A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF TOFACITINIB (CP-690,550) IN CHINESE SUBJECTS WITH ACTIVE PSORIATIC ARTHRITIS AND AN INADEQUATE RESPONSE TO AT LEAST ONE CONVENTIONAL SYNTHETIC DMARD

Investigational Product Number:	CP-690,550
Investigational Product Name:	Tofacitinib
Protocol Number:	A3921234
Phase:	3

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 4	4 Jun 2020	1. Sample size increase from approximately 195 to approximately 204 to preserve the study power, which is negatively impacted by the COVID-19 pandemic on the response rates and the rate difference of the primary endpoint. (Protocol summary, Section 3, Section 5.1, Section 9.1 and Section 9.2).
Amendment 3	13 May 2020	1. Exclusion Criteria Section 4.4 number 29 and Screening Section 6.1: add to evaluate the risk factors of venous thromboembolism before entering the study. 2. Add checking risk factors for venous thromboembolism in every visit (revisions are in Schedule of Activities, Section 3, Section 6.2, and new Reference #19 added). 3. Add Section 7.5.8 to list the venous thromboembolism risk factors that will be checked every visit and tofacitinib dosing guidance when a risk factor is identified. 4. Add confirmed venous thromboembolism into Section 6.3.2 Discontinuation Criteria. 5. Clarify that the DMARDs prohibition requirement ends at last dose in Appendix 3. After last dose of investigational drug, treatment will be left at the discretion of investigators to ensure subjects' benefit. 6. Clarify that all JAK inhibitors are prohibited in the study and require washout as described in Appendix 3. 7. Other Inclusion Criteria Section 4.3 - number 2: make changes based on 2020 WHO guideline and China local practice. To be consistent, update the chest radiography monitoring requirement accordingly in SOA and Section 7.5.3.3. 8. Exclusion Criteria Section 4.4 – number 31: clarify that patients with previous clinical experience of tofacitinib will be excluded to avoid bias. 9. Update Section 4.6.6 Contracepion part per current

Document	Version Date	Summary of Changes and Rationale
		effective protocol, in which male condom or female condom with spermicide are no longer considered as highly effective methods. Also add clarified requirements that are for background medications. 10. Incorporate all the revisions addressed in PACLs dated 31Oct2018, 13Mar2019, 27May2019 and 01April2020, respectively, as per bullet points below: • Other Inclusion Criteria Section 4.3 – number 4: specify the washout requirements for three TNFi biosimilar used widely in China. And clarify that other biosimilar biologics could follow washout requirements of reference product after confirming they have same half lives. • Correct misleading wording in Section 7.5.7.2 and Section 4.1.2 and correct some inaccurate wording of translation in Chinese version. • Section 8.1.4: To clarify requirement of differentiate AE reporting and the reporting of medical history that occurs before study intervention. • Add the contingency tactics during Corona Virus Disease 2019 into Section 7.7 Corona Virus Disease 2019.
Amendment 2	20 Aug 2018	1. Sample size is increased to 195 subjects to yield a higher power of at least 90%. The enrollment will be monitored to cap the proportion of subjects with baseline swollen joint count ≤5 at 40% (ie, ≤78 subjects) to keep study population similar to global pivotal study A3921091. 2. Inclusion criteria 4.1.2: the minimum treatment duration of sulfasalazine is changed to 3 months, which is in accordance with clinical practice in China. 3. Inclusion criteria 4.3: specify we intend to recruit Chinese adult subjects.

Document	Version Date	Summary of Changes and Rationale
		4. Exclusion criteria 4.4 item 8: wording is updated to make this criterion more comprehensive. 5. Update Appendix 3 Prohibited Concomitant Medications to include the possible DMARDs used in clinical practice. 6. Make clarifications for study visits to avoid inconsistent understanding. 7. Incorporate all the revisions addressed in PACL dated on 26 Feb 2018: • Section 4.4 Exclusion criteria: a change is made that 12-lead ECG will be read and determined by qualified cardiologist. • Correct the identified inconsistencies. • Some format adjustments are to make it clear. 8. Update safety part by protocol template. 9. This study is for China registration, so delete US IND number and EudraCT number.
Amendment 1	20 November 2017	1. Regional study is changed to China alone study: the study is designed to support PsA registration in China. 2. Treatment arm of tofacitinib 10 mg BID is removed: based on results of PsA global pivotal studies, recommended PsA posology globally is tofacitinib 5 mg BID only, the 10 mg BID dose is not included as part of the posology in PsA. 3. Primary endpoint is changed to ACR50 response rate at Month 3: ACR50 indicates higher degree of improvement with more clinical relevance. Based on data of A3921091, with ACR50 as primary endpoint makes it possible to detect a statistical difference between tofacitinib and placebo with adequate power. CCI [redacted]

Document	Version Date	Summary of Changes and Rationale
		CCI [redacted] 5. Template update.
Original protocol	11 July 2014	Not applicable (N/A)

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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APPENDICES

PROTOCOL SUMMARY

Background and Rationale:

Psoriatic arthritis (PsA) is a chronic inflammatory autoimmune disease characterized by joint inflammation and destruction, psoriatic skin lesions, enthesitis, dactylitis, spondylitis, progressive disability and adverse effects on quality of life. Tofacitinib (CP-690,550) is a potent and selective inhibitor of the Janus Kinase (JAK) family of kinases. While tofacitinib shows nanomolar inhibitory potency against all JAK family kinases in enzymatic assays, it shows functional specificity for JAK1 and JAK1/3 over JAK2 in cell-based assays. The broad effects of JAK1/3 inhibition on multiple cytokine pathways provide the rationale for developing tofacitinib as treatment for PsA.

Efficacy and safety of oral dosing with tofacitinib in Rheumatoid Arthritis (RA) subjects has been demonstrated in Phase 2 and 3 studies and received Federal Drug Administration (FDA) approval on 6 November 2012 for this indication. Tofacitinib citrate 5 mg twice daily (BID) dose was also approved in Japan and Korea, and both tofacitinib citrate 5 mg BID and 10 mg BID doses approved in Taiwan. In China, tofacitinib 5 mg BID was approved on 10 March 2017, for the indication to treat adult patients with moderately to severely active RA who have had inadequate response or intolerance to Methotrexate (MTX). Efficacy and safety of tofacitinib 5 mg BID has been demonstrated in 2 completed Phase 3 studies and 1 ongoing long term extension study of PsA. Data from the Global Phase 3 trials in PsA is under review by FDA.

This is a 6 month Phase 3 study designed to evaluate the efficacy and safety of tofacitinib 5 mg BID as a treatment for PsA in Chinese subjects with active PsA who have had an inadequate response in their PsA to at least one conventional synthetic disease-modifying anti-rheumatic drug (csDMARD).

Objectives:

- To compare efficacy of tofacitinib 5 mg BID versus placebo for treatment of rheumatological signs and symptoms of PsA in Chinese subjects with active PsA who have had an inadequate response to at least one csDMARD.

- To compare the safety and tolerability of tofacitinib 5 mg BID versus placebo in Chinese subjects with active PsA who have had an inadequate response in PsA to at least one csDMARD.

- To compare physical function status, health outcome measures and dermatological signs and symptoms after administration of tofacitinib 5 mg BID versus placebo in Chinese subjects with active PsA who have had an inadequate response in PsA to at least one csDMARD.

Study Design:

This is a Phase 3 randomized, 6-month, double-blind, placebo-controlled, parallel group study designed to evaluate the efficacy and safety of tofacitinib in adult, Chinese subjects with active PsA who had an inadequate response in their PsA to at least one csDMARD. A total of approximately 204 subjects will be randomized in a 2:1 ratio to one of the following two parallel treatment sequences. The enrollment will be monitored to cap the proportion of subjects with baseline swollen joint count ≤5 at approximately 38% (ie, approximately 78 subjects).

Treatment Sequence	Treatment	Planned Number of Randomized Subjects
Sequence A	Tofacitinib 5 mg BID	136
Sequence B	Placebo x 3 Months → Tofacitinib 5 mg BID[1]	68

[1.] At Month 3, subjects randomized into Treatment Sequence B will receive tofacitinib 5 mg BID in a blinded manner through Month 6.

Primary study endpoint of The American College of Rheumatology's definition for calculating improvement in RA (ACR50) responder rate will be obtained at Month 3. During the study, subjects are required to remain on a stable dose of one csDMARD, eg, methotrexate or sulfasalazine and should remain on that dose throughout the study.

Study Treatments:

Subjects are randomized to receive either tofacitinib 5 mg BID or placebo. At Month 3, all subjects receiving placebo will be advanced to tofacitinib 5 mg BID in a blinded manner for 3 months. Investigators, subjects and sponsor will remain blinded through the entire duration of the study until database release.

Statistical Methods:

The sample size and power analysis for the primary endpoint are based on the randomization of approximately204 subjects in a 2:1 ratio. The sample size for this study is driven by the ACR50 response rate.

On the assumption of a placebo response rate of 9.5% and factoring in the number of subjects with primary endpoint data missing due to COVID-19 (around 11 subjects as of 29 May 2020), this sample size of approximately 136 Chinese subjects in the tofacitinib treatment arm and 68 subjects in the placebo arm will yield at least 90% power to detect a difference of 18.5% from placebo in ACR50 response, based on normal approximation (without continuity correction) at the 2-sided significance level of 5%.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Visit Identifier and visit window[a]	**Screening**[1]	**Visit 1 Baseline Day 1**	**Visit 2 Week 2 (Day 15±3 days)**	**Visit 3 Month 1 (Day 29±3 days)**	**Visit 4 Month 2 (Day 57±7 days)**	**Visit 5 Month 3 (Day 85±7 days)**	**Visit 6 Month 4 (Day113±7 days)**	**Visit 7 Month 6 (169±7 days)**	**Early Termination**	**Follow-up Visit**[18]
Informed Consent	X									
PsA Diagnosis, Medical History[2]	X									
Concomitant/Prior Medications	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam[3]	X	X						X	X	
Targeted Physical Exam[3]			X	X	X	X	X			
Vital Signs, Temperature	X	X	X	X	X	X	X	X	X	
Waist and Hips Circumference		X						X	X	
Height	X									
12-Lead ECG	X							X	X	
QuantiFERON-TB Gold (or Mantoux/PPD Skin Test); Chest Radiographs[4]	X									
LABORATORY TESTING[19]										
Hematology[5]	X	X		X	X	X	X	X	X	X
Hemoglobin A1c (HbA1c)		X				X		X	X	
Lymphocyte subset analysis (FACS)		X				X		X	X	
Chemistry panel (fasting)[6]	X	X		X	X	X	X	X	X	X
Lipid Panel (fasting)[7]		X		X		X	X	X	X	X
Urinalysis[8]	X	X		X	X	X	X	X	X	
Urine pregnancy test (HCG)[9]	X	X	X	X	X	X	X	X	X	X
C-Reactive Protein (CRP)	X	X	X	X	X	X	X	X	X	
HIV serology, HBsAg, HBcAb, HCV Ab	X									
Prothrombin time (INR)[10]	X									
Rheumatoid Factor (RF), Cyclic Citrullinated Peptide Antibody (CCP)		X								

Visit Identifier and visit window[a]	Screening[1]	Visit 1 Baseline Day 1	Visit 2 Week 2 (Day 15±3 days)	Visit 3 Month 1 (Day 29±3 days)	Visit 4 Month 2 (Day 57±7 days)	Visit 5 Month 3 (Day 85±7 days)	Visit 6 Month 4 (Day113±7 days)	Visit 7 Month 6 (169±7 days)	Early Termination	Follow-up Visit[18]
Serum follicle stimulating hormone (FSH)[11]	X									
CLINICAL EVALUATION OF RHEUMATOLOGY ENDPOINTS[12]										
Tender/Painful Joint Count, Swollen Joint Count	X	X	X	X	X	X	X	X	X	
Physician's Global Assessment of Arthritis (VAS)		X	X	X	X	X	X	X	X	
Physician's Global Assessment of Psoriatic Arthritis (VAS)		X		X		X		X	X	
Dactylitis Assessment		X		X		X		X	X	
Enthesitis Assessment (Leeds Index)[13]		X		X		X		X	X	
CLINICAL EVALUATION OF DERMATOLOGY ENDPOINTS[12]										
Assessment of plaque psoriasis[14]	X									
Physician's Global Assessment of Psoriasis (PGA-PsO)[15]		X		X		X		X	X	
Psoriasis Area and Severity Index (PASI); Body Surface Area (BSA)[15]		X		X		X		X	X	
Nail Psoriasis Severity Index (NAPSI)[16]		X		X		X		X	X	
PATIENT REPORTED OUTCOMES[17]										
Patient's Assessment of Arthritis Pain (VAS); Patient's Global Assessment of Arthritis (VAS); HAQ-DI		X	X	X	X	X	X	X	X	
SF-36, EQ-5D		X		X		X		X	X	
WPAI-PsA		X				X		X	X	
OTHER ACTIVITIES										
Contraception check[20]		X	X	X	X	X	X	X	X	X
Randomization		X								
Drug Dispensing		X				X				
Dosing diary despensing		X								
Drug Accountability; review dosing diary			X	X	X	X	X	X	X	
Serious and non-serious adverse event monitoring	X	X	X	X	X	X	X	X	X	X

Visit Identifier and visit window[a]	Screening[1]	Visit 1 Baseline Day 1	Visit 2 Week 2 (Day 15±3 days)	Visit 3 Month 1 (Day 29±3 days)	Visit 4 Month 2 (Day 57±7 days)	Visit 5 Month 3 (Day 85±7 days)	Visit 6 Month 4 (Day113±7 days)	Visit 7 Month 6 (169±7 days)	Early Termination	Follow-up Visit[18]
Risk factor check for venous thromboembolism[21]	X	X	X	X	X	X	X	X	X	X

a. Day relative to start of study treatment (Day 1). For the purpose of this protocol, 1 Month is defined as 28 calendar days.

1. Screening visit occurs within 28 (+10) days prior to Baseline (Day 1) visit.
2. Psoriatic Arthritis (PsA) diagnosis is based upon Classification Criteria for Psoriatic Arthritis (CASPAR) at screening (see Section 4.1.1). For study inclusion, subject must have had signs and symptoms consistent with PsA diagnosed for at least 6 months. PsA disease subtype will be collected and documented in eCRF (see Section 6.2). Medical history includes cardiovascular (CV) risk factor assessment ie, smoking status, average weekly alcohol consumption, family history of premature coronary heart disease (CHD).
3. Complete physical exam includes weight, general appearance, skin, HEENT (head, eyes, ears, nose and throat), heart, lungs, abdomen, lower extremities, neurologic and lymph nodes. Targeted physical exam consists of weight, examination of heart, lungs, abdomen, lymph nodes and lower extremities.
4. For subjects with latent tuberculosis infection and treated with preventive anti-tuberculosis therapy during study, chest radiograph should be be monitored per local practice.
5. Hematology includes RBC, RBC morphology, WBC with differential, hemoglobin, hematocrit, reticulocyte count and platelet count.
6. Chemistry panel (fasting) includes urea nitrogen, creatinine, glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), albumin and creatine kinase (CK).
7. Lipid Panel (fasting) includes: fasting total cholesterol, LDL, HDL, triglycerides. In addition, apolipoprotein A-1 and B will be measured at baseline, Months 1, 3, 6 (or Early Termination) and Follow-Up Visit for eligible subjects. All lipid profile tests will be performed by the central laboratory.
8. Urinalysis includes specific gravity, pH, protein, glucose, ketones, blood and leukocyte esterase. Microscopy and/or culture to be performed if clinically indicated or if urinalysis results are positive (blood, protein or leukocyte esterase/WBC).
9. Urine pregnancy test (human chorionic gonadotrophin, HCG) is required only for women of child-bearing potential; may be repeated more frequently if required by local practices, if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected.
10. Prothrombin time (INR) will be performed at Screening and as needed in cases of elevated liver enzymes.
11. Post-menopausal status may be confirmed at the discretion of investigator by having a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females as per 4.1 Inclusion Criteria.
12. All rheumatologic and dermatologic evaluations performed at baseline and thereafter will be done by a qualified assessor who is blinded to the subject's safety data, previous efficacy data and treatment randomization.
13. Enthesitis will be assessed using Leeds Index (Section 7.2.8).
14. For study eligibility, subjects must have active plaque psoriasis at Screening which has been diagnosed or confirmed by a dermatologist or a Sponsor-approved rheumatologist.
15. Physician Global Assessment of Psoriasis (PGA-PsO), Psoriasis Area and Severity Index (PASI) and Body Surface Area (BSA). PASI performed only if ≥3% of BSA affected at baseline.
16. Nail Psoriasis Severity Index (NAPSI) will be performed on the target finger nail identified at baseline and be followed for duration of the study (Section 7.3.4).

17. Subject completed questionnaires include: Patient's Global Assessment of Arthritis (VAS), Patient's Global Assessment of Arthritis Pain (VAS), Health Assessment Questionnaire-Disability Index (HAQ-DI), Short-Form-36 Health Survey (Version 2, Acute) (SF-36), EuroQol 5 Dimensions (EQ5D) and The work productivity and Activity Impairment – Psoriatic Arthitis Questionnaire (WPAI-PsA). All patient reported outcomes should be completed prior to any other assessments made at each visit.
18. If a subject discontinues from or completes the study with abnormalities in hematology or clinical chemistry results (as defined in Section 6.3.2), or a subject discontinues from study due to an adverse event, a follow-up visit must be performed after the Early Termination study visit within 28 days (+14 days) of last dose of study treatment. In addition, all subjects who complete the study must have a follow-up visit within 28 days (+14 days) of end of study visit.
19. Testings that are to be done in central lab: hematology, HbA1c, Lymphocyte subset analysis (FACS), Chemistry panel, Lipid Panel, Urinalysis, C-Reactive Protein (CRP), HIV serology, HBsAg, HBcAb, HCV Ab, Prothrombin time (INR), Rheumatoid Factor (RF), QuantiFERON-TB Gold, FSH testing if needed.
20. Confirm and document that contraception, if assigned, is used consistently and correctly.
21. Per amendment 3, all subjects will be asked at every study visit if they have any newly-developed risk factors for venous thromboembolism as described in Section 7.5.8.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Tofacitinib is a highly selective inhibitor of the Janus kinase (JAK) family of kinases that is being developed for the treatment of adult, Chinese subjects with active psoriatic arthritis (PsA) who have had an inadequate response to csDMARD treatment for PsA.

1.2. Background and Rationale

PsA is a chronic inflammatory autoimmune disease characterized by joint inflammation and destruction, psoriatic skin lesions, enthesitis, dactylitis, spondylitis, progressive disability and adverse effects on quality of life.[1,2] PsA presents significant health and socioeconomic burdens for the individual and society. There is currently no cure for PsA. The goals of therapy for patients with PsA are: 1) to achieve the lowest possible level of disease activity in all disease domains; 2) to optimize functional status, improve quality of life and well-being; 3) to prevent structural damage to the greatest extent possible; and 4) to avoid or minimize complications, both from untreated active disease and from therapy.

