A LONG-TERM, OPEN-LABEL EXTENSION STUDY OF TOFACITINIB (CP-690,550) FOR THE TREATMENT OF PSORIATIC ARTHRITIS

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Investigational Product Name:	Tofacitinib
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Phase:	3

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 4	12 April 2017	• Updated template changes in appropriate sections and corrected typographical errors. • Protocol Summary updated to reflect new sub-study. • Sections 1.2.2., 1.2.3 and 1.2.4. Updated with information from Tofacitinib December 2016 Investigator's Brochure. • Incorporated administrative letters in Sections 5.6.1 and 7.6.9.1. • Section 9. Updated to reflect changes for the sub-study. • Section 16. Updated reference style, per template. • Updated abbreviations list, due to missing and with addition of sub-study. • Appendix 10-Methotrexate Withdrawal Sub-Study added and updated main protocol in appropriate sections in reference to the sub-study.
Amendment 3	01 February 2015	• Sections 4.2.1, 4.4.6.1, Appendix 9. Additional contraceptive requirement for women of childbearing potential in Canada based upon Health Canada Guidance document: Consideration for Inclusion of Women in Clinical Trials and Analysis of Sex Differences • Sections 4.2.1, 4.4, 5.6.2, Appendix 3. Clarification of prohibited medications, per regulatory request. • Sections 5.7, Appendix 6. Clarification of rescue medication use, per regulatory request. • Section 7.6.8, 9.6. Clarification of requirements for events for review/adjudication. Update of adjudicated safety review committees to include Gastrointestinal Perforation Review Committee.
Amendment 2	13 August 2014	• Section 4.1.2. Added "by the central laboratory" to inclusion #5. • Section 4.4.6. Inclusion of requirement for 2 highly effective contraceptive methods for women of child-bearing potential (United Kingdom only). • Section 9.6. Updated adjudication/review committee language. • Pfizer protocol template updates including Section 5.4 (Drug Storage), 5.5 (Drug Accountability), 8 (Adverse Event Reporting) and 15 (Publication of Study Results).
Amendment 1	07 February 2014	• Updated Introduction to reflect November 2013 tofacitinib Investigator's Brochure. • Included certoluzimab minimum treatment duration and washout information (Appendix 3) since recent marketing approval for PsA. • Section 4.2.1. Addition of infection exclusion criteria #11 and exclusion criteria (#15) for subjects

		at risk of GI perforation per regulatory request. • Section4.4.6. Clarification of use of sexual abstinence as contraceptive method only when consistent with preferred and usual subject lifestyle, per regulatory request. • Section 4.6. Modification of rater qualifications for Physician's Global Assessments to include healthcare professionals competent to perform the assessments. • Section 7.6.3. Inclusion of requirements for reviewer of TB tests per local standard of care per regulatory request.
Original protocol	14 May 2013	N/A

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

PROTOCOL SUMMARY

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 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 tofacitinib 5 mg twice a day (BID) received Food and Drug Administration (FDA) approval 6 November 2012 for this indication. Efficacy and safety of oral dosing with tofacitinib in subjects with plaque psoriasis has previously been demonstrated in a Phase 2 dose ranging study and is currently being investigated in Phase 3 registration studies.

This Phase 3 study is a long-term extension (LTE) study designed to evaluate the safety and tolerability of tofacitinib as a treatment for PsA.

An optional sub-study is included to assess the efficacy, safety and tolerability of tofacitinib 5 mg BID administered as monotherapy after methotrexate (MTX) withdrawal compared to tofacitinib 5 mg BID in combination with MTX. Subjects who have completed at least 24 months of participation in the long term extension study and are currently receiving tofacitinib 5 mg BID in combination with oral methotrexate are eligible to participate. Details are included in Appendix 10.

Objectives:

- To evaluate the long term safety and tolerability of treatment with tofacitinib (5 mg twice daily [BID] and 10 mg BID) in adult subjects with active PsA.
- To evaluate the long term efficacy of tofacitinib (5 mg BID and 10 mg BID) in adult subjects with active PsA.

Study Design:

This is a Phase 3, long-term, open-label extension study designed to evaluate the safety, tolerability and efficacy of tofacitinib in subjects with active PsA. Subjects with active PsA will have previously participated in randomized studies of tofacitinib. For subjects who are completing participation in a randomized study of tofacitinib, the final visit of the qualifying study can be combined with screening and baseline visit for this study. Additional assessments and inclusion/exclusion criteria are required for subjects who enroll >14 days

after completing treatment in their qualifying study. In this case, a separate screening visit to determine subject eligibility is required followed by a baseline visit.

All eligible subjects from qualifying studies A3921091 and A3921125 will receive open-label tofacitinib 5 mg BID upon entry into A3921092. Subjects from A3921091 will receive first dose of study medication ≥1 week after last injection of study medication in that qualifying study. Tofacitinib dose may be increased to 10 mg BID at study visits if, based upon investigator's discretion, subjects receiving tofacitinib 5 mg BID would benefit from a higher dose and are not experiencing any tofacitinib-related adverse events, including abnormalities in laboratory test results that are judged to be related to tofacitinib. Tofacitinib dose may be decreased (ie, 10 mg BID to 5 mg BID) for safety reasons at any time. Treatment duration for subjects participating in the main LTE study is approximately 3 years (36 standardized 4-week months). Subjects participating in the sub-study may have up to an additional 1 year (12 standardized 4-week months) of treatment for a maximum potential total of approximately 4 years (48 standardized 4-week months).

At various time points in this trial, safety measurements, including physical examination, clinical laboratory tests, adverse event monitoring, electrocardiograms (ECGs) and vital signs will be performed. All subjects will be monitored for clinical evidence of PsA response to treatment. Health Outcomes Measures (ie, Patient Reported Outcomes assessments for pain, quality of life, physical function, fatigue, work limitations, health care resource utilization and health status) will also be performed at various time points in this trial. In addition, subjects will be monitored for serious infections, lymphadenopathy and lymphoproliferative disorder (LPD).

Study design of the sub-study is found in Appendix 10.

Statistical Methods:

There will be 2 sets of analyses: one for the A3921092 long-term extension (LTE) and the other for the sub-study. For the A3921092 LTE, the safety analysis will include cumulative data from all the subjects and all the data (including the data collected in the sub-study). The efficacy analysis will include only the data collected in the A3921092 LTE (the efficacy data collected in the sub-study will be evaluated separately for the sub-study).

Statistical methods for the sub-study are found in Appendix 10.

The analyses for the primary endpoints will be descriptive in nature. Adverse events (AEs), Serious Adverse Events (SAEs), laboratory tests and vital signs will be summarized in accordance with Pfizer Data Standards. Secondary endpoints (including additional safety, efficacy and Health Outcome Measure endpoints) will be summarized by descriptive statistics at each visit at which they are collected.

Table 1. Schedule of Activities

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol. Subjects participating in the sub-study should refer to the Schedule of Activities in Appendix 10.

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.

Protocol Activity	Subjects >14 days after EOS Visit[1]		Combined with EOS Visit[2]	Separate Visit within 14 days after EOS Visit[3]	Month 1 (±7 days)	Month 3 (±7 days) then Q6 mos* (±10 days)	Month 6 then Q12 mos** (±10 days)	Month 12 then Q12 mos*** Or Early Termination (±10 days)	Follow-Up Phone Call[4]	Follow-up Visit[5]
					A	B	C	D		
	Screen	Baseline	Screening /Baseline	Screening /Baseline						
Informed Consent	X		X	X						
Medical History, Disease Activity Assessment[6]	X									
CV Risk Assessment[7]	X						X	X		
Register for subject identification number	X		X	X						
Complete Physical Exam[8]	X							X		
Targeted Physical Exam[8]		X		X	X	X	X			
Vital signs, temperature	X	X		X	X	X	X	X		
Waist and hips circumference		X			X		X	X		
12-Lead ECG[9]	X							X		
QuantiFERON or Mantoux PPD /Chest Radiograph, if Necessary[10]	X							X[10]		
LABORATORY TESTING										
Hematology, Chemistry Panel[11]	X	X		X	X	X	X	X		X
CRP[11]	X	X		X	X	X	X	X		
Hemoglobin A1c (HbA1c)[11]		X					X	X		

Protocol Activity	Subjects >14 days after EOS Visit[1]		Combined with EOS Visit[2]	Separate Visit within 14 days after EOS Visit[3]	Month 1 (±7 days)	Month 3 (±7 days) then Q6 mos* (±10 days)	Month 6 then Q12 mos** (±10 days)	Month 12 then Q12 mos*** Or Early Termination (±10 days)	Follow-Up Phone Call[4]	Follow-up Visit[5]
					A	B	C	D		
	Screen	Baseline	Screening /Baseline	Screening /Baseline						
Lipid panel (fasting)[12]		X				X[12]	X	X		X
CBC with Differential and Chemistry Labs[13]					As required for Standard Of Care					
Lymphocyte subset analysis (FACS)		X				X	X	X		
Urinalysis[14]	X	X		X	X	X	X	X		
Urine pregnancy test (hCG)[15]	X	X		X	X	X	X	X		X
HIV Serology, HBsAg, HBcAb, HCV Ab	X									
Stool Examination (Brazilian Sites Only)	X									
CLINICAL EVALUATION OF RHEUMATOLOGY ENDPOINTS										
Tender/Painful Joint Count, Swollen Joint Count	X	X		X	X	X	X	X		
Physician's Global Assessment of Arthritis (VAS)		X		X	X	X	X	X		
Dactylitis Assessment		X			X	X	X	X		
Enthesitis Assessment (SPARCC and Leeds Index)[16]		X			X	X	X	X		
CLINICAL EVALUATION OF RHEUMATOLOGY/DERMATOLOGY ENDPOINTS										
Physician's Global Assessment of Psoriatic Arthritis (VAS)		X			X	X	X	X		
CLINICAL EVALUATION OF DERMATOLOGY ENDPOINTS										
Physician's Global Assessment of Psoriasis (PGA-PsO)[17]		X			X	X	X	X		
Psoriasis Area and Severity Index (PASI); Body		X			X	X	X	X		

Protocol Activity	Subjects >14 days after EOS Visit[1]		Combined with EOS Visit[2]	Separate Visit within 14 days after EOS Visit[3]	Month 1 (±7 days)	Month 3 (±7 days) then Q6 mos* (±10 days)	Month 6 then Q12 mos** (±10 days)	Month 12 then Q12 mos*** Or Early Termination (±10 days)	Follow-Up Phone Call[4]	Follow-up Visit[5]
					A	B	C	D		
	Screen	Baseline	Screening /Baseline	Screening /Baseline						
Surface Area (BSA)[17]										
Nail Psoriasis Severity Index (NAPSI) [18]		X			X		X	X		
PATIENT REPORTED OUTCOMES[19]										
Patient's Assessment of Arthritis Pain (VAS); Patient's Global Assessment of Arthritis (VAS); HAQ-DI[20]		X		X	X	X	X	X		
Itch Severity Index (ISI)		X			X		X	X		
Patient's Global Joint and Skin Assessment (PGJS-VAS)		X			X	X	X	X		
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); Ankylosing Spondylitis Quality of Life (ASQOL)		X			X	X	X	X		
SF-36, FACIT-F, EuroQol EQ-5D, PsA-HCRU, WLQ, DLQI[20]		X			X		X	X		
OTHER ACTIVITIES										
Adverse Event Assessment		X		X	X	X	X	X	X	X
Prior/Concomitant Treatment	X	X		X	X	X	X	X		X
Dispense study medication/Accountability[21]		X	X	X	X[21]	X	X	X[21]		

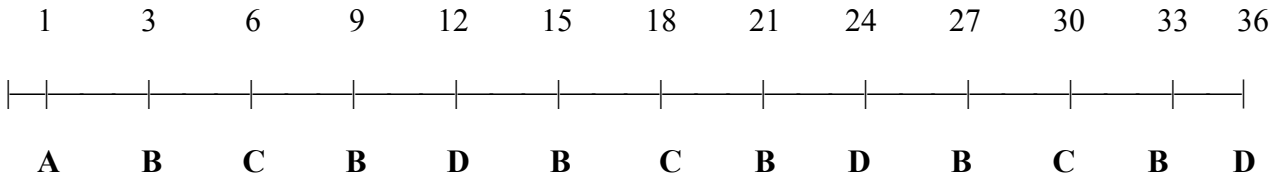
* Study visit Type B will occur every 6 months after Month 3 (eg, Month 9, 15, 21, 27,[22] 33[22]). See Figure 1.
**Study visit Type C will occur every 12 months after Month 6 (eg, Month 18, 30[22]). See Figure 1.
***Study visit Type D will occur every 12 Months after Month 12 (eg, Month 24,[22] 36[22]). See Figure 1.

