that the hazard ratios of the combined tofacitinib regimens versus the TNFi control regimen are less than 1.8. Assuming that the true hazard ratio is 1.0 the required number of events is 138 for malignancies to achieve 90% power and 103 for MACE to achieve 80% power.

The planned enrollment is approximately 4000 patients within 3 years (1000 in the first year and 1500 per year in the second and third years of recruitment). The assumed 'dropout or Loss to Follow-up' (LTFU) rate for MACE is 10% in the first year, 7% in the second and 5% per year, thereafter. For malignancies, because they will be followed after discontinuation the LTFU rate is assumed to be 5% in the first year, 3.5% in the second year and 2.5% per year thereafter. The assumed event rate for MACE is 1.0 event per hundred patient-years and the assumed rate for malignancy is 1.1 events per hundred patient-years; assumptions are based on results from the CORRONA database,[20] and also based on a meta-analysis of TNF-α inhibitors.[21] Based on those assumptions it is expected that the trial will accrue the desired number of events in approximately 5 years.

Additionally, the statistical objectives with respect to the primary safety endpoints include drawing inferences with 95% (two-sided) confidence that the hazard ratios of the tofacitinib 10 mg regimen to the tofacitinib 5 mg regimen are less than 2.0. Assuming that the true hazard ratio is 1.0 the required number of events is 87 for malignancies to achieve 90% power and 65 for MACE to achieve 80% power. Based on the same assumptions of patient enrollment, LTFU and event rates, the trial is expected to accrue the desired number of events in approximately 5 years.

The trial will conclude when the required number of events (138 malignancies and 103 MACE) has been observed. It is likely that more than the required events may be observed in one endpoint in order to get the required event in another, therefore the power may be higher for a given endpoint (eg, more than 103 MACE events may need to be observed in order to observe 138 malignancy events). The final analysis will utilize all observed events.

Software for sample size and power calculation was East 5®, Cytel Inc, Boston, MA, USA.

9.2. Safety Analysis

9.2.1. Analysis of Primary Safety Endpoint

The co-primary safety endpoints of malignancies and MACE will be analyzed to provide comparative rates for tofacitinib vs. the combined TNFi.

The primary statistical safety objective is the estimation of the hazard ratios relative to the TNFi control for the two tofacitinib doses combined and for each dose of tofacitinib separately for the adjudicated events of MACE and malignancy excluding non-melanoma skin cancer. Analysis of the primary safety endpoints will be based upon adjudicated events.

Hazard ratios for the safety events of main interest will be calculated separately for each primary endpoint. The ratios for both tofacitinib doses combined versus the control, for each tofacitinib dose versus the control, and for the two tofacitinib doses versus each other will be reported along with their 95% confidence intervals. Adjustments for multiplicity will not be applied.

The primary statistical method for deriving estimators for hazard ratios will be the fitting of proportional hazards (Cox) regression models. A model containing only the single independent variable for treatment group will be calculated and reported. The effects of adding other predictors to the model, such as geographic region, age, gender, and so forth will be fully explored and reported. An analysis by TNFi subset strata (ie, the sites/regions where either adalimumab or etanercept was used) will be conducted to assure consistency of results.

A Surveillance, Epidemiology, and End Results (SEER) analysis of the malignancy endpoint will be conducted.

Both total time (or ITT) and on treatment analyses of the main safety endpoints will be conducted. The total time analysis will not censor times to event and will ascribe events to randomized treatment.

The on-treatment analysis for MACE will censor subjects who crossover from tofacitinib, adalimumab or etanercept to standard of care at 60 days after standard of care is initiated. The principal analysis for malignancies will not censor for subjects crossing to standard of care (ie, will be the total time analysis).

9.2.2. Analysis of Secondary Safety Endpoints

The secondary safety endpoints will include an evaluation of the following events:

- Opportunistic infection events including tuberculosis (adjudicated).
- Hepatic events (adjudicated).
- Cardiovascular events other than MACE (adjudicated).
- All AEs, including SAEs.
- Clinically significant abnormal laboratory parameters.
- All cause mortality (adjudicated).
- Reasons for permanent or temporary discontinuation of study medication.