While non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are included in the 2016 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) guidance,[3] these medications are only mildly effective at relieving musculoskeletal signs and symptoms, and they have safety risks with long-term usage. Despite the relative paucity of randomized controlled data in PsA trials supporting their efficacy and safety, csDMARDs such as MTX are used for treatment of PsA peripheral arthritis, psoriasis, and dactylitis. csDMARDs are not recommended by GRAPPA for treatment of enthesitis or axial domains, due to lack of evidence for efficacy. Furthermore, their use can be limited by adverse events including liver toxicity (methotrexate, leflunomide), hypersensitivity and blood dyscrasias (sulfasalazine),[4] and nephrotoxicity (cyclosporine).[5,6,7] Limited or questionable effectiveness accompanied with potential toxicity suggest that a large proportion of PsA patients are inadequately treated with csDMARDs.

The targeted synthetic disease modifying anti-rheumatic drug (tsDMARD) apremilast is a selective inhibitor of the enzyme phosphodiesterase 4 (PDE4) which was recently approved for the treatment of PsA. It has demonstrated mild to modest efficacy on PsA signs and symptoms, evidenced by lack of statistical significance versus placebo for higher thresholds of efficacy for peripheral arthritis (eg, American College of Rheumatology criteria ≥50% improvement [ACR50] and American College of Rheumatology criteria ≥70% improvement [ACR70]). Apremilast also has no PsA structural assessment data, and its use can be limited by tolerability issues.

Currently 5 tumour necrosis factor inhibitors (TNFi) are approved by the US FDA for use in PsA: infliximab, etanercept, adalimumab, golimumab, and certolizumab.[8] Within the last few years, additional biologic disease-modifying anti-rheumatic drugs (bDMARDs) have been approved for PsA including ustekinumab (a human mAb interleukin-12 and IL-23 antagonist) and secukinumab (a human mAb interleukin-17A antagonist). These bDMARD therapies have demonstrated statistical significance versus placebo on ACR 20/50/70 responses; as well as efficacy in other PsA domains.

TNFi and Apremilast are not approved in China for the treatment of PsA. There is therefore unmet medical need for new disease-modifying anti-rheumatic drugs (DMARDs) in the PsA patient population in China where there is no approved biologic/TNFi for PsA and treatment alternatives are insufficient.

This trial will use placebo control in the study design to provide rigorous hypothesis testing and unequivocal scientific data to evaluate the efficacy and safety profile of tofacitinib in Chinese PsA patient population. The placebo control period will be 3 months in duration which should be adequate time to see effects of active treatment on signs/symptoms of PsA and minimize the amount of structural damage incurred. Subjects who enroll in this study should remain on their concomitant non-biologic DMARDs as noted in the inclusion/exclusion criteria. In addition, subjects may be offered an appropriate rescue medication (see Appendix 5) during the study if there is an increase in pain. Finally, if subjects do experience an increased or persistent clinical disease activity, they will have the option to withdraw from the study at any time.

This Phase 3 study will evaluate the efficacy and safety of tofacitinib, a highly selective inhibitor of the JAK family of kinases (including JAK3), for the treatment of active PsA in a double-blind, 6-month, placebo-controlled, randomized study in adult, Chinese subjects who have had an inadequate response to at least one csDMARD. Tofacitinib has previously demonstrated efficacy and safety in Phase 2 and Phase 3 studies of Rheumatoid Arthritis (RA) and 5 mg BID was approved by the FDA 6 November 2012 for treatment of moderate to severe RA. Tofacitinib citrate 5 mg dose was also approved in Japan and Korea, and both tofacitinib citrate 5 mg and 10 mg doses approved in Taiwan. In China, tofacitinib 5 mg BID was approved on 10 March 2017, for the indication to treat adult patients with moderately to severely active RA who have had inadequate response or intolerance to MTX. Efficacy and safety of tofacitinib 5 mg BID has been demonstrated in 2 completed Phase 3 studies and 1 ongoing long term extension study of PsA. Data from the Global Phase 3 trials in PsA is under review by FDA.

In this study, a similar study design to the global pivotal study A3921091 will be used to investigate the safety and efficacy of tofacitinib 5 mg BID in Chinese subjects with active PsA.

1.2.1. Mechanism of Action

Tofacitinib is a potent, selective inhibitor of the JAK family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent 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. Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain-containing receptors for several cytokines, including IL-2, -4,-7,-9, -15 and -21.[9,10,11] These cytokines are integral to lymphocyte activation, proliferation, and function and inhibition of their signaling may thus 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 type I

interferons. At higher exposures, inhibition of erythropoietin signaling could occur via inhibition of JAK2 signaling. Many of the cytokines that are associated specifically with the pathogenesis of PsA (eg, IL-2, IFN-γ, IL-12, IL-23) are modulated directly by JAK inhibition with tofacitinib. Furthermore, tofacitinib has been shown to suppress IL-22 cytokine signaling and IL-23 receptor expression and to inhibit T helper 17 (Th17) cell differentiation.[12,13] Tofacitinib suppresses the production of IL-17 by T cells isolated from synovium and peripheral blood of RA patients.[14] Treatment with tofacitinib dosed at 5 mg BID or 10 mg BID for 52 weeks in RA patients significantly decreased the level of IL-17 produced by circulating T cells.[15]

In summary, tofacitinib, via JAK inhibition, was predicted to have robust efficacy in the treatment of PsA. Tofacitinib efficacy has also been demonstrated in RA as well as in comorbid diseases frequently seen in PsA such as plaque psoriasis, inflammatory bowel disease, with some evidence of efficacy in AS.[16,17]

1.2.2. Summary of Efficacy

Efficacy of tofacitinib in patients with psoriatic arthritis was demonstrated in two Phase 3 studies: A3921091 and A3921125.

A3921091 was a randomized, placebo and active comparator controlled, double-blind, multi-site Phase 3 study in active PsA subjects who had inadequate response to at least one csDMARD. Of 422 randomized subjects, 406 completed Month 3 visit at which assessments of primary endpoints ACR20 and HAQ-DI were done. Significantly greater improvements in ACR20 response rates (5 mg BID vs placebo: 50.5% vs 33.3%, P=0.0102; 10 mg BID vs placebo: 60.6 vs 33.3%, P<0.0001) and ΔHAQ-DI (Health Assessment Questionnaire Disability Index) (5 mg BID vs placebo: -0.35 vs -0.18, P=0.0062; 10 mg BID vs placebo: -0.40 vs -0.18, P=0.0004) were observed for both tofacitinib 5 mg BID and 10 mg BID versus placebo at Month 3 and were maintained to Month 12. Tofacitinib 5 and 10 mg BID demonstrated superiority vs PBO for ACR20 response rate as early as Week 2 (22.4% and 31.7% vs 5.7%; p<0.001). ACR50 response rates were statistically significantly higher in active-treated arms than in the placebo arm at Month 3 during the double-blind placebo-controlled period. At Month 3, the ACR50 response rates were 28.04% for tofacitinib 5 mg BID, 40.38% for tofacitinib 10 mg BID, 33.02% for adalimumab 40 mg SC (subcutaneous) q 2 weeks, and 9.52% for placebo (P values were 0.0004, <0.0001 and <0.0001 for tofacitinib 5 mg BID vs Placebo, tofacitinib 10 mg BID vs Placebo and Adalimumab vs Placebo).

A3921125 was a randomized, placebo controlled, double-blind, multi-site Phase 3 study in active PsA subjects who had inadequate response to at least one TNF inhibitor. Of the 395 randomized subjects, 394 were treated, 364 (91.6%) completed Month 3 visit at which assessments of primary endpoints ACR20 and HAQ-DI were done. There were significantly greater improvements in ACR20 response (5 mg BID vs placebo: 49.6% vs 23.7%, P<0.0001; 10 mg BID vs placebo: 47.0% vs 23.7%, P<0.0001) and HAQ-DI (5 mg BID vs placebo: -0.39 vs -0.14, P<0.0001; 10 mg BID vs placebo: -0.35 vs -0.14, P=0.0009) for both tofacitinib doses compared to placebo at Month 3; improvements were maintained to Month 6. Tofacitinib 5 and 10 mg BID demonstrated superior ACR20 response vs placebo

as early as Week 2 (26.7% and 28.8% vs 13.0%; p≤0.05). At Month 3, the ACR50 response rates were 29.77% for tofacitinib 5 mg BID, 28.03% for tofacitinib 10 mg BID, and 14.5% for placebo (P values were 0.0025 and 0.0065 for tofacitinib 5 mg BID vs placebo and tofacitinib 10 mg BID vs placebo).

1.2.3. Summary of Safety

The clinical development program for tofacitinib includes healthy volunteers and subjects with RA, plaque psoriasis, Psoriatic Arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis and renal transplants enrolled in Phase 1, 2 and 3 studies.

As of January 2016, over 22,000 patients have received at least 1 study dose of oral tofacitinib, in either a randomized clinical study or in a long-term extension (LTE) study. In Phase 1 studies, tofacitinib has been administered to healthy volunteers or subjects in single doses ranging from 0.1 to 100 mg and in multiple dose regimens ranging from 5 to 50 mg BID, as well as 60 mg once daily (QD).

Potential safety risks for subjects treated with tofacitinib are based on the totality of the data including nonclinical observations, clinical observations, as well as safety risks reported for other therapies that may share common pathways with tofacitinib. These risks include serious and other important infections such as opportunistic infections and herpes zoster infections, potential for malignancies including lymphoma, and the potential for GI perforations. Laboratory changes associated with, or potentially associated with, tofacitinib treatment include decreases in hemoglobin levels and absolute neutrophil counts (ANC), and increases in lipids, transaminases, serum creatinine, and creatine kinase (CK); the clinical significance of the laboratory changes is uncertain. Although a potential increase risk in cardiovascular (CV) events may also be a concern, this is not supported based upon review of cardiovascular events in subjects with RA during both short and long-term treatment with tofacitinib. However, the number of events reported and resulting wide confidence intervals means that a definitive conclusion cannot be made at this time. The safety profile of tofacitinib in both rheumatoid arthritis and psoriasis subject populations is qualitatively similar. Tofacitinib treatment was well tolerated by subjects participating in the Phase 3 clinical trials in the PsA development program. The observed safety findings were consistent with those observed in both short and long-term data from the RA and psoriasis (PsO) development programs and with other drugs used to treat PsA. No new safety findings were identified and the risks associated with tofacitinib treatment can be mitigated or are manageable via the existing measures employed for the approved indication of RA described in the current prescribing information.

Both doses of tofacitinib were well tolerated. In PsA subjects treated with tofacitinib, serious infections were few, and did not increase over long-term exposure, with a minimal numerical dose dependent difference between 5 mg BID and 10 mg BID. Dose dependent incidence rates for serious infection events were consistent with those seen in RA and PsO, despite the relatively smaller PsA data set. Evidence for dose dependent differences in herpes zoster, serious infections, non-melanoma skin cancer, and laboratory abnormalities was identified in the RA and in PsO development programs.

Interpretation of these results and the possible risks associated with the administration of tofacitinib are summarized in Investigator's Brochure.

1.2.4. Overall Risk-Benefit

1.2.4.1. Potential Benefits

Given the chronic nature of this disorder and the limited available therapies, there remains an unmet medical need for an effective oral treatment for PsA, especially in China where neither TNFi nor other biologics are approved for PsA.

The benefits to individual subjects participating in this study will be the potential control of the disease activity by improving signs and symptoms. All subjects may also benefit from gaining knowledge about their health status through study tests and physician assessments, as well as having close monitoring of their disease.

1.2.4.2. Potential Risks

The risks associated with tofacitinib are similar to the risks associated with the use of other immunosuppressive agents, including a potential increased risk for serious and other important infections, eg, tuberculosis and viral reactivation such as herpes zoster. In RA subjects who have received tofacitinib, the rate of serious infections is higher in subjects 65 years of age and older. Rates of herpes zoster infections in tofacitinib-treated subjects with RA were increased compared with placebo-treated subjects and historical controls; this included an increased risk of herpes zoster infections in Asian RA patients compared with non-Asian RA patients. Decreases in white blood cell counts, particularly neutrophils and lymphocytes, and decreases in hemoglobin have been observed. These effects were usually mild to moderate and returned to normal after discontinuation of therapy. Infections, anemia and neutropenia are all consistent with the pharmacology of tofacitinib as a potent inhibitor of JAK3 with cross-over to JAK1 and moderate selectivity for JAK2. Treatment with tofacitinib was associated with increases in levels of low density lipoprotein(LDL) and high density lipoprotein (HDL) cholesterol, with the ratios of mean LDL/HDL cholesterol unchanged. In the previous controlled trials, elevation of LDL cholesterol generally returned to pre-treatment levels after discontinuation of tofacitinib. Review of cardiovascular events reported in the RA studies suggests that tofacitinib does not appear to increase ocurrence of Major Adverse Cardiac Events (MACE) in subjects with RA during both short- and long-term treatment. The long-term implications of these changes for cardiovascular risk are currently unknown. Also seen in previous studies were slight increases in measured serum creatinine and serum transaminases. This effect generally returned to baseline after discontinuation of therapy. A single RA subject experienced possible drug-induced liver injury (DILI) while being treated with tofacitinib and methotrexate. Tofacitinib was discontinued and she recovered following treatment with prednisone and azathioprine. The time course of her biochemical abnormalities were atypical for DILI; however, investigations did not reveal an alternative etiology. Potential risks that may also be associated with the use of tofacitinib include a potential increased risk of lymphoma and lymphoproliferative disorders, and other malignancies. Non-melanoma skin cancers have been reported in RA patients treated with tofacitinib and has been assessed as an adverse drug reaction based primarily on the review of RA data.

Cases of gastrointestinal (GI) perforation were observed in RA subjects taking tofacitinib, often in the setting of diverticulitis. All affected subjects were taking concomitant non-steroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids that have been associated with an increased risk of GI tract injury.[18] Isolated events of gastrointestinal perforation have also been reported in clinical trials in psoriasis and renal transplant subjects. These perforations were reported as diverticulitis or perforated diverticulum. In one report, the perforation occurred approximately two weeks after discontinuation of study therapy.

Interstitial lung disease (ILD), a complex co-morbidity in RA patients, has also been reported in RA patients receiving tofacitinib. While data from the RA development program do not identify a pulmonary toxicity for tofacitinib, an increased risk of ILD was observed in Asian RA patients as compared to non-Asian RA patients.

In the PsA development program, the serious infection rate was similar between tofacitinib doses, as well as between tofacitinib and adalimumab, and similar to the RA and PsO development programs.

The incidence rate of malignancy for the PsA program is within range of those observed in the RA and PsO programs. Rates in the RA and PsO long term extension (LTE) studies have not changed over time. The incidence rates for malignancies (excluding non-melanoma skin cancer, NMSC) in tofacitinib treated PsA subjects were found to be within the range of those that have been reported in the published PsA literature (including LTE trials) and comparable to published rates for other PsA approved therapies. The incidence rate for NMSC for the PsA program is within range of those observed in the RA and PsO programs.

Based on nonclinical data, there is a potential risk for teratogenicity with tofacitinib. A more detailed discussion of tofacitinib safety can be found in the Investigator's Brochure.

1.2.5. Clinical Pharmacokinetics

The pharmacokinetic (PK) profile of tofacitinib is characterized by rapid absorption, rapid elimination (terminal half-life of ~3 hours) and dose proportional PK. Co-administration with a high fat meal increased the tofacitinib area under the curve (AUC) by 14% and decreased C_{max} by 26%; no dosage adjustments or meal restrictions during chronic dosing are warranted. The clearance mechanisms for tofacitinib in humans appear to be both non-renal and renal excretion of the parent drug, the former accounting for approximately 2/3 of the total clearance. The metabolism of tofacitinib appears to be primarily mediated by CYP3A4 with minor contribution from CYP2C19 as suggested by data from poor metabolizers of CYP2C19. The PK of tofacitinib is similar between Caucasians, Chinese, and Japanese healthy volunteers.

In vitro studies have shown that tofacitinib does not significantly inhibit the major drug metabolizing CYPs, indicating a low potential for tofacitinib to increase the exposure of other drugs. This was demonstrated in a clinical study where tofacitinib did not have an effect on the pharmacokinetics of an oral dose of midazolam (a highly sensitive CYP3A substrate) in healthy volunteers. On the other hand, inhibitors and inducers of CYP3A4/5 are likely to alter the disposition of tofacitinib. Co-administration of tofacitinib

with fluconazole, a moderately potent inhibitor of CYP3A4 and a potent inhibitor of CYP2C19, resulted in 79% and 27% increases in the AUC and C_{max} of tofacitinib, respectively. Co-administration of tofacitinib with methotrexate had no effect on the PK of tofacitinib and resulted in an approximate 10% decrease in the AUC of methotrexate. The extent of decrease in methotrexate exposure does not warrant modifications to the individualized dosing of methotrexate. Co-administration of tofacitinib with cyclosporine and oral tacrolimus, moderate and weak CYP3A4 inhibitors, respectively, resulted in increases of 73% and 21% in AUC_{inf} of tofacitinib. In both cases, tofacitinib C_{max} was decreased slightly; ratio 91%, for tacrolimus and 83%, for cyclosporine.

Consistent with the ~30% contribution of renal clearance to the total clearance of tofacitinib, mean exposure in end stage renal disease (ESRD) subjects (on a non-dialysis day) was approximately 40% higher compared with historical healthy subject data. In contrast, in a separate study, mean exposure was approximately 125% higher in subjects with severe renal impairment compared with healthy subjects. Mild and moderate renally impaired subjects had 37% and 43% higher exposure, respectively, compared with healthy subjects.

Based on these data, subjects with estimated creatinine clearance <40 mL/min will be excluded from this study as will concomitant use of moderate to potent inhibitors of CYP3A4/5.

Further clinical pharmacology background information on tofacitinib can be found in the current version of the tofacitinib Investigator's Brochure.

1.2.6. Drug Development and Study Rationale

Completed studies for PsA include: A3921091, a Phase 3, randomized, double-blind, placebo-controlled, active-controlled study of the efficacy and safety of 2 doses of tofacitinib or adalimumab in subjects with active PsA who had an inadequate response to an oral csDMARD; and A3921125, a Phase 3, randomized, double-blind, placebo controlled study of the efficacy and safety of 2 doses of tofacitinib in subjects with active PsA who have had an inadequate response to at least one TNF inhibitor, and A3921092, an ongoing long-term, open-label extension study of tofacitinib for the treatment of PsA. ACR20 response rates, HAQ-DI and ACR50 at Month 3 for both tofacitinib 5 mg BID and 10 mg BID were significantly superior to placebo in both Study A3921091 and A3921125. The ACR20, HAQ-DI and ACR50 at Month 3 for the pooled data were consistent with the results of the individual study analyses. In Studies A3921091 and A3921125, onset of efficacy as measured by ACR20 response was shown at Week 2 (the first post-Baseline assessment) for both tofacitinib 5 mg BID and 10 mg BID as demonstrated by a statistically significant difference from placebo. In both Studies A3921091 and A3921125, the ACR20 response rates and HAQ-DI were maintained or improved for both tofacitinib 5 mg BID and 10 mg BID from Month 3 through the end of study. Tofacitinib 5 mg BID and 10 mg BID response rates at Month 3 for the efficacy endpoints of ACR50 and ACR70 were significantly superior to placebo in Study A3921091. In Study A3921125, ACR50 response rates at Month 3 for tofacitinib 5 mg BID and 10 mg BID were also significantly superior to placebo.