1. Subjects who are qualified to enter A3921092 extension study and do so >14 days (but ≤3 months) after early termination or end of study (EOS) visit in qualifying study must undergo re-screening procedures and have separate visit for baseline activities. Baseline visit must occur 2-28 days after Screening visit.
2. Subjects who are qualified to enter A3921092 extension study and do at the end of study (EOS) visit in qualifying study do not need to be rescreened or have an additional baseline visit.

3. Subjects who are qualified to enter A3921092 extension study and do not do so at the end of study (EOS) visit but <14 days after early termination or EOS in parent study do not need to be re-screened but require procedures performed for baseline.
4. For those subjects that complete the study, follow-up phone call will be made to subjects within 7 days after the 28 days following EOS visit and adverse events noted.
5. If a subject discontinues from the study due to abnormal hematology or clinical chemistry results which meet criteria as described in Appendix 4, or discontinues due to an adverse event, a follow-up visit must be performed after the Early Termination visit within 28 days (±7 days) of last dose of study treatment.
6. Disease Activity Assessment must be performed on subjects who enroll >14 days after end of study visit in qualifying study to determine if subject has sufficient evidence of PsA disease activity to warrant use of tofacitinib as a DMARD (Section 7.1.1).
7. Cardiovascular (CV) Risk Factor Assessment includes multiple assessments such as smoking status, average weekly alcohol consumption, and family history of premature coronary heart disease (CHD) (See Section 7.4 for complete list).
8. Complete physical exam should be performed annually (Month 12, 24 and 36) and includes: height, weight, general appearance, skin, HEENT (head, eyes, ears, nose and throat), heart, lungs, abdomen, lower extremities, neurologic and lymph nodes. Targeted physical exam should be performed at other scheduled visits and includes: weight, examination of heart, lungs, abdomen, lower extremities (for peripheral edema) and lymph nodes.
9. 12-lead ECG will be taken at annual visits (Month 12, 24 and 36) and Early Termination (ET) visit only. ECG will be evaluated by a central reader.
10. Tuberculosis screening procedures must be performed if not completed in the last 3 months. Subjects who have PPD must return within 48-72 hours for evaluation. Annual TB screening will be conducted using Quantiferon-TB® Gold In-Tube test (QFT) for subjects in those countries in which TB incidence has been reported at a rate of >50 cases per 100,000 persons (see Section 7.6.3). All subjects with positive results (and who tested negative at their last QFT) must have chest radiograph performed and reviewed by a radiologist or pulmonologist as per local standard of care.
11. Hematology includes: white blood cell (WBC) count/differential, hemoglobin, hematocrit, red blood cell (RBC) count and morphology, reticulocyte and platelet counts. Serum chemistry 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). All hematology, clinical chemistry tests and HbA1C will be performed by the central laboratory; C-reactive Protein (CRP) will also be measured by central laboratory.
12. A fasting lipid panel (total cholesterol, LDL, HDL, triglycerides, apolipoprotein A-1 and B) and other lipoprotein tests potentially including particle size measurements Table 8 will be collected at the baseline visit for subjects who enroll more than 14 days after their EOS visit from their qualifying study; for all subjects at Month 3, Month 6 (Study Visit Type C) and every 6 months thereafter (Study Visits Type C and D).
13. Clinical chemistry as appropriate for standard of care in subjects receiving background non-biologic DMARDs may include creatinine, albumin and liver function tests.
14. 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).
15. Urine pregnancy testing (human chorionic gonadotropin; β-hCG) is required only for women of childbearing potential.
16. Enthesitis will be assessed using the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index and Leeds Enthesitis Index.
17. 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 of qualifying study.
18. Nail Psoriasis Severity Index (NAPSI) will be performed on target nail identified at baseline/Visit 1 of qualifying study.

19. All Patient Reported Outcomes should be completed prior to any other assessments made at each visit.
20. Subject completed questionnaires include: Health Assessment Questionnaire-Disability Index (HAQ-DI), Short-Form-36 Health Survey (Version 2, Acute) (SF-36), EuroQol 5 Dimensions (EQ5D), Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F), Dermatology Quality of Life Index (DLQI), Work Limitation Questionnaire (WLQ).
21. Study medication will not be dispensed at Month 1 or End of Treatment or Early Termination visit; however, drug accountability will be performed. If the subject participates in the sub-study, the investigational product for the main LTE will be collected at the time of entry into the sub-study and accountability completed.
22. At Month 24, 27, 30, 33, or 36 of the LTE, subjects may enter the sub-study. Please refer to Appendix 10 for the sub-study requirements and procedures. These subjects will complete the study procedures scheduled at the chosen visit (Month 24, 27, 30, 33, or 36) of the LTE and the additional requirements and procedures of the sub-study (Appendix 10).

Figure 1. Assessments at Each Visit Grouped by Letter in Schedule of Activities



Letter indicates activities to be performed at that month (See Table 1. Schedule of Activities).

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1. INTRODUCTION

1.1. Indication

Tofacitinib is being developed for the treatment of adult subjects with active Psoriatic Arthritis (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 purpose of treatment is to control disease activity, alleviate signs and symptoms, maintain physical function, optimize quality of life, and, if possible, induce complete remission.

There is very little clinical study data to support the efficacy of traditional disease-modifying anti-rheumatic drugs (DMARDs) in PsA (eg, methotrexate, sulfasalazine).[2] Traditional DMARDs may not always slow or prevent progressive joint damage and may be associated with clinical tolerability and/or safety issues. Tumor Necrosis Factor inhibitors (TNFi) have demonstrated in published clinical studies evidence of both efficacy (signs, symptoms and retardation of joint damage) and safety and are the only biologic agents indicated for the treatment for PsA.[3] Use of TNF inhibitors remains limited with inconvenience of the required parenteral routes of administration and apparent loss of initial efficacy with continued use in a significant proportion of patients. There is therefore potential unmet medical need for new DMARDs in the PsA patient population.

This open-label study will evaluate the long-term safety and tolerability of tofacitinib for treatment of PsA.

An optional sub-study is included to assess the efficacy, safety and tolerability of tofacitinib 5 mg BID administered as monotherapy after methotrexate (MTX) withdrawal compared to tofacitinib 5 mg BID in combination with MTX. Subjects who have completed at least 24 months of participation in the long term extension study and are currently receiving tofacitinib 5 mg BID in combination with oral methotrexate are eligible to participate. Details are included in Appendix 10.

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.[4,5,6] These cytokines are integral to lymphocyte activation, proliferation, and function and inhibition of their signaling may thus result in suppression 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. In addition to interfering with Th1 and Th2 cell differentiation, tofacitinib has been shown to interfere with the production of inflammatory Th17 cells.[7] These effects provide the basis for use in diseases in which the immune response plays a pathogenic role such as PsA.[8,9]

1.2.2. Summary of Efficacy

1.2.2.1. Rheumatoid Arthritis

Efficacy and safety of oral dosing with tofacitinib in Rheumatoid Arthritis (RA) subjects has been demonstrated in Phase 2 and 3 studies and tofacitinib 5 mg BID received FDA approval for this indication.

In the tofacitinib twice daily RA program, there were 6300 adult patients exposed to tofacitinib BID as of May 2016 in the Phase 2 and Phase 3 studies and an ongoing Phase 3b/4 post authorization safety study. These studies, which are summarized in the tofacitinib Investigator's Brochure, ranged from 6 to 24 weeks in duration. Subjects enrolled in these qualifying studies had the opportunity to roll-over into either one of two long-term, open-label extension studies to continue with tofacitinib active treatment (A3921024 or A3921041, also summarized in the tofacitinib Investigator's Brochure).

The tofacitinib RA clinical development program has conclusively demonstrated the efficacy of tofacitinib 5 mg BID and 10 mg BID in treating moderate to severe RA in patients who had experienced an inadequate response or intolerance to DMARDs, most commonly MTX. Consistent and sustained improvements were observed in efficacy measures that are clinically relevant to patients and practitioners and across a variety of clinical scenarios within populations that would be eligible for treatment within the RA indication. A comparison of various measures of efficacy, including improvements in signs and symptoms, physical function and radiographic data indicated that the efficacy of tofacitinib is generally comparable between 5 mg BID and 10 mg BID, with potential for greater probability of response with the 10 mg BID dose in the more stringent outcomes such as remission and Low Disease Activity (LDA). Onset of benefit with tofacitinib use was rapid and response was durable. Improvement in signs and symptoms was demonstrated after as little as 2 weeks of treatment with tofacitinib, and maintained after more than 7 years of continued treatment in the uncontrolled LTE studies. More detailed information can be found in Section 6.2 of the Investigator's Brochure.

1.2.2.2. Plaque Psoriasis

The tofacitinib development program in patients with moderate to severe chronic plaque psoriasis was comprised of 2 Phase 3 randomized, placebo-controlled studies (A3921078 and A3921079), 1 Phase 3 placebo-controlled active comparator study (A3921080), 1 Phase 3 withdrawal/retreatment study (A3921111) and 1 Phase 3 open-label LTE study (A3921061). The primary efficacy outcomes in the program included the proportion of patients with a Physician's Global Assessment (PGA) response of "clear" or "almost clear" and the

proportion of patients with at least a 75% reduction in Psoriasis Area and Severity Index (PASI) relative to baseline (ie, PASI75) response.

Tofacitinib 5 mg BID or 10 mg BID treatment resulted in consistent and significant improvement in multiple variables:

- Clinically meaningful improvements in the PGA response of "clear" or "almost clear" and PASI75 response were demonstrated in the tofacitinib 5 mg BID and 10 mg BID dose groups relative to placebo. In studies A3921078 and A3921079, the PGA and PASI75 response rate were statistically superior to placebo at the 16-week primary time point.

- Tofacitinib 10 mg BID was statistically significantly superior to placebo and non-inferior to high-dose etanercept (50 mg twice weekly subcutaneously) at 12 weeks in the PGA and PASI75 responses in study A3921080.

Additional information on completed and ongoing psoriasis studies can be found in the current version of the tofacitinib Investigator's Brochure.

1.2.2.3. Phase 3 PsA Studies

The tofacitinib Phase 3 program was designed to evaluate the efficacy of tofacitinib 5 mg BID and 10 mg BID in patients with active PsA. The 2 tofacitinib Phase 3 pivotal studies (A3921091 and A3921125) compared the efficacy of both tofacitinib doses to that of placebo over 3 months for improvements in multiple PsA domains, examined the onset of efficacy, and assessed the persistence of efficacy of both tofacitinib doses in conventional synthetic disease-modifying anti-rheumatic drug-inadequate responder (csDMARD-IR) TNFi-naïve and TNFi-IR populations. All study participants randomized to placebo were advanced in a blinded fashion at Month 3 to either tofacitinib 5 mg BID or 10 mg BID and treatment duration was a total of 12 months in A3921091 and 6 months in A3921125.

The first Phase 3 PsA study, A3921091 has completed and the primary endpoints were met. The American College of Rheumatology 20% response rate (ACR20) was statistically significantly greater for both tofacitinib 5 mg BID and 10 mg BID dose treatment groups than the placebo treatment group at Month 3. The mean change from baseline (decrease) in the Health Assessment Questionnaire-Disability Index (HAQ-DI) was statistically significantly greater than placebo for both tofacitinib 5 mg BID and 10 mg BID dose treatment groups at Month 3. Evidence of efficacy was also observed across other PsA domains (secondary endpoints) and was maintained to Month 12.[10]

Results from the second Phase 3 PsA study, A3921125 demonstrated that there were significantly greater improvements in ACR20 response rate and ΔHAQ-DI for both doses versus placebo; improvement persisted to Month 6.[11]

1.2.3. Summary of Safety

The clinical development program for oral tofacitinib includes healthy volunteers and subjects with RA, plaque psoriasis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), ankylosing spondylitis, psoriatic arthritis and renal transplants enrolled in Phase 1, 2 and 3 studies.

Over 22,000 subjects have received at least one oral dose of tofacitinib in a clinical trial as of January 2016. Of these, approximately 8700 subjects have continued clinical trial participation by enrolling in long-term extension studies or other types of continuation studies.

Potential safety risks for subjects treated with tofacitinib are based on the totality of the data including nonclinical and clinical data across the entire tofacitinib development program with the majority of clinical data coming from studies in RA and PsO patient populations, including open-label extension studies. These risks include serious and other important infections such as tuberculosis, opportunistic infections and herpes zoster (HZ) infections, potential for malignancies including lymphoma, and the potential for gastrointestinal (GI) perforations. Subjects receiving tofacitinib may be at increased risk for non-melanoma skin cancer (NMSC). Based on nonclinical data, there is potential for tofacitinib to have effects on pregnancy and the fetus.

It has long been recognized that RA is associated with accelerated atherosclerosis and increased cardiovascular (CV) mortality and morbidity. The incidence of CV events during treatment with tofacitinib in RA patients was evaluated by an independent, external CV adjudication committee. No evidence of heightened CV risk was found. Tofacitinib was not associated with an increase in adjudicated CV events within the PsO development program.