Adverse events and clinical laboratory abnormalities (Section 2.2.1.2) will be summarized according to treatment received at the time of the event. Both ITT and on treatment analyses will be conducted for the other secondary endpoints listed in Section 2.2.1.2.

9.3. Efficacy Analysis

Efficacy endpoints will include:

- Change from baseline to each post-baseline scheduled visit in DAS28-4 (CRP). Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI).
- Rate of remission at each post-baseline scheduled visit including:
  - ACR-EULAR Boolean remission (defined as the subject satisfying all of the following: tender joint count ≤1, swollen joint count ≤1, CRP ≤1 mg/dL, patient global assessment ≤1 on a 0-10 scale).
  - SDAI ≤3.3.
  - CDAI ≤2.8.
- Rate of low disease activity (LDA) at each post-baseline scheduled visit including:
  - SDAI ≤11.
  - CDAI ≤10.
  - DAS28-4(CRP) ≤3.2.
- ACR20, ACR50, and ACR70 response rate of at each post-baseline scheduled visit.
- Change from baseline to each post-baseline scheduled visit in the HAQ-DI.

Descriptive statistics of efficacy endpoints for all subjects in the study will be provided from baseline to the declared end of the study. Differences between each tofacitinib regimen and the TNFi regimen, as well as between tofacitinib regimens, will be estimated.

Details may be found in the statistical analysis plan.

9.4. Interim Analysis

No interim analysis of the study data will be performed for use outside the DMC and the Steering Committee.

9.5. Data Monitoring Committee

This study will use an external Data Monitoring Committee (DMC).

The DMC will be responsible for ongoing monitoring of safety of subjects in the study in an unblinded manner according to the Charter. All safety data, including potential primary endpoint data will be forwarded to, and reviewed by, the DMC on a regular basis. Based on these reviews, the DMC will have the capacity to make recommendations to Pfizer that might impact the future conduct of the trial. The recommendations made by the DMC to alter the

conduct of the study will be forwarded to Pfizer and the Steering Committee for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

9.6. Steering Committee

The Steering Committee is a committee established by Pfizer to oversee the conduct of the trial, assess at intervals the progress of a clinical trial (ie, Performance Standards), the aggregate accumulation of primary endpoint events (ie, MACE and malignancies) meeting pre-specified criteria, and the attainment of 1500 subjects completing 3 years in the study. The Steering Committee will recommend to the study team whether to continue, modify or stop a trial, independently from the study team. The Steering Committee will include only non-Pfizer trial experts who are not members of the study team.

The Steering Committee will consider the ongoing accumulation of the adjudicated primary endpoint events and study performance standard metrics and may determine that sufficient events have occurred to assess the primary objectives of the study or that it is not feasible to continue the trial in pursuit of the stated objectives. These determinations by the Steering Committee will be made in accordance with pre-specified rules documented in the Steering Committee Charter and in the Statistical Analysis Plan and following consultations with the US FDA could result in recommendations for changes in study design, including changes in number of subjects studied or duration of study.

The Steering Committee Charter will pre-specify all reviews of the data that will be performed during the conduct of the study and how the data will be evaluated to determine that study completion can be declared.

The Steering Committee will be responsible for blinded review of adjudicated, aggregate primary endpoint data according to its charter.

Any recommendations made by the Steering Committee to alter the conduct of the study will be forwarded to the study team who will confer with the US FDA prior to implementation of any changes in the study design. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints to regulatory authorities, as appropriate.

The numbers of events necessary to achieve the targeted statistical power for the comparisons of the hazards for the primary endpoints with respect to the various combinations of treatment groups and boundaries were given in a previous section of this protocol.

Additionally, the Steering Committee will maintain detailed Performance Standards (refer to Section 13), periodically review metrics and implement corrective actions, as needed.