Tofacitinib treatment was well tolerated by subjects participating in the Phase 3 clinical trials in the PsA development program. The observed safety findings were consistent with those observed in both short and long-term data from the RA and PsO development programs and with other drugs used to treat PsA. No new safety findings were identified and the risks associated with tofacitinib treatment can be mitigated or are manageable via the existing measures employed for the approved indication of RA described in the current prescribing information. Safety risks identified in the PsA clinical trial program is consistent with tofacitinib 5 mg BID RA safety database on both the clinical development program and post marketing experience.

Study A3921234 is intended to support the indication of tofacitinib 5 mg BID for reducing signs and symptoms and improving physical function in adult, Chinese patients with active PsA who have had inadequate response to at least one csDMARD.

1.2.7. Dose Selection Rationale

A3921046 was a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study comparing the efficacy of tofacitinib in doses of 5 mg BID and 10 mg BID versus placebo for the treatment of signs and symptoms in patients with active RA who have had an inadequate response to a DMARD (traditional or biologic), as measured by ACR20 at Month 6, change of HAQ-DI from baseline at Month 3, rate of achieving disease activity score (DAS)28-4 (erythrocyte sedimentation rate [ESR])<2.6 at Month 6. 795 patients were randomized to treatment, and 792 received at least 1 dose of study medication; 651/792 (82.2%) patients completed the study. In this study, China had 218 subjects randomized to treatment and 216 received at least 1 dose of study medication. Statistical significance of the efficacy primary objectives was determined using the step-down procedure. The ACR20 response rates at Month 6 were statistically significantly different for both tofacitinib doses compared with placebo (tofacitinib 5 mg BID vs placebo, 52.73% vs 31.21%, P<0.0001; tofacitinib 10 mg BID vs placebo, 58.25% vs 31.21%, P<0.0001). The differences from placebo for mean changes from Baseline in HAQ-DI at Month 3 were also significantly different for both tofacitinib doses compared with placebo (tofacitinib 5 mg BID vs placebo, -0.46 vs -0.21, P<0.0001; tofacitinib 10 mg BID vs placebo, -0.56 vs -0.21, P<0.0001). The rate of patients achieving a DAS28-4(ESR) <2.6 at Month 6 for tofcitinib 5 mg and 10 mg was also significantly different from placebo (tofacitinib 5 mg BID vs placebo, 9.13% vs 2.70%, P<0.0038; tofacitinib 10 mg BID vs placebo, 13.33% vs 2.70%, P<0.0001). The ACR50 response rates at Month 3 and Month 6 were significantly different for both tofacitinib doses compared to placebo (at Month 3: tofacitinib 5 mg BID vs placebo, 27.33% vs 9.55%, P<0.0001; tofacitinib 10 mg BID vs placebo, 33.98% vs 9.55%, P<0.0001; at Month 6: tofacitinib 5 mg BID vs placebo, 33.76% vs 12.74%, P<0.0001; tofacitinib 10 mg BID vs placebo, 36.57% vs 12.74%, P<0.0001).

A3921174 was a 52-week study evaluating the efficacy and safety of tofacitinib 5 and 10 mg BID compared to placebo in subjects with moderate to severe chronic plaque psoriasis in China, Korea, and Taiwan. 266 subjects were randomized to treatment. All of these 266 subjects received at least 1 dose of study medication. At Week 16, tofacitinib 10 mg BID and 5 mg BID were both superior to placebo for the response of PGA “clear” or “almost clear” and the response of Psoriasis Area and Severity Index 75 (PASI75). The

proportions of subjects achieving PGA "clear" or "almost clear" and PASI75 responses at Week 16 (full analysis set, FAS/nonresponder imputation, NRI) were statistically significant in the tofacitinib 10 mg BID (75.56% and 81.11%, respectively) and 5 mg BID (52.27% and 54.55%, respectively) treatment groups compared to the placebo group (19.32% and 12.50%, respectively) with all $p < 0.0001$.

Tofacitinib 5 mg BID and 10 mg BID both demonstrated as effective doses for the treatment of active PsA across the 2 pivotal Phase 3 studies in TNFi-naïve and TNF-IR populations and across multiple PsA disease domains (peripheral arthritis, skin manifestation, enthesitis, and dactylitis). The observed differences between tofacitinib doses were modest, inconsistent in both magnitude and direction, and not considered clinically meaningful.

Tofacitinib treatment was generally well tolerated by PsA subjects participating in the Phase 3 clinical trials in the PsA development program. No new safety findings were identified. Evidence for dose dependent differences in herpes zoster, serious infection, non-melanoma skin cancer, and laboratory abnormalities was identified in the RA and in PsO development programs. Although PsA development program was limited in size, similar trends are expected in PsA patients treated with tofacitinib.

Given that in general, the efficacy of tofacitinib 5 BID and 10 mg BID are similar and the dose response relationship for certain safety events are established in the larger RA and PsO programs, the 5 mg BID dose optimizes the risk:benefit profile in the PsA population.

As tofacitinib has demonstrated efficacy and acceptable safety in both Chinese RA and plaque psoriasis patients, and global PsA pivotal studies has demonstrated efficacy and safety, there is rationale to expect that it will be efficacious and acceptably safe in Chinese PsA patients. Based on globally recommended posology, tofacitinib 5 mg BID is selected in this protocol. Complete information on tofacitinib can be obtained from the current version of the tofacitinib Investigator's Brochure, which is the single reference safety document (SRSD) for this study. A summary of selected, relevant information is presented in this Introduction.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

- To compare efficacy of tofacitinib 5 mg BID versus placebo for treatment of rheumatological signs and symptoms of PsA in Chinese subjects with active PsA who have had an inadequate response to at least one csDMARD.

- To compare the safety and tolerability of tofacitinib 5 mg BID versus placebo in Chinese subjects with active PsA who have had an inadequate response in PsA to at least one csDMARD.

2.1.2. Secondary Objectives

- To compare physical function status after administration of tofacitinib 5 mg BID versus placebo in Chinese subjects with active PsA who have had an inadequate response in PsA to at least one csDMARD.

- To compare the effects of tofacitinib 5 mg BID versus placebo on all health outcomes measures in Chinese subjects with active PsA who have had an inadequate response to at least one csDMARD.

- To compare the efficacy of tofacitinib 5 mg BID versus placebo for the treatment of dermatological signs and symptoms of PsA in Chinese subjects who have had an inadequate response to at least one csDMARD.

2.2. Endpoints

2.2.1. Primary Endpoint

- ACR50 responder rate at Month 3.

2.2.2. Secondary Endpoints

2.2.2.1. Secondary Efficacy Endpoints

- ACR20 and ACR70 responder rates at all timepoints;

- ACR50 responder rates at all timepoints other than Month 3;

- Change from baseline (Δ) in ACR response criteria components (HAQ-DI, C-reactive protein [CRP], Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis, swollen joint count, tender/painful joint count) at all timepoints;

- HAQ-DI response defined as a decrease from Baseline ≥0.30 for subjects with Baseline HAQ-DI ≥0.30 at all timepoints; HAQ-DI response defined as a decrease from Baseline ≥0.35 for subjects with Baseline HAQ-DI ≥0.35 at all timepoints;

- Psoriatic Arthritis Response Criteria (PsARC) at Month 1, Month 3 and Month 6;

- Physician's Global Assessment of Psoriasis (PGA-PsO) at Month 1, Month 3 and Month 6;

    - PGA-PsO response of clear or almost clear and a ≥2-step improvement from Baseline for subjects with Baseline PGA-PsO ≥2;

    - ΔPGA-PsO for subjects with Baseline PGA-PsO >0;

- Psoriasis Area and Severity Index 75 (PASI75) response at Month 1, Month 3 and Month 6 for subjects with Baseline psoriatic body surface area (BSA) ≥3% and Baseline PASI >0;

- Dactylitis severity score (DSS) at Month 1, Month 3 and Month 6 for subjects with Baseline DSS >0;

    - ΔDSS;

    - Resolution of dactylitis defined as a subject achieving DSS=0;

- Enthesitis score ([using Leeds enthesitis index (LEI))] at Month 1, Month 3 and Month 6 for subjects with Baseline LEI >0;

    - ΔLEI;

    - Resolution of enthesitis defined as a subject LEI=0.

2.2.2.2. Secondary Physical Function and Health Outcome Measures

Assessed at baseline, Months 1, 3 and 6:

- Short-Form-36 Health Survey (ΔSF-36) Version 2, Acute;

- EuroQol 5-Dimension Health State Profile (ΔEQ-5D).

2.2.3. Safety Endpoints

- Incidence and severity of adverse events.

2.2.4. Other Endpoints

2.2.4.1. Other Efficacy Endpoints

- ΔDAS28-3(CRP) at all timepoints;

- Physician's Global Assessment of Psoriatic Arthritis (ΔPGA-PsA) at Month 1, Month 3 and Month 6;

- %Δ in PASI and PASI clinical sign component scores at Month 1, Month 3 and Month 6 for subjects with Baseline BSA ≥3% and Baseline PASI >0;

- %ΔBSA at Month 1, Month 3 and Month 6 for subjects with Baseline BSA >0%;

- Nail Psoriasis Severity Index (ΔNAPSI) Score at Month 1, Month 3 and Month 6 for subjects with Baseline NAPSI >0.

Health Outcome Measures Assessed at baseline, Months 3 and 6:

- Work Productivity and Activity Impairment – Psoriatic Arthritis Questionnaire (ΔWPAI-PsA).

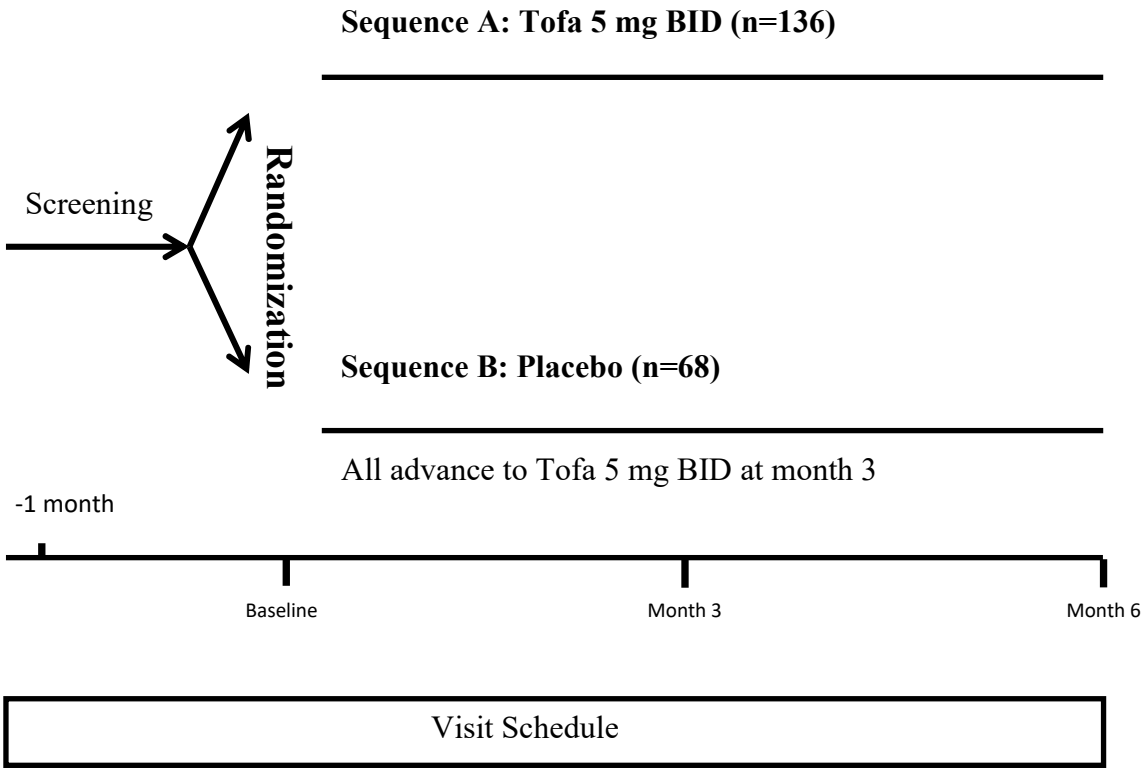
2.2.4.2. Other Safety Endpoints

- Clinical laboratory tests (eg, clinical chemistry, hematology);
- Vital sign measurements (blood pressure, pulse rate and temperature);
- Physical examinations;
- Electro-cardiogram (ECG) measurements.

3. STUDY DESIGN

This is a Phase 3 randomized, 6-month, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of tofacitinib in adult, Chinese subjects with active PsA who had an inadequate response in their PsA to at least one csDMARD. All subjects in the study will be evaluated for risk factors for venous thromboembolism.[19] See Risk Factor Check for VTE in Section 7.5.8 for tofacitinib dosing guidance when a risk factor is identified. A total of approximately 204 subjects will be randomized in a 2:1 ratio to one of the following two parallel treatment sequences. The enrollment will be monitored to cap the proportion of subjects with baseline swollen joint count ≤5 at approximately 38% (ie, approximately 78 subjects).

A schematic of the study design is shown below.



*Primary study endpoints of ACR50 will be obtained at Month 3. All subjects randomized to placebo will receive tofacitinib 5 mg BID in a blinded manner after Month 3.

During the study, subjects are required to remain on a stable dose of one csDMARD, eg, methotrexate or sulfasalazine, and should remain on that dose throughout the study.

4. SUBJECT ELIGIBILITY CRITERIA

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

PsA is a chronic inflammatory autoimmune disease characterized by joint inflammation and destruction, psoriatic skin lesions, enthesitis, dactylitis and spondylitis. A subject must meet the peripheral arthritis criteria and the ClASsification criteria for Psoriatic ARthritis[20] (CASPAR) for enrollment. However, not all of the eligible subjects will have presence of other PsA disease manifestations such as psoriasis, enthesitis or dactylitis at baseline.

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

4.1. Inclusion Criteria

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

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

2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.

   Female subjects of nonchildbearing potential must meet at least one of the following criteria:

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

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

4. The subject has signs and symptoms consistent with the diagnosis of PsA for at least 6 months and fulfills ClASsification criteria for Psoriatic ARthritis[20] (CASPAR) Criteria at screening and has evidence of active arthritis based upon number of tender/painful and swollen joints detailed in Section 4.1.1 below.

5. Ongoing treatment with a stable dose of a csDMARD (eg, methotrexate or sulfasalazine) (Section 4.1.2 below).

6. Meet all other eligibility criteria described in Sections 4.2, 4.3 and 4.4 below.

4.1.1. Active Psoriatic Arthritis

To be eligible for participation in this study, a subject must meet the following criteria:

1. To meet the CASPAR criteria, a subject must have inflammatory articular disease (joint, spine, or entheseal) with 3 points from the following 5 categories:

   a. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis. Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.† A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider. A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.

   b. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.

   c. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.

   d. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.

   e. Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

   †Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

2. The subject must have active arthritis at both screening and baseline, as defined by having both:

   a. ≥3 tender/painful joints on motion (out of 68 joints assessed); ***and***;

   b. ≥3 swollen joints (out of 66 joints assessed).

3. The subject must have active plaque psoriasis at Screening which has been diagnosed or confirmed by a dermatologist or a Sponsor-approved rheumatologist.

4.1.2. Background DMARDs

All local standard-of-care practices for the administration of permitted background DMARD therapy, including laboratory testing, contraceptive requirements, follow-up care and contraindications should be performed according to local standards of care throughout the study.

Subjects must receive permitted background csDMARDs and should remain on a stable dose of one csDMARD throughout the course of the study.

- Methotrexate: Maximum dose of 20 mg/week. Minimum duration of therapy 4 months and dose stable for 4 weeks prior to first dose of study drug. Subjects on methotrexate should be on an adequate and stable dose of folate supplementation (not less than 5 mg weekly based on folic acid, unless such doses would violate the local label guidelines or standard of care) for at least 4 weeks prior to the first dose of study drug (see Section 5.8). Subject must not have had previous serious toxicity while on methotrexate and not be expected to require evaluation for possible methotrexate toxicity (eg, require a liver biopsy for methotrexate toxicity) during the study.

- Sulfasalazine: Maximum dose of 3 g/day. Minimum duration of therapy 3 months and dose stable for 4 weeks prior to first dose of study drug.

4.2. PsA Patient Population

- Subjects who had a documented inadequate response to at least one csDMARD due to lack of efficacy or toxicity/lack of toleration.

- Subjects may have received a TNFi.

4.3. Other Inclusion Criteria

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

1. Subjects must be Chinese adults at least 18 years of age at the Screening visit.

2. No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined by **all** of the following:

    - A negative QuantiFERON-TB Gold (QFT-G) In-Tube test performed at or within 3 months prior to a given Screening visit. A negative purified protein derivative (PPD) test can be substituted for the QuantiFERON Gold (QFT-G) In-Tube test only if the central laboratory is unable to perform the test or cannot determine the results to be positive or negative and the Pfizer Study Clinician approves it, on a case by case basis. Subjects with a history of Bacille Calmette Guérin (BCG) vaccination will be tested with the QFT-G test.

    - No local QFT-G testing will be accepted for meeting the inclusion criterion.

- A chest radiograph taken at or within the 3 months prior to screening without changes suggestive of active TB infection as determined (and documented) by a qualified radiologist or pulmonologist as per local standard of care.

- No history of either untreated or inadequately treated latent or active TB infection.

- If a subject has previously received an adequate course of therapy for either latent (9 months of isoniazid or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection per local practice, neither a PPD test nor a QuantiFERON® TB Gold In-Tube®™ (QFT-G) need be obtained, but a chest radiograph must still be obtained if not done so within the prior 3 months. A subject who is currently being treated for either latent or active TB infection can only be enrolled with exclusion of close contacts of multi-drug resistant TB, documentation of an adequate treatment regimen, and prior approval of the Sponsor.