Interstitial lung disease (ILD) is a serious comorbidity in RA patients. Risk factors for the development of ILD in RA include Asian race, older age, male gender, higher RA disease activity and treatment with corticosteroids or MTX. The incidence rate of ILD and geographic variation seen in patients treated with tofacitinib are consistent with what has been reported in literature. For additional information, please refer to Section 6.2.3.1.5 of the IB.

Laboratory changes associated with the oral use of tofacitinib treatment in humans include decreases in hemoglobin levels, absolute neutrophil counts (ANC), and absolute lymphocyte count, increases in total cholesterol, HDL cholesterol, LDL cholesterol, transaminases, serum creatinine, and creatine kinase (CK). Recovery of laboratory changes upon discontinuation of tofacitinib treatment is characteristically observed. The safety profile of tofacitinib in both rheumatoid arthritis and psoriasis subject populations is qualitatively similar. The current safety profile for the treatment of PsA across both studies, A3921091 and A3921125 is similar to that reported for RA and no new risks have been identified.[10,11]

Interpretation of these results and the possible risks associated with the administration of tofacitinib are summarized in Section 6.2.3 (Special Safety) and Section 7 (Summary of Data and Guidance for the Investigator) of the 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.

The benefits to individual subjects participating in this study will be the potential continued control of their PsA disease activity including rheumatological signs and symptoms (eg, joint swelling/tenderness, enthesitis, dactylitis and spondylitis), dermatological manifestations (eg, skin plaques), physical function and fatigue. 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 the RA program, the serious infection rate in tofacitinib-treated subjects was consistent with the rates of serious infections in patients treated with other therapeutic interventions including biologic DMARDs. In the PsO program the serious infections overall rate was lower than was observed for the RA program. Serious infections were more frequent among the elderly (>65 years), subjects with diabetes mellitus and subjects treated previously with biological agents. Caution is also recommended in subject with a history of chronic lung disease as these patients may be more prone to infections. Rates of herpes zoster infections in tofacitinib-treated subjects with RA were increased compared with placebo-treated RA subjects and historical controls; this included an increased risk of herpes zoster infections in Asian RA patients compared with non-Asian RA patients. In the tofacitinib RA clinical development program, the rate of HZ varied significantly across countries and regions. The incidence rates of HZ in Japan and Korea were notably higher than the rates observed in other regions/countries. The reason for the increased risk of HZ in Japan and Korea is unclear.

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. Anemia is a possible consequence of JAK2 inhibition. Experience to date indicates that anemia is easily monitored, usually manageable without discontinuation of drug, and reversible upon discontinuation of tofacitinib. Neutropenia is of primary concern by virtue of its relationship to an increased risk of infection. Thus far, no association between the occurrence of neutropenia and infection has been observed in the tofacitinib program.

Treatment with tofacitinib was associated with increases in levels of LDL and 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. In light of the association of RA and accelerated atherosclerosis, CV mortality and morbidity CV events were evaluated by an independent CV adjudication committee. Review of cardiovascular events by the committee reported in

the RA and PsO studies suggests that tofacitinib was not associated with an increase in major adverse cardiovascular events.

Also seen in previous studies were slight increases in measured serum creatinine and serum transaminases. This effect generally returned to normal 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. No additional possible DILI cases and no confirmed Hy's Law cases have been identified during adjudication by the Hepatic Event Review Committee (HERC).

NMSC has been acknowledged as an adverse drug reaction for tofacitinib based on review of data in the RA subjects. There has been no identified increased risk of other types of malignancy for tofacitinib, although an increased incidence of post-transplant lymphoproliferative disorders (PTLD) was observed in tofacitinib-treated subjects in a renal transplant study where combination of multiple potent immunosuppressants was used in conjunction with tofacitinib. Other malignancies observed (at varying frequencies depending upon the population under study) include lung and breast cancer, lymphoma, melanoma, colon and prostate cancer. Pancreatic and other cancers have also been reported less frequently.

Cases of GI perforation were observed in RA subjects taking tofacitinib, often in the setting of diverticulitis. All affected subjects had underlying risk factors, including a history of concomitant drug treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids that have been associated with an increased risk of GI tract injury.[12,13] Isolated events of gastrointestinal perforation have also been reported in clinical trials in other tofacitinib indications including one (preferred term: appendicitis) in the A3921091 study.

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 but there was no consistent dose relationship.

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 in Section 6.2.3.

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 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 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

Tofacitinib has demonstrated efficacy in RA as both monotherapy (Phase 2 dose ranging Studies A3921019, A3921035, A3921040 and Phase 3 Study A3921045) and in combination with methotrexate (Phase 2 dose ranging studies A3921025, A3921039 and Phase 3 studies A3921032, A3921044, A3921046 [methotrexate, sulfasalazine and other traditional DMARDs] and A3921064). Efficacy in relieving signs and symptoms and in restoring physical function was demonstrated at the ACR20 primary endpoint, and secondary efficacy endpoints including ACR50, ACR70, Disease Activity Score 28 (DAS 28) and the HAQ-DI. The safety of tofacitinib in RA patients at doses lower than 15 mg was also demonstrated. After review of the Phase 2 dose ranging studies, tofacitinib doses of 5 mg and 10 mg BID were selected to be used in the Phase 3 registration program for RA.

Tofacitinib has demonstrated efficacy and safety in plaque psoriasis in the PsO program and more recently in the 2 Phase 3 PsA studies that have just completed.

This Phase 3 study is intended to provide long-term safety and tolerability data for tofacitinib when dosed at 5 mg BID or 10 mg BID in adult patients with PsA.

1.2.7. Dose Selection Rationale

Doses of tofacitinib (5 mg BID and 10 mg BID) that were previously demonstrated to be efficacious in the RA and psoriasis Phase 2 development programs are currently being, or have been, studied in their respective Phase 3 programs. These tofacitinib doses of 5 mg BID and 10 mg BID will also be evaluated in this long-term extension study in PsA subjects.

Tofacitinib doses of 5 and 10 mg BID were selected for the Phase 3 programs for each of these indications based on modeling of extensive Phase 2 dose-response data. The Phase 2 programs include 5 studies in RA patients (A3921019, A3921025, A3921035, A3921039 and A3921040) and 1 study in psoriatic patients (A3921047). The dose selection for RA was based primarily on study A3921025, which evaluated 5 doses (1, 3, 5, 10 and 15 mg BID tofacitinib and placebo for up to 24 weeks). The dose selection for psoriasis was based primarily on study A3921047 in which 3 doses of tofacitinib were studied (2, 5 and 15 mg BID) for up to 12 weeks.

For each program, a review of several efficacy and safety outcomes was performed to identify key drivers for dose selection. The selection of doses for RA was based on longitudinal dose-response modeling of the ACR20, ACR50 and ACR70 responses for efficacy and changes in hemoglobin (and associated anemia incidence) for safety. Similarly, the selection of doses for psoriasis was based on modeling of PASI75 and PGA endpoints for efficacy and changes in hemoglobin for safety. Dose selection was principally based on the probability of achieving a clinically meaningful target effect (PTE), where the target effect was defined in terms of a placebo-adjusted difference at a specific time point that is considered to be clinically meaningful. Doses that were considered for Phase 3 were those that achieved a PTE of approximately 50% or higher on each endpoint. The relationships between tofacitinib dose and PTE are displayed in Figure 2 and Figure 3 for RA and psoriasis, respectively. As shown in the figures, the 5 and 10 mg BID doses met the criteria (PTE of approximately 50% or higher on nearly all endpoints) for progression into Phase 3 for both indications.

Figure 2. Probability of Achieving Target Effect for Efficacy (ACR20, ACR50 and ACR70) and Safety (Incidence of Anemia) Endpoints Based on Modeling of Study A3921025 Data in RA Patients

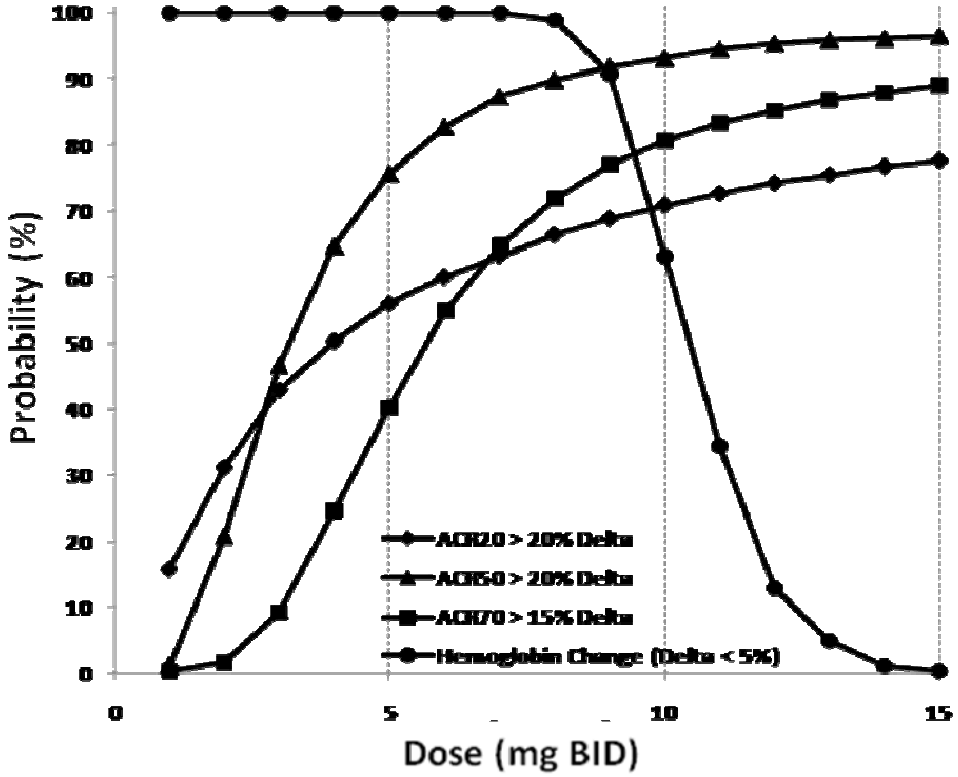
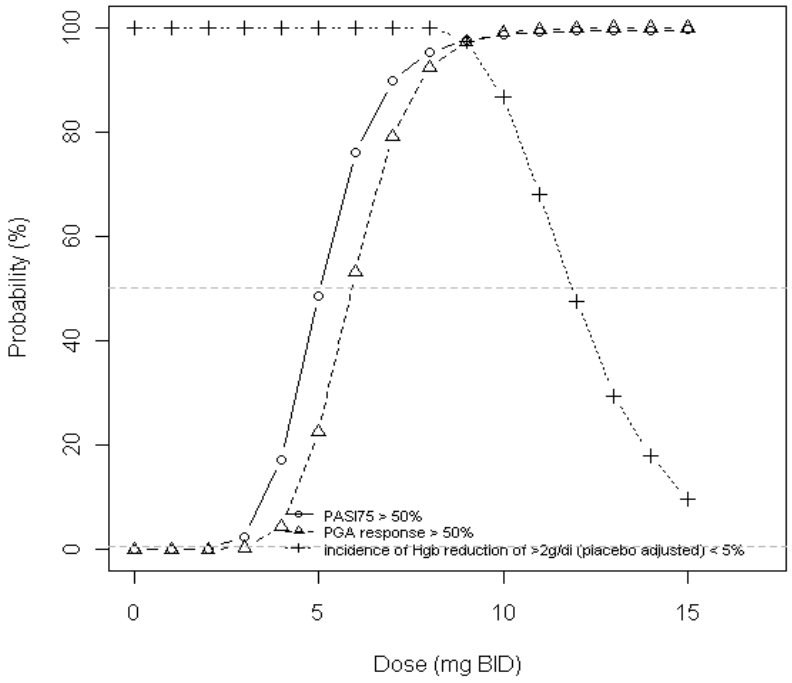


Figure 3. Probability of Achieving Target Effect for Efficacy (PASI75 and PGA Responses) and Safety (Incidence of Hemoglobin Change) Endpoints Based on Dose/Exposure Response Modeling of Study A3921047 Data in Psoriatic Patients



In RA patients, the inclusion of tofacitinib 5 mg BID as the lowest dose for Phase 3 reflects the predicted increased PTE over, for example, the 3 mg BID dose on ACR50 (77% for 5 mg BID vs 49% for 3 mg BID) and ACR70 (50% for 5 mg BID vs. 14% for 3 mg BID), without any loss in the PTE for anemia. The inclusion of tofacitinib 10 mg BID in the Phase 3 program reflects the possibility of increased benefit over the 5 mg BID dose on ACR70 (80% PTE for 10 mg BID vs 50% for 5 mg BID), and/or for structure preservation while maintaining a sufficiently conservative safety profile. ACR20/50/70 results observed in the RA Phase 3 studies confirmed the selection of tofacitinib 5 mg BID and 10 mg BID doses in that population.

