



**A PHASE 3B/4 RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED
STUDY OF METHOTREXATE (MTX) WITHDRAWAL IN SUBJECTS WITH
RHEUMATOID ARTHRITIS (RA) TREATED WITH TOFACITINIB 11MG
MODIFIED RELEASE (MR) FORMULATION**

Compound:	CP 690,550
Compound Name:	Tofacitinib citrate
United States (US) Investigational New Drug (IND) Number:	CCI [REDACTED]
European Clinical Trials Database (EudraCT) Number:	2016-001825-15
Protocol Number:	A3921192
Phase:	Phase 3B/4



Document History

Document	Version Date	Summary of Changes
Original protocol	09 May 2016	Not applicable (N/A)
Amendment 1	09 Feb 2017	<p>Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, United Kingdom country specific amendment. The following changes were made:</p> <ol style="list-style-type: none">1. Exclusion of subjects screened in Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and the United Kingdom who have resided in or traveled in areas of endemic tuberculosis or endemic mycoses.2. Addition of Quantiferon testing at week 24 for all patients.3. Addition of text to Section 1.2.1 that tofacitinib is under review in the EU and not yet approved.4. Clarification to the Schedule of Activities and Section 7.2 that careful assessment of the skin for melanoma and nonmelanoma skin cancer is part of the Assessment of New Physical Findings.5. Addition of a statement regarding the risk of administration of NSAIDs and methotrexate and the prohibition of the use of folate antagonists during the study.6. Clarification of discontinuation criteria.7. Change to Section 7.16 and 7.17 indicating that CRP and ESR are blinded to the investigator and site staff after randomization instead of screening.8. Changes to Section 4.4.5 Contraception and Reproductive Status section added in Appendix 7.

Amendment 2	04 Dec 2017	<p>The following changes were made:</p> <ol style="list-style-type: none"> 1. Addition of text to Section 1.2.1 that tofacitinib has been approved in the EU. 2. Addition of the ECG at End of Study visit in the Schedule of Activities and in Section 6.2.7. 3. The number of subjects enrolled was increased from 580 to 680. 4. The LDA assessment was changed from DAS28-4(ESR) <3.2 and DAS28-4(CRP) <3.2 to DAS28-4(ESR) ≤3.2 and DAS28-4(CRP) ≤3.2. 5. Stool examination for parasites in Peru (Table 4; Clinical Laboratory Tests) will be deleted since Peru is not involved this study. 6. Changes from baseline in tender/painful joint counts, swollen joint counts, subject assessment of arthritis pain, subject global assessment of arthritis, and physician global assessment of arthritis were added as other efficacy endpoints. <p>The following changes previously described in the protocol administrative change letters (PACL) dated 17Jun2016, 14Jul2016, 05Jul2017 and 07Sep2017 were made:</p> <ol style="list-style-type: none"> 1. In Section 7.4, Electrocardiogram, the electrocardiogram (ECG) at the End of Study visit was deleted and comparison of the End of Study ECG was not to be completed per the PACL dated 17Jun2016. However, the decision has been made to keep the ECG at the End of Study visit so this change will not be made. 2. In Sections 6.1 (screening), 6.2.4 (Visit 3) and 6.2.6 (Visit 5): the sentence “Subjects are required to fast for at least 6 hours prior to the visit” is deleted. 3. In Section 6.2.2 (Visit 1): “Smoking history and alcohol consumption” will be added as one of the information collected. 4. In Sections 7.16, C-Reactive Protein (CRP) and 7.17, Erythrocyte Sedimentation Rate
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		<p>(ESR) will be changed so that the Investigator and other site personnel participating in the study and Pfizer study personnel will be kept blinded of the results of this test after the randomization visit.</p> <ol style="list-style-type: none">5. In Section 4.2, Exclusion Criteria, Criterion 8b, has been revised to also exclude any prior JAK inhibitor usage.6. Section 9.6 has been retitled and includes information regarding potential safety and efficacy analyses of data obtained in the Open Label Phase of the study.7. In Appendix 3, Prohibited Concomitant Medications: The medication "baricitinib (Olumiant)" has been added to the Prohibited Concomitant Medications table, listed under Nonbiologic DMARDs.8. In Section 3.0, Study Design:<ol style="list-style-type: none">a. "The enrollment will be monitored by Sponsor to ensure approximately 50% of enrolled subjects will have moderate disease activity (defined as DAS28 (ESR) >3.2 and <5.1) and approximately 50% will have severe disease activity (defined as DAS28 (ESR) >5.1)." is removed from the protocol.b. "In addition, the proportion of subjects who have been exposed to one or more biologics prior to enrollment" is changed to "In addition, the proportion of subjects who have had an insufficient response to one or more biologics prior to enrollment"
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This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Background and Rationale

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

The Phase 2 and 3 studies in the RA development program have demonstrated that tofacitinib Immediate Release (IR) 5 mg twice daily (BID) consistently reduces signs and symptoms of rheumatoid arthritis (RA), improves physical function and other subject-reported outcomes such as fatigue, pain and health-related aspects of quality of life in subjects with moderate to severe RA. Combined with its inhibition of the progression of structural damage, the development program has demonstrated tofacitinib as an effective targeted synthetic disease-modifying antirheumatic drug (DMARD) in treating RA.⁵⁻¹⁰ Ongoing long-term extension and Phase 3b/4 post authorization safety studies are aimed to demonstrate sustained efficacy and a consistent safety profile as seen in the Phase 2 and 3 controlled clinical trials. Data from completed and ongoing clinical trials demonstrate tofacitinib's manageable safety profile. The overall benefit-risk profile of the tofacitinib IR formulation remains favorable (refers to Investigator Brochure (IB) for further details). Tofacitinib IR 5 mg BID is currently approved in the United States (US), European Union (EU), and 40 other countries for the treatment of adult patients with RA.

To enable once daily (QD) dosing, Pfizer has developed a modified release (MR) osmotic tablet formulation of tofacitinib at a dose strength of 11 mg. Seven Phase 1 healthy volunteer studies have been completed to characterize the biopharmaceutical aspects of the tofacitinib MR 11mg QD formulation and establish similarity in key pharmacokinetic (PK) exposure parameters and relative bioavailability (BA) as compared to the currently approved tofacitinib IR 5 mg BID formulation. The tofacitinib MR clinical pharmacology development program has demonstrated that the MR 11 mg QD dose has equivalent Area Under Concentration (AUC) and C_{max} compared to the currently approved IR 5 mg BID dose. Exposure-response (E-R) relationships from the IR development program show that C_{av} is the relevant parameter for efficacy and that the slightly lower (29%) C_{min} of the MR formulation is not clinically important to the efficacy of tofacitinib. These data support the consistent efficacy between MR 11 mg QD and IR 5 mg BID. Likewise, the overall

similarity in PK parameters and duration of JAK1/3 inhibition over the dosing interval, along with exposure-safety relationships from the IR program, indicate that the safety of MR 11 mg QD will be consistent with that of the IR 5 mg BID. The MR formulation of tofacitinib was also shown to be generally safe and well tolerated in 7 healthy volunteer studies.

Collectively, these data support a favorable benefit-risk profile for the MR 11 mg QD formulation for the treatment of adult patients with moderately to severely active RA, and the efficacy and safety of tofacitinib MR 11 mg QD are expected to be consistent with that demonstrated for tofacitinib IR 5 mg BID. A New Drug Application (NDA) for the MR osmotic tablet formulation of tofacitinib (dosed at 11 mg QD) for the treatment of RA is under review by the Food and Drug Administration (FDA).

The tofacitinib IR 5mg BID formulation has demonstrated efficacy both as a monotherapy and in combination with methotrexate (MTX) in previous trials. However, it remains unknown whether the tofacitinib efficacy will be sustained after the withdrawal of MTX among RA patients who achieve low disease activity following treatment with tofacitinib plus MTX. Results of the current study will inform the value of the continued MTX treatment among subjects who have responded to combined therapy of tofacitinib and MTX. A MR 11mg QD regimen has the potential to offer an additional dosing option to subjects, and based on the equivalence of key pharmacokinetic parameters, efficacy and safety are expected to be consistent with that demonstrated for tofacitinib IR 5 mg BID. Therefore, the current study will evaluate the sustained efficacy and safety of the tofacitinib MR 11 mg QD regimen among RA patients undergoing blinded withdrawal of MTX.

Complete information for tofacitinib may be found in the single reference safety document (SRSD), which for this study is the tofacitinib IB. The SRSD for MTX is the Summary of Product Characteristics (SPC).

STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES

Primary Objectives

To compare the efficacy of tofacitinib MR 11mg monotherapy to tofacitinib MR 11mg with continued MTX, as measured by the change in the Disease Activity Score utilizing 4 components including erythrocyte sedimentation rate (DAS28-4 (ESR)) from randomization (at Week 24) to the end of the double-blind MTX withdrawal phase (at Week 48).

Secondary Objectives

- To compare the efficacy of tofacitinib MR 11mg monotherapy to tofacitinib MR 11mg with continued MTX in the double-blind MTX withdrawal phase (at Week 36), as measured by DAS28-4 (ESR).

- To compare the efficacy of tofacitinib MR 11mg monotherapy to tofacitinib MR 11mg with continued MTX in the double-blind MTX withdrawal phase (at Weeks 48 and 36), as measured by Disease Activity Score 28-4 (C-reactive protein) (DAS28-4 (CRP)), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), Low Disease Activity (LDA), remission, ACR20, ACR 50, and ACR 70.
- To compare effects of tofacitinib MR 11mg monotherapy to tofacitinib MR 11mg with continued MTX on health outcome measures in the double-blind MTX withdrawal phase (at Weeks 48 and 36), as measured by Health Assessment Disability Questionnaire-Disability Index (HAQ-DI), Medical Outcomes Survey Short Form -36 (SF-36), Work Productivity and Activity Impairment (WPAI), European Quality of Life - 5 dimensions questionnaire (EuroQol EQ-5D), and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale.
- To evaluate the safety and tolerability of tofacitinib MR 11mg monotherapy versus tofacitinib MR 11mg with continued MTX.

Other Objectives

- To describe efficacy of treatment with tofacitinib 11mg with MTX in the open-label run-in phase (at Weeks 12 and 24), as measured by DAS28-4 (ESR), DAS28-4 (CRP), CDAI, SDAI, LDA, remission, ACR20, ACR 50, ACR70.
- To describe effects of treatment with tofacitinib MR 11mg with MTX on health outcome measures in the open-label run-in phase (at Weeks 12 and 24), as measured by HAQ-DI, SF-36, WPAI, EuroQol EQ-5D, and FACIT-Fatigue scale.

Exploratory Objectives

- To collect exploratory biomarker/genomics samples for bio-banking.
- US and Canada ONLY: To explore effects of treatment with tofacitinib MR 11mg with/without MTX on health outcome measure in the open-label run-in phase (at Weeks 12 and 24) and the double-blind MTX withdrawal phase (at Weeks 48 and 36), as measured by Routine Assessment of Patient Index Data 3 (RAPID3).

Endpoints

Efficacy Endpoints

Primary Efficacy Endpoint

Change in DAS28-4 (ESR) score from randomization (at Week 24) to the end of double-blind MTX withdrawal phase (at Week 48).

Secondary Efficacy Endpoints

- Change in the DAS28-4 (ESR) from Week 24 to Week 36;
- Changes in the DAS28-4 (CRP), CDAI and SDAI, respectively, from Week 24 to Week 48 and from Week 24 to Week 36;
- LDA as assessed by DAS28-4(ESR) ≤ 3.2 , DAS28-4(CRP) ≤ 3.2 , CDAI ≤ 10 and SDAI ≤ 11 , respectively, at Weeks 48 and 36;
- Remission as assessed by ACR-EULAR Boolean remission criteria,¹¹ DAS28-4 (ESR) < 2.6 , DAS28-4 (CRP) < 2.6 , CDAI ≤ 2.8 and SDAI ≤ 3.3 , respectively, at Weeks 48 and 36;
- ACR20, ACR 50, and ACR70 responses, respectively, at Weeks 48 and 36;
- Change in the HAQ-DI, the SF-36 (8 domain scores and 2 component scores), WPAI, EuroQol EQ-5D and the FACIT-Fatigue scale score, respectively, from Week 24 to Week 48 and from week 24 to Week 36;
- HAQ-DI response (ie, decrease of at least 0.22) at Weeks 48 and 36.

Other Efficacy Endpoints

- Changes in DAS28-4 (ESR), DAS28-4 (CRP), CDAI, SDAI, HAQ-DI, SF-36 (8 domain scores and 2 component scores), WPAI, EuroQol EQ-5D score and FACIT-Fatigue scale score, respectively, from day 1 to Week 12 and from day 1 to Week 24;
- LDA as assessed by DAS28-4(ESR) ≤ 3.2 , DAS28-4(CRP) ≤ 3.2 , CDAI ≤ 10 and SDAI ≤ 11 , respectively, at Weeks 12 and 24;
- Remission as assessed by ACR-EULAR Boolean remission criteria, DAS28-4 (ESR) < 2.6 , DAS28-4 (CRP) < 2.6 , CDAI ≤ 2.8 and SDAI ≤ 3.3 , respectively, at Weeks 12 and 24;
- ACR20, ACR 50, and ACR70 responses, respectively, at Weeks 12 and 24;
- HAQ-DI response (ie, decrease of at least 0.22) at Weeks 12 and 24.
- Changes in tender/painful joint counts, swollen joint counts, subject assessment of arthritis pain, subject global assessment of arthritis, physician global assessment of arthritis, and CRP, respectively, from day 1 to Week 12 and from day 1 to Week 24, from Week 24 to Week 48 and from week 24 to Week 36.