9.7. External Adjudication/Review Committees

The external, independent adjudication (or review) committees that are planned for use in this study are described below. All review committees will make a detailed assessment and follow-up of events to determine if the event meets pre-defined criteria. To assist in this process, sites may be asked to submit additional data to facilitate that assessment. The review and classification processes for each are defined in detail in the respective charters.

9.7.1. Hepatic Event Review Committee

The Hepatic Event Review Committee (HERC) will review, assess and categorize potential events of hepatic injury reported in this study. Case review and assessment by the HERC will be independent of Pfizer.

Events will be identified for adjudication by study investigators, Pfizer personnel (or designee) and/or by search of the clinical, safety and laboratory databases. Each reviewed event will be assessed as to whether the event represents drug-associated drug-induced liver injury (DILI). Each case reviewed will be classified for the following categories:

- Drug Induced Liver Injury (DILI).
- Pattern of Injury.
- Hy's Law Case.
- Severity of injury.
- Recovery.
- Liver Failure.
- Likely, competing or alternative cause(s).

The product of the HERC will be narrative in format. The process of adjudication will be defined in the Hepatic Event Review Committee's charter.

9.7.2. Opportunistic Infection Review Committee

The Opportunistic Infection Review Committee (OIRC) will review, assess and categorize potential opportunistic infections (OI) reported in this study. Case review and assessment by the OIRC will be independent of Pfizer.

Events will be identified for adjudication by study investigators, Pfizer personnel (or designee) and/or by search of the clinical and safety databases. Each potential OI will be assessed as to whether it meets specific criteria:

- Opportunistic Infection (type specified).
- Special Interest Infection (type specified).

- Does not meet criteria.
- Unevaluable or Undetermined.

The process of adjudication will be defined in the Opportunistic Infection Review Committee's charter.

Both the reported and adjudicated event terms will be reported in the study database; analyses will be based on adjudicated events.

9.7.3. Cardiovascular Safety Endpoint Adjudication Committee

The Cardiovascular Endpoint Adjudication Committee (CV-EAC) will evaluate and adjudicate selected CV safety events by a consistent set of criteria. Case review and assessment by the CV-EAC will be independent of Pfizer.

Events will be identified for adjudication by study investigators, Pfizer personnel (or designee) and/or by search of the clinical and safety databases. Cardiovascular events to be adjudicated include:

- Death (coronary and non-coronary).
- Myocardial Infarction.
- All Coronary Revascularization.
- Unstable Angina.
- New Ischemic Heart Disease.
- Stroke (fatal and non-fatal).
- Transient Ischemic Attack (TIA).
- Congestive Heart Failure (CHF).
- Peripheral Arterial Vascular Disease (PAVD) – first diagnosis or procedure.
- Deep Vein Thrombosis
- Pulmonary Embolism
- Arterial Embolism
- Arterial Thrombosis

The process of adjudication will be defined in the Cardiovascular Endpoint Adjudication Committee's charter.

Both the reported and adjudicated event terms will be reported in the study database; analyses will be based on adjudicated events.

9.7.4. Malignancy Adjudication Committee and Histopathology Over-read

The Malignancy Adjudication Committee (MAC) will review, assess and categorize potential malignancies reported in this study. Case review and assessment by the MAC will be independent of Pfizer.

Events will be identified for adjudication by study investigators, Pfizer personnel (or designee) and/or by search of the clinical and safety databases. Each potential event will be assessed as to whether 1) it meets criteria for classification as a malignancy and 2) the type of malignancy.

Additionally, any biopsy that is performed to evaluate the potential presence of a malignant process will be reviewed independently by blinded, board-certified pathologists at a central laboratory.