In psoriasis patients, the tofacitinib 5 and 10 mg BID doses provided acceptable PTE for PASI75 (49% and 99%, respectively) and a high probability of observing a placebo-adjusted incidence rate <5% for a hemoglobin decrease of >2 g/dL from baseline (100% and 87%, respectively), although 5 mg BID did not achieve the desired PTE for PGA response (23% ie, less than the target of 50%). However, the model predictions for the 5 mg BID suggested an adequate placebo-adjusted response rate for both PASI75 and PGA (50% and 46%, respectively) at this dose level. Thus, the inclusion of the 5 mg BID dose as the lowest dose for Phase 3 reflects the lowest dose that can achieve efficacy of the desired product profile. The inclusion of 10 mg BID in the Phase 3 studies reflects an increased benefit over the 5 mg BID dose on both PASI75 and PGA responses; predicted response rates are over 10% higher in the 10 mg BID dose group compared to the 5 mg BID group.

As tofacitinib has demonstrated efficacy and acceptable safety in both RA and plaque psoriasis, there is rationale to expect that it will be efficacious and acceptably safe in PsA.

Patients with peripheral joint involvement from PsA typically respond to those drugs that are indicated for the treatment of rheumatoid arthritis. The psoriatic skin involvement in PsA patients responds to those drugs that are indicated for the treatment for psoriasis. Thus drugs that are efficacious for both rheumatoid arthritis and psoriasis may therefore be expected to work in patients that have PsA. The doses of four TNFi currently approved for use in PsA are either the same or are very similar to the doses approved for their respective treatment of RA or psoriasis and all may be used with or without methotrexate. Although TNF inhibitors have a different mechanism of action than tofacitinib, there is rationale to expect that tofacitinib will demonstrate efficacy and safety in PsA comparable to that of tofacitinib treatment of RA.

Patients with PsA may be expected to respond to the same doses of tofacitinib that are safe and efficacious in rheumatoid arthritis and psoriasis. Tofacitinib 5 mg BID has been determined to be the minimum clinically important dose for both RA and plaque psoriasis, and this dose is selected as the lower dose to be studied in Phase 3 PsA parent studies (A3921091, A3921125). Additionally since tofacitinib 10 mg BID may offer benefit for patients with PsA, tofacitinib 10 mg BID was selected as the higher dose to be studied in the PsA Phase 3 studies. Therefore, both 5 mg BID and 10 mg BID tofacitinib doses will be included in this open label extension study.

Complete information for 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 Objective

- To evaluate the long term safety and tolerability of treatment with tofacitinib (5 mg twice daily [BID] and 10 mg BID) in adult subjects with active Psoriatic Arthritis (PsA).

2.1.2. Secondary Objective

- To evaluate the long term efficacy of treatment with tofacitinib (5 mg BID and 10 mg BID) in adult subjects with active Psoriatic Arthritis (PsA).

2.2. Endpoints

2.2.1. Primary Endpoints

- Incidence and severity of adverse events.

- Incidence of clinical abnormalities and change from baseline (in this and/or prior study) in clinical laboratory values during treatment.

2.2.2. Secondary Endpoints

- ACR20, ACR50 and ACR70 response rate at all time points.
- HAQ-DI score at all time points.
- Psoriatic Arthritis Response Criteria (PsARC) response at all time points.
- Physician's Global Assessment of Psoriasis (PGA-PsO) response at all time points.
- Psoriasis Area and Severity Index 75 (PASI75) response ie, the proportion of subjects achieving at least a 75% reduction in PASI relative to baseline (in this and/or prior study) and PASI/PASI component scores at all time points.
- Dactylitis severity score at all time points.
- Enthesitis score (using Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index and Leeds Index) at all time points.
- Bath Ankylosing Spondylitis Disease Assessment Index (BASDAI) at all time points.
- Physical function/other patient reported outcomes to be assessed at Month 1, Month 6 (and every 6 months thereafter): Short-Form 36 (version 2, Acute); EQ5D; Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F).

2.2.3. Other Endpoints

- DAS28-3 C-reactive protein (CRP) at all time points.
- Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity Index for Reactive Arthritis/PsA (DAREA/DAPSA), Composite Psoriasis Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PASDAS), Minimal Disease Activity (MDA) score and their components at all time points.
- Presence of dactylitis at all time points.
- Nail Psoriasis Severity Index (NAPSI) Score at Month 1, Month 6 (and every 6 months thereafter).
- Itch Severity Index (ISI) at Month 1, Month 6 (and every 6 months thereafter).
- Patient's Global Joint and Skin Assessment (PGJS-VAS) at all time points.
- Ankylosing Spondylitis Quality of Life questionnaire (ASQOL) at all time points.
- Physical function/other patient reported outcomes to be assessed at Month 1, Month 6 (and every 6 months thereafter): Dermatology Life Quality Index (DLQI); PsA Healthcare Resource Utilization Questionnaire (PsA HCRU); Work Limitations Questionnaire (WLQ).

- Incidence of investigator-reported clinically significant changes in physical examination from baseline (in this and/or prior study) during treatment.

- Incidence of electrocardiogram (ECG) abnormalities and change from baseline (in this and/or prior study) in ECG measurements during treatment.

- Incidence of vital sign (blood pressure and pulse rate) abnormalities and changes from baseline (in this and/or prior study) in vital sign measurements during treatment.

3. STUDY DESIGN

This is a Phase 3, long-term, open-label extension study designed to evaluate the safety, tolerability and efficacy of tofacitinib in subjects with active PsA who have previously participated in randomized PsA clinical studies with tofacitinib. For subjects who complete participation in such a randomized clinical study with tofacitinib, the final visit of the qualifying study can be combined with the screening and baseline visit for this study. Additional assessments and inclusion/exclusion criteria are required for subjects who enroll >14 days after completing treatment in their qualifying study. In this case, a separate screening visit to determine subject eligibility is required followed by a baseline visit.

All eligible subjects from qualifying studies A3921091 and A3921125 will receive open-label tofacitinib 5 mg BID upon entry into A3921092. Subjects from A3921091 will receive first dose of study medication ≥1 week after last injection of study medication in that qualifying study. Tofacitinib dose may be increased to 10 mg BID at study visits if, based upon investigator's discretion, subjects receiving tofacitinib 5 mg BID would benefit from a higher dose and are not experiencing any tofacitinib-related adverse events, including abnormalities in laboratory parameters that are judged to be related to tofacitinib. Tofacitinib dose may be decreased (ie, 10 mg BID to 5 mg BID) for safety reasons at any time during the study. Treatment duration for subjects participating in the LTE study is approximately 3 years (36 standardized 4-week months). Subjects participating in the sub-study may have up to an additional 1 year (12 standardized 4-week months) of treatment for a maximum potential total of approximately 4 years (48 standardized 4-week months).

At various time points in this trial, safety measurements, including physical examination, clinical laboratory tests, adverse event monitoring, electrocardiograms (ECGs) and vital signs will be performed. All subjects will be monitored for clinical evidence of response of PsA to treatment. Health Outcome Measures (ie, Patient Reported Outcomes assessment questionnaires for pain, quality of life, physical function, fatigue, work limitations, health care resource utilization and health status) will also be performed at various time points in this trial. In addition, subjects will be monitored for serious infections, lymphadenopathy and lymphoproliferative disorder (LPD).

Study design of the sub-study is found in Appendix 10.

4. SUBJECT SELECTION

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

4.1. Inclusion Criteria

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

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

4.1.1. Inclusion Criteria That Apply to All Subjects

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

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

3. Subjects must have a diagnosis of PsA and previously completed participation in a qualifying study of tofacitinib for the treatment of PsA or have required earlier discontinuation of treatment in a qualifying study for reasons other than treatment-related adverse events (exception being injection-related AEs) with the written approval of the Pfizer Clinician.

4. Subject must be at least 18 years of age (20 years old for subjects in Taiwan) or older at the Screening visit.

5. Subjects receiving permitted traditional non-biologic background DMARDs, eg, methotrexate, sulfasalazine or leflunomide, must be dosed in accordance with the local regulatory label.

   All local standard of care practices for administration of non-biologic background DMARD therapy, including laboratory testing, contraceptive requirements, follow-up care and contraindications, should be performed according to the local standards of care throughout 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 5.6). Subjects 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 gm/day. Minimum duration of therapy 2 months and dose stable for 4 weeks prior to first dose of study drug.

- Leflunomide: Maximum dose of 20 mg/day. Minimum duration of therapy 4 months and dose stable for 4 weeks prior to first dose of study drug.

- Other traditional non-biologic DMARDs not listed as a prohibited concomitant medication (see Appendix 3) may be considered after discussion with the Sponsor.

6. 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.

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

4.1.2. Inclusion Criteria That Apply to Subjects Who Enroll Into This Study After the 14 Day Window From the End of Study Visit of the Qualifying Study

1. Time from End of Study visit of qualifying study must be ≤3 months.

2. In the opinion of the investigator, the subject must have sufficient evidence of PsA disease activity to warrant use of tofacitinib as a DMARD.

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. Discontinuation criteria for biologics not otherwise mentioned must be discussed with the Pfizer Study Clinician.

4. Screening 12-lead electrocardiogram (ECG) that does not demonstrate clinically relevant abnormalities (as determined by central reader) 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).

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

   - A negative QuantiFERON-Gold® In-Tube test performed by the central laboratory within the 3 months prior to screening. 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 within the 3 months prior to screening and reviewed by a radiologist or pulmonologist as per local standard of care and documented to be without changes suggestive of active TB infection.

   - 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 in a locale where rates of primary multi-drug resistant TB infection are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, neither a PPD test nor a QuantiFERON-Gold® In-Tube test 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 confirmation of current incidence rates of multi-drug resistant TB infection, documentation of an adequate treatment regimen, and prior approval of the Sponsor.

4.2. Exclusion Criteria

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

4.2.1. Exclusion Criteria that Apply to All Subjects

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

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

3. Pregnant females, breastfeeding females and females of child-bearing potential who are unwilling or unable to use a highly effective method(s) 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 or females planning pregnancy. Women of childbearing potential must test negative for pregnancy prior to enrollment in this study. Subjects in Canada who are women of child-bearing potential, and sexually active, are required to use one highly effective method and one additional effective method of contraception (see Appendix 9). (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 4.4.6).

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

5. 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.

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

7. Functional Class IV status 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.[15]

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

9. 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.

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

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

    - Requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 3 months prior to the first dose of study medication;

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

12. 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.

13. 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 4.4.2 Vaccine Guidelines for further information regarding avoidance of household contacts who may be vaccinated).

14. 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.

15. A subject that is considered at increased risk for GI perforation (eg, patients with diverticulitis) by the Investigator or Sponsor.

16. 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.

17. A subject requiring prohibited concomitant medications (See Appendix 3). For a medical condition in which it is important for the subject's safety to continue a prohibited drug described in Appendix 3, and there is no study-permitted alternative, the subject must not participate in this study. Subjects receiving non-prohibited concomitant medications must be on a stable regimen which is defined as not starting a new drug or changing dosage within seven days or 5 half-lives (whichever is longer) prior to the baseline visit.

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

    - $HBsAg^+$ is exclusionary; subjects who are $HBsAg^-$ but $HBcAb^+$ must undergo further testing and be $HBsAb^+$ to be considered for enrollment.

    - Subjects who are HCV Ab^+ must undergo further testing for HCV RNA and are allowed to enroll if negative.

19. 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.

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

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

22. Participation in other studies involving investigational drug(s) (Phases 1-4) during study participation.

4.2.2. Exclusion Criteria That Apply to Subjects Who Enroll Into This Study After the 14 Day Window From the End of Study Visit of the Qualifying Study

Laboratory assessments at the Screening Visit or within 3 months prior to the baseline visit include:

- Evidence of hematopoietic disorders or evidence of hemoglobin levels <10 g/dL;
- An absolute white blood cell (WBC) count of $<3.0 \times 10^9$/L ($<3000/mm^3$);
- Absolute neutrophil count of $\leq 1.5 \times 10^9$/L ($\leq 1500/mm^3$);
- Absolute lymphocyte count $<1.0 \times 10^9$/L ($<1000/mm^3$);
- Platelet count $<100 \times 10^9$/L ($<100,000/mm^3$).

Laboratory assessments at the Screening Visit only:

- Estimated creatinine clearance <40 mL/min by Cockroft Gault equation (Appendix 2);
- Total bilirubin, Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) >1.5x the upper limit of normal at screening visit.

4.3. Enrollment Criteria

Subjects will be enrolled into the study provided they have signed an informed consent document to participate in the study, have undergone all screening procedures as required, and have met all inclusion and exclusion criteria for participation in the study at Baseline/Day 1. Subjects will be assigned a subject identification number that will be retained throughout the study.

4.4. 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.

- Avoid vaccinations with live or attenuated live vaccines and contact with individuals who have recently received live or attenuated live vaccines (See Section 4.4.2).