Safety Endpoints

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

Exploratory Endpoints

- Exploratory biomarker/genomics endpoints will be specified in a separate protocol and/or statistical analysis plan if exploratory analyses utilizing the bio-banked exploratory genomic and biomarker samples across tofacitinib studies or across multiple programs are conducted.
- US and Canada ONLY: RAPID3 summary score at Weeks 12, 24, 36 and 48.

STUDY DESIGN

Study A3921192 is a 12-month randomized, double-blind, placebo-controlled withdrawal study in a total of approximately 580 subjects with moderate to severe RA (defined as CDAI >10 and DAS28 (ESR) \geq 3.2) who are insufficiently responding to their stable dose of MTX treatment. The enrollment will be monitored by Sponsor to ensure approximately 50% of enrolled subjects will have moderate disease activity (defined as DAS28 (ESR) \geq 3.2 and \leq 5.1) and approximately 50% will have severe disease activity (defined as DAS28 (ESR) > 5.1). In addition, the proportion of subjects who have had an insufficient response to one or more biologics prior to the enrollment should be \leq 25% (ie, \leq 145 subjects).

After reviewing the rate of achievement of LDA and monitoring the discontinuation rate in the open-label period, the decision was made to increase in enrollment numbers from approximately 580 to 680 factoring in a discontinuation rate of approximately 15% during the open label run-in phase. As of 02 Aug 2017, study was 50% enrolled with 81% having severe disease activity. The LDA rate (~79% based upon a small sample size) was higher than protocol assumptions and historic data. It is expected that enrolling >50% of subjects with severe disease activity will result in a sufficient number of subjects with LDA at Week 24. Therefore, the enrollment requirement of 50% of subjects with severe disease activity and 50% with moderate disease activity was removed from the protocol.

Following enrollment, all subjects will receive open-label tofacitinib MR 11mg QD added to MTX at their previously stabilized dose for 24 weeks (run-in phase). At the end of the run-in phase (Week 24), only subjects who achieve low disease activity (LDA) as assessed by CDAI (ie, CDAI \leq 10) (approximately 232 subjects) will be randomized into the 24-week double-blind, placebo-controlled MTX withdrawal phase. Subjects who do not achieve LDA (defined by CDAI >10) at this time point will be discontinued from the study. Subjects entering the double-blind phase will be randomized in a 1:1 ratio to either continue the run-in phase treatment regimen (tofacitinib MR 11mg QD with blinded MTX) or to receive tofacitinib monotherapy (tofacitinib MR 11mg QD with blinded matching placebo for MTX). Randomization will be stratified by subject's prior exposure to a biologic DMARD. Randomized subjects will be followed up to the end of Week 48. The primary efficacy

endpoint is the change in DAS28-4 (ESR) from randomization (at Week 24) to the end of double-blind MTX withdrawal phase (at Week 48).

STATISTICAL METHODS

Based on estimated CDAI-defined low disease activity rate of 40% derived from prior Phase 3 studies and factoring in a discontinuation rate of approximately 15% during the open label run-in phase, approximately 680 subjects will be enrolled to the run-in phase with the aim of at least 232 subjects being randomized into the blinded MTX withdrawal phase at Week 24. With a two-sided Type-I error of 5% and an assumed standard deviation (SD) of 1.4 for the difference in change from randomization in DAS28-4 (ESR) between the two arms, a sample size of 232 subjects randomized at Week 24 would provide 90% power to declare non-inferiority of tofacitinib monotherapy relative to tofacitinib plus methotrexate with a non-inferiority margin of 0.6.

The primary endpoint of change from randomization in DAS28-4 (ESR) at Week 48 will be analyzed as a continuous variable using a linear mixed-effect model of repeated measures (MMRM) that includes the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological DMARD, and baseline DAS28-4 (ESR) value as a covariate. Within-subject variability will be accounted for using a random effect with an unstructured covariance matrix. Change from randomization at any visit post-randomization will be defined as the DAS28-4 (ESR) value at that visit minus the value at randomization.

The analysis will be based on the Full Analysis Set (FAS), which is defined as those subjects who received at least one dose of tofacitinib MR 11mg plus MTX during the open label run-in period, and were randomized and received at least one dose of the randomized investigational drug regimen (tofacitinib MR 11mg with MTX or tofacitinib MR 11mg with placebo for MTX) during the blinded MTX withdrawal period.

A robustness analysis based on a per-protocol analysis set will be performed. Sensitivity analyses using different methods of handling missing data will also be conducted; further details will be outlined in the SAP.

STATISTICAL DECISION RULES

The primary analysis will be a non-inferiority test to show that tofacitinib MR 11mg monotherapy is not less effective (non-inferior) than tofacitinib MR 11mg with continued MTX within the margin of non-inferiority set at 0.6 (ie, the difference in mean change from randomization in DAS 28-4 (ESR) between the two arms). In other words, the change from randomization in DAS28-4(ESR) for the tofacitinib MR 11mg with placebo for MTX arm may be less favorable than that for the tofacitinib MR 11mg with continued MTX arm by no more than 0.6.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the [STUDY PROCEDURES](#) and [ASSESSMENTS](#) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Protocol Activities	Screening Visit	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4 (Randomization)	Visit 5	Visit 6 (End of Study/Early Withdrawal) ^k	Telephone Follow-up ^o
	Day -30 (+10 days; ie, -40 days)	Day 1	Week 6 (Day 42) (±5 days)	Week 12 (Day 84) (±10 days)	Week 24 (Day 168) (±10 days)	Week 36 (Day 252) (±10 days)	Week 48 (Day 336)(±10 days)/early withdrawal	At least 28 days following last dose of study drugs (+14 days)
Informed Consent	X							
Medical History, Prior Medication	X							
RA diagnosis	X							
Complete Physical Examination	X	X ⁿ					X	
Assessment of New Physical Findings ^q			X	X	X	X		
Inclusion/Exclusion criteria	X	X						
Laboratory Testing								
Blood Chemistry	X	X	X	X	X	X	X	
CRP ^a	X	X		X	X	X	X	
ESR	X	X		X	X	X	X	
Hematology	X	X	X	X	X	X	X	
Banked biospecimens		X	X		X		X	
HIV Serology	X							
HBsAg, HBcAb, HBsAb ^b	X							
HCV Ab, HCV RNA ^b	X							
Lipid Profile (fasting)		X	X		X		X	
Pregnancy test, ^c Contraceptive Check and Documentation	X	X	X	X	X	X	X	
QuantiFERON-Gold [®] TM	X				X ^l			
Rheumatoid Factor	X							

Tofacitinib citrate

A3921192

Final Protocol Amendment 2, 04 Dec 2017

Protocol Activities	Screening Visit	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4 (Randomization)	Visit 5	Visit 6 (End of Study/Early Withdrawal) ^k	Telephone Follow-up ^o
	Day -30 (+10 days; ie, -40 days)	Day 1	Week 6 (Day 42) (±5 days)	Week 12 (Day 84) (±10 days)	Week 24 (Day 168) (±10 days)	Week 36 (Day 252) (±10 days)	Week 48 (Day 336)(±10 days)/early withdrawal	At least 28 days following last dose of study drugs (+14 days)
Anti-cyclic citrullinated peptide (Anti-CCP) antibody	X							
FSH (if applicable) ^d	X							
Urinalysis	X							
Chest X-ray or CT ^e	X							
ECG	X						X	
Randomization					X			
Investigational Product Dispensing		X		X	X	X		
Joint Count (28) ^f	X	X		X	X	X	X	
Subject Assessment of Arthritis Pain		X		X	X	X	X	
Subject Global Assessment of Arthritis		X		X	X	X	X	
Physician Global Assessment of Arthritis		X		X	X	X	X	
HAQ-DI ^g		X		X	X	X	X	
SF-36 (Version 2, Acute)		X		X	X	X	X	
EuroQol EQ-5D ^h		X		X	X	X	X	
Work Productivity and Activity Impairment (WPAI)		X		X	X	X	X	
FACIT-Fatigue ⁱ		X		X	X	X	X	
Routine Assessment of Patient Index Data 3 (RAPID3) (US and Canada ONLY)		X		X	X	X	X	
Safety Assessment/AE Reporting/Assessment for AEs Requiring Adjudication ^j	X ^m	X	X	X	X	X	X	X ^p
Concomitant Medication Review		X	X	X	X	X	X	
Provide/review dosing diary		X	X	X	X	X	X	
Return unused investigational products				X	X	X	X	

- a. After screening, the investigator and other site personnel participating in the study and Pfizer study personnel will be kept blinded of the results of CRP.
- b. See Exclusion Criteria 3 and Table 4 in Section 7.17 for details.
- c. Pregnancy tests (serum/urine) may also be repeated more frequently as per request of IRBs/ECs or if required by local regulations.
- d. To confirm post-menopausal status, if applicable.
- e. Chest radiograph or Chest CT scan unless previously performed and documented within 3 months prior to screening.
- f. Joint counts done by a blinded joint assessor.
- g. Health Assessment Questionnaire – Disability Index.
- h. European Quality of Life 5 Dimension Questionnaire.
- i. Functional assessment of chronic illness therapy-fatigue scale.
- j. Specific safety events will be submitted to the appropriate Safety Event Adjudication/Review Committee for adjudication.
- k. Subjects who do not achieve LDA at Week 24 and are therefore not randomized do not require a separate EOS visit except for QuantiFERON Gold[®]™ In-Tube Test.
- l. QuantiFERON Gold[®]™ in-Tube Test will be performed for ALL subjects (those who meet LDA and those who do not meet LDA at week 24) in Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and the United Kingdom. For all other countries the test will ONLY be performed for subjects who do not achieve LDA at Week 24 and are therefore not randomized.
- m. Report and assess AEs within appropriate reporting period. See Section 6.1 for details.
- n. Height will not be collected in the Case Report Form (CRF).
- o. Can be combined with the End of Study visit as long as the Telephone Follow-up occurs at least 28 days after last administration of study drugs.
- p. Includes a query of pregnancy status in addition to AEs.
- q. Assessment of new physical findings consists of an abbreviated physical examination assessing the following: weight, vital signs, skin examination including a careful examination for melanoma and nonmelanoma skin cancer, lungs, heart, lower extremities for peripheral edema, abdomen, and lymph nodes.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

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

1.2. Background and Rationale

1.2.1. Tofacitinib Immediate Release (IR) Formulation

The Phase 2 and 3 studies in RA development program demonstrated that tofacitinib IR 5 mg twice daily (BID) consistently reduces signs and symptoms of RA, improves physical function and other subject-reported outcomes such as fatigue, pain and health-related aspects of quality of life in subjects with moderate to severe RA. Combined with its inhibition of the progression of structural damage, the development program has demonstrated tofacitinib as an effective targeted synthetic DMARD in treating RA.⁵⁻¹⁰ Ongoing long-term extension and Phase 3b/4 post authorization safety studies are aimed to demonstrate sustained efficacy and a consistent safety profile as seen in the Phase 2 and 3 controlled clinical trials.

Data from completed and ongoing clinical studies demonstrate tofacitinib's manageable safety profile. As of April 2014, Over 10,000 subjects have received at least 1 study dose of oral tofacitinib in either a randomized clinical study or a long-term extension (LTE) study in multiple indications. Approximately 6100 adult RA subjects have been exposed to tofacitinib with greater than 16,800 subject years of exposure in Phase 2, 3, 3B/4 post-authorization and LTE studies. Potentially important safety risks that have been observed with the oral use of tofacitinib in the Phase 2 and Phase 3 studies include serious and other important infections, including tuberculosis (TB) and herpes zoster; the potential for malignancies including lymphoma; and the potential for gastrointestinal (GI) perforations. Subjects receiving tofacitinib may also be at increased risk of nonmelanoma skin cancers (NMSC). Cardiovascular disease and interstitial lung disease (ILD) are findings seen in RA subjects receiving tofacitinib, and are recognized comorbidities for RA as well as being associated with other RA therapies. Changes in laboratory values have also been observed including a dose-dependent increase in low density lipoprotein (LDL) cholesterol and dose-dependent decreases in neutrophils and hemoglobin. Other laboratory changes

observed with tofacitinib treatment include decreases in lymphocytes and increases in transaminases, serum creatinine, and creatine kinase (CK). Laboratory changes observed with tofacitinib treatment are manageable; recovery of laboratory changes upon discontinuation of tofacitinib treatment is characteristically observed. Based on nonclinical data, there is the potential for tofacitinib to have effects on pregnancy and the fetus. More details of identified risks with tofacitinib in RA are presented in the XELJANZ™ (tofacitinib citrate) Investigator Brochure (IB).

Based on the most recent data from clinical trials and post-marketing experience, the overall benefit-risk profile of the tofacitinib IR formulation remains favorable (refer to tofacitinib IB for further details). Tofacitinib IR 5 mg BID is currently approved in the United States (US), European Union (EU), and 40 other countries.

1.2.2. Tofacitinib Modified Release (MR) Formulation

To enable once daily (QD) dosing, Pfizer has developed a modified release (MR) osmotic tablet formulation of tofacitinib at a dose strength of 11 mg. Seven Phase 1 healthy volunteer studies have been completed to characterize the biopharmaceutical aspects of the tofacitinib MR 11 mg QD formulation and establish similarity in key pharmacokinetic (PK) exposure parameters and relative bioavailability (BA) as compared to the currently approved tofacitinib IR 5 mg BID formulation. The clinical pharmacology development program has demonstrated that the MR 11 mg QD dose has equivalent Area Under Concentration (AUC) and C_{max} compared to the currently approved IR 5 mg BID. Exposure-response (E-R) relationships from the IR development program show that C_{av} is the relevant parameter for efficacy and that the slightly lower (29%) C_{min} of the MR formulation is not clinically important to the efficacy of tofacitinib. These data support the consistent efficacy between MR 11 mg QD and IR 5 mg BID.