3. Subject has discontinued all disallowed concomitant medications for the required time prior to the first dose of study medication and is taking only those concomitant medications in doses and frequency allowed by the protocol (see Appendix 3). Subjects who are receiving any investigational or marketed treatment for PsA or psoriasis not mentioned elsewhere must have that treatment discontinued for 4 weeks or 5 half-lives, whichever is longer. All biologic agents not otherwise mentioned (eg, inclusion criteria #4 and exclusion criteria #16) must be discontinued for a minimum of 6 months prior to the first dose of study drug.

4. Subjects must not be receiving TNFi. Subjects on TNFi must discontinue according to the following criteria:

   - Etanercept and its biosimilar biological products (Enbrel®, Yisaipu, Qiangke, Anbainuo): Discontinued at least 4 weeks prior to the first dose of study drug;

   - Adalimumab (Humira®): Discontinued at least 10 weeks prior to first dose of study drug;

   - Infliximab (Remicade®): Discontinued at least 8 weeks prior to the first dose of study drug;

   - Golimumab (Simponi®): Discontinued at least 10 weeks prior to the first dose of study drug;

   - Certoluzimab (Cimzia®): Discontinued at least 10 weeks prior to first dose of study drug;

   - Other biosimilar biological products could follow the requirements of their reference product after confirming they have same half lives.

5. Subjects who are already taking oral corticosteroids (but not injectable) may participate in the study:

   - Oral corticosteroids: Subjects who are already receiving oral corticosteroids must be on a stable dose of ≤10 mg/day of prednisone or equivalent for 4 weeks prior to first dose of study drug.

   - Injected (eg, intraarticular, intramuscular or intravenous) corticosteroids: Discontinued 4 weeks prior to the first dose of study drug.

6. Subjects who are already taking NSAIDs/Cyclooxygenase-2 (COX-2) inhibitors may participate in the study provided that the dose is stable for one week prior to first dose of study drug.

7. Subjects are to discontinue active psoriasis treatments prior to being enrolled in the study.

   - Biologics: All biologic agents, which includes investigational and marketed agents, and are not otherwise mentioned (eg, exclusion criteria #16) must be discontinued for a minimum of 6 months prior to first dose of study drug.

   - Topical treatments that could affect psoriasis, eg, corticosteroids, tars, keratolytics, anthralin, vitamin D analogs, and retinoids must be discontinued at least 2 weeks prior to first dose of study drug. Exceptions- the following topical treatments are allowed: non-medicated emollients for use over the whole body; topical steroids including hydrocortisone and hydrocortisone acetate ≤1% for the palms, soles, face, and intertriginous areas only; tar and salicylic acid preparations for the scalp only and shampoos free of corticosteroid for the scalp only.

   - Ultra-violet B (UVB) (narrowband or broadband) phototherapy must be discontinued at least 2 weeks prior to first dose of study drug. Psoralens + UVA phototherapy (PUVA) must be discontinued at least 4 weeks prior to first dose of study drug.

4.4. Exclusion Criteria

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

1. Currently have non-plaque forms of psoriasis, eg erythrodermic, guttate or pustular, with the exception of nail psoriasis, which is allowed.

2. Investigator 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, including their family members, directly involved in the conduct of the study.

3. Participation in other interventional studies involving investigational drug(s) (Phases 1-4) within 4 weeks before the current study begins and/or during study participation. Participation in any observational studies during study participation is permitted.

4. Pregnant female subjects, breastfeeding female subjects, female subjects of child-bearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least one ovulatory cycle after last dose of investigational product. Women of childbearing potential must test negative for pregnancy prior to enrollment in this study. (Further description of the requirements and a list of contraceptives considered highly effective and acceptable for use in this study will be found in Section 4.6.6).

5. Blood dyscrasias within 3 months prior to the first dose of study drug including confirmed:

   a. Hemoglobin <10 g/dL (<100 g/L);

   b. White blood cell count <3.0 x 10^9/L (<3000 mm^3);

   c. Absolute neutrophil count <1.5 x 10^9/L (<1500 mm^3);

   d. Absolute lymphocyte count of <1.0 x 10^9/L (<1000/mm^3);

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

6. Estimated Creatinine Clearance <40 ml/min based on Cockcroft-Gault equation (Appendix 2).

7. Total bilirubin, aspartate amniotransferase (AST) or alanine aminotransferase (ALT) more than 1.5 times the upper limit of normal (ULN) at screening visit.

8. Current or recent history of a severe, progressive or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic (including hypercholesterolemia), endocrine, pulmonary, cardiovascular, or neurologic disease.

9. History of any autoimmune rheumatic disease other than PsA (including systemic lupus erythematosis, mixed connective tissue disease, scleroderma, polymyositis) or known diagnosis of fibromyalgia, without approval by Sponsor. Also excluded are subjects with prior history of, or current, rheumatic inflammatory disease other than PsA (eg, gout, reactive arthritis, chronic Lyme disease) without approval by Sponsor.

10. A subject with known immunodeficiency disorder or a first degree relative with a hereditary immunodeficiency.

11. Functional Class IV as defined by the American College of Rheumatology classification of functional status for RA, ie, limited in ability to perform usual self-care, vocational and avocational activities.[21]

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

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

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

15. History of active infection (including localized infection):

    - Requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 6 months prior to the first dose of study medication;

    - Requiring oral antimicrobial therapy within 2 weeks prior to the first dose of study medication.

16. Any prior treatment with non-B cell-specific lymphocyte depleting agents/therapies [eg, alemtuzumab (Campath®), efalizumab (Raptiva®)], alkylating agents (eg, cyclophosphamide or chlorambucil), or total lymphoid irradiation. Subjects who have received rituximab or other selective B-lymphocyte depleting agents (including experimental agents) are eligible if they have not received such therapy for at least 1 year prior to first dose of study drug and have normal $CD19/20^{+}$ counts by fluorescence activated cell sorter (FACS) analysis.

17. Any subject who has been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of study medication or is to be vaccinated with these vaccines at any time during treatment or within 6 weeks following discontinuation of study medication. (See Section 4.6.2. Vaccine Guidelines for further information regarding avoidance of household contacts who may be vaccinated).

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

19. History of alcohol or drug abuse unless in full remission for greater than 6 months prior to first dose of study medication.

20. Screening 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities (as determined by aqualified cardiologist) which may affect subject safety (eg, pattern of acute myocardial infarction, acute ischemia or serious arrhythmia) or interpretation of study results (eg, continuously paced ventricular rhythm or complete left bundle branch block).

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

22. Significant trauma or surgery procedure within 1 month prior to first dose of study medication, or any planned elective surgery during the study period.

23. A subject requiring prohibited concomitant medications (See Appendix 3).

24. A subject known to be infected with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) or any chronic infection.

25. Hepatitis B surface antigen positive ($HBsAg^+$) is exclusionary; subjects who are $HBsAg^-$ but Hepatitis B core antibody positive ($HBcAb^+$) must undergo further testing and be Hepatitis B surface antibody positive ($HBsAb^+$) to be considered for enrollment.

26. Subjects who are $HCVAb^+$ must undergo further testing for HCV RNA and are allowed to enroll if negative.

27. A subject with evidence of skin conditions (eg, eczema) at the time of the screening or baseline visit that would interfere with evaluation of psoriasis.

28. A subject that is considered at increased risk for gastrointestinal perforation (eg, patient with diverticulitis) by the Investigator or Sponsor.

29. Any factors or clinical characteristics potentially related to the risk of venous thromboembolism (see Section 7.5.8, Risk Factor Check for VTE) 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.

30. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior 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.

31. A subject who has previously participated in any study of tofacitinib or has any previous clinical experience of tofacitinib.

32. A subject who, in the opinion of the investigator or Pfizer (or designee), will be uncooperative or unable to comply with study procedures.

4.5. Randomization Criteria

A subject who has signed an informed consent document to participate in the study, has undergone all screening procedures, and meets all inclusion and no Exclusion Criteria for participation in the study at the baseline visit, may be randomized into this study. Subjects will be randomized in a 2:1 ratio to one of the two parallel treatment sequences. A centralized computer-generated randomization schedule will be used to assign subjects to the treatment groups. Subjects will be assigned a subject identification number in the order of their screening for the study. The identifying number will be retained throughout the study.

At Month 3, subjects originally randomized to Treatment Sequence B will be advanced to tofacitinib 5 mg BID treatment in a blinded fashion for the remainder of the study. Study blinding will be maintained for all groups throughout the study (see Section 6.2).

4.6. Life Style Guidelines

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

- On designated study visit days, comply with fasting requirements for at least 9 hours prior to visit (See Section 6).
- On study visit days, do not smoke or ingest caffeine (eg, tea, coffee, some soft drinks/colas/energy drinks and power bars) during the 30 minutes prior to blood pressure and pulse (heart) rate measurements.
- On study visit days, showering or bathing is permitted prior to attending the study visit, but do not moisturize.
- On study visit days, take prescribed permitted concomitant medication, as needed, prior to the study visit, if it can be administered with water only.
- Avoid vaccinations with live or attenuated live vaccines and contact with individuals who have recently received live or attenuated live vaccines (See Section 4.6.2).
- Discontinue and avoid using certain medications and treatments (see Inclusion Criteria and list of prohibited medications Appendix 3).
- Contact the study site investigator if there are any changes or additions to concomitant medications.
- Avoid having elective surgery (See Section 4.6.5).
- Agree to use acceptable contraceptive methods per Section 4.6.6.

4.6.1. Non-Pharmacologic Interventions

The subject should continue all non-pharmacological therapies, such as physical therapy, as indicated. However, the subject should avoid changing the type or intensity of therapy or initiating new therapy until after Month 3, but preferably after Month 6 visit.

4.6.2. Vaccine Guidelines

4.6.2.1. Subject Vaccination

Subjects should be vaccinated appropriately prior to screening for the study.

Vaccination with any live vaccine (whether attenuated or not) is prohibited during the study and for 6 weeks after last dose of study drug. Vaccines that are allowed would include: inactivated, subunit, toxoid and DNA. It is recommended that subjects be up to date on vaccinations prior to enrollment in this study.

4.6.2.2. Household Contact with Others Vaccinated

During the study and for 6 weeks following the last dose of study drug, subjects should avoid routine household contact with children or adults who have been vaccinated with live or attenuated live vaccines. Some of these vaccines include varicella ("chickenpox") vaccine, oral polio vaccine, and the inhaled flu vaccine. Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is potential risk that the virus may be transmitted. General guidelines suggest that exposure should be avoided following vaccination with these vaccines for the stated period:

a. Varicella or attenuated typhoid fever vaccination for 4 weeks following vaccination;

b. Oral polio vaccination for 6 weeks following vaccination;

c. Attenuated rotavirus vaccine for 10 days following vaccination;

d. FluMist® (inhaled flu vaccine) for 1 week following vaccination.

4.6.3. 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 CYP3A inhibition or induction. Otherwise, herbals with pharmaceutical properties must be discontinued for at least 4 weeks prior to first dose of study drug, 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). Please direct any questions to the Sponsor.

Glucosamine sulfate and chondroitin sulfate are allowed in the study but should be stably dosed beginning at least 1 week prior to first dose of study medicine.

4.6.4. Fasting Visit Requirements

On visit days when fasting lipid panels are scheduled to be collected, all subjects should refrain from all food and liquids (water and medications permitted, if appropriate) for at least 9 hours prior to scheduled safety laboratory tests. Visits that require fasting are Baseline (Visit 1), Month 1 (Visit 3), Month 3 (Visit 5), Month 4 (Visit 6), Month 6 (Visit 7), Early Termination and Follow-Up Visit (if required).

4.6.5. Elective Surgery

During the course of this study, no elective surgery should be scheduled and will be considered a protocol deviation if it occurs. Elective surgery should only be scheduled >1 month before study start or delayed to after the study.

Subjects who do require surgery should temporarily discontinue study drug for one week prior to the surgical procedure and remain off study drug after the surgical procedure until sutures/staples are removed. If absorbing sutures or chemical closure methods are utilized, study drug can be resumed when the operative site is sufficiently healed and risk of infection is minimal.

4.6.6. Contraceptive

The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his/her partner(s) from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP).

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

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:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;

    - Intravaginal;

    - Transdermal;

    - Injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;

    - Injectable.

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

No effects of tofacitinib have been seen in male fertility or offspring of dosed males in any preclinical studies conducted to date. However, male subjects who are on background medications (including DMARDs) that require male contraceptive precautions according to the local drug label must do so if they are sexually active with women of child bearing potential during the study and after therapy for 3 months or for the duration specified in the local drug label. Subjects who are receiving concomitant drugs (eg, methotrexate) that require contraceptive precautions in their labeling should follow the most stringent precautions.

4.7. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list that is located in the study portal.

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

4.8. Rater Qualifications

Individuals who perform the Physician's Global Assessment of Arthritis and Physician's Global Assessment of PsA must be a physician or other healthcare professional who is competent to peform the assessments. Individuals who perform Physician's Global Assessment of Psoriasis will be similarly qualified, however, with previous psoriasis clinical experience. The following procedures require a health care professional who is competent to perform the assessments: tender/painful joint count; swollen joint count; assessment of dactylitis; assessment of enthesitis; PASI, body surface area (BSA); and NAPSI.

Completion of the study "Delegation Log" (including date of training completion) for the assessors will constitute verification that the individual is competent to conduct these assessments.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator 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).

For this study, the investigational products are Tofacitinib 5 mg tablets and Placebo tablets that match tofacitinib tablets.

5.1. Allocation to Treatment

Study Treatments:

Subjects are randomized to receive either tofacitinib 5 mg BID or placebo. At Month 3, all subjects receiving placebo will be advanced to tofacitinib 5 mg BID in a blinded manner for 3 months. Investigators, subjects and sponsor will remain blinded through the entire duration of the study until database release.

Subjects will be randomized in a 2:1 ratio to one of the following two parallel treatment sequences:

- **Treatment Sequence A**: Tofacitinib 5 mg BID;
- **Treatment Sequence B**: Placebo → Tofacitinib 5 mg BID at Month 3;

The following medication will be supplied by Pfizer Inc:

- Tofacitinib 5 mg tablets;
- Placebo tablets that match tofacitinib tablets.

Treatment Sequence	Treatment	Planned Number of Randomized Subjects
Sequence A	Tofacitinib 5 mg BID	136
Sequence B	Placebo x 3 Months → Tofacitinib 5 mg BID[1]	68

[1.] At Month 3, subjects randomized into Treatment Sequence B will receive tofacitinib 5 mg BID in a blinded manner through Month 6.

Subjects will be randomized in a 2:1 ratio to Treatment Sequence A or Treatment Sequence B. Assignment to treatment sequence will be accomplished using an automated web/telephone randomization system (IVRS). The IVRS system contains the randomization schedule. At the Screening Visit, the investigative site will contact the IVRS (online or by telephone call). The site will enroll the subject into the IVRS by indicating minimal information sufficient to distinguish one subject from another (eg, date of birth and gender) and receive a unique subject identification number. At the Baseline/Day 1 (Visit 1), the system will associate that subject with the next available treatment on the randomization schedule and provide the randomization number. The system will then give the investigative site a code which corresponds to study drug that was previously shipped to the site and is in the site's inventory ready to be dispensed. This code corresponds to the study drug of that period in the treatment sequence in which the subject has just been randomized.

The site will call the system on study visit days when study drug is to be dispensed. The randomization schedule will contain sufficient treatment allocations to allow for over-enrollment; however when a sufficient number of subjects have enrolled, the randomization part of the system will be stopped. The part of the system that supplies codes will continue until the last subject randomized has been dispensed the last supply of study drug.

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 an automated web/telephone randomization system provided by the Sponsor for breaking the blind. Blinding should only be broken in emergency situations for reasons of subject safety. The Investigator should attempt to contact Pfizer before breaking the blind. When the blind for a subject has been broken, the reason must be fully documented.

5.3. Subject Compliance

Subject compliance with dosing administration will be verified by accounting of returned containers and trial medication at visits Week 2 and Month 1, 2, 3, 4 and 6 or Early Termination. When trial medication is administered at the research facility, it will be administered under the supervision of study personnel.

Compliance of the study drug will be monitored by the accounting of unused medication and will be documented. Subjects who demonstrate <80% compliance should be counseled by the investigator or designee and ensure steps are taken to improve compliance. The subjects who are determined by investigators or sponsors to be unable to comply with dosage

regimen, should be withdrawn. Subjects who are <80% compliant with dosage regimen for any two consecutive visit periods should be withdrawn from the study.

If the subject overconsumes study drug (>120% of medication, intentional or accidental) the investigator or designee is to counsel the subject and ensure correct understanding of the study drug dosing regimen. The investigator should contact the Pfizer Study Clinician promptly with any over-compliance that may potentially impact the safe use of study drug or that may result in a serious adverse event.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

The Sponsor will provide tofacitinib as 5 mg tablets with corresponding matching placebo tablets. The blinded assignment will consist of one active 5 mg tablet for the 5 mg dose sequence or one placebo tablet for the placebo sequence. Tablets will be supplied in bottles as appropriate for the treatment sequence to which the subject is randomized. The subject will be instructed to take one tablet from assigned bottle twice daily. Each bottle will be labeled as appropriate for this placebo-controlled, double-blind study.

5.4.2. Preparation and Dispensing

Study drug will be dispensed in bottles. At each dispensing visit, subjects will receive a sufficient quantity of study drug to last until their next scheduled dispensing visit.

5.5. Administration

The study drug will be labeled in such a manner that the subject and study staff will be unable to determine from the dispensed packaging to which treatment sequence the subject is assigned. Each bottle will be labeled with appropriate directions for administration.

Study drug will be dispensed to subjects for self administration after appropriate training and specific instructions will be provided. A dosing diary will be provided to the subjects to record the administration of study drug.

On the day of a scheduled study visit, the study drug should be taken after completing all the study procedures at the clinic.

Tofacitinib tablets and matching placebo for oral administration will be dispensed in bottles and may be taken with or without food. Subjects will swallow the study medication whole, and will not manipulate or chew the medication prior to swallowing. Subjects will be instructed to take their study drug twice daily (once in the morning and once in the evening approximately 12 hours apart) at approximately the same times each day.

If the investigator deems it necessary to withhold study medication to treat a non-serious infection or other medical condition, temporary withholding is permitted for up to 5 days which should be well documented in medical record and case report form (CRF). If study medication interruption exceeding 5 days is required for a medical reason, the investigator must contact the Pfizer Study Clinician for approval.

Temporary withholding of the study medication, as described above, is permitted once during the study without obtaining prior approval from the Pfizer Study Clinician. Any additional request(s) for temporary withholding of study drug require(s) documented approval by the Pfizer Study Clinician.

5.6. Investigational Product Storage

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

Investigational product should be stored in its original container and in accordance with the drug label. See the drug label for storage conditions of the product. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt and throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

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

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer 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 storage requirements for take home medications including how to report temperature excursions.

5.7. Investigational Product Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies. All investigational products will be accounted for using a drug accountability form/record.

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

All study drug bottles must be returned to the investigator by the subject and the investigator will return the bottles to Pfizer.