- Discontinue and avoid using certain medications and treatments used to treat PsA or psoriasis (see Inclusion Criteria and list of prohibited medications Appendix 3). Discontinue and avoid using certain other prohibited medications and treatment (see Appendix 3) not used to treat PsA or psoriasis. For a medical condition in which it is important for the subject's safety to continue using the prohibited drug, and there is no study-permitted alternative, the subject must not participate in this study.

- Contact the study site investigator if there are any changes or additions to concomitant medications.

- Avoid having elective surgery (See Section 4.4.5).

- Agree to use highly effective contraceptive methods per Section 4.4.6.

4.4.1. Non-Pharmacologic Interventions

The subject should continue all non-pharmacological therapies, such as physical therapy, as indicated.

4.4.2. Vaccine Guidelines

4.4.2.1. Subject Vaccination

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.

4.4.2.2. 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.

4.4.3. Dietary Supplements

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

Vitamins, minerals and purified food substances are allowed in amounts not known to be associated with adverse effects (such as hypervitaminosis). Herbals with pharmaceutical properties are allowed only if there is acceptable evidence of no 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.

4.4.4. 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 (if subject enrolls in A3921092 >14 days after end of qualifying study visit), Month 3, Month 6 and every 6 months thereafter, End of Treatment/Early Termination Visit and Follow-Up Visit (if required).

4.4.5. Elective Surgery

During the course of this trial, no elective surgery should be scheduled without first consulting the Pfizer Clinician.

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.

4.4.6. Contraception

4.4.6.1. Contraceptive Methods in Women of Childbearing Potential

Administration of tofacitinib in preclinical studies was shown to have teratogenic effects on the offspring of treated rats and viability of their fetuses. Due to this hypothetical risk, women of childbearing potential will not be administered tofacitinib until pregnancy is excluded and should use a highly effective method(s) of contraception during therapy with

tofacitinib and for at least one ovulatory cycle after study treatment is discontinued. They must have a negative urine pregnancy test at the baseline visit prior to the first dose of study drug and at every visit during the study (or more frequently if required by local practices), if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected or if the subject has become sexually active.

For the purposes of this protocol, female subjects must either use adequate contraception or be of non-childbearing potential. The investigator, in consultation with the subject, will select an appropriate method(s) of contraception for women of child-bearing potential who are sexually active from the permitted list of contraception methods, and instruct the subject in their consistent and correct use. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the subject to call immediately if a selected birth control method(s) is discontinued or if pregnancy is known or suspected. Subjects in the United Kingdom that are women of childbearing potential are required to use two highly effective methods of birth control. Subjects in Canada who are women of childbearing potential, and sexually active, are required to use one highly effective method and one additional effective method of contraception (see Appendix 9).

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

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

2. Correctly placed copper containing intrauterine device (IUD) or intrauterine system (IUS).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Sterilization of male partner with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.

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

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

4.4.6.2. Women of Non-Childbearing Potential

Female subjects of non-childbearing potential must meet **at least one of the following criteria**:

- Have undergone documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure; or
- 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 serum follicle stimulating hormone (FSH) level within the laboratory's reference range for post-menopausal females.

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

4.4.7. Contraceptive Methods in Male Subjects

Administration of tofacitinib in preclinical trials demonstrated no effects on male sperm or offspring in any studies conducted to date. No effect on human male fertility is expected and male subjects need not take contraceptive precautions unless required by other concomitant medications (eg, methotrexate).

4.5. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list 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 contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should 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 contact number is not intended for use by the subject directly and if a subject calls that number, they will be directed back to the investigational site.

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).

Study drug will be dispensed to subjects to self-administer after appropriate training and specific written instructions are provided. Tofacitinib will be taken orally 5 mg BID (approximately every 12 hours). The investigator has the option to increase the dose to 10 mg BID in those subjects who are receiving 5 mg BID and, in the investigator's opinion, has PsA symptoms that are not adequately controlled. Changes in the dose are only permitted at scheduled study visits, unless a reduction to 5 mg BID is required due to safety abnormalities as outlined in Appendix 4. Study treatment will continue in the LTE portion of the study until the subject discontinues from the study or has received approximately 3 years (36 standardized 4-week months) of treatment.

5.1. Allocation to Treatment

Subjects who enroll in this study from qualifying studies will first receive tofacitinib 5 mg BID, administered orally, in open-label dosing. Allocation of subjects to treatment will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject's number. The site personnel will then be provided with a randomization number and container number(s) when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number, randomization number and container number(s) assigned. The confirmation report must be stored in the site's files.

5.2. Breaking the Blind

This is an open-label study. Assignment to tofacitinib will be open to the Investigator, subjects and Pfizer study team.

5.3. Drug Supplies

Each tofacitinib bottle will be labeled as appropriate for this open-label study. Study medication will be taken according to the instructions provided to the subject. The specific subject instructions will also direct the subject to bring the study medication bottle(s) to the clinic on study visit days. Any permitted dose adjustments that may occur between scheduled study visits (ie, dose reduction for safety reasons) must be clearly documented on the subject's chart and verified for start date and dose when the subject returns for their next scheduled visit.

5.3.1. Preparation and Dispensing

Tofacitinib medication will be dispensed in bulk bottles. At each dispensing visit, subjects will receive a sufficient quantity of study drug to last until their next scheduled dispensing visit. For subjects who are taking 5 mg BID, one bottle of study drug will be dispensed at each dispensing visit. If a subject is receiving 10 mg BID, 2 bottles will be dispensed. At all study visits, subjects must return all containers and unused study medications for accountability and the amount of study drug returned will be recorded.

5.3.2. Administration

Tofacitinib should be administered orally, twice daily, approximately 12 hours apart, once in the morning and once in the evening. Subjects receiving 5 mg BID will receive 1 tablet in the morning and 1 tablet in the evening. Subjects receiving 10 mg BID will receive 2 tablets in the morning and 2 tablets in the evening. Tofacitinib may be administered with or without food. If a tofacitinib dose is missed and the interval to the next scheduled dose is less than 6 hours, the missed dose of tofacitinib should not be administered. Subjects should be instructed to document any missed doses.

5.3.3. Compliance

Subject compliance with dosing administration will be verified by accounting of returned containers and trial medication at each visit.

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

If the subject is over-compliant with study drug (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 (>120% in a visit period) that may potentially impact the safe use of study drug or that may result in a serious adverse event.

5.4. Drug Storage

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

Investigational product should be stored in its original container and in accordance with the drug label. See the drug label for storage conditions of the product.

Storage conditions stated in the single reference safety document (SRSD), ie Investigator's Brochure (IB) will be superseded by the storage conditions stated in the labeling.

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

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

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. 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 investigational products.

5.5. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss or other disposition of the investigational product supplies. To ensure adequate records, all investigational product supplies will be accounted for in the drug accountability inventory forms as instructed by Pfizer and will be monitored by the accounting of unused investigational product returned by the subjects. All study drug bottles must be returned to the investigator by the subject and the investigator will return the bottles to Pfizer. 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.

5.5.1. Destruction of Investigational Product Supplies

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

For all containers returned to the investigator by the subject, the investigator will maintain the returned supply until destruction is authorized or release to a third party for destruction is granted.

5.6. Concomitant Treatment(s)

It is important to be aware of, and document, **all** concomitant treatments 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 to receive 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.

Treatments 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 treatments. Treatments taken after the first dose of study drug has been administered will be documented as concomitant treatments. All concomitant treatments taken during the study must be recorded in the study records with indication (as appropriate), daily dose and start and stop dates of administration. Subjects will be queried about concomitant treatments 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.

5.6.1. Stable Background Pain or Other Arthritis Therapy

Use of background medication (eg, methotrexate, leflunomide or sulfasalazine) by a subject is not a requirement. However, if used, the concomitant DMARD should be the same medication as the subject was receiving in the qualifying study. Adjustment of background medications are allowed for reasons of inadequate efficacy of current treatment, or may be tapered or discontinued due to disease improvement. Adjustments for safety reasons may be done at any time, but if this leads to changes in excess of those allowed, the investigator must receive approval from the Pfizer Clinician to allow the subject to continue in the trial. Dose adjustments of the permitted concomitant DMARDs should not occur any more frequently than every 3 months. If adjustment of the concomitant DMARD is required for safety, it can occur at any time. If the concomitant DMARD requires adjustment for efficacy, it should be completed at the visit or within 14 days.

If a concomitant DMARD is discontinued during the course of the study, it should not be re-initiated. Addition of any new concomitant DMARD is not allowed; subjects are only permitted to receive one concomitant DMARD in the study.

Dose adjustments may be made, or background NSAID/COX-2 inhibitors may be switched, but should be no more frequently than every 3 months, and should be more than 14 days prior to a study visit. Oral corticosteroid dose should not exceed 10 mg prednisone or its equivalent daily. Daily dosage of NSAIDs/COX-2 inhibitors and corticosteroids must not be modified within the 24 hours prior to any study visit, except if adjustment is needed to protect a subject's safety.

Methotrexate doses may be adjusted no more frequently than every 3 months (and remaining ≤20 mg/week). Adjustments should not be made more than 4 weeks prior to a study visit. Intra-articular steroids should be administered in a total dosage of no more than 80 mg of methylprednisolone or equivalent every 6 months. Intra-articular hyaluronate sodium injections may be administered for indications in accordance with the local label. Injected joints will be considered to have their pre-injection status for efficacy assessments during the remainder of the study. Intra-articular injections should be administered more than 6 weeks prior to a study visit (See Appendix 6).

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 5, Appendix 6).

Daily dosage of 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.

5.6.2. Other Medications

Prohibited drugs and dietary supplements must be discontinued according to protocol guidelines: a list of prohibited drugs with specific discontinuation recommendations is listed in Appendix 3. 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). All concomitant treatment taken during the study must be recorded with indication (as required), daily dose, and start and stop dates of administration.

5.7. Rescue Therapy

The only medications that are allowed for rescue are listed in Appendix 6. Subjects who require rescue medication 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 must not be dosed with rescue medication during the 24 hours prior to a study visit except if adjustment is needed because subject is experiencing intolerable pain. Baseline stable use of acetaminophen/paracetamol or opioids should NOT be discontinued in advance of study visits.

5.8. Dosage Reduction and Withholding

All subjects will receive tofacitinib 5 mg BID upon entry into A3921092. Dosage of tofacitinib may be increased to 10 mg BID only at scheduled study visits to provide greater control of the subject's PsA, if the investigator feels the subject would benefit and the subject is not experiencing any tofacitinib-related adverse events, including abnormalities in laboratory parameters that are judged to be related to tofacitinib.

For those subjects whose tofacitinib dose has been increased to 10 mg:

- Dosage of tofacitinib may be reduced back to 5 mg BID for mild to moderate cytopenias, other mild to moderate AEs, or any other safety-related issues, either temporarily or for the duration of the study.
- Definitions of mild to moderate cytopenias are as follows:
    - Mild to moderate neutropenia: 1000-1500 neutrophils/mm^3, confirmed;
    - Mild to moderate anemia: a decrease of hemoglobin from 1.0-2.0 g/dL from baseline, inclusive, provided the hemoglobin remains >8.0 g/dL;
    - Mild to moderate thrombocytopenia: 75,000-100,000 platelets/mm^3.

For all subjects:

- Dosage of tofacitinib may be temporarily discontinued for up to 28 consecutive days, for more severe cytopenias, for infections which do not meet criteria for serious infections (ie, those requiring parenteral antimicrobial therapy or hospitalization), for surgical procedures or other moderately severe AEs.
- Treatment with tofacitinib will be discontinued and the subject withdrawn from this study for toxicities as defined in Appendix 4.

6. STUDY PROCEDURES

Subjects from any qualifying tofacitinib PsA study who elect to participate should complete a combined screening/baseline visit on the same day they end participation in the previous randomized tofacitinib study or within 14 days to be eligible for rollover into A3921092. Eligible subjects enrolling outside of the 14 day window (but ≤3 months) will be required to participate in the full Screening visit and Baseline visit.

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

Subjects who are on prohibited medications, and are deriving a beneficial response from them, should not be entered into this study.

6.1. Screening and Baseline

6.1.1. Subjects Requiring Separate Screening and Baseline Visits

Subjects who enter this study from their qualifying study outside of the 14 day window after their last study visit in the prior study must participate in a Screening Visit to determine eligibility and a Baseline Visit for enrollment in this study. To be eligible, enrollment into A3921092 must occur ≤3 months after last visit in the qualifying study.