Likewise, the overall similarity in PK parameters and duration of JAK1/3 inhibition over the dosing interval, along with exposure-safety relationships from the IR program, indicate that the safety of MR 11 mg QD will be consistent with that of the IR 5 mg BID. Of the 172 total subjects in the 7 healthy volunteer studies, 67 reported adverse events (AEs). AEs were generally similar between the MR formulations and the IR tablets. There were no deaths, serious adverse events (SAEs), severe AEs, or dose reductions/temporary discontinuations due to AEs. The majority of AEs were considered to be mild and related to treatment, and none of the reported AEs were considered clinically important.

Collectively, these data support a favorable benefit-risk profile for the MR 11 mg QD formulation for the treatment of adult patients with moderately to severely active RA, and showed the efficacy and safety of tofacitinib MR 11 mg QD are expected to be consistent with that demonstrated for tofacitinib IR 5 mg BID. A New Drug Application (NDA) for the MR osmotic tablet formulation of tofacitinib (dosed at 11 mg QD) for the treatment of RA is under review by the Food and Drug Administration (FDA).

1.2.3. Rationale

The tofacitinib IR 5mg BID formulation has demonstrated efficacy both as a monotherapy and in combination with methotrexate (MTX) in previous trials. However, it remains unknown whether the tofacitinib efficacy will be sustained after the withdrawal of MTX among RA patients who achieve low disease activity following treatment with MTX plus tofacitinib. Results of the current study will inform the value of the continued MTX treatment among subjects who have responded to combined therapy of tofacitinib and MTX. A MR 11mg QD regimen has the potential to offer an additional dosing option to subjects, and based on the equivalence of key pharmacokinetic parameters, efficacy and safety are expected to be consistent with that demonstrated for tofacitinib IR 5 mg BID. Therefore, the current study will evaluate the sustained efficacy and safety of the tofacitinib MR 11 mg QD regimen among RA patients undergoing blinded withdrawal of MTX.

1.2.4. Single Reference Safety Document (SRSD)

Complete information for tofacitinib may be found in the single reference safety document (SRSD), which for this study is the tofacitinib IB. The SRSD for MTX is the Summary of Product Characteristics (SPC).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

To compare the efficacy of tofacitinib MR 11mg monotherapy to tofacitinib MR 11mg with continued MTX, as measured by the change in the Disease Activity Score utilizing 4 components including erythrocyte sedimentation rate (DAS28-4 (ESR)) from randomization (at Week 24) to the end of the double-blind MTX withdrawal phase (at Week 48).

2.1.2. Secondary Objectives

- To compare the efficacy of tofacitinib MR 11mg monotherapy to tofacitinib MR 11mg with continued MTX in the double-blind MTX withdrawal phase (at Week 36), as measured by DAS28-4 (ESR).
- To compare the efficacy of tofacitinib MR 11mg monotherapy to tofacitinib MR 11mg with continued MTX in the double-blind MTX withdrawal phase (at Weeks 48 and 36), as measured by Disease Activity Score 28-4 (C reactive protein) (DAS28-4 (CRP)), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), Low Disease Activity (LDA), remission, ACR20, ACR 50, and ACR 70.

- To compare effects of tofacitinib MR 11mg monotherapy to tofacitinib MR 11mg with continued MTX on health outcome measures in the double-blind MTX withdrawal phase (at Weeks 48 and 36), as measured by Health Assessment Disability Questionnaire-Disability Index (HAQ DI), Medical Outcomes Survey Short Form -36 (SF-36), Work Productivity and Activity Impairment (WPAI), European Quality of Life 5 dimensions questionnaire (EuroQol EQ 5D), and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale.
- To evaluate the safety and tolerability of tofacitinib MR 11mg monotherapy versus tofacitinib MR 11mg with continued MTX.

2.1.3. Other Objectives

- To describe efficacy of treatment with tofacitinib 11mg with MTX in the open-label run-in phase (at Weeks 12 and 24), as measured by DAS28-4 (ESR), DAS28-4 (CRP), CDAI, SDAI, LDA, remission, ACR20, ACR 50 and ACR70.
- To describe effects of treatment with tofacitinib MR 11mg with MTX on health outcome measures in the open-label run-in phase (at Weeks 12 and 24), as measured by HAQ-DI, SF-36, WPAI, EuroQol EQ-5D, and FACIT-Fatigue scale.

2.1.4. Exploratory Objectives

- To collect exploratory biomarker/genomics samples for bio-banking.
- US and Canada ONLY: To explore effects of treatment with tofacitinib MR 11mg with/without MTX on health outcome measure in the open-label run-in phase (at Weeks 12 and 24) and the double-blind MTX withdrawal phase (at Weeks 48 and 36), as measured by Routine Assessment of Patient Index Data 3 (RAPID3).

2.2. Endpoints

2.2.1. Efficacy Endpoints

2.2.1.1. Primary Efficacy Endpoint

Change in DAS28-4 (ESR) score from randomization (at Week 24) to the end of double-blind MTX withdrawal phase (at Week 48).

2.2.1.2. Secondary Efficacy Endpoints

- Change in the DAS28-4(ESR) from Week 24 to Week 36;
- Changes in the DAS28-4 (CRP), CDAI and SDAI, respectively, from Week 24 to Week 48 and from Week 24 to Week 36;
- LDA as assessed by DAS28-4(ESR) ≤ 3.2 , DAS28-4(CRP) ≤ 3.2 , CDAI ≤ 10 and SDAI ≤ 11 , respectively, at Weeks 48 and 36;

- Remission as assessed by ACR-EULAR Boolean remission criteria,¹¹ DAS28-4 (ESR)<2.6, DAS28-4 (CRP)<2.6, CDAI≤2.8 and SDAI≤3.3, respectively, at Weeks 48 and 36;
- ACR20, ACR 50, and ACR70 responses, respectively, at Weeks 48 and 36;
- Change in the HAQ-DI, the SF-36 (8 domain scores and 2 component scores), WPAI, EuroQol EQ-5D and the FACIT-Fatigue scale score, respectively, from Week 24 to Week 48 and from Week 24 to Week 36;
- HAQ-DI response (ie, decrease of at least 0.22) at Weeks 48 and 36.

2.2.1.3. Other Efficacy Endpoints

- Changes in DAS28-4 (ESR), DAS28-4 (CRP), CDAI, SDAI, HAQ-DI, SF-36 (8 domain scores and 2 component scores), WPAI, EuroQol EQ-5D score and FACIT-Fatigue scale score, respectively, from day 1 to Week 12 and from Day 1 to Week 24;
- LDA as assessed by DAS28-4(ESR)≤3.2, DAS28-4(CRP)≤3.2, CDAI≤10 and SDAI≤11, respectively, at Weeks 12 and 24;
- Remission as assessed by ACR-EULAR Boolean remission criteria, DAS28-4 (ESR)<2.6, DAS28-4 (CRP)<2.6, CDAI≤2.8 and SDAI≤3.3, respectively, at Weeks 12 and 24;
- ACR20, ACR 50, and ACR70 responses, respectively, at Weeks 12 and 24;
- HAQ-DI response (ie, decrease of at least 0.22) at Weeks 12 and 24;
- Changes in tender/painful joint counts, swollen joint counts, subject assessment of arthritis pain, subject global assessment of arthritis, physician global assessment of arthritis, and CRP, respectively, from day 1 to Week 12 and from day 1 to Week 24, from Week 24 to Week 48 and from week 24 to Week 36.

2.2.1.4. Safety Endpoints

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

2.2.1.5. Exploratory Endpoints

- Exploratory biomarker/genomics endpoints will be specified in a separate protocol and/or statistical analysis plan if exploratory analyses utilizing the bio-banked exploratory genomic and biomarker samples across tofacitinib studies or across multiple programs are conducted;

- US and Canada ONLY: RAPID3 summary scores at Weeks 12, 24, 36 and 48.

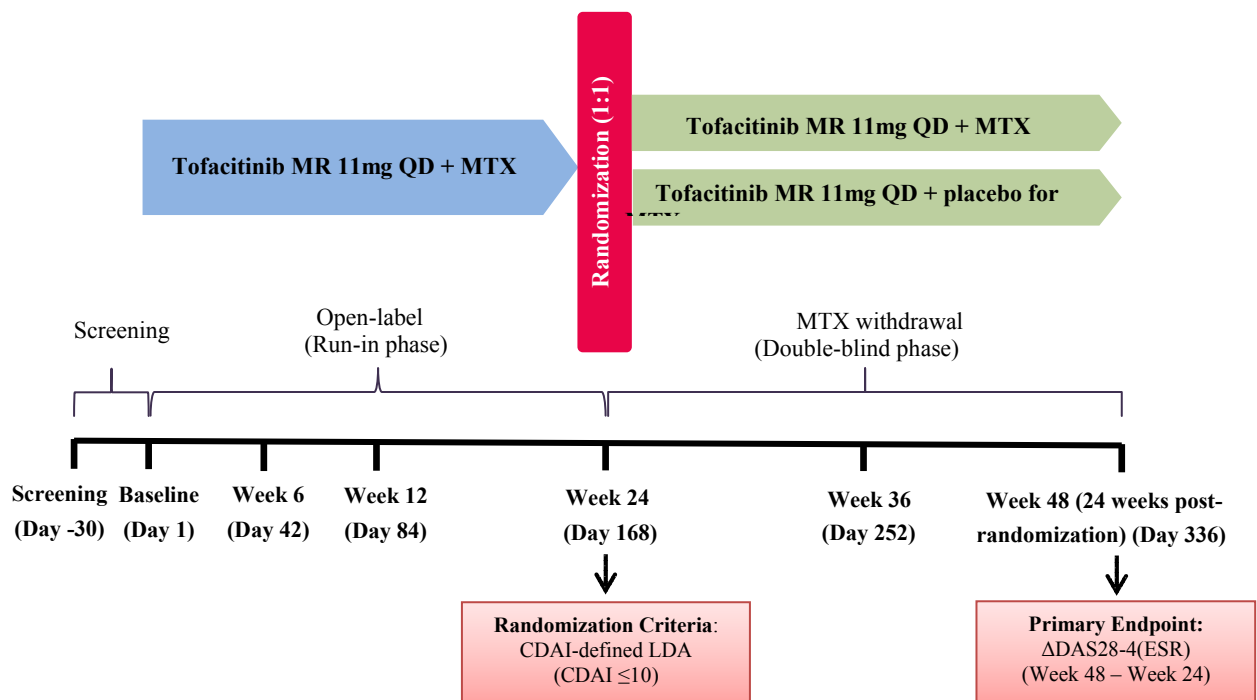
3. STUDY DESIGN

Study A3921192 is a 12-month randomized, double-blind, placebo-controlled withdrawal study in a total of approximately 580 subjects with moderate to severe RA (defined as CDAI >10 and DAS28 (ESR) \geq 3.2) who are insufficiently responding to their stable dose of MTX treatment. The enrollment will be monitored by Sponsor to ensure approximately 50% of enrolled subjects will have moderate disease activity (defined as DAS28 (ESR) \geq 3.2 and \leq 5.1) and approximately 50% will have severe disease activity (defined as DAS28 (ESR) \geq 5.1). In addition, the proportion of subjects who have had an insufficient response to one or more biologics prior to the enrollment should be \leq 25% (ie, \leq 145 subjects).

After reviewing the rate of achievement of LDA and monitoring the discontinuation rate in the open-label period, the decision was made to increase in enrollment numbers from approximately 580 to 680 factoring in a discontinuation rate of approximately 15% during the open label run-in phase. As of 02 Aug 2017, study was 50% enrolled with 81% having severe disease activity. The LDA rate (\sim 79% based upon a small sample size) was higher than protocol assumptions and historic data. It is expected that enrolling >50% of subjects with severe disease activity will result in a sufficient number of subjects with LDA at Week 24. Therefore, the enrollment requirement of 50% of subjects with severe disease activity and 50% with moderate disease activity was removed from the protocol.

Following enrollment, all subjects will receive open-label tofacitinib MR 11mg QD added to MTX at their previously stabilized dose for 24 weeks (run-in phase). At the end of the run-in phase (Week 24), only subjects who achieve low disease activity (LDA) as assessed by CDAI (ie, CDAI \leq 10) (approximately 232 subjects) will be randomized into the 24-week double-blind, placebo-controlled MTX withdrawal phase. Subjects who do not achieve LDA (defined by CDAI >10) at this time point will be discontinued from the study. Subjects entering the double-blind phase will be randomized in a 1:1 ratio to either continue the run-in phase treatment regimen (tofacitinib MR 11mg QD with blinded MTX) or to receive tofacitinib monotherapy (tofacitinib MR 11mg QD with blinded matching placebo for MTX). Randomization will be stratified by subject's prior exposure to a biologic DMARD. Randomized subjects will be followed up to the end of Week 48. The primary efficacy endpoint is the change in DAS28-4 (ESR) from randomization (at Week 24) to the end of double-blind MTX withdrawal phase (at Week 48).

Figure 1. Study Design



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 participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria

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

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

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
2. Subjects are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Must be 18 years of age or older.