5.8. Concomitant Medication(s)

It is important to be aware of, and document, **all** concomitant medications including: prescription, non-prescription (ie, over-the-counter) and herbal medications.

A subject who is receiving an allowed concomitant medication for any reason must be on a locally-approved medication and dose that is considered standard-of-care for the treated indication, and this must be documented in the case report form. Subjects are not allowed on any other investigational drug during the study.

It is recommended that subjects avoid changing non-prohibited prescription or non-prescription drugs, vitamins, and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication and prior to study visits unless otherwise noted below, throughout the study.

Medications that are taken in the Screening period (after informed consent is obtained and before the first dose of study drug) will be documented as prior medications. Medications taken after the first dose of study drug has been administered will be documented as concomitant medications. All concomitant medications taken during the study must be recorded in the study records with indication (as appropriate), daily dose, administration route and start and stop dates of administration. Subjects will be queried about concomitant medications at each study visit.

Minimum guidelines for folate supplementation during study: Subjects on methotrexate **must** receive folate supplementation according to local methotrexate label guidelines and standard of care. A minimum of 5 mg weekly based on folic acid should be given unless local guidelines or standard of care state otherwise.

5.8.1. Stable Background Pain or Other Arthritis Therapy

For csDMARDs which have been discontinued prior to first dose of study drug, the following minimum washout criteria apply: Methotrexate, Sulfasalazine: must have been discontinued for 4 weeks prior to the first dose of study drug.

Subjects taking permitted csDMARDs (eg, methotrexate (≤20 mg/week), sulfasalazine (≤3 gm/day)), nonsteroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), and/or corticosteroids (≤10 mg prednisone mg/day) should remain on the same dose regimen throughout the study except if adjustment is needed to protect the subject's safety. Daily dosages of NSAIDs/COX-2 inhibitors, corticosteroids, opioids, and acetaminophen/paracetamol must be stable for 1 week prior to first study dose and must remain so during the study treatment period through Month 3 except if adjustment is needed to protect a subject's safety. Daily dosage of NSAIDs/COX-2 inhibitors, corticosteroids, opioids and acetaminophen/paracetamol must not be modified within the 24 hours prior to any study visit, except if adjustment is needed to protect a subject's safety.

The total daily dose of acetaminophen may not exceed 2.6 grams per day, and the total daily dose of opioid may not exceed the potency equivalent of 30 mg of orally-administered morphine (See Appendix 4 and Appendix 5).

Intravenous or intramuscular corticosteroids are not allowed during this study either as a stable concomitant medication or as rescue medication. Intra-articular corticosteroids and hyaluronate sodium are allowed but only as rescue therapy (See Appendix 5).

5.8.2. Other Medications

Prohibited drugs and dietary supplements must be discontinued at least 30 days or 5 half lives (whichever is longer) before the first dose of study drug. Herbals with pharmaceutical properties are allowed only if there is acceptable evidence of no CYP3A inhibition or induction. Otherwise, herbals with pharmaceutical properties must be discontinued for at least 4 weeks prior to first dose of study drug, 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). A list of prohibited drugs with specific discontinuation recommendations is listed in Appendix 3. Please note that certain medications should be discontinued at least 30 days prior to first dose of study drug based on the half-life of these drugs and amiodarone should be discontinued at least 290 days prior to first dose of study drug based on a half-life of 58 days. All concomitant medication taken during the study must be recorded with indication (as required), daily dose, administration route and start and stop dates of administration.

Traditional Chinese Medicine: ***Tripterygium wilfordii***, or **léi gōng téng** sometimes called **thunder god vine** but more properly translated **thunder duke vine**, is a vine used in traditional Chinese medicine for treatment arthritis, and is prohibited during the study.

5.9. Rescue Therapy

The only medications that are allowed for rescue are listed in Appendix 5.

Increases of acetaminophen/paracetamol and opioids are allowable as rescue medication for no more than 10 consecutive days. Acetaminophen/paracetamol may be added or increased to a maximum of 2.6 gm/day. Opioids may be added or increased to a maximum potency equivalent of 30 mg of orally-administered morphine. 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 total acetaminophen/paracetamol dose will exceed 2.6 gm/day.

Subjects who require rescue for more than 10 consecutive days should be discontinued from the study. There is no limit to the duration of nonconsecutive use of rescue medications. In addition, subjects may not be dosed with rescue medication during the 24 hours prior to a study visit. Baseline stable use acetaminophen/paracetamol or opioids should NOT be discontinued in advance of study visits.

A maximum of 40 mg methylprednisolone or equivalent of intraarticular corticosteroids will be allowed as rescue medication at or after the Month 3 visit; intraarticular corticosteroid injections should not be performed within the 4 weeks prior to a study visit. The total allowed intraarticular corticosteroid dose may be divided into separate injections (eg, 20 mg, 20 mg). Intra-articular hyaluronate sodium injections may be administered for indications in accordance with the local label at or after the Month 3 visit in no more than two joints. If performed at Month 3 visit, intra-articular injections must be given after the assessments are completed.

6. STUDY PROCEDURES

6.1. Screening

All the Days/Months are relative to start of study treatment (Day 1). For the purpose of this protocol, 1 Month is defined as 28 calendar days.

Subjects will be screened within 28 (+10) days prior to administration of study medication to confirm that they meet the entrance criteria for the study. Subjects may not be rescreened unless approved by the Sponsor. Rescreening of subjects will be allowed in a limited number of circumstances as determined by the Pfizer Study Clinician (eg, subject requires washout of prohibited medications, requires antimicrobial therapy within 2 weeks prior to the first dose of study medication, requires emergency surgery) and should be confirmed with the Pfizer Study Clinician when rescreening can occur.

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 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 4 week screening duration. For these subjects, written informed consent and a unique subject number obtained through the IVRS system must be obtained prior to initiation of the washout period. No other screening activities should be performed at this time. These subjects should return for a Screening Visit within the 4 weeks prior to Baseline/Day 1, at which time all screening procedures should be completed.

Subjects are required to fast for at least 9 hours prior to the visit.

If the Mantoux PPD tuberculin skin test is given, subject must return 48-72 hours post test for induration evaluation.

The following procedures will be performed:

- Informed consent;
- Confirmation of PsA diagnosis: The subject must have a diagnosis of PsA based upon the CASPAR Criteria (See Section 4). PsA disease subtype will be documented in case report form (CRF);
- Medical history: Include history of previous vaccinations, specifically influenza, pneumococcal, and zoster. The medical history should also include smoking status, average weekly alcohol consumption, and family history of premature coronary heart disease (CHD). Premature coronary heart disease is defined as CHD in a male first-degree relative first observed at <55 years or CHD in female first-degree relative first observed at <65 years;
- Prior medications: Current and prior Traditional Chinese medicine, *Tripterydium hypoglaucum* (thunder god vine), requires a 4 week washout period prior to first dose of study treatment. Current and prior medications (noting exclusions and required DMARD restrictions), including a complete history of all DMARDs (including biologics) ever taken with reasons for discontinuation (those taken during the 1 year prior to the first dose of study drug should include dose and duration of treatment). Complete history of all drugs (including nonprescription drugs, vitamins, and dietary supplements), taken within 4 weeks prior to screening procedures; Complete physical examination (plus Height): Weight, height, general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (presence of peripheral edema), abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes;
- Vital signs: blood pressure, pulse rate and temperature (tympanic, oral or temporal preferred);

- PsA Disease Activity: Tender/Painful Joint Count (68), Swollen Joint Count (66);
- Psoriasis Dermatological Assessment: Active plaque psoriasis;
- Risk factor check for venous thromboembolism (see Section 4.4 – Number 30);
- Laboratory testing:
  - Hematology, Urinalysis, Chemistry Panel, HIV Serology, HBsAg, HBcAb, HCV Ab, C-Reactive Protein (CRP), and Prothrombin time (PT/INR). Screening lab tests may be repeated a single time if the initial result is inconsistent with previous documented subject laboratory history;
  - Urine Pregnancy Test (for women of childbearing potential only);
  - Serum FSH concentrations (optional, see Section 4.1) for postmenopausal females who are not on hormone replacement therapy and with no prior history of hysterectomy;
  - QuantiFERON-Gold®™ or Mantoux PPD tuberculin skin test: Must be performed unless previously tested and documented within 3 months of screening visit or unless subject has previously received an adequate course of therapy for either latent or active TB infection. If the Mantoux PPD tuberculin skin test is done, the subject must return 48-72 hours post test for evaluation;
- 12-lead electrocardiogram;
- Radiograph of chest: Unless performed within 3 months of screening visit and review documented by radiologist or pulmonologist per local standard of care;
- Monitoring of adverse events.

6.2. Study Period

Subjects who have met all the Inclusion Criteria and have no Exclusion Criteria present may participate in the study.

Blood collection for laboratory testing requiring a fasting state (at least 9 hours) may be taken up to 48 hours following the Baseline/Day 1 visit or up to 48 hours following other post-baseline double-blind study period visits as necessary to ensure samples are collected in a fasting state. If the subject has not fasted for at least 9 hours, the visit should be rescheduled to occur within 48 hours in the fasting state.

Subjects should complete the patient reported outcome (PRO) questionnaires at the clinic prior to any other study procedures. This sequence of study procedures will reduce the risk of inadvertently introducing bias in a subject's responses through study staff interactions. In the unlikely event that a PRO questionnaire(s) is not able to be administered by the study site

staff and completed by the subject at the clinic visit, the PRO questionnaire(s) should not be administered.

All rheumatological and dermatological assessments will be performed by qualified, trained assessors who are blinded to the subject's safety data, previous efficacy data and treatment randomization. To ensure consistency and reduce intra-individual variability, the same qualified assessor should score all evaluations for a particular assessment for a given subject throughout the study.

6.2.1. Visit 1, Baseline Day 1

Subjects are required to fast for at least 9 hours prior to the visit, however, blood collection for laboratory testing may be taken up to 48 hours following the Baseline/Day 1 visit as necessary to ensure the samples are collected in a fasting state.

All PROs should be performed before any other study procedures. These include the following:

- Patient's Assessment of Arthritis Pain (Visual Analog Scale, VAS);
- Patient's Global Assessment of Arthritis (VAS);
- HAQ-DI;
- SF-36 Version 2 (Acute);
- EuroQol 5 Dimensions (EQ-5D);
- Work Productivity and Activity Impairment – Psoriatic Arthritis Questionnaires (WPAI-PsA).

Procedures that will be performed prior to randomization on Visit 1, Day 1 for baseline include:

- Complete Physical Examination: Weight, general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (presence of peripheral edema), abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes;
- Vital signs: blood pressure, pulse rate and temperature (tympanic, oral or temporal preferred);
- Waist and hips circumference;
- Risk factor check for venous thromboembolism (see Section 7.5.8).

- Laboratory testing:
  - Hematology, Chemistry Panel, Hemoglobin A1c (HbA1c), C-Reactive Protein (CRP), Rheumatoid Factor (RF), Cyclic Citrullinated Peptide Antibody (CCP), Lipid Profile (fasting), Urinalysis; Lymphocyte subset analysis (FACS);
  - Urine Pregnancy Test (for women of childbearing potential only);
- Contraception check: Confirm and document that proper contraception is being used.
- Clinical Evaluation of Rheumatology Endpoints (by blinded assessor):
  - Tender/painful joint counts (68);
  - Swollen joint counts (66);
  - Physician's Global Assessment of Arthritis (VAS);
  - Assessment of dactylitis using DSS;
  - Assessment of enthesitis using LEI.
- Clinical Evaluation of Dermatology Endpoints (by blinded assessor):
  - PGA-PsO;
  - PASI;
  - BSA;
  - NAPSI.
- Clinical Evaluation of Rheumatology and Dermatology Endpoint (by blinded assessor): PGA-PsA (VAS);
  - Randomization;

Procedures that will be performed after randomization on Visit 1, Day 1 include:

- Drug and dosing diary dispensing;
- Monitoring of adverse events and concomitant medication;
- Observe subject taking the study drug following completion of all the study procedures at the clinic with the record logged in the dosing CRF, and also make a record of csDMARD taking.

6.2.2. Visit 2, Week 2, Day 15

There is a ±3 day window for this visit.

All PROs should be completed prior to any other study procedures. These include the following:

- Patient's Assessment of Arthritis Pain (VAS);
- Patient's Global Assessment of Arthritis (VAS);
- HAQ-DI.

Procedures that will be performed include:

- Targeted physical examination (weight, examination of heart, lungs, abdomen, lower extremities and lymph nodes);
- Vital signs: blood pressure, pulse rate and temperature (tympanic, oral or temporal preferred);
- Risk factor check for venous thromboembolism (see Section 7.5.8);
- Laboratory testing: Urine Pregnancy Test (for women of childbearing potential only), CRP;
- Contraception check: Confirm and document that proper contraception is being used;
- Clinical Evaluation of Rheumatology Endpoints:
  - Tender/Painful Joint Counts (68);
  - Swollen Joint Count (66);
  - Physician's Global Assessment of Arthritis (VAS);
- Monitoring of adverse events and concomitant medications. Record any modifications, deletions or additions;
- Dosing diary check and Drug accountability;
- Instruct subject to bring the bottles with them to the visit.

6.2.3. Visit 3, Month 1, Day 29

There is a ±3 day window for this visit.

Subjects are required to fast for at least 9 hours prior to the visit. Blood collection may be taken up to 48 hours following this visit as necessary to ensure samples are collected in a fasted state.

All PROs should be performed before any other study procedures. These include the following:

- Patient's Assessment of Arthritis Pain (VAS);
- Patient's Global Assessment of Arthritis (VAS);
- HAQ-DI;
- SF-36;
- EQ-5D.

Procedures that will be performed include:

- Vital signs: blood pressure, pulse rate and temperature (tympanic, oral or temporal preferred);
- Risk factor check for venous thromboembolism (see Section 7.5.8);
- Laboratory testing: Hematology, Chemistry Panel, CRP, Urinalysis, Lipid Panel (fasting), Urine Pregnancy Test (for women of childbearing potential only);
- Contraception check: Confirm and document that proper contraception is being used;
- Targeted physical examination (weight, examination of heart, lungs, abdomen, extremities and lymph nodes).
- Clinical Evaluation of Rheumatology Endpoints (by blinded assessor):
    - Tender/Painful Joint Counts (68);
    - Swollen Joint Count (66);
    - Physician's Global Assessment of Arthritis (VAS);
    - Assessment of of dactylitis using DSS;
    - Assessment of enthesitis using LEI.

- Clinical Evaluation of Dermatology Endpoints (by blinded assessor):
  - PGA-PsO;
  - PASI;
  - BSA;
  - NAPSI.
- Clinical Evaluation of Rheumatology and Dermatology Endpoint (by blinded assessor): PGA-PsA (VAS);
- Monitoring of adverse events and concomitant medications. Record any modifications, deletions or additions;
- Dosing diary check and Drug accountability;
- Instruct subject to bring the bottles with them to the visit.

6.2.4. Visit 4, Month 2, Day 57

There is a ±7 day window for this visit.

Subjects are required to fast for at least 9 hours prior to the visit. Blood collection may be taken up to 48 hours following this visit as necessary to ensure samples are collected in a fasted state.

All PROs should be completed prior to any other study procedures. These include the following:

- Patient's Assessment of Arthritis Pain (VAS);
- Patient's Global Assessment of Arthritis (VAS);
- HAQ-DI.

Procedures that will be performed include:

- Targeted physical examination (weight, examination of heart, lungs, abdomen, lower extremities and lymph nodes);
- Vital signs: blood pressure, pulse rate and temperature (tympanic, oral or temporal preferred);
- Risk factor check for venous thromboembolism (see Section 7.5.8);

- Laboratory testing: Urinalysis, Hematology, Chemistry panel, CRP, Urine pregnancy test (for women of childbearing potential only);
- Contraception check: Confirm and document that proper contraception is being used.
- Clinical Evaluation of Rheumatology Endpoints:
  - Tender/Painful Joint Counts (68);
  - Swollen Joint Count (66);
  - Physician's Global Assessment of Arthritis (VAS).
- Monitoring of adverse events and concomitant medications. Record any modifications, deletions or additions;
- Dosing diary check and Drug accountability;
- Instruct subject to bring the bottles with them to the visit.

6.2.5. Visit 5, Month 3, Day 85

There is a ±7 day window for this visit.

Subjects are required to fast for at least 9 hours prior to this visit. Blood collection may be taken up to 48 hours following this visit as necessary to ensure samples are collected in a fasted state.

All PROS should be completed prior to any other study procedures. These include the following:

- Patient's Assessment of Arthritis Pain (VAS);
- Patient's Global Assessment of Arthritis (VAS);
- HAQ-DI;
- SF-36 Version 2 (Acute);
- EQ-5D;
- WPAI-PsA.

Procedures that will be performed include:

- Targeted physical examination (weight, examination of heart, lungs, abdomen, lower extremities, and lymph nodes);

- Vital signs: blood pressure, pulse rate and temperature (tympanic, oral or temporal preferred);
- Risk factor check for venous thromboembolism (see Section 7.5.8);
- Laboratory testing: Hematology, Chemistry Panel, CRP, HbA1c, Lipid Panel (fasting), Urinalysis; Lymphocyte subset analysis (FACS), Urine Pregnancy Test (for women of childbearing potential only);
- Contraception check: Confirm and document that proper contraception is being used;
- Clinical Evaluation of Rheumatology Endpoints (by blinded assessor):
  - Tender/Painful Joint Counts (68);
  - Swollen Joint Count (66);
  - Physician's Global Assessment of Arthritis (VAS);
  - Assessment of dactylitis using DSS;
  - Assessment of enthesitis using LEI.
- Clinical Evaluation of Dermatology Endpoints (by blinded assessor):
  - PGA-PsO;
  - PASI;
  - BSA;
  - NAPSI;
  - Clinical Evaluation of Rheumatology and Dermatology Endpoint (by blinded assessor): PGA-PSA (VAS).
- Monitoring of adverse events and concomitant medications. Record any modifications, deletions or additions;
- Dosing diary check and Drug accountability;
- Drug dispensing;
- Instruct subject to bring the bottles with them to the visit.

6.2.6. Visit 6, Month 4, Day 113

There is a ±7 day window for this visit.

Subjects are required to fast for at least 9 hours prior to the visit. Blood collection may be taken up to 48 hours following this visit as necessary to ensure samples are collected in a fasted state.

All PROs must be performed before any other study procedures. These include the following:

- Patient's Assessment of Arthritis Pain (VAS);
- Patient's Global Assessment of Arthritis (VAS);
- HAQ-DI.