6.1.1.1. Screening Visit

- Informed consent obtained.
- Register for subject identification number.
- Medical history: Include history of previous vaccinations, specifically influenza, pneumococcal and zoster. The medical history should also include Cardiovascular (CV) Risk Factor Assessment (Section 7.4) which includes 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.
- Disease Activity Assessment (Section 7.1.1).
- Prior/concomitant treatments ongoing or started since last visit in the qualifying study not exceeding the last 12 months.
- Temperature (oral, tympanic or temporal preferred), blood pressure and pulse rate (vital signs).
- 12-lead ECG.
- Complete Physical Examination: Height, weight, general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (presence of peripheral edema), abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes.
- QuantiFERON Gold® test or Mantoux Purified Protein Derivative (PPD) skin test where applicable and/or chest radiograph where applicable (unless done in the prior 3 months). Subjects who have PPD must return within 48-72 hours for evaluation.
- Blood and urine specimen testing: Central laboratory tests including: Hematology, Chemistry Panel, Urinalysis, CRP, HIV serology, HBsAg, HBcAb, HCV Ab, Stool examination for parasites (Brazil only). 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 child-bearing potential only.
- Tender/Painful Joint Count (68), Swollen Joint Count (66).

6.1.1.2. Baseline Visit

This visit must occur 2-28 days after screening visit.

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 hour prior to the Baseline/Day 0 visit as necessary to ensure the samples are collected in a fasting state.

All Patient Reported Outcomes 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).
- Health Assessment Questionnaire – Disability Index (HAQ-DI).
- BASDAI.
- ASQOL.
- Patient's Global Joint and Skin Assessment (PGJS-VAS).
- SF-36 Version 2 (Acute).
- DLQI.
- FACIT Fatigue Scale.
- EuroQol 5 Dimensions (EQ-5D).
- ISI.
- WLQ.
- PsA-HCRU.

Procedures that will be performed prior to enrollment and the first dose of study drug on Visit 1, Day 1 for baseline include:

- Targeted Physical Examination: (weight, examination of hearts, lungs, abdomen, lower extremities and lymph nodes).
- Vital signs: blood pressure, pulse rate and temperature (tympanic, oral or temporal preferred).

- Waist and hips circumference.
- Blood and urine specimen testing: Central laboratory tests include: Hematology, Chemistry Panel, Lymphocyte subset analysis (FACS), Hemoglobin A1c (HbA1c), C-Reactive Protein (CRP), Lipid Profile (fasting), Urinalysis.
- Urine Pregnancy Test (for women of childbearing potential only).
- Clinical Evaluation of Rheumatology Endpoints:
    - Tender/painful joint counts (68);
    - Swollen joint counts (66);
    - Physician's Global Assessment of Arthritis (VAS);
    - Assessment of presence and severity of dactylitis;
    - Assessment of enthesitis using the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index and Leeds Enthesitis Index.
- Clinical Evaluation of Dermatology Endpoints:
    - Physician's Global Assessment of Psoriasis (PGA-PsO);
    - Psoriasis Area and Severity Index (PASI);
    - Body Surface Area (BSA);
    - Nail Psoriasis Severity Index (NAPSI).
- Clinical Evaluation of Rheumatology and Dermatology Endpoint: Physician's Global Assessment of Psoriatic Arthritis (VAS).
- Drug dispensing.
- Monitoring of adverse events and concomitant treatment.

6.1.2. Subjects with Combined End of Study Visit/Baseline Visit

For subjects combining the End of Study (EOS) Visit from qualifying study with Screening/Baseline visit for A3921092, subjects must complete activities as indicated from EOS visit and the following procedures:

- Informed consent obtained.
- Register for subject identification number.
- Dispense study medication/schedule next visit.

6.1.3. Subjects with End of Study Visit Separate From Combined Screening/Baseline Visit

Subjects who complete their combined screening/baseline visit within 14 days of the last visit of the qualifying study but not on the same day must complete the following procedures at the combined screening/baseline visit.

- Informed consent obtained.
- Register for subject identification number.

All Patient Reported Outcomes 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).
- Health Assessment Questionnaire – Disability Index (HAQ-DI).

Procedures that will be performed prior to enrollment and the first dose of study drug on Visit 1, Day 1 for baseline include:

- Targeted Physical Examination: (weight, examination of hearts, lungs, abdomen, lower extremities and lymph nodes).
- Vital signs: blood pressure, pulse rate and temperature (tympanic, oral or temporal preferred).
- Blood and urine specimen testing: Central laboratory tests include: Hematology, Chemistry Panel, C-Reactive Protein (CRP), Urinalysis.
- Urine Pregnancy Test (for women of childbearing potential only).
- Clinical Evaluation of Rheumatology Endpoints:
    - Tender/painful joint counts (68);
    - Swollen joint counts (66);
    - Physician's Global Assessment of Arthritis (VAS).
- Drug dispensing.
- Monitoring of adverse events and concomitant treatments.

6.2. Study Period

Subjects who have met all inclusion criteria and have no exclusion criteria present may participate in the study.

Standard of Care Testing. Safety laboratory tests should be repeated as appropriate for subjects receiving permitted concomitant non-biologic DMARD therapy, eg, subjects on background methotrexate should have complete blood count (CBC) and differential count with safety chemistries as appropriate for the local standard of care.

The blood collection for laboratory testing at specified visits [eg, Month 3, Month 6 (and every 6 months thereafter), Month 12 (and every 12 months thereafter)] requiring a fasting state (at least 9 hours) may be taken up to 48 hours prior to or after the visit 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.

Prior to attending the study visits, subjects are allowed to shower or bathe that morning but should not moisturize with topical emollient.

Subjects should complete the Patient Reported Outcome 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 Patient Reported Outcome (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. 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. The visit window for this study as well as the qualifying study utilizes 28 days for a month.

6.2.1. Type A Visit: Month 1

The window for this visit is ±7 days.

All Patient Reported Outcomes 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).
- Health Assessment Questionnaire – Disability Index (HAQ-DI).
- Patient's Global Joint and Skin Assessment (PGJS-VAS).
- BASDAI.

- ASQOL.
- SF-36 Version 2 (Acute).
- DLQI.
- FACIT Fatigue Scale.
- EuroQol 5 Dimensions (EQ-5D).
- WLQ.
- PsA-HCRU.
- ISI.

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).
- Waist and hips circumference.
- Blood and urine specimen testing: Central laboratory tests including: Hematology, Chemistry Panel, CRP, Urinalysis.
- Urine Pregnancy Test (for women of women of childbearing potential only).
- Clinical Evaluation of Rheumatology Endpoints:
    - Tender/Painful Joint Counts (68);
    - Swollen Joint Count (66);
    - Physician's Global Assessment of Arthritis (VAS);
    - Assessment of presence and severity of dactylitis;
    - Assessment of enthesitis using the Spondyloarthritis Research Consortium of Canada [SPARCC] Enthesitis Index and Leeds Index.
- Clinical Evaluation of Dermatology Endpoints:
    - Physician's Global Assessment of Psoriasis (PGA-PsO);

  - Psoriasis Area and Severity Index (PASI);
  - Body Surface Area (BSA);
  - Nail Psoriasis Severity Index (NAPSI).
- Clinical Evaluation of Rheumatology and Dermatology Endpoint: Physician's Global Assessment of Psoriatic Arthritis (VAS).
- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions.
- Drug accountability.

6.2.2. Type B Visit: Months 3, 9, 15, 21, 27* and 33*

The window for the Month 3 visit is ±7 days and ±10 days for visits thereafter.

At the Month 3 visit only, subjects are required to fast for at least 9 hours prior to the visit. Blood collection may be taken up to 48 hours prior to or following this visit as necessary to ensure samples are collected in a fasted state.

All Patient Reported Outcomes 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).
- BASDAI.
- ASQOL.
- Patient's Global Joint and Skin Assessment (PGJS-VAS).
- Health Assessment Questionnaire – Disability Index (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).

- Blood and urine specimen testing: Central laboratory tests including: Hematology, Chemistry Panel, Lymphocyte subset analysis (FACS), CRP, Urinalysis, Lipid panel (fasting) at Month 3 only.
- Urine Pregnancy Test (for women of women of childbearing potential only).
- Clinical Evaluation of Rheumatology Endpoints:
    - Tender/Painful Joint Counts (68);
    - Swollen Joint Count (66);
    - Physician's Global Assessment of Arthritis (VAS);
    - Assessment of presence and severity of dactylitis;
    - Assessment of enthesitis using the Spondyloarthritis Research Consortium of Canada [SPARCC] Enthesitis Index and Leeds Index.
- Clinical Evaluation of Dermatology Endpoints:
    - Physician's Global Assessment of Psoriasis (PGA-PsO);
    - Psoriasis Area and Severity Index (PASI);
    - Body Surface Area (BSA).
- Clinical Evaluation of Rheumatology and Dermatology Endpoint: Physician's Global Assessment of Psoriatic Arthritis (VAS).
- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions.
- Drug accountability.
- Drug dispensing.

*At Month 27 or Month 33, subjects who meet entry criteria of the sub-study can be enrolled in the sub-study. These subjects will complete the study procedures at this visit and will end study participation in the LTE. At the Switch/Baseline visit of the sub-study, all investigational product from the main A3921092 LTE study will be collected for accountability under the main protocol. New tofacitinib supplies will be dispensed under the sub-study. Please refer to Appendix 10 for additional requirements and procedures.

6.2.3. Type C Visit: Months 6, 18 and 30*

The window for these visits is ±10 days.

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

All Patient Reported Outcomes 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).
- BASDAI.
- ASQOL.
- Patient's Global Joint and Skin Assessment (PGJS-VAS).
- Health Assessment Questionnaire – Disability Index (HAQ-DI).
- SF-36 Version 2 (Acute).
- DLQI.
- FACIT Fatigue Scale.
- EuroQol EQ-5D.
- ISI.
- WLQ.
- PsA-HCRU.

Procedures that will be performed include:

- Cardiovascular Risk Assessment: smoking status, average weekly alcohol consumption and family history of premature coronary heart disease (see Section 7.4).
- Physical Examination: 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).

- Blood and urine specimen testing: Central laboratory tests including: Hematology, Chemistry Panel, CRP, HbA1c, Lipid Panel (fasting), Urinalysis, Lymphocyte subset analysis (FACS).
- Urine Pregnancy Test (for women of childbearing potential only).
- Waist and hips circumference.
- Clinical Evaluation of Rheumatology Endpoints:
    - Tender/Painful Joint Counts (68);
    - Swollen Joint Count (66);
    - Physician's Global Assessment of Arthritis (VAS);
    - Assessment of presence and severity of dactylitis;
    - Assessment of enthesitis using the Spondyloarthritis Research Consortium of Canada [SPARCC] Enthesitis Index and Leeds Index.
- Clinical Evaluation of Dermatology Endpoints:
    - Physician's Global Assessment of Psoriasis (PGA-PsO);
    - Psoriasis Area and Severity Index (PASI);
    - Body Surface Area (BSA);
    - Nail Psoriasis Severity Index (NAPSI).
- Clinical Evaluation of Rheumatology and Dermatology Endpoint: Physician's Global Assessment of Psoriatic Arthritis (VAS).
- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions.
- Drug accountability.
- Drug dispensing.

*At Month 30, subjects who meet entry criteria of the sub-study can be enrolled in the sub-study. These subjects will complete the study procedures at this visit and will end study participation in the LTE. At the Switch/Baseline visit of the sub-study, all investigational product from the main A3921092 LTE study will be collected for accountability under the main protocol. New tofacitinib supplies will be dispensed under the sub-study. Please refer to Appendix 10 for additional requirements and procedures.

6.2.4. Type D Visit: Month 12, 24* and 36*

The window for these visits is ±10 days.

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

All Patient Reported Outcomes 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).
- BASDAI.
- ASQOL.
- Patient's Global Joint and Skin Assessment (PGJS-VAS).
- Health Assessment Questionnaire – Disability Index (HAQ-DI).
- SF-36 Version 2 (Acute).
- DLQI.
- FACIT Fatigue Scale.
- EuroQol EQ-5D.
- ISI.
- WLQ.
- PsA-HCRU.

Procedures that will be performed include:

- Cardiovascular Risk Assessment: smoking status, average weekly alcohol consumption and family history of premature coronary heart disease (see Section 7.4).
- Physical Examination: Complete physical examination (height, weight, general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), extremity exam (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).

- Blood and urine specimen testing: Central laboratory tests including: Hematology, Chemistry Panel, CRP, HbA1c, Lipid Profile (fasting), Urinalysis, Lymphocyte subset analysis (FACS).

- QuantiFERON Gold® In-Tube Test (QFT) only for subjects: 1) in countries for which TB incidence has been reported >50 cases per 100,000 persons (see Section 7.6.3) and 2) who tested negative at their last QFT. Subjects newly testing positive must have chest radiograph performed and reviewed by a radiologist or pulmonologist as per local standard of care. Please note: subjects with a new positive QFT and a chest x-ray that does not show active disease (and no other evidence of active disease) are required to be treated for latent tuberculosis infection.

- Urine Pregnancy Test (for women of childbearing potential only).

- Waist and hips circumference.

- 12-lead electrocardiogram.

- Clinical Evaluation of Rheumatology Endpoints:

    - Tender/Painful Joint Counts (68);

    - Swollen Joint Count (66);

    - Physician's Global Assessment of Arthritis (VAS);

    - Assessment of presence and severity of dactylitis;

    - Assessment of enthesitis using the Spondyloarthritis Research Consortium of Canada [SPARCC] Enthesitis Index and Leeds Index.