4. Have a score of 6 or greater on the 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis at and/or prior to Screening Visit.
5. Have ≥ 4 tender/painful joints on motion and ≥ 4 swollen joints (28 joint counts) at both Screening Visit and Baseline Visit (Visit 1).
6. Have moderate to severe disease activity as defined by CDAI >10 and DAS28-4(ESR) ≥ 3.2 at Baseline Visit.
7. Have taken an oral MTX treatment regimen (15-25mg/week) continuously for at least 4 months prior to the screening visit and has taken a stable weekly dose of oral MTX with supplemental folic acid or folinic acid for at least 4 weeks prior to the baseline visit (conversion from parenteral MTX to oral MTX will require stabilization of the treatment regimen for at least 1 month):
 - MTX doses between 10mg/week and <15 mg/week are allowed only if there is documented intolerance or toxicity from higher doses in the source documentation.
 - MTX doses less than 10mg/week or more than 25mg/week are not permitted under any circumstances.
 - a. 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.
 - Subjects must have an inadequate clinical response to MTX, defined as the presence of sufficient residual disease activity to meet the entry criteria.
8. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 3 months after the last dose of assigned treatment. For contraception details to be applied in Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and the United Kingdom see [Appendix 7](#).
9. Female subjects of childbearing potential must test negative for pregnancy at screening visit and baseline visit.
10. Female subjects who are not of childbearing potential (ie, meet at least 1 of the following criteria):
 - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
 - Have medically confirmed ovarian failure; or

- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state.

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

11. Subjects must screen negative for active tuberculosis or inadequately treated tuberculosis infection (active or latent) as evidenced by all of 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 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 (or chest Computed Tomography (CT) scan, if available) taken at screening without changes suggestive of active tuberculosis (TB) infection, unless previously performed and documented within 3 months prior to screening.

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

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

active disease; the chest radiograph must be obtained at screening or, if previously performed and documented, within 3 months prior to screening.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.
2. Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant; male subjects able to father children and female subjects of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 3 months after the last dose of investigational product. For contraception details to be applied in Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and the United Kingdom see [Appendix 7](#).
3. Subjects with any of the following infection or infection history:
 - a. Any infection requiring treatment within 2 weeks prior to the Baseline Visit (Visit 1).
 - b. Any infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged to be an opportunistic infection or 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 where adequate treatment cannot be documented.
 - i. Subjects screened in Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and the United Kingdom who have resided or traveled in areas with endemic tuberculosis or endemic mycoses will be excluded.
4. 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.
 5. Subjects with any uncontrolled clinically significant laboratory abnormality or any of the following laboratory abnormalities:
 - 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) <40 mL/min using the Cockcroft-Gault formula.
 6. Subjects with a history of insufficient response to ≥ 2 biologics, regardless of the class.
 7. Participation in other studies involving investigational drug(s) within 4 weeks or 5 half-lives (whichever is longer) after discontinuation of the investigational compound prior to the current study entry and/or during study participation, unless further restrictions to class of compound are specified in [Section 4.2](#) (exclusion criteria) and [Section 5.8](#) (concomitant treatment).
 8. Subjects requiring or have received any prohibited concomitant medication as outlined in [Appendix 3: Prohibited Concomitant Medication](#), including:

- a. Subjects who have received live or live attenuated vaccines within 4 weeks prior to the first dose of study drug or are planning to receive live or live attenuated vaccines at any time during treatment or within 6 weeks following discontinuation of study drug.
 - b. Subjects who have previously been treated with tofacitinib, baricitinib, or any other investigational JAK inhibitors.
 - c. Subjects who are being treated with biologic or non-biologic DMARDs (including antimalarials) other than MTX within their specified washout window at study entry (defined in [Appendix 3: Prohibited Concomitant Medications](#), and [Section 5.8.2: Disallowed Concomitant Medications](#)).
 - d. Subjects who are being treated with corticosteroids, other than stable low dose oral corticosteroids in doses equivalent to ≤ 10 mg prednisone per day, within 4 weeks prior to the first dose of the study drug.
 - e. 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 CYP3A4 inducers (defined in [Appendix 3: Prohibited Concomitant Medications](#)).
9. 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).
 10. Subjects who had significant trauma or surgical procedure within 1 month prior to the Baseline Visit (Visit 1).
 11. Subjects with any rheumatic autoimmune disease, other than RA and Sjogren's syndrome.
 12. 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).
 13. 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.
 14. Subjects with history of, or current evidence for, severe gastrointestinal narrowing (pathologic or iatrogenic); eg, esophageal motility disorders, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, chronic intestinal pseudoobstruction, or Meckel's diverticulum.

15. Subjects with history of documented diverticulitis in the source documentation.
16. Alcohol or substance abuse unless in full remission for more than 6 months prior to first dose of investigational drugs.
17. 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

All eligible subjects enrolled in the study will initially receive open-label tofacitinib combined with MTX for 24 weeks (run-in phase). At the end of the 24-week open-label run-in phase, only subjects who achieve Low Disease Activity (LDA) (as assessed by CDAI ≤ 10) will be randomized to the 24-week double-blind, placebo-controlled, MTX withdrawal phase. Subjects who do not achieve the LDA (as assessed by CDAI > 10) at this time point will be discontinued from the study.

Subjects who enter the 24-week double-blind phase will be randomized in a 1:1 ratio to either continue the run-in phase treatment (tofacitinib MR 11mg QD with blinded MTX) or to receive tofacitinib monotherapy (tofacitinib MR 11mg QD with blinded placebo for MTX).

Randomization will be stratified by whether or not the subject was ever exposed to a biologic DMARD previously.

4.4. Lifestyle Guidelines

4.4.1. Non-Pharmacologic Interventions

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

4.4.2. Vaccine and Exposure to Infections Guidelines

It is recommended that subjects be up to date on all recommended vaccination (including pneumococcal vaccine and flu vaccine) per local practice guideline prior to enrollment.

Vaccination with live components is prohibited within the 4 weeks prior to first dose of investigational product to 6 weeks after last dose of investigational product. 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, measles, mumps, rubella, varicella (“chickenpox”) vaccine or varicella-zoster vaccine, oral polio vaccine, rotavirus, Yellow Fever and the intranasal (inhaled) flu vaccine.

Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted. General guidelines for immunosuppressed subjects suggest that household contact with children and others who have been vaccinated with live vaccine components should be avoided following their vaccination with the following vaccines for the stated time period:

- Attenuated typhoid fever vaccination for 4 weeks following vaccination;
- Oral polio vaccination for 6 weeks following vaccination;
- Attenuated rotavirus vaccine for 10 days following vaccination;
- FluMist[®] (intranasal flu vaccine) for 1 week following vaccination.

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 potent CYP3A4 inhibition or induction, or both moderate CYP3A4 and potent CYP2C19 inhibition. Otherwise, herbals with pharmaceutical properties must be discontinued for at least 4 weeks prior to first dose of investigational product, unless there is sufficient data available regarding the duration of an herbal medication's pharmacokinetic and pharmacodynamic effects to allow a shorter washout to be specified (eg, 5 half-lives).

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.

4.4.4. Surgery

During the course of this study, no elective surgery should be scheduled without first consulting with the Pfizer study clinician. Preferably, elective surgery should be scheduled before the study entry or delayed until participation in the study is completed.

It is recommended that subjects who require major surgery temporarily discontinue tofacitinib approximately 1 week prior to the surgical procedure and remain off tofacitinib after the surgical procedure until sutures/staples are removed. Investigational products can be resumed when the sutures/staples are removed. If absorbing sutures or chemical closure methods are utilized, investigational product can be resumed when the operative site is sufficiently healed and risk of infection is minimal.

4.4.5. Contraception and Reproductive Status

In this study, male subjects who are able to father children and female subjects who are of childbearing potential will receive MTX, which has been associated with teratogenic risk, and tofacitinib, which has been associated with teratogenic risk in animals (further information can be found in the single safety reference document). Those who, in the opinion of the investigator, are sexually active and at risk for pregnancy with their partner(s) must agree to use with their partner(s) two (2) methods of highly effective contraception throughout the study and continue for at least 3 months after the last dose. The investigator or his or her designee, in consultation with the subject, will select 2 appropriate methods of contraception for the individual subject and his/her partner(s) from the list of permitted contraception methods (see below) and instruct the subject in their consistent and correct use. The investigator or his or her designee will discuss with the subject the need to use 2 highly effective methods of contraception consistently and correctly according to the [schedule of activities](#) and document such conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if a selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

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

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (ie, oral, inserted, injected, implanted, transdermal) provided the subject (or the subject's partner(s)) plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD) or intrauterine system.
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the postvasectomy ejaculate.
5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

Pregnancy testing will be performed and documented at every visit unless the non-childbearing potential is confirmed and documented. The specific contraceptive methods will be documented and at every visit, their consistent and correct use will be ascertained and documented in the subject's case report form.

For contraception and reproductive status details to be applied in Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and the United Kingdom see [Appendix 7](#).

4.5. Sponsor's Qualified Medical Personnel

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

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 numbers, contact information for the investigational site, and contact details for a contact center 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 contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

4.6. Rater Qualifications

A Joint Count Assessor blinded to subject data (including adverse events, subject reported outcomes and physician assessments of disease activity and/or severity) will assess the number of swollen and tender/painful joints, as part of the assessment of RA activity. The Joint Count Assessor at each site is required to be a health care professional who has been trained in rheumatology and specializes in the treatment of subjects 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

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33). Tofacitinib and MTX are investigational products in this study.

All subjects enrolled in the study will initially receive open-label tofacitinib and MTX for 24 weeks (run-in phase). Subjects who achieve LDA (as assessed by CDAI ≤ 10) at the end of the run-in phase will be randomly allocated (in a 1:1 ratio) to either tofacitinib with continued MTX arm or tofacitinib with placebo arm as presented in [Table 1](#).

Table 1. Treatment Arms

Open-label phase (all subjects)
One tablet open-label tofacitinib MR 11mg orally QD + open-label MTX capsule(s) orally every week at prior stabilized dose
Double-blind phase (subjects will be randomized to one of the two arms below)
Arm 1 (tofacitinib MR 11mg QD with blinded MTX): One tablet open-label tofacitinib 11 mg orally QD + blinded MTX capsule(s) orally every week at prior stabilized dose
OR
Arm 2 (tofacitinib MR 11mg QD with blinded placebo for MTX, ie, tofacitinib MR 11mg QD monotherapy): One tablet open-label tofacitinib 11 mg orally QD + blinded matching placebo capsule(s) for MTX orally every week at prior stabilized dose

5.1. Allocation to Treatment

Allocation of subjects to treatment arms will proceed through the use of an automatic Interactive Web-based Response (IWR) system provided by the Sponsor. There is a 24-hour-a-day, 365-days-a-year IWR helpdesk available for any questions or issues. The study specific IWR reference manual will provide the contact information and further details on the use of the IWR system.

At the screening visit, the site personnel (study coordinator or specified designee) will enter the subject into the IWR by indicating minimal information sufficient to distinguish one subject from another (eg, the date of birth and initials of the subject) and receive the unique subject identification (ID) number generated by the IWR for each subject. The subject who is failed to pass the screening will not be enrolled into the study. The subject who passes the screening will be enrolled into the study and assigned with the open-label treatments.

Following the confirmation of LDA status at the end of the run-in phase, the site personnel will be required to enter or select information including but not limited to the protocol number, the subject ID number, the date of birth and/or initials of the subject, the LDA status and the prior use of biologic DMARDs in the IWR. The site personnel will then be provided with a treatment assignment code which corresponds to the number on the dispensable unit (DU) or container in the site's inventory. The corresponding DU or container will be dispensed to the subject. The IWR system will provide a confirmation report containing the subject number and DU or container number assigned. The confirmation report must be stored in the site's files.

5.2. Breaking the Blind

This study will be subject-, investigator-, and sponsor-blinded. At the initiation of the study, the study site will be instructed on using IWR for breaking the blind. The blind should only be broken in emergency situations for reasons of subject safety. Whenever possible, the

investigator should attempt to contact the Pfizer study team before breaking the blind. When the blind for a subject is broken, the reason must be fully documented and entered on the case report form (CRF). At all other times, treatment and randomization information will be kept confidential and will not be released to the investigator/study staff until the conclusion of the study.

5.3. Subject Compliance

Compliance with expected consumption of dispensed investigational product will be assessed by comparing the expected number of doses to be taken to the number of doses returned during any given time period, keeping in mind that subjects may have their investigational product temporarily withheld due to abnormal laboratory tests, adverse events, or the need to take a short course of a prohibited concomitant medication. Doses of investigational products 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 on the CRF with the reason for reduced drug consumption.

Compliance of less than 80% of the expected number of doses for any one of the investigational products in the interval should be documented in the dosing log of the subject's CRF with the reason for non-compliance (less than expected consumption), 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. Subjects who are less than 80% compliant with the dosage regimen for any two consecutive visit periods during the study should be withdrawn from the study.

Compliance of more than 120% of the expected number of doses for any one of the investigational products in the interval should be documented in the dosing log of the subject's CRF with the reason for non-compliance (more than expected consumption), and should be reported as a protocol deviation and recorded as a dosing error.

Subjects who are non-compliant will be counseled and the site will implement appropriate measures to secure subject compliance, as appropriate to the site and reason for non-compliance.

Subjects will record all Tofacitinib and MTX dosing in a dosing diary. It will be reviewed with the subject at every study visit for compliance.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

During the run-in phase, tofacitinib citrate MR 11 mg tablets and MTX 2.5 mg capsules will be provided in open-label bottles for oral administration by Sponsor. During the double-blind phase, open-label bottles of tofacitinib MR 11mg tablets and blinded bottles of MTX 2.5 mg capsules or matching placebo capsules for MTX will be provided for oral administration by Sponsor.