Procedures that will be performed include:

- Vital signs: blood pressure, pulse rate and temperature (tympanic, oral or temporal preferred);
- Risk factor check for venous thromboembolism (see Section 7.5.8);
- Laboratory testing: Hematology, Chemistry Panel, CRP, Lipid Panel (fasting), Urinalysis, Urine Pregnancy Test (for women of childbearing potential only);
- Contraception check: Confirm and document that proper contraception is being used;
- Targeted physical examination (weight, examination of heart, lungs, abdomen, lower extremities, and lymph nodes).
- Clinical Evaluation of Rheumatology Endpoints (by blinded assessor):
    - Tender/Painful Joint Counts (68);
    - Swollen Joint Count (66);
    - Physician's Global Assessment of Arthritis (VAS).
- Monitoring of adverse events and concomitant medications. Record any modifications, deletions or additions;
- Dosing diary check and Drug accountability.

6.2.7. Visit 7, Month 6, Day 169 or Early Termination Visit

There is a ±7 day window for the Month 6 visit.

Subjects are required to fast for at least 9 hours prior to the visit. Blood collection may be taken up to 48 hours following this visit as necessary to ensure samples are collected in a fasted state.

All PROs should be completed prior to any other study procedures. These include the following:

- Patient's Assessment of Arthritis Pain (VAS);
- Patient's Global Assessment of Arthritis (VAS);
- HAQ-DI;
- SF-36 Version 2 (Acute);
- EQ-5D;
- WPAI-PsA.

Procedures that will be performed include:

- Vital signs: blood pressure, pulse rate and temperature (tympanic, oral or temporal preferred);
- Risk factor check for venous thromboembolism (see Section 7.5.8);
- Laboratory testing: Hematology, Chemistry Panel, CRP, HbA1c, Lipid Panel (fasting), Urinalysis; Lymphocyte subset analysis (FACS), Urine Pregnancy Test (for women of childbearing potential only);
- Contraception check: Confirm and document that proper contraception is being used;
- Complete Physical Examination: weight, general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), extremity exam (presence of peripheral edema), abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes;
- Waist and hips circumference;
- 12-lead electrocardiogram.

- Clinical Evaluation of Rheumatology Endpoints (by blinded assessor):
  - Tender/Painful Joint Counts (68);
  - Swollen Joint Count (66);
  - Physician's Global Assessment of Arthritis (VAS);
  - Assessment of dactylitis using DSS;
  - Assessment of enthesitis using Leed's Index.
- Clinical Evaluation of Dermatology Endpoints (by blinded assessor):
  - PGA-PsO;
  - PASI;
  - BSA;
  - NAPSI;
  - Clinical Evaluation of Rheumatology and Dermatology Endpoint (by blinded assessor): PGA-PsA,
- Monitoring of adverse events and concomitant medications. Record any modifications, deletions or additions;
- Dosing diary check and Drug accountability;
- Review subject laboratory abnormalities to assess need for potential additional safety follow-up.

6.2.8. Follow-up Visit

Subjects are required to fast for at least 9 hours prior to the visit. Blood collection may be taken up to 48 hours following this visit as necessary to ensure samples are collected in a fasted state.

If a subject discontinues from or completes the study with abnormalities in hematology or clinical chemistry results which meet criteria as defined in Section 6.3.2, or a subject discontinues from the study due to an adverse event, a follow-up visit must be performed after the Early Termination study visit and at least 28 calendar days and up to 42 calendar days after last dose of study treatment. In addition, subjects who complete this study will have a follow-up visit at least 28 calendar days and up to 42 calendar days after the last administration of investigational product. The following procedures will be performed:

- Laboratory testing: Hematology, Chemistry Panel; Lipid Panel (fasting), Urine Pregnancy Test (for women of childbearing potential only);
- Risk factor check for venous thromboembolism (see Section 7.5.8);
- Contraception check: Confirm and document that proper contraception is being used;
- Adverse event reporting and concomitant medication use.

If abnormalities in hematology or clinical chemistry results are still observed at the follow-up visit, the subject must continue to be followed until the laboratory abnormality stabilizes or returns to baseline levels as approved by the Sponsor.

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 (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject return for a final visit and follow-up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response according to the definition of adverse event noted in Section 8.2.1. Withdrawal due to a subject being no longer willing to participate in the study should be distinguished from withdrawal due to "lost to follow-up" (LTFU). Every effort should be made to identify and contact subjects who are potentially LTFU. A subject should not be considered a withdrawal due to LTFU until at least 3 attempts to contact the subject by multiple methods have been unsuccessful. All methods of attempted contact with the subject must be clearly documented (dated and initialed) in the subject's source documents and recorded on appropriate CRF page. All potential LTFU subjects must be discussed with the Pfizer study team or designee prior to assigning LTFU status. If a subject discontinues from the study due to an adverse event (AE) or any abnormality in hematology or clinical chemistry results which meet the criteria as defined in Section 6.3.2, a follow-up visit must be performed within 28 days (±7 days) of last dose of study treatment. The investigator must determine and document the primary reason for subject withdrawal.

If a subject has any clinically significant, treatment-emergent, abnormalities at the conclusion of the study, the Sponsor (or designated representative) should be notified and every effort should be made to arrange follow-up evaluations at appropriate intervals to document the course of the abnormality. All abnormal laboratory events of clinical significance should be followed until the laboratory values have returned to normal or baseline levels.

6.3.1. Monitoring Criteria

The following laboratory abnormalities require prompt retesting, ideally within one week:

- Any single hemoglobin value that drops >2 g/dL (or >20 g/L) below baseline;
- Absolute neutrophil count <1.2 x 10^9/L (<1200/mm^3);
- Absolute lymphocyte counts <0.5 x 10^9/L (<500/mm^3);
- Platelet count <100 x 10^9/L (<100,000/mm^3);
- Serum creatinine increase >50% OR an absolute increase in serum creatinine >0.5 mg/dL (or 44 μmol/l) over the average of the screening and baseline values;
- Any creatine kinase (CK) >5x ULN (repeat laboratory testing should also include cardiac troponin).

If the abnormality is confirmed after re-test, follow-up should be discussed with the Sponsor and frequency of monitoring increased. Confirmation should be done based upon central laboratory results, but local laboratory results will be acceptable, particularly if these may be done more promptly.

In case of potential DILI, repeat laboratory tests should be taken within 48 hours of awareness. See Section 8.4.2 Potential Cases of Drug-Induced Liver Injury.

6.3.2. Discontinuation Criteria

Study drug will be discontinued and the subject withdrawn from the study in the event of any of the following:

- Requirement of rescue medication for more than 10 consecutive days;
- Subjects who are <80% compliant with dosage regimen for any two consecutive visit periods should be withdrawn from the study;
- Subjects interrupting study drug for more than 14 consecutive days;
- 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 (see Section 8.4.4);

- Two sequential absolute neutrophil counts $<1.0 \times 10^9$/L ($<1000/mm^3$);
- Two sequential hemoglobin values <8.0 g/dL (80 g/L) or decreases of >30% from baseline value;
- Two sequential absolute lymphocyte counts $<0.5 \times 10^9$/L ($<500/mm^3$);
- Two sequential platelet counts $<75 \times 10^9$/L ($<75,000/mm^3$);
- Two sequential AST or ALT elevations ≥3 × ULN with at least one total bilirubin value ≥2 × ULNl;[a]
- Two sequential AST or ALT elevations ≥3 × ULN accompanied by signs or symptoms consistent with hepatic injury (eg, new onset elevated PT/INR);[a]
- Two sequential AST or ALT elevations >5 × ULN, regardless of total bilirubin or accompanying signs or symptoms;[a]
- Two sequential increases in serum creatinine >50% AND an absolute increase in serum creatinine >0.5 mg/dL (44 μmol/l) over the average of the screening and baseline values;
- Two sequential creatine kinase (CK) elevations >10 × ULN, unless the causality is known not to be medically serious (eg, exercise or trauma induced);
- A confirmed positive urine pregnancy test in a woman of childbearing potential;
- Any opportunistic infections considered significant by the investigator or the Sponsor;
- Confirmed venous thromboembolism;
- Other serious or severe adverse events, in the opinion of the investigator or Sponsor. Whenever possible, the investigator should consult with a member of the Pfizer study team before discontinuation of the subject.

If a subject discontinues from the study due to abnormalities in hematology or clinical chemistry parameters which meet criteria as defined in this section, a follow-up visit must be performed within 28 days (±7 days) of last dose of study treatment. For a confirmed increase in serum creatinine of >50% and >0.5 mg/dL above the average of screening and baseline, laboratory values will be followed with retesting until the creatinine elevation has stabilized (ie, stopped increasing) over at least 3 consecutive tests obtained monthly.

a. In each case, there is a need for additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with the Sponsor or designee.

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, which may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the subject. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions that he/she has taken to ensure that normal processes are adhered to as soon as possible. Single missed assessments, if justified, would not be considered as non-adherence to protocol; reason for missed evaluation must be documented. Two or more consecutively missed assessments for any endpoint would be considered non-adherence and be reported. The study team will be informed of these incidents in a timely manner.

7.1. Efficacy Endpoints

7.1.1. ACR Assessments

The American College of Rheumatology's definition for calculating improvement in RA (ACR50) is calculated as a ≥50% improvement in tender and swollen joint counts and ≥50% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant. Similarly, ACR20 and ACR70 are calculated with the respective percent improvement.[22] This efficacy measurement will be made at every study visit. The specific components of the ACR Assessments that will be used in this study are:

1. Tender/Painful Joint count (68);
2. Swollen Joint Count (66);
3. Patient's Assessment of Arthritis Pain (VAS);
4. Patient's Global Assessment of Arthritis (VAS);
5. Physician's Global Assessment of Arthritis (VAS);
6. C-Reactive Protein (CRP);
7. Health Assessment Questionnaire – Disability Index (HAQ-DI).

7.1.2. DAS Assessment

The Disease Activity Score (DAS)[23] is a derived measurement with differential weighting given to each component. DAS 28-3 (CRP) will be calculated from measurements made at all study visits.

The components of the DAS 28-3 arthritis assessment are:

1. Tender/Painful Joint Count (28);

2. Swollen Joint Count (28);

3. C-Reactive Protein (CRP).

Tender/painful and swollen joint counts used are as described in Sections 7.2.2 and 7.2.4.

7.1.3. PsA Response Criteria (PsARC)

The PsARC[24,25] will be calculated at all study visits in addition to the ACR response criteria. The PsARC consists of 4 measurements:

1. Tender joint count (68);

2. Swollen joint count (66);

3. Physician's Global Assessment of Arthritis (VAS);

4. Patient's Global Assessment of Arthritis (VAS).

The same tender/painful joint count and swollen joint count used for ACR response criteria will be applied to the PsARC. In order to be a 'PsARC responder', subjects must achieve improvement in 2 of 4 measures, one of which must be joint pain or swelling, without worsening in any measure.

7.2. Clinical Evaluation of Rheumatology Endpoints

The PsA subtype for each subject will be documented in the CRF. PsA subtype will be based upon whether or not the disease: is oligoarticular (<5 joints involved), polyarticular (≥5 joints involved), has distal interphalangeal joint involvement, spondylitis (spinal involvement) or is characterized by arthritis mutilans (aggressive joint destruction).

All rheumatological evaluations will be performed by qualified, trained assessors who are blinded to the subject's safety data, previous efficacy data and treatment randomization. To ensure consistency and reduce intra-individual variability, the same qualified assessor should score all evaluations for a given assessment for a given subject throughout the study.

7.2.1. Tender/Painful Joint Count (68)

Sixty-eight (68) joints will be assessed by a blinded 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 or missing joints). Artificial joints will not be assessed.

The 68 joints to be assessed are:

- Upper Body: temporomandibular, sternoclavicular, acromioclavicular;

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

7.2.2. Tender/Painful Joint Count (28)

Twenty-eight tender/painful joint counts include the following joints: shoulders, elbows, wrists, metacarpophalangeal joints (MCP), proximal interphalangeal joints (PIP), and knees. This count will be calculated by Sponsor from the 68 tender/painful joint count assessed by the blinded joint assessor as described in Section 7.2.1.

7.2.3. Swollen Joint Count (66)

The blinded assessor will also assess joints for swelling using the following scale: Present/Absent/Not Done/Not Applicable (to be used for artificial or missing joints).

Sixty-six (66) joints will be assessed for swelling, the same as those listed above for tenderness/pain, except that the right and left hip joints are not included in the swollen joint count. Artificial joints will not be assessed.

7.2.4. Swollen Joint Count (28)

This measurement will include the same joints as described in Section 7.2.3 and will be calculated by Sponsor from the 66 swollen joint count assessed by the blinded assessor.

7.2.5. Physician's Global Assessment of Arthritis

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

THE PATIENT'S ARTHRITIS AT THIS TIME IS:
(PLEASE MAKE AN X MARK ON THE LINE BELOW.)

Very Good _____ Very Poor

[Note: Scale will be 100 mm in length]

7.2.6. Physician's Global Assessment of Psoriatic Arthritis

The blinded investigator or qualified assessor will assess how the subject's overall PsA appears at the time of the visit. This may include any element of the disease that is related to their PsA and may include arthritis, psoriasis, enthesitis, dactylitis or spondylitis. The investigator's response will be recorded using a 100 mm visual analog scale (VAS).

THE PATIENT'S OVERALL PSORIATIC ARTHRITIS AT THIS TIME IS:
(PLEASE MAKE AN X MARK ON THE LINE BELOW.)

Not active at all _____Extremely active

[Note: Scale will be 100 mm in length]

7.2.7. Assessment of Dactylitis

The number of digits in hands and feet with dactylitis will be evaluated by a blinded assessor. In addition, dactylitis severity will be scored based upon digit tenderness using a scale of 0-3, where 0 = no tenderness and 3 = extreme tenderness, in each digit of the hands and feet. The range of total dactylitis scores for a subject would be 0-60.

7.2.8. Assessment of Enthesitis

Number of sites with enthesitis will be evaluated by a blinded assessor using Leeds Enthesitis Index.[26] The 6 sites assessed using the Leeds Enthesitis Index include (right and left): lateral epicondyle humerus, medial femoral condyle and Achilles tendon insertion.

7.2.9. C-Reactive Protein (CRP)

Blood samples will be collected at each visit (except follow-up) for analysis of CRP using an assay by the central laboratory. The investigator and Sponsor will be kept blinded to the results of this test at all visits except the Screening Visit.

7.3. Clinical Evaluation of Dermatologic Endpoints

All dermatological evaluations will be performed by qualified, trained assessors who are blinded to the subject's safety data, previous efficacy data and treatment randomization. To ensure consistency and reduce intra-individual variability, the same qualified assessor should score all evaluations for a given assessment for a given subject throughout the study.

7.3.1. Physician's Global Assessment of Psoriasis (PGA-PsO)

The Physician's Global Assessment of Psoriasis is scored on a 5-point scale, reflecting a global consideration of the erythema, induration and scaling across all psoriatic lesions. Average erythema, induration and scaling are scored separately over the whole body according to a 5-point severity scale (0 to 4) as defined by morphologic descriptors (Table 1). The severity scores are summed and averaged after which the total average is rounded to the nearest whole number score to determine the PGA-PsO score and category presenting greater severity of psoriasis (Table 2).

Table 1. Component Scoring Criteria for the Physician's Global Assessment (PGA-PsO)

Component Score	Description
Erythema (E)	
0	No evidence of erythema (post-inflammatory hyperpigmentation and/or hypopigmentation may be present)
1	Light pink
2	Light red
3	Red
4	Dark, deep red
Induration (I)	
0	No evidence of plaque elevation
1	Barely palpable
2	Slight, but definite elevation, indistinct edges
3	Elevated with distinct edges
4	Marked plaque elevation, hard/sharp borders
Scaling (S)	
0	No evidence of scaling
1	Occasional fine scale
2	Fine scale predominates
3	Coarse scale predominates
4	Thick, coarse scale predominates

Table 2. Physician's Global Assessment (PGA-PsO) Score

Physician's Global Assessment		Description
0	Clear	Cleared, except for any residual discoloration
1	Almost Clear	Majority of lesions have individual scores for (E + I + S)/3 that rounds to 1
2	Mild	Majority of lesions have individual scores for (E + I + S)/3 that rounds to 2
3	Moderate	Majority of lesions have individual scores for (E + I + S)/3 that rounds to 3
4	Severe	Majority of lesions have individual scores for (E + I + S)/3 that rounds to 4

Note: Calculated arithmetic average of individual signs severity scores [(E + I + S)/3] is rounded to the nearest whole number score (eg, if total ≤2.49, score = 2; if total ≥2.50, score = 3).

7.3.2. Psoriasis Area and Severity Index (PASI)

The Psoriasis Area and Severity Index (PASI)[27] quantifies the severity of a subject's psoriasis based on both lesion severity and the percent of body surface area (BSA) affected. PASI is a composite scoring by the investigator of degree of erythema, induration, and scaling (each scored separately) for each of four body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to

the whole body. The calculation of BSA is described in Section 7.3.3. Note: PASI should only be performed if ≥3% of subject's BSA is affected at baseline.

Lesion Severity: the basic characteristics of psoriatic lesions – erythema, induration and scaling – provide a means for assessing the severity of lesions. Assessment of these three main signs is performed separately for four body regions: head and neck, upper limbs, trunk, (including axillae and groin) and lower limbs (including buttocks). Average erythema, induration and scaling are scored for each body region according to a 5-point scale: 0, no involvement; 1, slight; 2, moderate; 3, marked; 4, very marked. Appropriate morphologic descriptors for each severity score are shown below (Table 3).

Table 3. Component Scoring Criteria for the Psoriasis Area and Severity Index (PASI)

Component Score		Description
Erythema (E)		
0	No involvement	None; may have residual hyperpigmentation
1	Slight	Pink or light red
2	Moderate	Darker pink-red
3	Marked	Red
4	Very Marked	Extremely red, "beefy" red
Induration (I)		
0	No involvement	None
1	Slight	Minimal elevation relative to normal surrounding skin
2	Moderate	Easily palpable with rounded edges
3	Marked	Elevated with hard, sharp borders
4	Very Marked	Very elevated with very hard, sharp borders
Scaling (S)		
0	No involvement	None
1	Slight	Mainly fine scale, some lesion partially covered
2	Moderate	Coarser thin scale, most lesions partially covered
3	Marked	Coarser thick scale, nearly all lesions covered, rough
4	Very Marked	Very thick scale, all lesions covered, very rough

Percent BSA with Psoriasis: the extent (%) to which each of the four body regions is involved with psoriasis is categorized using a non-linear scaling method to a numerical area score according to the following BSA scoring criteria (Table 4).

Table 4. Psoriasis Area and Severity Index (PASI) Area Score Criteria

Percent Body Surface Area (BSA) with Psoriasis	Area Score
0%	0
>0-9%	1
10-29%	2
30-49%	3
50-69%	4
70-89%	5
90-100%	6

Body Region Weighting: each body region is weighted according to its approximate percentage of the whole body (Table 5).