- Clinical Evaluation of Dermatology Endpoints:

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

    - Psoriasis Area and Severity Index (PASI);

    - Body Surface Area (BSA);

    - Nail Psoriasis Severity Index (NAPSI).

- Clinical Evaluation of Rheumatology and Dermatology Endpoint: Physician's Global Assessment of Psoriatic Arthritis (VAS).

- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions.
- Drug accountability.
- Drug dispensing (except at Month 36 visit).

*At Month 24 or Month 36, subjects who meet entry criteria of the sub-study can be enrolled in the sub-study. These subjects will complete the study procedures at this visit and will end study participation in the LTE. At the Switch/Baseline visit of the sub-study, all investigational product from the main A3921092 LTE study will be collected for accountability under the main protocol. New tofacitinib supplies will be dispensed under the sub-study. Please refer to Appendix 10 for additional requirements and procedures.

6.2.5. End of Study Follow-up Phone Call

Subjects will be contacted within 7 days after the 28 days following End of Study visit and any adverse events will be documented.

6.2.6. Early Termination Visit

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

All Patient Reported Outcomes 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).
- Health Assessment Questionnaire – Disability Index (HAQ-DI).
- Patient's Global Joint and Skin Assessment (PGJS-VAS).
- BASDAI.
- ASQOL.
- SF-36 Version 2 (Acute).
- DLQI.
- FACIT Fatigue Scale.
- EuroQol EQ-5D.

- ISI.
- WLQ.
- PsA-HCRU

Procedures that will be performed include:

- Cardiovascular Risk Assessment: smoking status, average weekly alcohol consumption and family history of premature coronary heart disease (see Section 7.4).
- 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.
- Vital signs: blood pressure, pulse rate and temperature (tympanic, oral or temporal preferred).
- Blood and urine specimen testing: Central laboratory tests including: Hematology, Chemistry Panel, Lymphocyte subset analysis (FACS), CRP, HbA1c, Lipid Profile (fasting), Urinalysis.
- Urine Pregnancy Test (for women of childbearing potential only).
- Waist and hips circumference.
- 12-lead electrocardiogram.
- Clinical Evaluation of Rheumatology Endpoints:
    - Tender/Painful Joint Counts (68);
    - Swollen Joint Count (66);
    - Physician's Global Assessment of Arthritis (VAS);
    - Assessment of presence and severity of dactylitis;
    - Assessment of enthesitis using the Spondyloarthritis Research Consortium of Canada [SPARCC] Enthesitis Index and Leeds Index.
- Clinical Evaluation of Dermatology Endpoints:
    - Physician's Global Assessment of Psoriasis (PGA-PsO);

  - Psoriasis Area and Severity Index (PASI);
  - Body Surface Area (BSA);
  - Nail Psoriasis Severity Index (NAPSI).
- Clinical Evaluation of Rheumatology and Dermatology Endpoint: Physician's Global Assessment of Psoriatic Arthritis (VAS).
- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions.
- Drug accountability.

6.3. Follow-up Visit

If a subject discontinues from the study with abnormalities in hematology or clinical chemistry results which meet criteria as defined in Appendix 4, 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 within 28 days (±7 days) of last dose of study treatment.

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

The following procedures will be performed:

- Blood testing: Central laboratory tests may include: Hematology, Chemistry Panel; Lipid Panel (fasting).
- Urine Pregnancy Test (for women of childbearing potential only).
- Adverse event reporting and concomitant treatment 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.

6.4. Subject Withdrawal

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

If 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

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 8.3. 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 case report form (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 any abnormality in hematology or clinical chemistry results which meet the criteria as defined in Appendix 4, a follow-up visit must be performed within 28 days (±7 days) of last dose of study treatment.

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.

Subjects who require rescue doses of acetaminophen/paracetamol or opioid for more than 10 consecutive days, subjects interrupting study drug for more than 28 consecutive days (see Appendix 4), or subjects who are <80% compliant with the dosage regimen for any two consecutive visit periods should be withdrawn from the study.

7. ASSESSMENTS

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

7.1. Efficacy Endpoints

7.1.1. Disease Activity Assessment

Subjects who enroll >14 days after their End of Study Visit in their qualifying study must, in the opinion of the investigator, have sufficient evidence of PsA disease activity to warrant use of tofacitinib as a DMARD (Inclusion criteria #2, Section 4.1.2).

7.1.2. ACR Assessments

The American College of Rheumatology's definition for calculating improvement in RA (ACR20) is calculated as a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant.[16] Similarly, ACR50, 70 and 90 are calculated with the respective percent improvement. 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).

7.1.3. Disease Activity Score Assessment

The Disease Activity Score (DAS)[17] 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).
4. Tender/painful and swollen joint counts used are as described in Sections 7.2.2 and 7.2.4.

7.1.4. PsA Response Criteria (PsARC)

The PsARC[18,19] will be collected 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 PsA Response Criteria. 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.

7.1.5. PsA Joint Activity Index (PsAJAI)

The PsA Joint Activity Index (PsAJAI)[20] is a weighted sum of 30% improvement in the 7 core measures of the ACR with weights of 2 given to the joint count measures (JNT), CRP and the Physician's Global Assessment of Arthritis (MDGDA). Weights of 1 are given to the remaining 30% improvement measures including Patient's Assessment of Arthritis Pain (PAIN), Patient's Global Assessment of Arthritis (PtGDA) and HAQ. The values are summed to get a score out of 9. The score is calculated as follows:

PsAJAI= 2 x 30%↓ JNT + 2 x 30%↓ CRP + 2 x 30%↓ MDGDA + 30%↓ PtGDA + 30%↓ PAIN + 30%↓ HAQ.

7.1.6. Disease Activity Index for Reactive Arthritis/Psoriatic Arthritis (DAREA/DAPSA)

DAREA/DAPSA[21] is a composite instrument to assess peripheral joint involvement that is based upon numerical summation of 5 variables of disease activity: tender/painful joint count + swollen joint count (using SJC66/ TJC68 assessments), Patient's Global Assessment of Arthritis (PtGA), Patient's Assessment of Arthritis Pain (PAIN) and CRP (in mg/dL). Since DAREA/DAPSA reflects domains found important in PsA, it has been proposed to serve as a Disease Activity Index for Psoriatic Arthritis (DAPSA). DAREA/DAPSA is calculated as follows:

DAREA/DAPSA = SJC66 + TJC68 + PtGA + PAIN + CRP.

7.1.7. Composite Psoriatic Disease Activity Index in Psoriatic Arthritis (CPDAI)

CPDAI[22] is a composite psoriatic disease activity index incorporating 5 domains including joint disease, skin involvement, enthesitis, dactylitis and spinal disease. For dactylitis, a simple dactylitic digit count is applied. For enthesitis, the Leeds Enthesitis Index (LEI) is used. For spinal involvement, the Bath Ankylosing Disease Activity Index (BASDAI) and

the Ankylosing Spondylitis Quality of Life questionnaire (ASQOL) are used. In addition, the dermatology quality of life index (DLQI) is used as a measure of the impact of skin disease. Using these instruments, and ranges of values based upon literature review, disease activity under each domain will be graded as not involved, mild, moderate and severe giving a range of attainable CPDAI scores of between 0 and 15 [See Appendix 7].

7.1.8. Minimal Disease Activity Score

A psoriatic arthritis patient is defined as having Minimal Disease Activity (MDA)[23] when the subject meets ≥5 of the 7 following criteria: 1) tender/painful joint count ≤1; 2) swollen joint count ≤1; 3) PASI score ≤1 or BSA ≤3%; 4) Patient Assessment of Arthritis Pain (VAS) ≤15 mm; 5) Patient's Global Assessment of Arthritis (VAS) ≤20 mm; 6) HAQ-DI score ≤0.5; 7) tender entheseal points (using Leeds Enthesitis Index) ≤1.

7.1.9. Psoriatic Arthritis Disease Activity Score (PASDAS)

PASDAS[24] is a composite PsA disease activity score that includes the following components: Patient's Global Skin and Joint Assessment (VAS), Physician's Global Assessment of Psoriatic Arthritis (VAS), swollen and tender/painful joint counts (66/68), Leeds Enthesitis Index score, tender dactylitic digit score, physical component summary score (PCS) of SF-36 and CRP.

7.2. Clinical Evaluation of Rheumatology Endpoints

All rheumatological evaluations will be performed by qualified, trained assessors. 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 joint assessor to determine the number of joints that are considered tender or painful. The response to pressure/motion on each joint will be assessed using the following scale: Present/Absent/Not Done/Not Applicable (to be used for artificial or missing joints). Artificial joints will not be assessed. Injected joints will be counted according to their pre-injection status for the remainder of the study.

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 joint assessor as described in Section 7.2.1.

7.2.3. Swollen Joint Count (66)

The joint 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. Injected joints will be counted according to their pre-injection status for the remainder of the study.

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 joint assessor.

7.2.5. Physician's Global Assessment of Arthritis

The 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 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 qualified 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 dactylitis, 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 qualified assessor using the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index[25] and Leeds Enthesitis Index.[26] The 16 sites assessed using SPARCC Index include (right and left): medial epicondyle humerus, lateral epicondyle humerus, supraspinatus insertion into greater tuberosity of humerus, greater trochanter, quadriceps insertion into superior border of patella, patellar ligament insertion into inferior pole of patella or tibial tubercle, Achilles tendon insertion into calcaneum and plantar fascia insertion into calcaneum. 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 for analysis of CRP using an assay analyzed by the central laboratory.

7.3. Clinical Evaluation of Dermatologic Endpoints

All dermatological evaluations will be performed by qualified, trained assessors. 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 2). 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 3).

Table 2. 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 3. 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 was 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 4).

Table 4. 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 5).

Table 5. 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 6).

Table 6. 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:

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

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 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).[28] The percent surface area with psoriasis is estimated by means of the handprint method, where the full palmar hand of the patient (ie, the subject's fully extended palm, fingers and thumb together) represents approximately 1% of the total BSA. The total BSA with psoriasis is the sum of the numbers of handprints over the 4 body regions, which ranges from 0 to 100% (Table 7).

Table 7. Handprint Determination of Body Region Surface Area

Body Region	Total Number of Handprints in Body Region	Surface Area of Body Region Equivalent of One Handprint
Head and Neck	10	10%
Upper Limbs	20	5%
Trunk (including axillae and groin)	30	3.33%
Lower Limbs (including buttocks)	40	2.5%

7.3.4. Nail Psoriasis Severity Index (NAPSI) Score

A target nail that was selected at the Baseline/Visit 1 in the qualifying study will continue to be assessed using the NAPSI scale.[29] 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. Cardiovascular (CV) Risk Factor Assessment

The CV Risk Factor Assessment should be addressed at the time of medical history review at Screening for subjects who enroll >14 days after their end of study visit in the qualifying study. This will be updated every 6 months through Month 36.

- Smoking status.
- Average weekly alcohol consumption: units/week, where a unit contains 12 g of pure alcohol, an amount equivalent to that contained in 5 oz (a glass) of wine, 12 oz of beer, or 1.5 oz of 90 proof spirits.
- Atrial fibrillation, diabetes mellitus, hypertension.
- Coronary heart disease (CHD).
- Carotid artery disease.
- Family history of premature CHD: CHD in a male first degree relative <55 years of age, CHD in a female first degree relative <65 years of age.

7.5. 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.

7.5.1. 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]

7.5.2. 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]

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

The HAQ-DI[30] assesses the degree of difficulty a subject has experienced during the past week in 8 domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities. Each activity category consists of 2-3 items. For each question in the questionnaire, the level of difficulty is scored from 0 to 3 with 0 representing "no difficulty," 1 as "some difficulty," 2 as "much difficulty," and 3 as "unable to do." Any activity that requires assistance from another individual or requires the use of an assistive device adjusts to a minimum score of 2 to represent a more limited functional status.

7.5.4. Patient's Global Joint and Skin Assessment (PGJS-VAS)

Subject's perception of disease will be assessed using a 100 mm visual analog scale (VAS) by placing a mark on the scale between 0 (excellent) and 100 (poor).[31] The rating corresponds to the way in which the subject felt over the past week in terms of how they were affected by their: 1) psoriasis and arthritis (global, PGA); 2) arthritis only (PJA) and 3) psoriasis only (PSA).

- Global (PGA)

In all the ways in which your PSORIASIS and ARTHRITIS, as a whole, affects you, how would you rate the way you felt over the past week?

Excellent _____ Poor

- Joints (PJA)

In all the ways your ARTHRITIS affects you, how would you rate the way in which you felt over the past week?

Excellent _____ Poor

- Skin (PSA)

In all the ways your PSORIASIS affects you, how would you rate the way in which you felt over the past week?