5.4.2. Preparation and Dispensing

At each dispensing visit (Baseline Visit/Visit 1, and Visits 3, 4 and 5), subjects will receive a sufficient quantity of investigational products to last until their next scheduled dispensing visit plus an additional amount to accommodate the allowable visit windows. Investigational products, along with written dosing instructions (dosing cards), will be dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance. The amount of investigational products dispensed at each visit must be recorded.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

5.5. Administration

All investigational products will be self-administered by the subject as specified in the dosing card with written instructions.

Investigational products may be taken with or without food, other than on study visit days where fasting is required. Subjects will swallow the investigational product whole and intact, and will not manipulate (eg, crush or split) or chew the medication prior to swallowing.

Subjects will take their tablets (tofacitinib) once daily in the morning, and take their capsules (MTX or matching placebo for MTX) once a week (the same day of the week and approximately the same time each week) unless dose division is required to manage intolerance.

At the beginning of the enrollment (ie, baseline visit/visit 1), subjects must discontinue the use of their personal (commercial) supply of MTX. All tofacitinib and MTX drug supplies will be provided by the Sponsor during study participation after the screening period.

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 4 weeks prior to the baseline visit (visit 1). Dosages of MTX (oral administration of up to 25 mg/week) are as approved in the respective Single Reference Safety Document (SRSD), as identified in [Section 1.2.4](#) of this protocol. MTX doses between 10mg/week and 15 mg/week are allowed only in the presence of documented intolerance to or toxicity from higher doses in the source documentation. Doses less than 10 mg/week or more than 25 mg/week are not permitted under any circumstances. The pre-study stable dose of MTX will be continued in the study period. The dose of MTX or matching placebo for MTX will be maintained throughout study participation unless dose reductions are further required due to drug toxicity. Dose reductions will be documented in the CRF.

Subjects who are randomized to placebo for MTX arm will receive full withdrawal of MTX (ie, no tapering) at the time of randomization.

The typical local standard of care practices for the administration of MTX include: laboratory testing, follow up care, contraindications, and folate supplementation. MTX laboratory testing is typically every 3 months once a subject is stabilized on MTX. However, in some regions, more frequent MTX testing and procedures are required; therefore MTX tests and procedures should be performed according to local standards of care throughout the study, regardless of study assignment. 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.

5.6. Investigational Product Storage

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

The investigational drug product should be stored in its original container and in accordance with the label. See the dosing card for storage conditions of the product. Storage conditions stated in the single reference safety document (SRSD) (tofacitinib IB and MTX SPC revised December 2012) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This is to be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

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

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct subjects on the proper storage requirements for take home investigational products.

Please refer to dosing card for additional details on the investigational drug storage dispensed to subjects.

5.7. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. At each study visit (except baseline /visit1 and Week 6/Visit 2), the subject must return the containers of investigational products to the investigator and the amount of any unused medications will be recorded. 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 investigational products returned by the subjects.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.8. Concomitant Treatment(s)

All concomitant medication taken during the study must be recorded with the 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.

Medications taken after informed consent but before the first dose of investigational products will be documented as prior medications. Medications taken after the first dose of investigational products will be documented as concomitant medications.

5.8.1. Allowed Concomitant Medications

All concomitant DMARDs including antimalarials are excluded at Baseline Visit/Visit 1, except MTX.

5.8.1.1. Treatment for Latent Tuberculosis

Subjects who are diagnosed as having latent tuberculosis (ie, positive tuberculosis test, chest x-ray or CT negative for active tuberculosis, and no evidence of active disease) at screening 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. A subject may enroll into the study after at least one month of isoniazid therapy or per local guideline.

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

5.8.1.2. Stable Background Arthritis Therapy

Subjects will continue on their stable background arthritis therapy, which can include nonsteroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), opioids, acetaminophen, and/or low dose oral corticosteroids (≤ 10 mg prednisone or equivalent per day) throughout the trial. Dosages of NSAIDs/COX-2 inhibitors, opioids, acetaminophen, and corticosteroids must have been stable for at least 4 weeks prior to first study dose and should remain so during the study treatment period, except if adjustment is needed to protect a subject's safety. However, the total daily dose of acetaminophen may not exceed the locally approved recommended daily dose, and the total daily dose of opioid must not exceed the potency equivalent of 30 mg of orally-administered morphine ([Appendix 5: Approximate Equivalent Morphine Doses of Opioid Analgesics](#)). Please note that administration of NSAIDs with MTX (usually at high doses) can lead to serious adverse reactions including gastrointestinal and hematological toxicity.

Low dose oral corticosteroids in doses equivalent to ≤ 10 mg prednisone per day is allowed during the study period. However, the prednisone dose increase should not exceed the initial dose during the study period.

Intra-articular corticosteroids may be given during the first 3 months of the run-in phase in no more than two joints, in a cumulative dose of no more than 80 mg methylprednisolone or its equivalent during any 6 month study period. Injections are not allowed after 3 months. Injected joints will also be considered as having their pre-injection status (tender/painful or swollen) for the remainder of the trial.

Intravenous or intramuscular corticosteroids are not allowed during this study.

Biologic DMARDs and non-biologic DMARDs (other than MTX) are not allowed during this study.

5.8.2. Disallowed Concomitant Medications

5.8.2.1. Disease Modifying Antirheumatic Drugs (DMARDs)

All DMARDs (except MTX) are disallowed during the study period. All prohibited concomitant DMARDs should be discontinued at least 4 weeks or 5 half-lives (whichever is longer) prior to the first dose of investigational products (Baseline Visit/Visit 1). Specific medications and required discontinuation (washout) times are listed in Table 2.

Table 2. DMARDs – Required Washout Period

Required Washout Period Prior to Baseline/Visit 1	
52 weeks	Rituximab or other selective B lymphocyte depleting agents (both marketed and investigational): discontinued for 1 year prior to the first dose of investigational products and if CD19/20+ counts are normal by fluorescence-activated cell sorting (FACS) analysis
20 weeks	Gold compounds, including auranofin (Ridaura), and injectable gold (aurothioglucose or aurothiomalate)
18 weeks	Canakinumab
12 weeks	Abatacept, certolizumab pegol, tocilizumab
10 weeks	Golimumab
8 weeks	Infliximab, leflunomide*
6 weeks	Adalimumab
4 weeks	Anakinra, azathioprine, cyclosporine, etanercept, tacrolimus, mizoribin, tetracycline, minocycline, penicillamine, sulfasalazine, bucillamine, chloroquine, hydroxychloroquine

* Leflunomide (Arava®) must be discontinued 8 weeks prior to the first dose of study drug if no elimination procedure is followed. Alternately, it should be discontinued with the following elimination procedure at least 4 weeks prior to the first dose of study drug: Cholestyramine at a dosage of 8 grams three times daily for at least 24 hours, or activated charcoal at a dosage of 50 grams 4 times a day for at least 24 hours (US PI, Elimination Procedure to significantly lower leflunomide drug levels).

5.8.2.2. Immune-Modulating Biologic Products

While receiving study drug, no immune-modulating biologic products are allowed to be administered, including biologic DMARDs (except MTX).

5.8.2.3. 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).

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 4 weeks or 5 half-lives (whichever is longer) prior to the Baseline Visit (Visit 1). Only systemically administered drugs listed in [Appendix 3](#) (Prohibited Concomitant Medication) require discontinuation; other routes of administration (eg, topical, vaginal, ophthalmic) are not prohibited.

If a medication that is a potent CYP3A4 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, tofacitinib should be interrupted during treatment.

If a medication that is a potent CYP3A4 inducer is administered during the study for any reason, including the treatment of an adverse event, tofacitinib may be continued, but the concomitant administration of the medication should be noted as a protocol deviation.

5.8.2.4. Immunizations

Live or live-attenuated vaccines should not be given concurrently with investigational products (refer to [Section 4.4.2](#) for more details).

5.8.2.5. Investigational medication

Any investigational medications must be discontinued prior to baseline visit (visit 1) for 4 weeks or 5 half-lives, whichever is longer. No investigational compounds (other than tofacitinib and MTX) may be taken during the study period.

5.9. Rescue Medication

Please refer to [Appendix 5](#) (Approximate Equivalent Morphine Doses of Opioid Analgesics) and [Appendix 6](#) (Rescue Therapy) for details.

6. STUDY PROCEDURES

Please refer to [Section 7](#) (Assessment) for details of exams and tests listed in this section.

6.1. Screening

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 will be screened 30 days (+10 day window, ie, 40 days) prior to administration of investigational products to confirm that they meet the entrance criteria for the study. Subjects must complete all screening procedures and assessments and have test results available prior to the baseline visit (visit 1). If a subject is not enrolled within 30 days (+10 days window) after the screening visit, all screening procedures and assessment must be

repeated unless otherwise noted (below). Sponsor approval must be obtained prior to re-screening a subject.

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 5.8: Concomitant Medication](#) and [Appendix 3: Prohibited Concomitant Medication](#)). For these subjects, written informed consent and the study subject identification (SSID) number must be obtained prior to initiation of the washout period. The screening assessments should be scheduled towards the end of the washout period to meet the 30-day (+10 days) screening duration. Additionally, screening procedures may need to be repeated to provide valid data (eg, laboratory testing) and turnaround time may extend beyond the screening duration. In this case, sponsor approval must be obtained. In no instance should the extended screening duration exceed 3 months.

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

Screening laboratory tests can be repeated once if deemed clinically appropriate (judged by the principal investigator) except for the following tests: 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.

Subjects will continue their usual stable dose of MTX during the screening period.

Procedures to be performed during the screening period include:

- Informed Consent.
- Review of inclusion/exclusion criteria.
- Prior 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.
- Medical History: include previous vaccination.
- Complete Physical Examination: height, weight, vital signs, general appearance, skin (presence of rash, skin lesions with malignant features), 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.
- Laboratory testing (Blood Chemistry, Hematology, CRP, ESR, HIV Serology, HBsAg, HBcAb, HBsAb, HCV Ab, HCV RNA, FSH (required to confirm postmenopausal status, if applicable), Rheumatoid Factor, anti-cyclic citrullinated peptide antibodies (anti-CCP), Urinalysis. All required laboratory testing must be complete and reported; any invalid specimens must be retested and reported prior to the Baseline Visit (Visit 1).
 - Pregnancy testing must be completed for all women of childbearing potential: all subjects must test negative; confirmation and documentation of the use of two highly effective methods of contraception by subjects of childbearing potential or their partners must be done. Non childbearing potential must be documented. For contraception and reproductive status details to be applied in Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and the United Kingdom see [Appendix 7](#).
 - QuantiFERON Gold[®]™ In-Tube Test: unless the subject has previously received an adequate course of therapy for either latent or active TB infection (see [Section 5.8.1.1: 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 Radiography](#)).
 - 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.
 - Serious Adverse Event (SAE) Reporting (after the subject provides informed consent).
 - Assess safety events (ie, reportable safety events within the appropriate reporting period) for adjudication by the appropriate adjudication or review committee and collect biopsies of potential malignancy events for central laboratory pathologist over read and report to Pfizer Study Team or designee.

6.2. Study Period

As part of adverse event monitoring, site personnel will assess safety events for adjudication and potential malignancy events for biopsy submission and central laboratory pathologist over read. Specific safety events will be submitted to the appropriate Safety Event Adjudication/Review Committee for adjudication as described in [Section 9.8](#).

Site personnel will report safety events and potential malignancy events to the Pfizer Study Team or designee based on the following reference time points:

- Events that are serious adverse events (SAEs) occurring after the time of informed consent will be submitted for adjudication/review or central histopathology review, as appropriate.
- Events that are non-serious AEs occurring after the time of first dose of study drug will be submitted for adjudication/review or central histopathology review, as appropriate.

6.2.1. Visit Windows

The screening period is expected to be no longer than 30 days (+ 10 day window) prior to the Baseline Visit (Visit 1), unless exceptions noted in [Section 6.1](#) are documented. All visits 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. Visit 1 is the baseline visit; the visit window for Visit 2 will be ± 5 days; the visit windows for Visit 3 to Visit 6 will be ± 10 days; and the visit window for telephone follow-up will be +14 days to ensure capture of all data.

Partial and unplanned 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.

6.2.2. Visit 1 (Baseline Visit; Day 1)

At Visit 1 (Baseline Visit), subjects will convert their personal (commercial) supply of MTX to the MTX supplied by the Sponsor with the stable dose established before the screening period.

Subjects are required to fast for at least 6 hours prior to the visit.

Procedures to be performed at Baseline Visit/Visit 1 include:

- Complete Physical Examination (excluding height): weight, vital signs, general appearance, skin (skin lesions with malignant features), 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. In addition, smoking history and alcohol consumption will be documented.
- Review of inclusion/exclusion criteria.
- Laboratory testing including blood chemistry, hematology, CRP, lipid profile (fasting), ESR.
- Biospecimen collection for banking.