This includes any biopsy performed to evaluate a potential malignancy in which the local pathology evaluation is consistent with either a benign process, a "pre-malignant process" or dysplasia, and includes cases of basal cell carcinoma and squamous cell carcinoma of the skin, and carcinoma in situ of the cervix. Pathology review will also include procedures performed for other reasons (ie, cosmetic surgery or removal of ischemic tissue) in which a malignancy is identified by the local pathology evaluation. Histopathology review will not encompass routine screening procedures for dysplasia such as a Papanicolaou (Pap) smear but will encompass cervical biopsy procedures as follow-up for abnormal Pap smear findings.

The MAC will review case information including patient history, diagnostic tests such as imaging, local biopsy results, central pathologist's diagnosis, surgical outcomes and other medical records as appropriate and available.

The local pathologist's diagnosis and the central pathologist's diagnosis, as well as both the reported and adjudicated event terms will be reported in the study database.

9.8. Additional Safety Event Review Committees

Additional safety event review committees may be established for review of specific events, such as interstitial lung disease and gastrointestinal (GI) perforations, to enhance the specificity and accuracy of reporting for these events.

These safety event review committees may be internal or external and will be independent of the study teams.

The review process will be defined in the respective committee charters. As for external review committees, sites may be asked to submit additional data to facilitate that assessment.

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 is 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)/Independent Ethics Committee (IEC), 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 is true. Any corrections to entries made in the CRFs, 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 records 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, eg, 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 (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), 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 (eg, 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 to 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)/Independent Ethics Committee (IEC)

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

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC 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 comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study subject, or his/her legal representative, 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 or the subject's legal representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

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 which 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. PERFORMANCE STANDARDS

During the study, the following performance standards will be monitored and evaluated. Metrics will be reported to the Steering Committee and additional measures may be taken by the Steering Committee to ensure the study integrity and timely completion of the study. The Steering Committee will maintain a Performance Standard Document with a complete description of the performance standards applied to this study, acceptable targets and remedial steps to be taken if not satisfactorily met. An overview of the performance standards is presented here.

13.1. Enrollment Rate Performance Standard

The purpose of this performance standard is to identify an acceptable rate of enrollment that allows subjects to be enrolled in the study at a rate sufficient to provide acceptable data to allow interpretation of the study endpoints within the requirements of this protocol. An acceptable target rate of enrollment provides guidance to the operational study team in determining the country footprint of the study and ultimately the selection of sites.

During the first 12 months of the study, sites will be in various stages of start-up; the recruitment rate is expected to gradually increase relative to the number of sites actively recruiting and then remain stable through the recruitment period. The sample size and recruitment period may vary dependent upon the Steering Committee's recommendations to the study team. A minimum of approximately 4000 subjects randomized over approximately a 3-year recruitment period with at least 1500 subjects completing approximately 3 years in the study is expected and the target number of events for MACE and malignancies has been achieved.

The target rate of enrollment for this study is to randomize all subjects by the end of the recruitment period. Recruitment rates are followed monthly by study, region and investigator site.

This study is being managed by an Alliance Partner. The Alliance Partner will have risk/mitigation plans in place to identify specific remedial actions to be taken, depending on the reason for variance from the expected recruitment rate; these actions will be implemented as appropriate (Clinical Trial Process Quality Standard (CTPQS)-106 Plan and Manage Study Execution, Version 3, Effective Date: 15-Feb-2013).

If recruitment falls below 100 subjects per month for 3 consecutive months and all sites planned have been initiated, the study team will identify the issues impacting recruitment and implement appropriate strategies if feasible, which may include increasing the number of sites participating in the study, providing recruitment tools to sites, which may include the development of site-specific advertisements and brochures, and/or retraining of sites to increase enrollment.

13.2. Target Population Performance Standard

The purpose of this performance standard is to identify the acceptable target population to be recruited into this study.

The acceptable population is defined as subjects 50 years of age or older with active rheumatoid arthritis and cardiovascular risk factors that meet all inclusion criteria for the study as defined in Section 4.1 Inclusion Criteria and that do not have evidence of any exclusion criteria as defined in Section 4.2 Exclusion Criteria.