Table 5. Psoriasis Area and Severity Index (PASI) Lesions Body Region Weighting

Body Region	Body Region Weighting
Head and Neck	0.1
Upper Limbs	0.2
Trunk (including axillae and groin)	0.3
Lower Limbs (including buttocks)	0.4

In each body region, the sum of the Severity Scores for erythema, induration and scaling is multiplied by the Area Score and by the Body Region Weighting to provide a body region value, which is then summed across all four body regions resulting in a PASI score as described in the following equation:

$$PASI = 0.1Ah(Eh+Ih+Sh) + 0.2Au(Eu+Iu+Su) + 0.3At(Et+It+St) + 0.4Al(El+Il+Sl)$$

where A = Area Score; E = erythema; I =induration; S = scaling; h = head and neck; u = upper limbs; t = trunk; l = lower limbs.

The PASI score can vary in increments of 0.1 and range from 0.0 to 72.0, with higher scores representing greater severity of psoriasis.

7.3.3. Body Surface Area (BSA)

Assessment of BSA[28] with psoriasis will be performed separately for four body regions: head and neck, upper limbs, trunk (including axillae and groin), and lower limbs (including buttocks). The percent surface area with psoriasis is estimated by means of the handprint method, where the full palmar hand of the subject (ie, the subject's fully extended palm, fingers and thumb together) represents approximately 1% of the total BSA. The BSA with psoriasis (%) is the sum of the numbers of the handpoints across the 4 body regions.

7.3.4. Nail Psoriasis Severity Index (NAPSI) Score

A target finger nail will be evaluated by the blinded assessor using the NAPSI scale.[29] At the baseline visit, the worst case fingernail should be chosen and the same nail evaluated consistently through the entire study. Each quadrant of the target nail is graded for nail matrix psoriasis (including any of the following parameters: pitting, leukonychia, red spots in lunula, nail plate crumbling) and nail bed psoriasis (including any of the following parameters: onycholysis, splinter hemorrhages, oil drop (salmon patch) discoloration, nail bed hyperkeratosis), giving that 1 target nail a score of 0-8.

7.4. Health Outcome Measures

All questionnaires should be completed by subjects prior to any procedures being performed at the study visit. Forms should be checked by site staff for completeness.

In the unlikely event that a PRO questionnaire(s) is not able to be administered by study site staff and completed by the subject as directed at the clinic visit, the PRO questionnaire(s) should not be administered. PRO questionnaires should also be reviewed for potential adverse events.

7.4.1. Patient's 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.

MY PAIN AT THIS TIME IS:
(PLEASE MAKE AN X MARK ON THE LINE BELOW.)

No Pain _____ Most Severe Pain

[Note: Scale will be 100 mm in length]

7.4.2. Patient's Global Assessment of Arthritis

Subjects will answer the following question, "Considering all the ways your arthritis affects you, how are you feeling today?" The subject's response will be recorded using a 100 mm visual analog scale (VAS).

CONSIDERING ALL THE WAYS YOUR ARTHRITIS AFFECTS YOU, HOW ARE YOU FEELING TODAY?
(PLEASE MAKE AN X MARK ON THE LINE BELOW.)

Very Well _____ Very Poorly

[Note: Scale will be 100 mm in length]

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

The HAQ-DI assesses the degree of difficulty a subject has experienced during the past week in 8 domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities.[30] 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.

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

The SF-36 v.2 (Acute)[31] is a 36-item generic health status measure. It measures 8 general health domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. These domains can also be summarized as physical and mental component summary scores.

7.4.5. EuroQol EQ-5D Health State Profile

The EuroQol EQ-5D Health State Profile is a copyrighted, patient 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.[32] 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 PsA and rheumatoid arthritis.

7.4.6. Work Productivity and Activity Impairment – Psoriatic Arthritis Questionnaire

The work productivity and Activity Impairment – Psoriatic Arthitis Questionnaire[33] is a six item questionnaire that measures absenteeism (work time missed), presenteesism (impairment at work/reduced on –the-job effectiveness), work productivity loss (overall work impairment/absenteeism plus presenteeism) and activity impairment. WPAI-PsA outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. The validity and reliability of the WPAI has been well established.

7.5. Safety

Safety will be assessed by the spontaneous reporting of AEs, physical examinations and clinical laboratory results in all subjects who receive at least one dose of study drug. Investigators and Pfizer clinicians will review individual subject data throughout the conduct of the study to ensure the subjects' well-being.

7.5.1. Vital Signs and Temperature

Body temperature, blood pressure and pulse rate will be measured at every study visit except the follow-up visit.

It is preferred that body temperature be collected using the tympanic, oral or temporal methods. The method chosen should be used consistently by the investigational site throughout the study.

Blood pressure (BP) will be measured using a standard calibrated blood pressure measuring device. The following method should be used to record the blood pressure:

- Subjects should be seated in a chair with feet flat on the floor, back supported and their arms bared (free of restrictions, such as rolled up sleeves, etc) and supported at heart level.

- Measurements should be taken on the same arm at each visit (preferably nondominant arm).
- Subjects should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurements.
- Measurements should begin after at least 5 minutes of rest.
- BP should be recorded to the nearest mmHg value.
- When the timing of BP and pulse (pulse rate) measurements coincides with a blood collection or other study procedures, BP and pulse (heart) rate should be obtained first.

7.5.2. Electrocardiogram

Twelve-lead electrocardiograms (ECGs) will be obtained on all subjects at the Screening and the Month 6 (or Early Termination) visit. All ECGs should be performed after the patient has rested quietly for at least 10 minutes. Screening visit ECG results will be used as a screening tool and should be maintained in the subject's source documentation. ECGs obtained at Month 6 will be compared to Screening ECGs. Any clinically significant changes from the Screening ECG will be recorded as adverse events and evaluated further, as clinically warranted.

7.5.3. Tuberculosis Screening

During the Screening period, it must be determined and documented that a subject does not have evidence of active or latent or inadequately treated infection with *Mycobacterium tuberculosis* (TB) per the Inclusion Criteria. The results of TB screening conducted in the 3 months prior to Screening visit or during the screening period must be documented in study records prior to Baseline (Visit 1).

7.5.3.1. Quantiferon®- TB Gold In-Tube Test

QuantiFERON®-TB Gold In-Tube is an in vitro diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10 and TB 7.7 proteins to stimulate cells in heparinized whole blood.[34] Detection of interferon-γ by Enzyme-Linked Immunosorbent Assay is used to identify in vitro responses to these peptide antigens that are associated with *Mycobacterium tuberculosis* infection. QuantiFERON®-TB Gold In-Tube is an indirect test for *M. tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

Test results will be reported as positive, negative or indeterminate. In the case of an indeterminate result, repeat tests may be permitted for the purpose of determining eligibility of subjects to enroll in this study. PPD testing will be allowed if there are two repeated indeterminate results at the discretion of the Sponsor. The procedure for using this test and interpreting the results is described fully in the laboratory manual, which will be provided to investigators.

7.5.3.2. Purified Protein Derivative (PPD) Tuberculin Test

If the QuantiFERON®-TB Gold In-Tube test is indeterminate, a second sample may be tested and, if still indeterminate, subjects can be screened using a Mantoux Purified Protein Derivative (PPD) test using 5 tuberculin units (5 TU) per 0.1 mL within the 3 months prior to a given screening visit at the discretion of the Pfizer Study Clinician. Subjects must have a PPD tuberculin test administered and then evaluated by a health care professional in order to be eligible for the study, unless this test has been performed and documented within the last 3 months.

If 5 TU is not available, then the PPD may be peformed according to local standards in 0.1 mL of solution on the volar aspect of the forearm, using a short beveled 26-or 27-gauge needle (Mantoux test). The test is read 48-72 hours later. A negative Mantoux/PPD tuberculin skin test result (5 TU PPD result of <5 mm of induration) is required to meet inclusion criteria.

7.5.3.3. Chest Radiograph (CXR)

A chest radiograph will be obtained at the Screening Visit in all subjects unless it has been taken and documented within the 3 months prior. To be considered eligible for the study, the radiograph must be reviewed by a radiologist or pulmonologist as per local standard of care and documented as negative for active tuberculosis infection.

For subjects with latent TB infection and treated with preventive anti-TB therapy during study, chest radiograph should be be monitored per local practice.

7.5.4. Complete Physical Examination

A standard complete physical examination will be performed at Screening visit, Baseline (Visit 1), Month 6 ((Visit 7) or Early Termination). The following parameters and body systems will be examined and any abnormalities described: height (at Screening Visit only), weight, general appearance, skin (presence of rash), HEENT (head, ears, eyes, nose, throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremity exam, abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes. Any clinically significant changes from Baseline (Visit 1) should be recorded as adverse events (AEs).

Recommendations for evaluation of emergent lymphadenopathy or other findings suggestive of lymphoproliferative disorder are provided in Appendix 6.

7.5.5. Targeted Examination

At all other visits except follow-up, an abbreviated physical examination will be performed assessing the following: weight, lungs, heart, abdomen, lower extremities and lymph nodes. Any clinically significant changes from Baseline (Visit 1) should be recorded as adverse events (AEs).

7.5.6. Weight, Waist and Hips Circumference and Height

It is recommended that weight be measured in kilograms (kg) with shoes removed. Waist and hip measurements should in centimeters (cm) and be taken directly on the skin without clothing, in the standing position, and at the end of normal expiration. Waist circumference should be measured immediately above the iliac crest. Hip circumference should be measured by positioning the measure tape around the maximum circumference of the buttocks; for women typically at the groin level and for men, typically 2-4 inches (5.1-10.2 cm) below the navel. Additional guidelines for weight and for waist and hip circumference measurement will be provided to study sites.

Weight should be measured to the nearest 0.1 kg. Waist and hip measurements should be measured to the nearest 0.1 cm.

It is recommended that height be measured in centimeters (cm) with shoes removed.

7.5.7. Clinical Safety Laboratory Tests

Blood and urine samples will be collected at the time points identified in the protocol for clinical safety laboratory tests (Table 6). Unscheduled clinical laboratory tests may be performed at any time during the study to assess any perceived safety concerns. Any laboratory test that is not analyzable should be repeated as soon as possible, but no later than the next visit.

7.5.7.1. Hepatitis B and C Virus Testing

Subjects with known hepatitis B infection will be excluded from the study. All subjects will be tested for HBsAg and HBcAb at Screening. Any subject who is $HBsAg^{+}$ must be excluded from study participation. Subjects who are $HBsAg^{-}$ but $HBcAb^{+}$ must undergo further testing for HBsAb by the central laboratory to be considered for enrollment. Subjects who are $HBsAg^{-}/HBcAb^{+}/HBsAb^{+}$ may be eligible for enrollment. Subjects who are $HBsAg^{-}/HBcAb^{+}/HBsAb^{-}$ are excluded from study participation.

Subjects will also be excluded for hepatitis C infection. At the Screening visit, all subjects will be tested for HCV Ab and, if positive, must undergo further testing for HCV RNA and allowed to enroll if negative.

Table 6. Clinical Laboratory Testing

Laboratory Testing Profile	Tests Included
Laboratory Tests Required at Screening Only	QuantiFERON®-TB Gold In-Tube, hepatitis C virus antibody (HCV Ab), hepatitis C virus RNA (HCV RNA),[a] hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb),[b] HIV-1/HIV-2 antibody screen, Prothrombin time (PT/INR);[c] FSH (optional for post-menopausal women only).
Hematology	Hemoglobin, hematocrit, RBC, RBC morphology, reticulocyte (abs); White blood cell (WBC) count and differential, [neutrophils (%, abs), lymphocytes (%, abs), monocytes (%, abs), eosinophils (%, abs), basophils (%, abs)], Lymphocyte subset analysis (FACS) [CD3+ (%, abs), CD3+CD4+ (%, abs), CD3+CD8+ (%, abs), CD19+ (%, abs), CD16+/CD56+ (%, abs)], platelets Hemaglobin A1c (HbA1c).
Chemistry Panel (fasting)	Urea nitrogen, creatinine, glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), albumin, creatine kinase (CK). Rheumatoid Factor (RF), Cyclic Citrullinated Peptide Antibody (CCP).
Lipid Panel (fasting)	Fasting total cholesterol, HDL, LDL, triglyceride; apolipoprotein A-1, B.
Urinalysis	Specific gravity, pH, protein, glucose, ketones, blood, leukocyte esterase. Urine HCG pregnancy testing for women of childbearing potential. Microscopy and/or culture to be performed if clinically indicated or if urinalysis results positive (blood, protein or leukocyte esterase/WBC).
Acute Phase Reactants	C-reactive protein (CRP, tested centrally).

Testings that are to be done in central lab: hematology, HbA1c, Lymphocyte subset analysis (FACS), Chemistry panel, Lipid Panel, Urinalysis, C-Reactive Protein (CRP), HIV serology, HBsAg, HBcAb, HCV Ab, Prothrombin time (INR), Rheumatoid Factor (RF), QuantiFERON-TB Gold, FSH testing if needed.

a. Only subjects who are HCV Ab positive should be reflex tested for HCV RNA.

b. Only subjects who are $HBsAg^-$ and $HBcAb^+$ should be reflex tested for HBsAb.

c. All subjects will be screened for normal prothrombin time (PT/INR). PT should also be evaluated to rule out acute hepatic injury in cases of hepatic enzyme elevations.

Abnormal test results determined to be caused from laboratory error should not be reported as AEs. Subjects who present with clinically significant laboratory findings at the final assessment must have a follow-up visit within 28 days ±7 days after last dose of study treatment. Clinically significant laboratory findings should be followed to resolution or until determined by the Investigator to be stabilized. Repeat tests may be needed to establish this.

7.5.7.2. Pregnancy Testing

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. For female subjects of childbearing potential, 2 negative pregnancy tests are required before receiving investigational products (1 negative pregnancy test at screening and 1 at the baseline visit immediately before investigational products administration). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy test result will then be required at the baseline visit before the subject may receive the investigational product. Pregnancy tests will also be repeated at every visit and at the end of the study to confirm that the subject has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period and when potential pregnancy is otherwise suspected, and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product the subject will be withdrawn from the study and all necessary follow-up will be conducted.

7.5.8. Risk Factor Check for Venous Thromboembolism

All subjects will undergo a risk factor check at each study visit to check for newly developed risk factors for venous thromboembolism.[19] This information is to be captured in the subject's source file and on the relevant case report form.

A subject may be at high risk for venous thromboembolism if he/she:

- has heart failure or prior myocardial infarction within past 3 months;
- has inherited coagulation disorders;
- has had venous thromboembolism, either deep venous thrombosis or pulmonary embolism;
- is taking combined hormonal contraceptives or hormone replacement therapy;
- has malignancy (association is strongest with cancers other than non-melanoma skin cancers);
- is undergoing major surgery or is immobilized.

Additional risk factors for venous thromboembolism, such as age, diabetes, obesity (BMI>30 kg/m^2), smoking status, hypertension, and first degree family history of VTE should also be taken into consideration by the investigator and the Sponsor medical monitor when evaluating the benefit:risk for each individual subject.

If a subject has one or more of the risk factors for venous thromboembolism listed above, investigator judgement based on Exclusion Criteria 30 (Section 4.4) will apply to determine whether subject is appropriate for entry into this study.

If a subject has one or more of the risk factors for venous thromboembolism listed above under Amendment 3 and is receiving tofacitinib 5 mg BID, they may remain on tofacitinib 5 mg BID after careful investigator assessment of benefit:risk.

For subjects who do not have any of the risk factors for venous thromboembolism listed above under Amendment 3, he/she will remain on their assigned tofacitinib dose.

Per Amendment 3, for subjects with suspected venous thromboembolism, treatment with tofacitinib should be temporarily withheld while the subject is evaluated. If venous thromboembolism is confirmed, discontinue treatment with tofacitinib and withdraw the subject from the study (Section 6.3.2, Discontinuation Criteria).

7.6. Cardiovascular and Malignancy Events

The identification of a cardiovascular event will be made by the study site and communicated to Pfizer or designee. Cardiovascular or malignancy events may also be identified by the Pfizer Study Team or designee during the review of subject data listings or by site monitors during routine monitoring of subject's study records. The Pfizer Study Team or designee will notify the study site of any cardiovascular events should they identify any ahead of a study site.

Cardiovascular events should be reported to the Pfizer Study Team or designee according to the following reference timepoints:

- Report any events that are serious adverse events (SAEs) occurring after the time of informed consent;
- Report any events that are non-serious adverse events (AEs) occurring after the time of informed consent.

7.6.1. Cardiovascular Events

Criteria for defining specific cardiovascular events will be provided to investigators in a separate study manual. The Pfizer Study Team or designee will provide a listing of specific documents needed to support cardiovascular event adjudication (see Section 9.6). Obtaining the documentation will be the responsibility of the study site. Cardiovascular event documentation will include, but is not limited to any of the following: hospital discharge summaries, operative reports, clinic notes, ECGs, diagnostic enzymes, results of other diagnostic tests, autopsy reports and death certificate information.

7.6.2. Malignancy Events

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

For all biopsies of potentially malignant tumors, suspicious lymphadenopathy, or possible extranodal lymphoproliferative disorder (LPD), the study site will request the pathologist to send the original slides used to make the definitive diagnosis, ancillary study reports, and the pathologist's report to the central laboratory for a blinded review by a central pathologist. See Appendix 6 for the steps to take in the event of potentially malignant tumors, lymphadenopathy or possible extra-nodal lymphoproliferative disorder (LPD) which might arise in the course of this study.

Malignancy event samples and documentation will include, but are not limited to any of the following: stained and unstained slides for each tissue block, and local pathology report(s).

7.7. Corona Virus Disease 2019 (COVID-19)

For participants with study visits or procedures impacted by the COVID-19 pandemic, the following guidance applies. Once a study participant is able to travel to the study site and the study site is operational, these changes outlined this Protocol Section 7.7 will no longer apply.

- Every effort should be made to follow-up on the safety of the study participant. In the event that in-clinic study visits cannot be conducted, remote visits will be allowed.

- Minimally, phone contact will be required at the scheduled or unscheduled visit when an in-clinic visit is not possible due to COVID-19. Video contact can be used if permitted by local regulations. During the remote visit, the following assessments should be performed:

    - Review and record any AEs and SAEs since the last contact, including but not limited to COVID-19-related events. The AE and SAE reporting process as noted in the protocol should be followed.

    - Review and record study treatment including compliance and missed doses. If allowed by local regulations, photos of remaining tablets can be collected. Review and record any changes or new concomitant medications since last contact.

    - PROs can be mailed via postal services or electronically if allowed and in accordance with local regulations to the study participant in advance of remote visits and verify they have been completed. These can either be mailed back to the site or held until a site visit is permissible. PROs cannot be completed by phone/video with the study participant.

    - Review and verify that contraceptive methods are being followed in those study participants that meet requirements for contraception.

    - In-clinic dose for the last dose of tofacitinib at the visit 7 can be administered during the remote visit and documented in the source.