- Pregnancy testing must be completed for all women of childbearing potential: all subjects must test negative; confirmation and documentation of the use of two highly effective methods of contraception by subjects of childbearing potential or their partners must be done. Non childbearing potential must be documented. For contraception and reproductive status details to be applied in Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and the United Kingdom see [Appendix 7](#).
- 28 tender /painful and swollen joint count.
- Completion of the following assessments:
 - Subject assessment of arthritis pain.
 - Subject global assessment of arthritis.
 - Physician global assessment of arthritis.
 - Health Assessment Questionnaire – Disability Index (HAQ DI).
 - SF 36 (Version 2, Acute).
 - European Quality of Life 5 Dimension Questionnaire (EuroQol EQ 5D).
 - Work Productivity and Activity Impairment (WPAI) Questionnaire.
 - Functional assessment of chronic illness therapy fatigue (FACIT Fatigue Scale).
 - US and Canada ONLY: RAPID3.
- Safety assessment and AE reporting.
- Assess safety events for adjudication by the appropriate adjudication or review committee and collect biopsies of potential malignancy events for central laboratory pathologist over read and report to Pfizer Study Team or designee.
- Concomitant Medication Review.
- Dispense investigational products as identified by the drug dispensing system. Dispense dosing diary to subject and instruct subject on proper use of the diary.
- Schedule the subject to return for Visit 2.

6.2.3. Visit 2 (Week 6; Day 42)

There is a ± 5 day window for this visit. Subjects are required to fast for at least 6 hours prior to the visit. Procedures to be performed at Visit 2 include:

- Assessment of new physical findings (weight, vital signs, skin examination including careful examination for melanoma and nonmelanoma skin cancer, lungs, heart, lower extremities for peripheral edema, abdomen and lymph nodes). Laboratory testing including blood chemistry, hematology, lipid profile (fasting).
- Biospecimen collection for banking.
- Pregnancy testing must be completed for all women of childbearing potential: all subjects must test negative; confirmation and documentation of the use of two highly effective methods of contraception by subjects of childbearing potential or their partners must be done. For contraception and reproductive status details to be applied in Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and the United Kingdom see [Appendix 7](#).
- Safety Assessment and AE Reporting.
- Assess safety events for adjudication by the appropriate adjudication/ review committee and collect biopsies of potential malignancy events for central laboratory pathologist over read and report to Pfizer Study Team or designee.
- Concomitant Medication Review.
- Review dosing diary with the subject.
- Schedule the subject to return for Visit 3.

6.2.4. Visit 3 (Week 12; Day 84)

There is a ± 10 day window for this visit. Procedures to be performed at Visit 3 include:

- Assessment of new physical findings (weight, vital signs, skin examination including careful examination for melanoma and nonmelanoma skin cancer, lungs, heart, lower extremities for peripheral edema, abdomen and lymph nodes).
- Laboratory testing including blood chemistry, hematology, CRP, ESR.
- Pregnancy testing must be completed for all women of childbearing potential: all subjects must test negative; confirmation and documentation of the use of two highly effective methods of contraception by subjects of childbearing potential or their partners must be done. For contraception and reproductive status details to be applied in Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and the United Kingdom see [Appendix 7](#).

- 28 tender /painful and swollen joint counts.
- Completion of the following assessments:
 - Subject assessment of arthritis pain.
 - Subject global assessment of arthritis.
 - Physician global assessment of arthritis.
 - HAQ DI.
 - SF 36 (Version 2, Acute).
 - EuroQol EQ 5D.
 - WPAI Questionnaire.
 - FACIT-Fatigue Scale.
 - US and Canada ONLY: RAPID3.
- Safety Assessment and AE Reporting.
- Assess safety events for adjudication by the appropriate adjudication/ review committee and collect biopsies of potential malignancy events for central laboratory pathologist over read and report to Pfizer Study Team or designee.
- Concomitant Medication Review.
- Return unused investigational products.
- Review dosing diary with the subject.
- Dispense investigational products as identified by the drug dispensing system.
- Schedule the subject to return for Visit 4 (Randomization).

6.2.5. Visit 4 (Randomization; Week 24; Day 168)

There is a ± 10 day window for this visit. Subjects are required to fast for at least 6 hours prior to the visit. Procedures to be performed at Visit 4 include:

- Assessment of new physical findings (weight, vital signs, skin examination including careful examination for melanoma and nonmelanoma skin cancer, lungs, heart, lower extremities for peripheral edema, abdomen and lymph nodes).

- Laboratory testing including blood chemistry, hematology, CRP, ESR, lipid profile (fasting).
- Biospecimen collection for banking.
- Pregnancy testing must be completed for all women of childbearing potential: all subjects must test negative; confirmation and documentation of the use of two highly effective methods of contraception by subjects of childbearing potential or their partners must be done. For contraception and reproductive status details to be applied in Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and the United Kingdom see [Appendix 7](#).
- 28 tender /painful and swollen joint counts.
- Completion of the following assessments:
 - Subject assessment of arthritis pain.
 - Subject global assessment of arthritis.
 - Physician global assessment of arthritis.
 - HAQ DI.
 - SF 36 (Version 2, Acute).
 - EuroQol EQ 5D.
 - WPAI Questionnaire.
 - FACIT -Fatigue Scale.
 - US and Canada ONLY: RAPID3.
- Review dosing diary with the subject.
- Safety Assessment and AE Reporting.
- Assess safety events for adjudication by the appropriate adjudication or review committee and collect biopsies of potential malignancy events for central laboratory pathologist over read and report to Pfizer Study Team or designee.
- Concomitant Medication Review.
- Return unused investigational products.

- Confirm the subject is eligible for randomization (achieve LDA as assessed by CDAI).
- Randomize eligible subjects and dispense investigational products as identified by the randomization/drug dispensing system.
- Schedule the subject to return for Visit 5.
- QuantiFERON Gold[®]™ In-Tube Test will be performed for all subjects (those who meet LDA and those who do not meet LDA at week 24) in Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and the United Kingdom. For all other countries the test will ONLY be performed for subjects who do not achieve LDA at Week 24 and are therefore not randomized.

6.2.6. Visit 5 (Week 36; Day 252)

There is a ±10 day window for this visit. Procedures to be performed at Visit 5 include:

- All Visit 3 assessments (refer to [Section 6.2.4](#)).
- Schedule the subject to return for Visit 6 (End of Study Visit).

6.2.7. Visit 6 (End of Study Visit; Week 48; Day 336/Early Withdrawal Visit)

Subjects who did not achieve LDA at Week 24 and were therefore not randomized do not require a separate EOS visit except for QuantiFERON Gold[®]™ In-Tube Test.

There is a ±10 day window for this visit. Subjects are required to fast for 6 hours prior to the visit. Procedures to be performed at Visit 6 include:

- Complete Physical Examination: height, weight, vital signs, general appearance, skin (presence of rash or suspicious lesions), 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.
- Laboratory testing including blood chemistry, hematology, CRP, lipid profile (fasting), ESR.
- 12-lead electrocardiogram.
- Biospecimen collection for banking.
- Pregnancy testing must be completed for all women of childbearing potential: all subjects must test negative; confirmation and documentation of the use of 2 highly effective methods of contraception by subjects of childbearing potential or their

partners must be done. For contraception and reproductive status details to be applied in Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and the United Kingdom see [Appendix 7](#).

- 28 tender /painful and swollen joint counts.
- Completion of the following assessments:
 - Subject assessment of arthritis pain.
 - Subject global assessment of arthritis.
 - Physician global assessment of arthritis.
 - HAQ DI.
 - SF 36 (Version 2, Acute).
 - EuroQol EQ 5D.
 - WPAI Questionnaire.
 - FACIT Fatigue Scale.
 - US and Canada ONLY: RAPID3.
- Safety Assessment and AE reporting.
- Assess safety events for adjudication by the appropriate adjudication or review committee and collect biopsies of potential malignancy events for central laboratory pathologist over read and report to Pfizer Study Team or designee.
- Concomitant Medication Review.
- Review of dosing diary with the subject (the diary will be returned at this visit).
- Return unused investigational products.

6.2.8. Telephone Follow-up (At least 28 days following last dose of study drugs)

This visit should occur at least 28 days following the last dose of study drugs. This visit can be combined with the End of Study visit as long as it occurs at least 28 days following the last dose of study drugs. If it is not combined with the End of Study visit, this visit can be performed over the phone. There is a +14 day window for the telephone follow-up.

- AE assessment.
- Pregnancy status.

6.3. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site. A complete list of specific discontinuation criteria for this study is listed in [Section 7.23](#).

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. 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 that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

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

If a subject has discontinued investigational product for greater than 14 consecutive days, the subject will be discontinued from the study.

Subjects who experience a single episode of disease flare at any time during the study (including the open-label run-in and double-blind phase) that could not be controlled by rescue medications will be discontinued from the study.

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 is to take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator is to document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team is to be informed of these incidents in a timely fashion.

7.1. Physical Examination

A complete physical examination will be performed at the Screening Visit, Baseline Visit (Visit 1) and End of Study Visit (Visit 6). The following parameters and body systems will be examined and any abnormalities described: height (not required for Baseline Visit/Visit1), weight, vital signs, general appearance, skin (presence of rash, skin lesions with malignant features), 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

At all other visits (Visits 2-5), an abbreviated physical examination will be performed assessing the following: weight, vital signs, skin examination including careful examination for melanoma and non-melanoma skin cancer, lungs, heart, lower extremities for peripheral edema, abdomen and lymph nodes. Any clinically significant changes from the last complete physical examination should be recorded as AEs; ongoing AEs should be updated, as appropriate.

7.3. Chest Radiograph

A chest radiograph or chest CT scan 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 chest radiograph must be negative for active tuberculosis infection.

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 (see [Section 5.8.1.1](#)).

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 need a new 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, 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 3](#) below.

Table 3. Disease Activity Indicators

Indicator	Definition/Calculation
DAS28-4 (CRP)	$0.56*\sqrt{(TJC28)} + 0.28*\sqrt{(SJC28)} + 0.36*\ln(\text{CRP in mg/l} + 1) + 0.014*\text{PtGA in mm} + 0.96$
DAS28-4 (ESR)	$0.56*\sqrt{(TJC28)} + 0.28*\sqrt{(SJC28)} + 0.70*\ln(\text{ESR in mm/ hour}) + 0.014*\text{PtGA in mm}$
Simplified Disease Activity Index (SDAI)	$(28TJC) + (28SJC) + [\text{PhyGA in cm}] + [\text{PtGA in cm}] + [\text{CRP in mg/dL}]$
Clinical Disease Activity Index (CDAI)	$(28TJC) + (28SJC) + [\text{PhyGA in cm}] + [\text{PtGA in cm}]$
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: subject and physician global assessments, pain, disability, and an acute-phase reactant (eg, CRP). Similarly, ACR50 and 70 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, subject'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; ESR = erythrocyte sedimentation rate in mm/first hour, PtGA = subject'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 blinded 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 (MCP) joints, proximal interphalangeal (PIP) joints, and knees. Artificial joints will not be assessed.

7.6.2. Swollen Joint Count (28 Joint Count)

The blinded 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. Subject Assessment of Arthritis Pain

Subjects will assess the severity of their arthritis pain using a 100 mm visual analog scale (VAS) by 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. Subject Global Assessment of Arthritis

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

7.9. 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 Subject’s Global Assessment of Arthritis. The Investigator’s response will be recorded using a 100 mm VAS.

7.10. Health Assessment Questionnaire – Disability Index (HAQ-DI)

The HAQ-DI¹² 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. 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.

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

The SF-36 (v.2, Acute)¹³ 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.

7.12. EuroQol EQ-5D Health State Profile

The EuroQol EQ-5D Health State Profile¹⁴ 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. The form should then be checked by site staff for completeness.

7.13. 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.¹⁵ WPAI outcomes are expressed as impairment percentages with higher numbers indicating greater impairment and less productivity.

7.14. Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue Scale

The FACIT – Fatigue Scale is a subject completed questionnaire¹⁶ consisting of 13 items that assess fatigue. Instrument scoring yields a range from 0 to 52, with higher scores representing better subject status (less fatigue). This questionnaire should be completed by the subject prior to any procedures being performed at the visit, if possible. The form should then be checked by site staff for completeness.

7.15. Routine Assessment of Patient Index Data 3 (RAPID3)

RAPID3 is a pooled index of the 3 patient-reported American College of Rheumatology rheumatoid arthritis (RA) Core Data Set measures: function, pain, and patient global estimate of status. Each of the 3 individual measures is scored 0 to 10, for a total of 30. Disease severity may be classified on the basis of RAPID3 scores: >12 = high; 6.1-12 = moderate; 3.1-6 = low; < or =3 = remission.¹⁷

7.16. C-reactive Protein (CRP)

The CRP will be collected at the time points identified in the [Schedule of Activity](#) and analyzed by a central laboratory. It will be used in the calculation of several efficacy parameters. After randomization, the Investigator and other site personnel participating in the study and Pfizer study personnel will be kept blinded of the results of this test.

7.17. Erythrocyte Sedimentation Rate (ESR)

The ESR will be analyzed by a local laboratory using the Westergren method. The local laboratory will report results to the central laboratory. After randomization, the investigator and other site personnel participating in the study and Pfizer study personnel will be kept blinded of the results of this test.

7.18. Clinical Laboratory Tests

Blood and urine samples will be collected at the time points identified in the [Schedule Of Activities](#). Unscheduled clinical laboratory tests may be obtained at any time during the study to assess any perceived safety concerns.