The performance standard for this study is that all subjects enrolled in the study meet the definition for inclusion.

Inclusion and exclusion criteria are monitored as subjects are enrolled in the study. Subjects are noted as protocol deviations if they do not meet the criteria for inclusion in the study (see Section 13.4 Subject Ineligibility Performance Standard). If a subject who is identified as not meeting the criteria is randomized to study drug, appropriate steps will be taken by the study team, including immediate withdrawal of the subject, if warranted to protect the safety of the subject.

Subjects who were not completely eligible for inclusion in the study for reasons that impact the analysis of the study endpoints will be excluded from the Per Protocol Analysis Set, but included in the Full Analysis Set.

This study is being managed by an Alliance Partner. The Alliance Partner will have risk/mitigation plans in place to identify specific remedial actions to be taken, depending on the reason for deviation for including subjects that do not meet the inclusion/exclusion criteria; these actions will be implemented as appropriate (CTPQS-106 Plan and Manage Study Execution, Version 3, Effective Date: 15-Feb-2013).

13.3. Primary Endpoint Safety Event Rate Performance Standard

The purpose of this performance standard is to prospectively identify the presumed rate at which the primary endpoint safety events occur during the study to inform decisions regarding enrollment or length of the study.

There are two co-primary endpoints in this study; major adverse cardiovascular events (MACE) and malignancies.

The performance standard for this study is the rate of MACE, which is 1.0 event per hundred patient-years, and the assumed rate for malignancy, which is 1.1 events per hundred patient-years.

Rates of events will be calculated for the blinded treatment groups for use by the Steering Committee periodically and will guide the Steering Committee in making recommendations regarding the sample size or length of study needed to evaluate the comparative endpoints. Rates significantly higher than expected may result in recommendation for a smaller study, while rates significantly lower than expected may result in a recommendation for a larger,

longer study or discontinuation of the study for infeasibility. All modifications to the study design will be made only following consultations with the US FDA.

13.4. Subject Ineligibility Performance Standard

The purpose of this performance standard is to identify the standard by which deviations from the protocol are identified that may render subjects ineligible for continued inclusion in the study or in statistical analyses of the study.

Protocol deviation identification and documentation will be accomplished for this study according to the Sponsor's standard operating procedures (SOPs) that require periodic review of individual protocol deviations and periodic review of aggregated cumulative protocol deviations. Prior to initiation of the study, a list of potentially important protocol deviations (pIPDs) is developed in alignment with the requirements of the protocol. This list is updated, as necessary, to include other deviations identified during the course of the study. Monitors identify and log all protocol deviations during the course of the study at each participating site. Additionally, pIPDs are prospectively identified; pIPDs are used by the statistician and clinician in determining eligibility for inclusion in the statistical analysis of the study and are considered for inclusion in the body of the clinical study report. An initial assessment of the individual protocol deviations is made by the study clinician. Review of individual and aggregate cumulative protocol deviations, which include all aspects of subject participation in the study, are used by the study team to understand study issues and evaluate the protocol, including operational procedures, to identify areas where retraining may be required or modification to procedures are necessary for compliance to the protocol.

Periodic and aggregate cumulative adverse events, serious adverse events and abnormal laboratory findings are reviewed by the study clinician to identify expected and unexpected safety signals and to identify subjects who potentially should be discontinued from the study. If an event is identified that would require subject discontinuation, the site is informed of this finding by the study team and if the subject is found to require discontinuation, discontinuation is required.

The performance standard for this study is at least monthly review of individual protocol deviations, adverse events and laboratory abnormalities with aggregate cumulative review of these events at least quarterly during the conduct of the study and once after database lock.

If the clinician determines that a protocol deviation affected the safe use of study drug in a manner that directly resulted in a serious adverse event (SAE), exposure during pregnancy, or was likely to recur and could affect the safe use of the drug in a manner that would likely result in an SAE or exposure during pregnancy, the event is forwarded to a cross-functional team that assesses the documentation and determines if the event meets the criteria, a protocol deviation alert letter, explaining the deviation is sent to participating investigators.