    - Missed or partially completed procedures and assessments, based on the Schedule of Activities, must be reported as a protocol deviation.

- Procedures or tests which are missed due to COVID-19 disruptions should be performed at the next available opportunity, even if outside of a protocol-specified visit window.

- Protocol-defined laboratory tests may be collected and resulted at an alternative clinical laboratory facility ONLY if testing at the study site using the central laboratory is not possible due to COVID-19 disruptions.

- Local laboratory results or central laboratory results will be needed in order to ship study medication to a study participant. This is to ensure no monitoring criteria have been met prior to receipt of study medication. Local laboratory results should include all assays as required by the protocol except for C-reactive protein as this is a blinded assay. If local laboratory results are obtained, your CRA will need to collect the laboratory accreditation and laboratory reference ranges electronically or when they are back onsite. These local laboratory results will need to be entered in the eCRF page.

    - Women of child-bearing potential will require a negative pregnancy test (completed at the site or local laboratory) prior to shipping investigational product to the study participant.

- If courier delivery of the study medication from the study sites is allowable by law and local guidance, the study participant must provide verbal consent for providing the contact details for shipping purposes. Document the verbal consent in the source documents. Tracking records of shipment including temperature monitoring records and the chain of custody of the study medication must be kept in the participant's medical records. Investigational product that is dispensed to the study participant via courier should correspond to the amount that is dispensed at the specific study visit and all dispensing activity should be registered in Impala.

- For study participants that must be discontinued from the study drug and study participation due to inability to comply with the protocol visits and procedures within the timeframes of the protocol, these discontinuations should be reported as "Other" for the Status on both Disposition (End of Treatment and Follow-Up) pages of the eCRF and in the "Specify Status" field, enter "COVID-19".

    - If the study participant discontinues due to a COVID-19 infection, record COVID-19 infection on the AE page and record the infection details on the Treated Infections Details page. The reason for discontinuation from investigational product would be "Adverse Event" on the Disposition-End of Treatment eCRF page.

If the sponsor determines that the impact of COVID-19 on protocol visits and procedures and associated timeframe needs to be reported on a case report form (CRF), this will be requested. For study medication interruption attributable to logistic restrictions during COVID-19, record it in Oral Dosing page as below: enter first day of interruption in "Start Date" and last day in "End Date", enter 0 in "Total Daily Dose", select Other for "Reason for Changed or Missed Dose" and enter COVID-19 in free typing area.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

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

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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.

8.1.1. Additional Details On Recording Adverse Event on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)

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

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety 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 must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

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.

8.1.5. 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 on the CRF, 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. 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, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. 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.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study 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 signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

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

- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- 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 any protocol-specified 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 recording as an AE.

8.2.3. 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.

Or that is considered to be:

- An important medical event.

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.

8.2.4. 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 is 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 outpatient/same-day/ambulatory procedures).

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a 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 SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, 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.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample).

In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator 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 and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications),

recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

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

- 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).
- 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 subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT 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) to Pfizer Safety 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 Safety 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 to Pfizer Safety 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 sponsor. 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 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.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. 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 Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- 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.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

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

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.5. Infections

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

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

8.5.1. Serious Infections

A serious infection is any infection that requires hospitalization for treatment or requires parenteral antimicrobial therapy or meets other criteria that require it to be classified as a serious adverse event. A subject who experiences a serious infection should be discontinued from the study and the serious adverse event should be listed as the reason for discontinuation in the Case Report Form. 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 7.7 on Adverse Event Reporting.

8.5.2. Treated Infections

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

The sample size and power analysis for the primary endpoint are based on the randomization of approximately 204 subjects in a 2:1 ratio. The sample size for this study is driven by the ACR50 response rate.

Assuming a placebo response rate of 9.5% and factoring in the number of subjects with primary endpoint missing due to COVID-19 (around 11 subjects as of 29 May 2020), a sample size of approximately 204 Chinese subjects (approximately 136 subjects in the tofacitinib treatment arm and 68 subjects in the placebo arm) randomized in a 2:1 ratio to tofacitinib and placebo arms will yield at least 90% power to detect a difference of 18.5% from placebo in ACR50 response rate, based on normal approximation (without continuity correction) at the 2-sided 5% significance level.

9.2. Efficacy Analysis

9.2.1. Analysis of Primary Endpoint of ACR50 Response Rate

The normal approximation to the difference in binomial proportions will be used to test the difference between tofacitinib 5 mg BID and placebo and to generate 95% confidence interval for the difference in response rates.

Missing values for any reason, eg, due to a subject dropping from the study or due to the impact of COVID-19 pandemic will be handled by setting the ACR50 value to nonresponsive. The SAP will also specify additional analyses to assess the sensitivity of the primary analysis to departures from the assumed missing data mechanism.

The analysis will include all randomized subjects who receive at least 1 dose of study drug.

9.2.2. Analysis of Secondary Endpoints

Binary endpoints will be analyzed similarly as for the primary analysis of ACR50.

The ΔHAQ-DI will be analyzed using a repeated measure model that includes the fixed effects of treatment, visit (Week 2, Months 1, 2, 3, 4 and 6), treatment by visit interaction, and baseline value, and an unstructured variance covariance matrix for within-subject correlation (an alternative variance covariance matrix will be used if the model does not converge under the unstructured variance covariance matrix). Other continuous endpoints will be analyzed similarly.

Details of the analysis methods for all the endpoints will be enumerated in the SAP.

9.3. Analysis of Other Endpoints

Other endpoints will be analyzed similarly as for the secondary endpoints.

9.4. Safety Analysis

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

- Incidence and severity of adverse events;
- Categorical summary of absolute vital signs and vital sign changes compared to baseline by subject;
- Incidence of adjudicated safety events;
- Serious infections will be summarized separately;
- Any safety events that trigger withdrawal of a subject;
- Safety laboratory tests will be summarized according to Pfizer standards;

- Special attention will be given to the following safety criteria: neutrophil counts, lymphocyte counts, serum creatinine levels, platelet counts, transaminase levels, bilirubin levels (and other measures of liver function), events of anemia.

9.5. Data Monitoring Committee

This study will use an External Data Monitoring Committee (E-DMC).

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

Information about the E-DMC can be found in the E-DMC Charter, which outlines the operating procedures of the committee, including specific description of the scope of their responsibilities, including a plan where communication timelines are defined.

9.6. Safety Endpoints Adjudication Committees (SEAC)

To help assess the specific safety events in this and other Phase 3 studies for the oral tofacitinib PsA program, 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), Opportunistic Infection Review Committtee (OIRC), Malignancy Adjudication Committee (MAC), and Hepatic Event Review Committee (HERC). 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 Committee, ILDRC). Further information about these committees can be found in their respective charters, including specific descriptions of the scope of their responsibilities and the process and definitions to review and assess specific safety events.

Additional safety event adjudication review committees may be established as considered appropriate. 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 review committees described above, all biopsies of potentially malignant tumors, suspicious lymphadenopathy, or possible extranodal lymphoproliferative disorder (LPD), should be submitted to the central laboratory pathologist. If biopsies are not available, digital photos of the stained slides for each tissue block, digital image of the slides and local pathology report(s) should be submitted. In some instances, additional expert pathology review of submitted samples may be requested external to the central laboratory. Description of the scope of review and the processes used to obtain and assess biopsies is

described in the Malignancy Histopathology Adjudication charters. Further details on central laboratory review of biopsies of suspected malignancies are found in Appendix 6.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent 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 investigator site may be subject to review by the IRB/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 investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. 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 or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/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 (IRB)/ Ethics Committee (EC)

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

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 numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator 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 and any subject recruitment materials 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 and any subject recruitment materials must be reviewed and approved by Pfizer, 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.

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

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

12.4. 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 regulatory 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

End of Trial is defined as Last Subject Last Visit.

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 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 180 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 patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

EudraCT

Pfizer posts European Union (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 PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

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

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

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Appendix 1. Abbreviations

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

Abbreviation	Term
Ab	Antibody
AE	Adverse Event
ACR	American College of Rheumatology
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Counts
Anti-CCP	Anti-cyclic citrullinated protein antibody
AST	Aspartate Aminotransferase
AUC	Area Under Curve
BCG	Bacille Calmette Guérin
bDMARD	Biological Disease-Modifying Anti-Rheumatic Drug
BID	Twice daily
BMI	Body Mass Index
BSA	Body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CCP	Cyclic Citrullinated Peptide
CDS	Core data sheet
CHD	Coronary Heart Disease
CK	Creatine Kinase
CL/F	Oral Clearance
COVID-19	Corona Virus Disease 2019
COX-2	Cyclooxygenase-2
CRF	Case Report Form
CRP	C-reactive Protein
csDMARD	Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug
CTA	Clinical Trial Application
CV-EAC	Cardiovascular Endpoint Adjudication Committee
CYP	Cytochrome P
CXR	Chest X-ray
DAS	Disease Activity Score
DILI	Drug Induced Liver Injury
DIP	Distal interphalangeal
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
DNA	Deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
EDMC	External Data Monitoring Committee
EDP	exposure during pregnancy
EQ-5D	The EuroQol EQ-5D Health State Profile
EU	European Union

Abbreviation	Term
EudraCT	European Clinical Trial Database
FACS	Fluoresence Activated Cell Sorting
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
gm	Gram
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire-Disability Index
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HBsAb	Hepatitis B surface antibody
HBcAb	Hepatitis B core antibody
HBV	Hepatitis B virus
HCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C virus
HDL	High Density Lipoprotein
HEENT	Head, eyes, ears, nose, throat
HIV	Human Immunodeficiency Virus
IB	investigator's brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IND	Investigational New Drug
INR	international normalized ratio
IP	Interphalangeal
IRB	Institutional Review Board
IRC	Internal Review Committee
IUD	Intrauterine Device
IUS	Interuterine System
IVRS	Interactive Randomization System
JAK	Janus kinase
LDL	Low density Lipoprotein
LEI	Leeds Enthesitis Index
LFT	liver function test
LPD	Lymphoproliferative Disease
LSLV	Last Subject Last Visit
LTE	long term extension
LTFU	Long-Term Follow-Up
MACE	Major Adverse Cardiac Events
MCP	Metacarpophalangeals
MCTD	Mixed Connective Tissue Disease

Abbreviation	Term
mg	Milligrams
MTP	Metatarsophalangeal
MTX	Methotrexate
NAPSI	Nail Psoriasis Severity Score
NRI	Nonresponder imputation
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PASI	Psoriasis Area Severity Index
PASI75	Psoriasis Area and Severity Index 75
PDE4	Phosphodiesterase 4
PGA-PsO	Physician's Global Assessment of Psoriasis
PIP	Proximal Interphalangeals
PK	Pharmacokinetics
PPD	Purified Protein Derivative
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
PsARC	Psoriatic Arthritis Response Criteria
PsO	Psoriasis
PT	Prothrombin Time
PUVA	Psoralens + UVA phototherapy
Qd	Once Daily
QFT-G	Quantiferon Gold
RA	Rheumatoid Arthritis
RBC	Red Blood Cell
RF	Rheumatoid Factor
RNA	ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-36	36-Item Short-Form Health Survey
SLE	Systemic Lupus Erythematosus
SRSD	Single Reference Safety Document
TB	Tuberculosis
TNFi	Tumour Necrosis Factor Inhibitor
tsDMARD	Targeted Synthetic Disease Modifying Anti-Rheumatic Drug
ULN	Upper Limit of Normal
US	United States
UVB	Ultraviolet B
VAS	Visual Analog Scale
VTE	Venous thromboembolism
WBC	White Blood Cell
WPAI-PsA	Work Productivity and Activity Impairment – Psoriatic Arthritis

Appendix 2. Cockcroft-Gault Calculation

Creatinine Clearance (estimated) / Conventional mL/min =

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

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

Appendix 3. Prohibited Concomitant Medications

All **biologic DMARDs** are prohibited. See Section 4.3 regarding washout period for TNFi. Other biologic agents are prohibited (eg, ustekinumab or investigational agents) and require a 6 month washout period unless otherwise specified.

The following nonbiologic DMARDs are prohibited before the last dose of investigational drug: Leflunomide, azathioprine, cyclosporine, bucillamine, iguratimod, mizoribin, tacrolimus, tetracycline (used as a DMARD) and any JAK inhibitor. All of these prohibited DMARDs require a 4 week washout period prior to first dose of study treatment. Leflunomide(Arava®) must have been discontinued 8 weeks prior to the first dose of study drug if no elimination procedure is followed. Alternately, it should have been 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.

Traditional Chinese medicine, *Tripterydium hypoglaucum* (thunder god vine), requires a 4 week washout period prior to first dose of study treatment.

All Investigational Drugs not otherwise specified are prohibited and require a 4 week (≥5 half-lives) washout period prior to first dose of study treatment.

All other prohibited drugs (see below) require at least a 7 day or 5 half-life (whichever is longer) washout period prior to the first dose of study treatment. In the table version below, those drugs requiring washout longer than 7 days are in bold and italicized. Note: efavirenz, nevirapine, barbiturates, carbamezipine, Phenobarbital, St. John's Wort, rifabutin and rifapentene should be discontinued at least 30 days prior to first dose of study drug based on half-life of these drugs, and that amiodarone should be discontinued at least 290 days prior to the first dose of study drug based on a half life of 58 days.

- Topical (including skin or mucous membranes) application of antibacterial (eg, clarithromycin, erythromycin and norfloxacin) and antifungal (fluconazole, ketoconazole, clotrimazole and itraconazole) medications is permitted.

- Potent inhibitors and inducers of CYP3A (shown below) are not permitted in the study except in emergency situations requiring no more than one day of administration or as approved by Pfizer Study Clinician.

Potent CYP3A Inhibitors	Potent CYP3A Inducers
HIV antivirals: -indinavir (Crixivan) -nelfinavir (Viracept) -ritonavir (Kaletra, Norvir)	***efavirenz (Sustiva)***
clarithromycin (Biaxin, Prevpac)	***nevirapine (Viramune)***
itraconazole (Sporanox)	***Barbiturates***
ketoconazole (Nizoral)	***carbamazepine (Carbatrol, Tegretol)***
nefazodone (Serzone)	modafinil (Provigil)
	phenobarbital
	phenytoin (Dilantin, Phenytek)
	rifabutin (Mycobutin)
	rifampin (Rifadin, Rifamate, Rifater)
	rifapentine (Priftin)

- Subjects may be initiated on moderate inhibitors (except amiodarone) and inducers (shown below), as required, if the total duration of treatment lasts less than or equal to 7 days.

- Consumption of juice from grapefruit, pomelos and Seville oranges is permitted up to 8 oz or 236 mL (total) in a day. It is recommended to separate their coadministration with study medication by at least ±1 hour.

Moderate CYP3A Inhibitors	Moderate CYP3A Inducers
HIV antivirals: - atazanavir (Reyataz) - delavirdine (Rescriptor) - saquinavir (Fortovase)	***St. John's wort***
amiodarone (Cordarone, Pacerone)	
cimetidine (Tagamet)	
Clotrimazole	
diethyl-dithiocarbamate	
diltiazem (Cardizem, Tiazac)	
Erythromycin	
fluconazole (Diflucan)	
fluvoxamine (Luvox)	
grapefruit or grapefruit-related citrus fruits, juices (eg, Seville oranges, pomelos)	
Mibefradil	
mifepristone (Mifeprex, RU486)	
norfloxacin (Shibroxin, Noroxin)	
verapamil (Calan SR, Covera HS, Isoptin SR, Tarka, Verelan)	
Voriconazole	

Prohibited are topical treatments that could affect psoriasis, eg, corticosteroids, tars, keratolytics, anthralin, vitamin D analogs, and retinoids and must be discontinued at least 2 weeks prior to first dose of study drug.

- Exceptions- the following topical treatments are allowed: non-medicated emollients for use over the whole body; topical steroids including hydrocortisone and hydrocortisone acetate ≤1% for the palms, soles,face and intertriginous areas only; tar and salicylic acid preparations for the scalp only and shampoos free of corticosteroid for the scalp only.

Also prohibited is UVB (narrowband or broadband) phototherapy that must be discontinued at least 2 weeks prior to first dose of study drug. Psoralens + UVA phototherapy (PUVA) must be discontinued at least 4 weeks prior to first dose of study drug.

Appendix 4. 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 5. Rescue Therapy

Acetaminophen/ paracetamol is allowable as rescue medication if dosed no more than 2.6 gm/day 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 2.6 gm/day for up to 10 consecutive days for rescue purposes.

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 (with or without acetaminophen/paracetamol), not to exceed 30 mg total daily dose.

2. Oxycodone (with or without acetaminophen/paracetamol), not to exceed 15 mg total daily dose.

3. Tramadol (with or without acetaminophen/paracetamol), not to exceed 300 mg total daily dose.

For subjects who ARE on stable, background opioid therapy:

- They may NOT add a second opioid agent for rescue;

- 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;

- If their background medication is a short-acting (half-life <5 hrs, Appendix 4) 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 4]) for rescue purposes;

- Sustained release opioid formulations (eg, OxyContin®, MS Contin®) and opioids with half lives greater than 5 hours (eg, methadone, propoxyphene) may NOT be USED for rescue medication.

Sustained release opioid formulations (eg, OxyContin®, MS Contin®) and opioids with half lives greater than 5 hours (eg, methadone, propoxyphene; see also Appendix 4) may NOT be INCREASED for rescue purposes.

Intravenous or intramuscular corticosteroids, biologic response modifiers and DMARDs, other than methotrexate and sulfasalazine, are not allowed during this study. Intra-articular corticosteroids may be given at or after the Month 3 visit in no more than two joints, in a cumulative dose of no more than 40 mg methylprednisolone or its equivalent in any 6 month study period. The total allowed intraarticular corticosteroid dose may be divided into separate injections (eg, 20 mg, 20 mg). Intra-articular hyaluronate sodium injections may be administered for indications in accordance with the local label at or after the Month 3 visit in no more than two joints in any 6 month study period. If performed at Month 3 visit, intra-articular injections must be given after assessments are completed. Intra-articular corticosteroids should not be administered within 4 weeks prior to a study visit.

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 2.6 gm/day. 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. Baseline stable acetaminophen/paracetamol or opioids should NOT be discontinued in advance of study visits.

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

Appendix 6. Evaluation of Potentially Malignant Tumors, Suspicious Lymphadenopathy, Possible Extranodal Lymphoproliferative Disorder (LPD)

The following steps should be taken in the event of potentially malignant tumors, lymphadenopathy or possible extranodal lymphoproliferative disorder (LPD) which might arise in the course of this study.

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

If a biopsy for lymphadenopathy or lymphoma is to be performed, the investigator or consultant should refer to the instructional slide deck in the Lymph Node Biopsy kit and review the following points with the surgeon and pathologist:

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

For all biopsies, please request the pathologist to send the original slides used to make the definitive diagnosis, ancillary study reports, and the pathologist's report to the central laboratory.