Table 4. Clinical Laboratory Tests

Tests	Comments
Chemistry: Urea nitrogen, creatinine, glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), albumin, creatine kinase (CK)	Creatinine clearance is calculated by the central laboratory according to the Cockcroft-Gault Formula at Screening Visit (Appendix 4) See Section 7.23 for retesting requirements for ALT and AST elevated ≥ 3 X ULN
Hematology: Hemoglobin, Hematocrit, RBC, RBC morphology, WBC, Neutrophils (% , abs), Lymphocytes (% , abs), Monocytes (% , abs), Eosinophils (% , abs), Basophils (% , abs), Platelets	See Section 7.22 for monitoring requirements related to hemoglobin, neutrophil and lymphocyte counts
CRP	Refer to Section 7.16
ESR	Refer to Section 7.17
Banked Biospecimens	Refer to Section 7.21
Rheumatoid factor	
Anti-cyclic citrullinated peptide	
FSH	To confirm post-menopausal status, if applicable
HIV Serology	
Hepatitis B Surface antigen (HBsAg) Hepatitis B Core Antibody (HBcAb) Hepatitis B Surface Antibody (HBsAb)	Subjects with a positive hepatitis B surface antigen (HBsAg) test will be excluded from the study. Subjects with 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.
Hepatitis C virus antibody (HCV Ab) Hepatitis C RNA (HCV RNA)	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)	Subjects should be fasting for at least 6 hours prior to obtaining specimen.

Table 4. Clinical Laboratory Tests

Tests	Comments
Serum or Urine Pregnancy Testing	All female subjects of childbearing potential, regardless of whether or not they are sexually active. Two negative pregnancy tests are required before receiving investigational product. 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 7.19) May be repeated if pregnancy is suspected or at the request of the IRB/EC or local regulations.
QuantiFERON TB Gold [®] ™ in Tube Test	See Sections 5.8.1.1 and 7.3 for further details on management of positive tests.
Urinalysis: Specific Gravity, pH, Protein, Glucose Ketones, Blood, Leukocyte Esterase	
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	See Section 8.7.2 for further details on management of elevations.
ALT = alanine aminotransferase (SGPT); AST = aspartate aminostransferase (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;	

It is recommended that for potential herpes zoster adverse events a laboratory diagnosis of varicella zoster virus infection be confirmed and that the virus be characterized. (Specimens should be obtained from vesicular fluid, maculopapular lesions, or crusts from lesions). Details of the test, method and laboratory details will be provided in a separate manual.

7.19. Pregnancy Testing

For female subjects of childbearing potential, 2 negative pregnancy tests are required before receiving investigational products. The second negative test should be obtained at least 19 days after the first and should be done during the first 5 days of the menstrual period immediately preceding the first dose of investigational product. In the absence of regular menstrual bleeding, the study candidate should have used 2 forms of contraception for at least 1 month before the second pregnancy test. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), and repeated at all study visits (from screening visit to the end of

study visit) to confirm that the subject has not become pregnant during the study. All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study. Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

7.20. Adjudicated Events

The Pfizer Study Team or designee will provide a listing of specific documents needed to support event adjudication by the Adjudication Committees (see [Section 9.6](#)). Obtaining and submitting the documentation will be the responsibility of the study site. Event documentation will vary with the event requiring adjudication and may include (but not be limited to): hospital discharge summaries, operative reports, clinic notes, ECGs, diagnostic tests, pathology reports, autopsy reports and death certificate information, as applicable.

7.21. Banked Biospecimens

7.21.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects 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 identification (ID) number. Samples will be kept in a facility accessible only by swiping a badge. 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 be used only for the purposes described here and in the informed consent document/subject information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also postmarketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any

remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/subject information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians, nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical study.

A 4-mL blood biospecimen **Prep D1 (K₂ edetic acid [ethylenediaminetetraacetic acid] [EDTA] whole blood collection optimized for DNA analysis)** will be collected at visits 1 (baseline visit) to be retained for potential pharmacogenomic/biomarker analyses related to drug response. 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.

Prep R1 (PAXGene whole blood collection optimized for RNA analysis): Two 2.5-mL blood biospecimens (2 paxgene tubes, 2.5 ml/tube) will be collected at visits 1, 2, 4 and 6, respectively, for potential pharmacogenomics/biomarker analyses related to drug response.

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 visits 1, 2, 4, and 6;
- Prep B2 (serum collection optimized for biomarker/ proteomics/metabonomic analysis): a 10 mL blood biospecimen will be collected at visits 1, 2, 4, and 6.

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/subject information sheet that they will not be compensated in this event.

7.21.2. Additional Research

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

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

- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation among people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

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

7.22. Assessment of Suicidal Ideation and Behavior (SIB)

There are no current medically significant suicidality concerns for tofacitinib or methotrexate 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.

7.23. Triggered Requirements for Monitoring and Discontinuation Criteria

Conditions in which Prompt Retesting is Required	
Condition	Action
Neutrophil counts <1000 cells/mm ³	The subject should return to the study site for prompt retesting, <u>ideally within 3-5 days</u> .
Platelet counts <100,000 platelets/mm ³	The subject should return to the study site for prompt retesting, <u>ideally within 3-5 days</u> .
Lymphocyte counts <500 lymphocytes/mm ³	The subject should return to the study site for prompt retesting, <u>ideally within 3-5 days</u> .
Any single AST and/or ALT elevation >3 times the upper limit of normal (ULN)*	The subject should return to the study site for prompt retesting, <u>ideally within 3-5 days*</u> .
Any single hemoglobin value <8.0 g/dL or one that drops ≥2 g/dL below baseline.	The subject should return to the study site for prompt retesting, <u>ideally within 3-5 days</u> .
Any serum creatinine increase >50% over the average of screening (most recent value prior to baseline) and baseline values OR an absolute increase in serum creatinine >0.5 mg/dL (>44.2 μmol/L) over the average of screening (most recent value prior to baseline) and baseline values	The subject should return to the study site for prompt retesting, <u>ideally within 3-5 days</u> .
* 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. A subject with a total bilirubin value ≥2 × ULN concurrently may need to return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results (refer to Section 8.7.2).	

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

Pregnancy or refusal to use appropriate contraception	Permanently withdraw the subject from the study and follow any pregnancy to resolution.
Use of rescue medications for more than 10 consecutive days	Treatment with all study drugs will be discontinued and the subject withdrawn from this study (see Appendix 6 for details).
Anaphylactic or other serious allergic reaction	Immediately discontinue study drug and institute appropriate therapy.
Symptoms suggestive of a lupus-like syndrome	Discontinue study drug and institute appropriate therapy
Other Triggered Requirements for Monitoring	
Condition	Action
Increase lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)	Monitor and treat according to local guidance (eg, diet and behavior modification, statin therapy)
Surgery	Interrupt study drug 1 week prior to a scheduled surgical procedure and may resume when operative site is sufficiently healed and risk of infection is minimal. (Study drug administration can be resumed only if the off-drug period is ≤14 consecutive days.)
Use of potent CYP3A4 and CYP2C19 Inhibitors and CYP3A4 Inducers	Treatment with potent CYP3A4 inhibitors or with medications that are both a moderate CYP3A4 inhibitor and potent inhibitor of CYP2C19 require that tofacitinib is interrupted during treatment. Treatment with a potent CYP3A4 does not require tofacitinib discontinuation but should be noted as a protocol deviation. See Appendix 3 for a list of CYP3A4 and CYP2C19 Inhibitors and CYP3A4 Inducers.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; g/dL = grams per deciliter; GGT = gamma-glutamyl transpeptidase, HDL= high density lipoprotein; LDL= low density lipoprotein; 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 a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

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

8.2. Reporting Period

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

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

8.3. Definition of an Adverse Event

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

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

- Drug dependency.

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

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

8.4. Medication Errors

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

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

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

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

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.

Examples of overdose for each investigational product are listed in [Sections 8.4.1](#) and [8.4.2](#).

8.4.1. Tofacitinib Overdose

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

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

≤100 mg tofacitinib daily for up to 2 weeks.

≤60 mg tofacitinib daily for up to 6 weeks.

≤30 mg tofacitinib daily for up to 6 months.

Please note, that concomitant treatment with a prohibited potent CYP3A4 inhibitor ([Appendix 3](#)) is assumed to result in a doubling of exposure. For further details, please refer to the tofacitinib Investigator Brochure.

8.4.2. Methotrexate Overdose

Leucovorin is indicated to diminish the toxicity and counteract the effect of methotrexate overdose. Leucovorin administration should begin as promptly as possible. As the time interval between MTX administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum MTX concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdose, hydration and urinary alkalization may be necessary to prevent the precipitation of MTX and/or its metabolites in the renal tubules. For further details, please refer to the product label for MTX.

8.5. Serious Infections

A serious infection is any infection (viral, bacterial, and fungal) 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 be discontinued from the study and the serious adverse event should be listed as the reason for discontinuation in the CRF. 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 8.1](#) on Adverse Event Reporting.

8.6. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) 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.

Clinically significant laboratory findings at the final assessment should be followed to resolution or until determined by the investigator to be stabilized. Repeat tests may be indicated to establish this.

8.7. Serious Adverse Events

A serious adverse event 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 may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

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

8.7.1. Protocol-Specified Serious Adverse Events

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

8.7.2. Potential Cases of Drug-Induced Liver Injury

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

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

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥ 3 times the upper limit of normal (\times ULN) concurrent with a total bilirubin value $\geq 2 \times$ ULN with no evidence of hemolysis and an alkaline phosphatase value $\leq 2 \times$ ULN or not available;
- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:
 - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥ 2 times the baseline values and $\geq 3 \times$ ULN, or $\geq 8 \times$ ULN (whichever is smaller).

Concurrent with

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

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

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

8.8. Hospitalization

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

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outsubject/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 workup of persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);

- Administrative admission (eg, for yearly physical examination);
- 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;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;

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

8.9. Severity Assessment

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

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

8.10. Causality Assessment

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

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

8.11. Exposure During Pregnancy

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

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

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

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

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an 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 general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless 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 baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

- Additional information about pregnancy outcomes that are reported as SAEs follows:
 - Spontaneous abortion includes miscarriage and missed abortion;
 - Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP 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 in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.12. Occupational Exposure

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

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

8.13. Withdrawal Due to Adverse Events (See Also the Section on [Subject Withdrawal](#))

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page. A complete list of specific discontinuation criteria for this study is listed in [Section 7.23](#).

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

8.14. Eliciting Adverse Event Information

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

8.15. Reporting Requirements

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

8.15.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

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

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.15.2. Non-serious Adverse Event Reporting Requirements

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

8.15.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

Based on estimated CDAI-based low disease activity rate of 40% derived from prior phase 3 studies and factoring in a discontinuation rate of approximately 15% during the open label run-in phase, approximately 680 subjects will be enrolled to the run-in phase with the aim of at least 232 subjects being randomized into the blinded MTX withdrawal phase at Week 24. With a two-sided Type-I error of 5% and an assumed standard deviation of 1.4 for the difference in change from randomization in DAS28-4 (ESR) between the two arms, a sample size of approximately 232 subjects randomized at Week 24 would provide 90% power to declare non-inferiority of tofacitinib monotherapy relative to tofacitinib plus methotrexate with a non-inferiority margin of 0.6.

9.2. Descriptive Analysis

Patient and clinical characteristics at baseline and randomization (ie, the end of open-label phase) will be summarized with the use of descriptive statistics. Frequencies and percentages will be used to describe categorical variables and mean and standard deviations (or median with interquartile range [IQR] and range, where appropriate) will be calculated for continuous variables.

Descriptive statistics will also be provided for all efficacy and safety endpoints at each visit in open-label phase or double-blind withdrawal phase as appropriate. Further details will be outlined in the SAP.

9.3. Efficacy Analysis

9.3.1. Analysis of the Primary Endpoint

The primary endpoint of change from randomization in DAS28-4(ESR) at Week 48 will be analyzed as a continuous variable using a linear mixed-effect model of repeated measures (MMRM) that includes the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological DMARD, and baseline DAS28-4 (ESR) value as a covariate. Within-subject variability will be accounted for using a random effect with an unstructured covariance matrix. Change from randomization at any visit post-randomization will be defined as the DAS28-4 (ESR) value at that visit minus the value at randomization.

The primary analysis will be a non-inferiority test to show that tofacitinib MR 11mg QD monotherapy is not less effective (non-inferior) than tofacitinib MR 11mg QD with MTX within the margin of non-inferiority set at 0.6 (ie, the difference in mean change from randomization in DAS28-4 (ESR) between the two arms). In other words, the change from randomization in DAS28-4(ESR) for the tofacitinib MR 11mg QD monotherapy arm may be less favorable than that for the tofacitinib MR 11mg QD with continued MTX arm by no more than 0.6. The estimated treatment difference and the associated 95% confidence interval (CI) will be presented. If the upper bound of the 95% two-sided CI for the difference (tofacitinib monotherapy arm minus tofacitinib with MTX arm) in change from randomization in DAS 28-4 (ESR) between the two arms is lower than 0.6, then tofacitinib monotherapy will be declared to be non-inferior to the tofacitinib with continued MTX treatment.

The analysis will be based on the Full Analysis Set (FAS), which is defined as those subjects who received at least one dose of tofacitinib plus MTX during the open label period and were randomized and received at least one dose of the randomized investigational drug (tofacitinib MR 11mg QD with placebo for MTX or tofacitinib MR 11mg QD with MTX) during the blinded MTX withdrawal period.

A robustness analysis based on a per-protocol analysis set will be performed. Sensitivity analyses using different methods of handling missing data will also be conducted; further details will be outlined in the SAP.

9.3.2. Analysis of Secondary Endpoints

Binary secondary endpoints will be analyzed using the normal approximation for the difference in binomial proportions.

Continuous secondary endpoints will be analyzed using similar methods as the primary endpoint, ie, a linear mixed-effect model of repeated measures (MMRM) that includes the fixed effects of treatment, visit, treatment-by-visit interaction, and baseline value as a covariate. Within-subject variability will be accounted for using a random effect with an unstructured covariance matrix.

The estimated treatment difference and the associated 95% confidence interval (CI) will be presented.

9.4. Analysis of Other Efficacy and Exploratory Endpoints

Analyses for other efficacy endpoints and exploratory endpoints will be discussed and detailed in the SAP.