If unexpected signals are identified in the safety database, the event(s) will be brought to the Safety Risk Management Committee for review and evaluation across all studies in the tofacitinib program and reported internally and externally, as required for the event.

Subjects with pIPDs that could impact endpoint analysis will be excluded from the Per Protocol Analysis Set, but included in the Full Analysis Set.

This study is being managed by an Alliance Partner. The Alliance Partner will have risk/mitigation plans in place to identify specific remedial actions to be taken, depending on the reason for ineligibility of the subject; these actions will be implemented with specific steps taken dependent upon the reason for the deviation (CTPQS-106 Plan and Manage Study Execution, Version 3, Effective Date: 15-Feb-2013).

13.5. Adherence to Assigned Treatment Performance Standard

The purpose of this performance standard is to identify the standard by which subjects are determined to be compliant with their assigned treatment during the study and how they will be handled in the analysis of study data.

Adherence to the assigned treatment is necessary to the integrity of the study analysis, which is dependent upon exposure to the assigned treatments. Compliance is determined by pill and syringe counts as described in Section 5.3.5 and study treatment and concomitant medication dosing logs.

There are several performance standards for compliance for this study:

- < 80% compliant with the dosage regimen for any one of the orally administered study medications or have not used 2 or more injectable syringes expected to be used over the time between scheduled visits.
    - These subjects will be counseled and the site will implement appropriate measures to secure subject compliance, including instituting interim visits to evaluate and encourage compliance, as appropriate to the site and reason for non-compliance.
- < 70% compliant with the dosage regimen for any one of the orally administered study medications or have not used 2 or more injectable syringes expected to be used over the time between scheduled visits.
    - The reason for non-compliance with the dosing regimen should be documented in the dosing log of the subject's case report form, and should be reported as a protocol deviation and unless there is a protocol stipulated reason for non-compliance with the dosing regimen, this should be recorded as a dosing error.
- > 120% compliance with the dosing regimen for any one of the orally administered study medications or have not used 2 or more injectable syringes expected to be used over the time between scheduled visits.
    - The reason for non-compliance (more than expected consumption) with the dosing regimen should be documented in the dosing log of the subject's case

report form with the reason for non-compliance, reported as a protocol deviation, and recorded as a dosing error.

Subjects who are found to be <70% or >120% compliant with the dosage regimen for any one of the study medications at any time during the study will be censored from efficacy analyses utilizing the Per Protocol Analysis Set, but will be included in analyses utilizing the Full Analysis Set.

This study is being managed by an Alliance Partner. The Alliance Partner will have risk/mitigation plans in place to identify specific remedial actions to be taken, depending on the reason non-compliance with the dosing regimen; these actions will be implemented if the event exceeds the respective performance standard (CTPQS-106 Plan and Manage Study Execution, Version 3, Effective Date: 15-Feb-2013).

13.6. Cross-Ins Performance Standard

Subjects will either remain in their respective assigned treatment (tofacitinib 5 mg BID, tofacitinib 10 mg BID, adalimumab 40 mg QOW or etanercept 50 mg weekly) or be identified as being switched to standard of care, which may include tofacitinib, adalimumab or etanercept if those compounds are standard of care in their locality. Therefore, a performance standard for Cross-Ins is not relevant to this study.

13.7. Subject Retention Performance Standard

The purpose of this performance standard is to identify subject retention performance standards and to define the actions to be taken if the performance standard is not met.

The performance standard for subject retention within their assigned treatment group is an assigned treatment discontinuation rate of approximately 15% annually during the conduct of the study with higher discontinuation rates seen during the first year of the study.

The expected assigned treatment discontinuation rates were developed from overall discontinuation rates seen in tofacitinib RA Phase 2/3 studies and the Long-Term Extension Studies and have been applied to this study as the projected performance standard for subject retention within their assigned treatment group.