9.5. Safety Analysis

The safety analysis set is defined as those subjects who received at least one dose of tofacitinib MR 11mg QD with MTX at entry into the study. All displays of safety data will be separated by the open-label phase and the double-blind phase.

CCI [REDACTED]

[REDACTED]

9.7. Data Monitoring Committee

This study will use an External Data Monitoring Committee (EDMC).

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

9.8. Safety Event Adjudication/Review Committees

To help assess specific safety events in this study, external adjudication committees have been established to harmonize and standardize selected safety event assessment. Members of these safety event adjudication committees will be blinded to treatment assignment in order to allow for unbiased assessments. These committees include a Cardiovascular Endpoint Adjudication Committee (CV EAC), Malignancy Adjudication Committee (MAC), Opportunistic Infection Review Committee (OIRC), Hepatic Event Review Committee (HERC) and Gastrointestinal Perforation Review Committee (GIPRC). Further information about these committees can be found in the respective charters, including specific descriptions of the scope of their responsibilities and the processes and definitions used to review and assess specific safety events.

In addition to these external committees, an internal committee of medically qualified Pfizer personnel with expertise in the assessment and diagnosis of respiratory disease will review and categorize potential events of interstitial lung disease (Interstitial Lung Disease Review Committee, ILDRC).

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

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative 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, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (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 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/Ethics Committee

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/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

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

12.2. Ethical Conduct of the Study

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

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

12.3. Subject Information and Consent

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

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

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

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

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

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

12.4. Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in 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 a sufficient number of 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.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of tofacitinib for use in subjects 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 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

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

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

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

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

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3. Murray PJ. The JAK-STAT signaling pathway: input and output integration. *J Immunol* 2007;178(5):2623-9.
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5. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. *Arthritis and rheumatism*. 2012;64(3):617-29. Epub 2011/09/29.
6. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *The New England journal of medicine*. 2012; 367(6):495-507. Epub 2012/08/10.
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8. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Annals of internal medicine*. 2013;159(4):253-61. Epub 2013/09/13.
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10. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Mejjide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *The New England journal of medicine*. 2012;367(6):508-19. Epub 2012/08/10.
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Appendix 1. Abbreviations

This is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ACIP	advisory Committee on Immunization Practices
ACPA	anti-cyclic citrullinated peptide
ACR	american college of rheumatology
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC _{inf}	area under the concentration-time curve from time 0 to infinity
BCG	Bacille Calmette Guérin
BID	twice daily
CD	cluster of differentiation
CDAI	clinical disease activity index
CHD	coronary heart disease
C _{av}	average observed concentration
C _{max}	peak or maximum observed concentration
C _{min}	minimum observed concentration
COX	cyclooxygenase
CRF	case report form
CRP	c-reactive protein
CSA	clinical study agreement
CT	computed tomography
CTA	clinical trial application
DAS	disease activity score
DAI	dosage and administration instructions
DMARD	disease-modifying antirheumatic drug
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
ESR	erythrocyte sedimentation rate
EQ-5D	European Quality of Life - 5 dimensions questionnaire
EU	European Union
EudraCT	European Clinical Trials Database
EuroQol	European Quality of Life
FACIT	Functional Assessment of Chronic Illness Therapy

FACS	fluorescence-activated cell sorting
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen
HDL	high density lipoprotein
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
HRQL	health-related quality of life
HZ	herpes zoster
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	identification
IFN γ	Interferon gamma
IL	interleukin
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRC	internal review committee
IUD	intrauterine device
IVRS	interactive voice response system
JAK	janus kinase
IWR	interactive web response
LDA	low disease activity
LDL	low density lipoprotein
LFT	liver function test
LSLV	last subject last visit
LTE	long-term extension
MCP	metacarpophalangeal
MTX	methotrexate
N/A	not applicable
NK	Natural killer
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York heart association
PCD	primary completion date
PhyGA	physician's global assessment of health

PIP	proximal interphalangeal
PT	prothrombin time
PtGA	subject's global assessment of health
QD	once daily
RA	rheumatoid arthritis
RAPID3	Routine Assessment of Patient Index Data 3
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDAI	simplified disease activity index
SF-36	short form (36) health survey
SIB	suicidal ideation and behavior
SJC	swollen joint count
SOA	schedule of activities
SOP	standard operating procedure
SPC	summary of product characteristics
SRSD	single reference safety document
SSID	study subject identification
TB	tuberculosis
TJC	tender joint count
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
TST	tuberculin skin test
TYK	tyrosine kinase
ULN	upper limit of normal
US	United States
USPI	United States package insert
UTN	Universal Trial Number
VAS	visual analogue scale
VZV	varicella zoster virus
WPAI	Work Productivity and Activity Impairment

Appendix 2. The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis

	Score
Target population (Who should be tested?): Patients who Have at least 1 joint with definite clinical synovitis (swelling)*	
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 $\geq 6/10$ 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 3. Prohibited Concomitant Medications

All prohibited investigational compounds require discontinuation for at least 4 weeks or 5 half-lives (whichever is longer) prior the Baseline Visit.

All investigational compounds, other than study drugs (tofacitinib and MTX), are prohibited during the study.

Please refer to [Appendix 6](#) for prohibited corticosteroids.

Only systemically administered drugs listed below are prohibited; topical, ophthalmic, or intravaginal administration is allowed.

The use of folate antagonists such as trimethoprim is prohibited during the study.

Prohibited Concomitant Medications	
CYP3A4 and/or CYP2C19 Inhibitors	CYP3A4 Inducers
Protease inhibitors: indinavir (Crixivan) nelfinavir (Viracept) ritonavir (Kaletra, Norvir) Saquinavir (Invirase)	Protease inhibitors: efavirenz (Sustiva)* nevirapine (Viramune)*
Macrolide antibiotics: clarithromycin (Biaxin, Prevpac) telithromycin (Ketek)	Anticonvulsants: barbiturates* phenobarbital* phenytoin (Dilantin, Phenytek) carbamazepine (Carbatrol, Tegretol)*
Other antibiotics: chloramphenicol	Antibiotics: rifampicin/rifampin (Rifadin, Rifamate) rifabutin (Mycobutin)* Rifapentene (Priftin)*
Antifungals: fluconazole (Diflucan) ketoconazole (Nizoral) itraconazole (Sporanox) voriconazole (Vfend)	Antidepressants: St. John's Wort*
Antidepressants: fluvoxamine (Luvox) nefazodone (Serzone)	Other compounds: modafinil (Provigil) troglitazone (Rezulin)
Prohibited Concomitant DMARDs**	
Biologic DMARDs	Nonbiologic DMARDs
Rituximab, anakinra (Kineret), etanercept (Enbrel), infliximab (Remicade), abatacept (Orencia), tocilizumab (Actemra), certolizumab pegol (Cimzia®), Golimumab (Simponi TM), adalimumab (Humira),	Oral gold (auranofin), injectable gold (aurothioglucose, aurothiomalate), sulfasalazine, d-penicillamine, bucillamine, mizoribin, azathioprine, leflunomide (Arava), cyclosporine, tacrolimus, tetracyclines (unless prescribed for acne), antimalarials (chloroquine, hydroxychloroquine), baricitinib

*Discontinue for at least 30 days

** See [Section 5.8](#) for specific washout requirements.

Appendix 4. Cockcroft-Gault Formula for Estimating GFR

$$\text{Creatinine Clearance (estimated) / Conventional mL/min} = \frac{((140 - \text{Age (years)}) \times \text{Weight (kg)} \times \text{Factor}^a)}{(72 \times \text{Serum Creatinine (mg/dL)})}$$

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

Appendix 5. Approximate Equivalent Morphine Doses Of Opioid Analgesics

Common opioid analgesics

Drug	Maximum Allowed Total Daily Dose	Relative potency to oral morphine	Half-Life
Morphine	30 mg	1	1.5 – 4 hrs
Hydrocodone (Vicodin, Lortab)	30 mg	1	3.8 – 4.5 hrs
Hydromorphone (Dilaudid)	7.5 mg	4	2.5 hrs
Meperidine (Demerol, Pethidine)	300 mg	0.1	3.2 – 3.7 hrs
Methadone (Dolophine, Methadose, Physeptone)	10 mg	3.0	23 hrs
Codeine (Paveral, Tylenol #2 and #3)	200 mg	0.15	2.5 – 3.5 hrs
Oxycodone [Roxicodone; Percocet, Tylox]	15 mg	~2	3.2 hrs
Tramadol [Ultram, Zydol; Zamadol, Ultracet, Tramal]	300 mg	~0.1	4.7 – 5.1 hrs

Sites should contact project team for acceptable alternative preparations and related data.

References:

1. Twycross R, Wilcock A, Thorp S. Palliative Care Formulary. Abingdon: Radcliffe Medical Press, 1998.
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Appendix 6. Rescue Therapy

Acetaminophen/ paracetamol is allowable as rescue medication if dosed no more than the locally approved recommended daily dose for no more than 10 consecutive days. If a subject is already taking stable background doses of acetaminophen/ paracetamol, s/he may increase the dose up to the locally approved recommended daily dose for up to 10 consecutive days for rescue purposes.

Acetaminophen/paracetamol is not permitted as a part of combination products such as over-the-counter “cold remedies” or in combination with opioids if the acetaminophen/paracetamol dose will exceed the locally approved recommended daily dose. Subjects who require rescue for more than 10 consecutive days should be discontinued from the trial. In addition, subjects should not be dosed with rescue acetaminophen/paracetamol or opioids within 24 hours prior to a study visit. However, baseline stable acetaminophen/paracetamol or opioids should NOT be discontinued in advance of study visits.

Low dose oral corticosteroids in doses equivalent to ≤ 10 mg prednisone per day is allowed during the study period. However, the prednisone dose increase should not exceed the initial dose during the study period.

Intra-articular corticosteroids may be given during the first 3 months of the run-in phase in no more than two joints, in a cumulative dose of no more than 80 mg methylprednisolone or its equivalent during any 6 month study period. Injections are not allowed after 3 months. Injected joints will also be considered as having their pre-injection status (tender/painful or swollen) for the remainder of the trial.

Intravenous or intramuscular corticosteroids are not allowed during this study.

Biologic response modifiers are not allowed during this study.

Subjects should not be dosed with any rescue intervention within 24 hours prior to a study visit.

The following paradigm should be used to determine appropriate opioid rescue therapy:

For subjects who are NOT on stable, background opioid therapy: any of the following single opioid agents may be given as rescue medication (with or without acetaminophen/ paracetamol) for no more than 10 consecutive days in the following total daily doses:

1. Hydrocodone, not to exceed 30 mg total daily dose.
2. Oxycodone, not to exceed 15 mg total daily dose.
3. Tramadol, not to exceed 300 mg total daily dose.

For subjects who ARE on stable, background opioid therapy:

1. They may NOT add a second opioid agent for rescue.
2. If their background medication is 1 of the 3 listed above, they may, within the above maximum total dosage limits, increase the dosage for up to 10 consecutive days for rescue purposes.
3. If their background medication is a short-acting (half-life <5 hours, [Appendix 5](#)) opioid that is not one of those listed above, they may increase the dosage for up to 10 consecutive days (up to a total daily dose which must not exceed the potency equivalent of 30 mg of orally-administered morphine ([Appendix 5](#)) for rescue purposes.
4. Sustained release opioid formulations (eg, OxyContin[®], MS Contin[®]) and opioids with half-lives greater than 5 hours (eg, methadone) may NOT be USED for rescue medication.
5. Sustained release opioid formulations (eg, OxyContin[®], MS Contin[®]) and opioids with half-lives greater than 5 hours (eg, methadone; see also [Appendix 4](#)) may NOT be INCREASED for rescue purposes.

Appendix 7. Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and United Kingdom Specific Protocol Requirements

In Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Spain, and the United Kingdom, the following changes are made to the protocol:

4.4.5 Contraception and Reproductive Status

In this study, male subjects who are able to father children and female subjects who are of childbearing potential will receive MTX, which has been associated with teratogenic risk in humans, and tofacitinib which has been associated with teratogenic risk in animals (further information can be found in the single safety reference document). Those who, in the opinion of the investigator, are sexually active and at risk for pregnancy with their partner(s) must agree to use with their partner(s) highly effective contraception throughout the study and continue for at least 6 months after the last dose. The investigator or his or her designee, in consultation with the subject, will select the appropriate method of contraception for the individual subject and his/her partner(s) from the list of permitted contraception methods below and instruct the subject in their consistent and correct use. The investigator or his or her designee will discuss with the subject the need to use a highly effective method of contraception consistently and correctly according to the [schedule of activities](#) and document such conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if a selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

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).

One of the below options must be used to satisfy the requirement for highly effective contraception:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (ie, oral, inserted, injected, implanted, transdermal) with either:
 - a. male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available, this option is not appropriate;
 - b. male sterilization.
2. Correctly placed copper-containing intrauterine device (IUD) or intrauterine system combined with either:
 - a. male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available, this option is not appropriate;

- b. male sterilization.
3. Male sterilization with absence of sperm in the postvasectomy ejaculate combined with:
 - a. male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository. For countries where spermicide is not available, this option is not appropriate;
 - b. bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure.
 4. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label) combined with:
 - a. IUD or intrauterine system;
 - b. male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available, this option is not appropriate;
 - c. male sterilization.

Pregnancy testing will be performed and documented at every visit unless the non-childbearing potential is confirmed and documented. The specific contraceptive methods will be documented and at every visit, their consistent and correct use will be ascertained and documented in the subject's case report form.