Discontinuation rates, including reason for discontinuation, are collected and reviewed by the study clinician periodically during the study. Discontinuation rates will be evaluated at least monthly for trends in total rates and components of these rates (eg, adverse events, insufficient clinical response, no longer willing to participate).

This study is being managed by an Alliance Partner. The Alliance Partner will have risk/mitigation plans in place to identify specific remedial actions to be taken, depending on the reason for the increased rate in discontinuation; these actions will be implemented if the rate of discontinuation exceeds the performance standard. However, intermediate interventions may be applied if component rates are trending upwards and reasons can be identified and addressed by the study team (eg, inappropriate subject selection, retraining of

sites, etc) (CTPQS-106 Plan and Manage Study Execution, Version 3, Effective Date: 15-Feb-2013).

13.8. Timeliness of Data Performance Standard

The purpose of this performance standard is to evaluate timeliness of data entry and define actions to be taken if the performance standard is not met.

The performance standard for timeliness of data entry is compliance to the requirement that investigators complete data entry into the case report form (CRF) within four (4) calendar days of that data becoming available.

This study is being managed by an Alliance Partner. The Alliance Partner will have a process in place to monitor timely CRF data entry that includes monthly monitor review of investigator performance to data entry timelines and a structured action plan and escalation/communication process triggered by site performance with data entry timelines (CTPQS-113 Study Site Initiation, Monitoring and Closure, Version 5, Effective Date: 15-Feb-2013).

14. DEFINITION OF END OF TRIAL

14.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

14.2. End of Trial in all Other Participating

End of Trial in all other participating countries is defined as that time when sufficient subjects have been recruited and completed the study (or the study is prematurely terminated by the Sponsor) and the database has been locked for the final study analysis.

15. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, a recommendation by the DMC, a recommendation by the Steering Committee, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of tofacitinib for use in patients with rheumatoid arthritis 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.

16. PUBLICATION OF STUDY RESULTS

16.1. 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). Pfizer registers study protocols and posts Basic Results on ClincialTrials.gov for Pfizer-sponsored interventional studies in human subjects that evaluate the safety and/or efficacy of a Pfizer product.

The results are posted in a tabular format called Basic Results.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, FDA-approved products, Pfizer posts results within one year of the primary completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV);

- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval, or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year of discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).

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 trial concluded according to the pre-specified protocol or was terminated.

16.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

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, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

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 multi-centre study, 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, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, 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 Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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Appendix 1. The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis[16]

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

*The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.
†Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider an expert rheumatologist should be consulted.
‡Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.
§Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.
¶"Large joints" refers to shoulders, elbows, hips, knees, and ankles.

#"Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.
**In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (eg., temporomandibular, acromioclavicular, sternoclavicular, etc.).
†† Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti-citrullinated protein antibody.
‡‡Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
§§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (eg, pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Appendix 2. Prohibited Concomitant Medications

Prohibited drugs, including investigational compounds, require discontinuation for at least 7 days or 5 half lives (whichever is longer) prior the Baseline visit. All investigational compounds, other than study drug, are prohibited during the study. Only systemically administered drugs listed below are prohibited; topical, ophthalmic, or intravaginal administration is allowed.

<table>
<tr><th colspan="2">Prohibited Concomitant Medications</th></tr>
<tr><th>Potent CYP3A/CYP2C19 Inhibitors</th><th>Moderate or Potent CYP3A Inducers</th></tr>
<tr><td>Protease inhibitors:
indinavir (Crixivan)
nelfinavir (Viracept)
ritonavir (Kaletra, Norvir)
Saquinavir (Invirase)</td><td>Protease inhibitors:
efavirenz (Sustiva)*
nevirapine (Viramune)*</td></tr>
<tr><td>Macrolide antibiotics:
clarithromycin (Biaxin, Prevpac)
telithromycin (Ketek)</td><td>Anticonvulsants:
barbiturates*
phenobarbital*
phenytoin (Dilantin, Phenytek)
carbamazepine (Carbatrol, Tegretol)*</td></tr>
<tr><td>Other antibiotics:
chloramphenicol</td><td rowspan="2">Antibiotics:
rifampicin/rifampin (Rifadin, Rifamate)
rifabutin (Mycobutin)*
rifapentene (Priftin)*</td></tr>
<tr><td>Antifungals:
fluconazole (Diflucan)
ketoconazole (Nizoral)
itraconazole (Sporanox)
voriconazole (Vfend)</td></tr>
<tr><td>Antidepressants:
fluvoxamine (Luvox)
nefazodone (Serzone)</td><td>Antidepressants:
St. John's Wort*</td></tr>
<tr><td></td><td>Other compounds:
modafinil (Provigil)
troglitazone (Rezulin)</td></tr>
<tr><td colspan="2">Prohibited Concomitant DMARDs**</td></tr>
<tr><th>Biologic DMARDs</th><th>Nonbiologic DMARDs</th></tr>
<tr><td>anakinra (Kineret), etanercept (Enbrel), adalimumab (Humira), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), rituximab (Rituxan, Mabthera)</td><td>Oral gold (auranofin), injectable gold (aurothioglucose, aurothiomalate), sulfasalazine, d-penicillamine, bucillamine, mizoribin, azathioprine, leflunomide (Arava), cyclosporine, tacrolimus</td></tr>
</table>

* Discontinue for at least 30 days
**See Section 5.5.2 for specific washout requirements and Section 5.6.1 for using standard of care treatment in subjects who are not controlled with their respective study drug.

Appendix 3. Cockcroft-Gault Formula for Estimating GFR

Creatinine Clearance (estimated) / Conventional mL/min =

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

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

Appendix 4. Sweden-Specific Protocol Requirements

The content of this Appendix is deleted as no subject was screened or enrolled in Sweden.

Appendix 5. Czech Republic, Spain and United Kingdom Specific Protocol Requirements

In the Czech Republic, Spain and the United Kingdom, the following changes have been made to the protocol sections listed:

4.2. Exclusion Criteria

Additional exclusion criteria apply:

6. c. Absolute lymphocyte count $<0.75 \times 10^9$/L ($<750/mm^3$)

6. d. Absolute neutrophil count $<1.2 \times 10^9$/L ($<1200/mm^3$)

7.10 Clinical Laboratory Tests

Subjects in the listed countries who are randomized to and are receiving tofacitinib will have additional laboratory testing performed. Lymphocyte subset assessments will be conducted at each study visit (Baseline, Month 2, Month 3 and every 3 months thereafter). The lymphocyte subsets and markers to be tested are identified in Table 4.

Table 4. Lymphocyte Subsets and Markers

Subsets	Markers
Total T cells	CD3+
CD4+ T cells	CD3+CD4+
CD8+ T cells	CD3+CD8+
NK cells	CD3-CD16+CD56+
B cells	CD3-CD19+

7.15 Triggered Requirements for Monitoring

Additional requirements for discontinuation of study drug include:

- Opportunistic infection judged significant by the investigator.
- Two sequential neutrophil counts <1000 neutrophils/mm^3.

Appendix 6. Canada Specific Requirements for the Use of Two Methods of Effective Contraception.

Subjects in Canada who are woman of childbearing potential and sexually active must use two contraceptive methods at the same time, one highly effective contraceptive method and one additional effective contraceptive method.

Highly effective contraceptive methods may include hormonal contraceptives (eg, combined oral contraceptives, patch, vaginal ring, injectables, and implants), intrauterine device (IUD) or intrauterine system (IUS), vasectomy or tubal ligation.

Effective methods may include barrier methods of contraception (eg, male condom, female condom, cervical cap, diaphragm or contraceptive sponge). The proper use of diaphragm or cervical cap includes use of spermicide and is considered one barrier method. The cervical cap and contraceptive sponge are less effective in parous women. The use of spermicide alone is not considered a suitable barrier method for contraception.

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