Excellent _____ Poor

[Note: Scale will be 100 mm in length]

7.5.5. Assessment of Spondylitis

Subject spondylitis symptoms will be evaluated using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Quality of Life (ASQOL) questionnaire.[32,33] BASDAI consists of VAS scales that will be used by subjects to answer six questions pertaining to 5 symptoms including: fatigue, spinal pain, joint pain/swelling, areas of localized tenderness and morning stiffness. ASQOL questionnaire consists of 18 questions for assessing quality of life in subjects with spondylitis.

7.5.6. Dermatology of Life Quality Index (DLQI)

The DLQI[34] is a general dermatology questionnaire that consists of 10 items that assess subject health-related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment). It has been extensively used in clinical trials for psoriasis. The DLQI is a psychometrically valid and reliable instrument that has been translated into several languages, and the DLQI total scores have been shown to be responsive to change. The minimally important difference for the DLQI has been estimated as a 2 to 5 point change from baseline.

7.5.7. Itch Severity Item (ISI)

The severity of itch (pruritus) due to psoriasis will be assessed using the ISI, a single-item, horizontal numeric rating scale. Subjects will be asked to rate "your worst itching due to psoriasis over the past 24 hours" on a numeric rating scale anchored by the terms "No itching" (0) and "Worst possible itching" (10) at the ends.

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

The FACIT – Fatigue Scale[35] is a patient completed questionnaire consisting of 13 items that assess fatigue. Instrument scoring yields a range from 0 to 52, with higher scores representing better subject status (less fatigue).

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

The SF-36 v.2 (Acute) is a 36-item generic health status measure.[36] 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 scores.

7.5.10. EuroQol EQ-5D Health State Profile

The EuroQol EQ-5D Health State Profile[37] 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. Additionally, scores from the five domains may be used to calculate a single index value, also known as a utility score. The validity and reliability of the EuroQol EQ-5D has been established in a number of disease states, including rheumatoid arthritis.

7.5.11. PsA Healthcare Resource Utilization Questionnaire

The PsA Healthcare Resource Utilization Questionnaire (PsA-HCRU) is a seventeen-item questionnaire that is designed to assess healthcare usage during the previous three months across a wide number of direct medical cost domains. The scale also assesses indirect costs associated with functional disability and impaired productivity at home and at work.

7.5.12. Work Limitations Questionnaire

The Work Limitations Questionnaire (WLQ)[38] is a twenty five-item scale that evaluates the degree to which health problems interfere with an ability to perform job roles along four dimensions. The Time Management scale (Question 1) contains five items addressing difficulty performing a job's time and scheduling demands. The Physical Demands scale (Question 2) covers a person's ability to perform job tasks that involve bodily strength, movement, endurance, coordination and flexibility. The Mental/Interpersonal Demands Scale (Questions 3 and 4) has nine items. Six items pertain to difficulty performing cognitive job tasks and/or tasks involving the processing of sensory information. Three items address a person's problems interacting with people on-the-job. The Output Demands scale (Question 5) contains five items concerning decrements in a person's ability to meet demands for quantity, quality, and timeliness of completed work.

7.6. Safety

Safety will be assessed by the spontaneous reporting of adverse events (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.

7.6.1. Vital Signs and Temperature

Body temperature, blood pressure and pulse rate will be measured at every study 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.

7.6.2. Electrocardiogram

Twelve-lead electrocardiograms (ECGs) will be obtained on subjects who enroll into this study >14 days after end of study visit in qualifying study, at annual (Month 12, 24 and 36) and Early Termination visits. All ECGs should be performed after the subject has rested quietly for at least 10 minutes. ECG data will be submitted to a central laboratory for measurement. Any clinically significant changes from the baseline ECG (from qualifying study for those subjects who enroll <14 days after end of study visit or from Screening visit in A3921092 for those subjects who enroll into this study >14 days after end of study visit in qualifying study), will be recorded as adverse events and evaluated further, as clinically warranted.

7.6.3. Tuberculosis Screening

For those subjects who enroll into this study >14 days after end of study visit in qualifying study, 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. The reviewer or reviewers, as per local standard of care, of the results of the Quantiferon-TB Gold In-Tube Test (QFT) and/or Mantoux Purified Protein Derivative (PPD) test and the x-ray and must provide his/her opinion about the eligibility of each patient for the study; this opinion must be documented in the subject's study records.

Annual TB testing will be performed using the QFT for subjects in those countries for which TB incidence has been reported at a rate of >50 cases per 100,000 persons, eg, Russian Federation and Taiwan [using China incidence rate] (World Health Organization, 2016).[39] All subjects with positive results must have a chest radiograph performed and reviewed by a radiologist or pulmonologist as per local standard of care and the radiograph must be negative for active TB infection for the subject to continue study participation. Subjects identified as having latent TB should be treated appropriately; for subjects remaining on study during their treatment, the only acceptable regimen is 9 months of isoniazid. Note: QFT should not be performed in subjects who had positive result during prior testing (screening visit or prior annual visits) and/or previously received adequate treatment for TB.

7.6.3.1. 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. 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.[40]

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.

7.6.3.2. 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 or evaluated at the annual visit using a Mantoux Purified Protein Derivative (PPD) test using 5 tuberculin units per 0.1 mL within the 3 months prior to a given screening visit at the discretion of the Sponsor. 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 Tuberculin Units (TU) is not available, then the PPD may be performed 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.

7.6.3.3. 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.

In addition, annual screening for latent and/or active TB will be conducted using QFT for subjects in those countries for which TB incidence has been reported at a rate of >50 cases per 100,000 persons. All subjects with a new positive QFT must have a chest radiograph performed and reviewed by a radiologist or pulmonologist as per local standard of care and the radiograph must be negative for active TB infection for the subject to remain in the study.

7.6.4. Complete Physical Examination

A standard complete physical examination will be performed at Screening (for those subjects who enroll in A3921092 >14 days after end of study visit in qualifying study), annual study visits (Month 12, 24 and 36) and Early Termination visit. The following parameters and body systems will be examined and any abnormalities described: height, 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 (for peripheral edema), abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes. Any clinically significant changes from Baseline should be recorded as adverse events (AEs). Baseline is defined according to the time subject entered A3921092 from qualifying study (see Appendix 8).

Recommendations for evaluation of emergent lymphadenopathy or other findings suggestive of lymphoproliferative disorder are provided in Appendix 8.

7.6.5. Targeted Examination

At all other visits, an abbreviated physical examination will be performed assessing the following: weight, lungs, heart, abdomen, lower extremities (for peripheral edema) and lymph nodes. Any clinically significant changes from baseline should be recorded as adverse events (AEs). Baseline is defined according to the time subject entered A3921092 from qualifying study (see Appendix 4).

7.6.6. 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 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.

7.6.7. Clinical Safety Laboratory Tests

Blood and urine samples will be collected at the time points identified in the protocol. 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.

Subjects will be excluded for hepatitis B infection. Subjects enrolling >14 days after end of qualifying study visit 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. Subjects enrolling >14 days after end of qualifying study visit will be tested for HCV Ab and, if positive, must undergo further testing for HCV RNA and may be allowed to enroll if negative.

Table 8. Clinical Laboratory Testing

Laboratory Testing Profile	Tests Included
Laboratory Tests Required at Screening Only	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, stool examination for parasites (Brazil only). 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)], platelets Hemoglobin A1c (HbA1c)
Chemistry Panel	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)
Lipid Panel	Fasting total cholesterol, HDL, LDL, triglyceride; apolipoprotein A-1, B and other lipoprotein tests potentially including particle size measurements
Tuberculosis Screening	QuantiFERON®-TB Gold In-Tube[c]
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)
FACS Analysis of Lymphocyte Subsets	CD3(%, abs), CD3+CD4+ (%, abs), CD3+CD8+ (%, abs), CD19+ (%, abs), CD56+CD16+ (%, abs)

[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] Performed at Screening Visit and annually for those subjects in countries which have high endemic TB rates and who tested negative at their last QFT.

Abnormal test results determined to be caused from laboratory error should not be reported as AEs. Patients 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.

7.6.7.1. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, before investigational product administration at the baseline visit and at each visit. A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study to confirm the subject has not

become pregnant during the study. Pregnancy tests may also be repeated as per request of Institutional Review Board/Independent Ethics Committees (IRB/IECs) or if required by local regulations.

If at any point during the study there is a case of a positive urine human Chorionic Gonadotropin (hCG) test, the subject will have the study drug stopped and the subject will be withdrawn from the study and all necessary follow-up be conducted.

7.6.8. Events for Adjudication/Review Committee Submission

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

7.6.9. Triggered Requirements

7.6.9.1. 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, if indicated after review by the Pfizer Study Clinician or Investigator. Factors that will be considered include stability of hemoglobin values, and their relationship to the standard reference range.
- 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 screening and baseline values, if indicated after review by the Pfizer Study Clinician or Investigator. Factors that will be considered include stability of the serum creatinine values, and their relationship to the standard reference range.
- Any creatine kinase (CK) >5x upper limit of normal (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.

For additional laboratory abnormalities that require prompt retesting, preferably within 48 hours from awareness of the abnormal results, see Section 8.7.2 Potential Cases of Drug-Induced Liver Injury.

7.6.9.2. 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 medications for more than 10 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 8.7).
- Two sequential absolute neutrophil counts <1.0 x 10^9/L (<1000/mm^3).
- Two sequential absolute lymphocyte counts <0.5x10^9/L (<500/mm^3).
- Two sequential hemoglobin values <8.0 g/dL (80 g/L) or decreases of >30% from baseline value.
- Two sequential platelet counts <75 x 10^9/L (<75,000/mm^3).
- Two sequential AST or ALT elevations ≥3 times the upper limit of normal with at least one total bilirubin value ≥2 times the upper limit of normal.[a]
- Two sequential AST or ALT elevations ≥3 times the upper limit of normal accompanied by signs or symptoms consistent with hepatic injury (eg, new onset elevated Prothrombin Time/International Normalized Ratio [PT/INR]).[a]
- Two sequential AST or ALT elevations >5 times the upper limit of normal, 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 screening and baseline values.
- Two sequential creatine kinase (CK) elevations >10 times the upper limit of normal, 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 infection considered significant by investigator or Sponsor.

- 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 Appendix 4, 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.

7.6.10. Country Specific Laboratory Testing Requirements

Brazil: Parasitological testing of the stool should be performed in accordance with Brazilian regulatory guidelines at the Screening Visit for those subjects who enroll in this study >14 days after end of study visit in their qualifying study.

7.7. Exploratory Biomarkers

7.7.1. Lymphocyte Subset Analysis

Fluorescence-activated Cell Sorting (FACS) analysis for lymphocyte subset markers will be performed to assess the effects of repeat doses of tofacitinib on T cell ($CD4^+CD3^+$, $CD8^+$), B cell ($CD19^+$) and NK cell ($CD16^+CD56^+$ cell) numbers. Whole blood samples will be collected at Baseline (for subjects who enter study >14 days after end of study visit or early termination in qualifying study), Month 3 and every 3 months thereafter.

7.8. 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 perform 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); 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.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

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

8.2. Reporting Period

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

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

8.3. Definition of an Adverse Event

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

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

- Drug dependency.

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

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

8.4. Medication Errors

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

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

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

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

8.5. Abnormal Test Findings

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

Test result is associated with accompanying symptoms, and/or

- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

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

8.6. 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.

8.6.1. 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 8 on Adverse Event Reporting.

8.6.2. 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 study drug temporarily discontinued during antimicrobial therapy in consultation with the Sponsor. This information should be noted in the Case Report Form.

8.7. Serious Adverse Events

A Serious Adverse Event is any untoward medical occurrence at any dose that:

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

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

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

8.7.1. Protocol-Specified Serious Adverse Events

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

8.7.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

- Concurrent with

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

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.8. Hospitalization

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

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);

- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment 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;
- Pre-planned 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 non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.9. Severity Assessment

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

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

8.10. Causality Assessment

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

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

8.11. Exposure During Pregnancy

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

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

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

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

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

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

8.12. Occupational Exposure

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

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

8.13. Withdrawal Due to Adverse Events (See Also the Section 6.4 Subject Withdrawal)

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

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

8.14. Eliciting Adverse Event Information

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

8.15. Reporting Requirements

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

8.15.1. Serious Adverse Event Reporting Requirements

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

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

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

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

8.15.2. Non-Serious Adverse Event Reporting Requirements

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

8.15.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

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, which will be dated and maintained by Pfizer. This analysis plan may modify what is outlined in the protocol; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

There will be 2 sets of analyses: one for the A3921092 LTE and the other for the sub-study. For the A3921092 LTE, the safety analysis will include cumulative data from all the subjects and all the data (including the data collected in the sub-study). The efficacy analysis for the LTE will only include the data collected in the A3921092 LTE (the efficacy data collected in the sub-study will be excluded from the LTE analysis).

Statistical methods for the sub-study are found in Appendix 10.

9.1. Sample Size Determination

The sample size of this study is determined by the number of subjects who enroll from qualifying randomized PsA studies with tofacitinib.

9.2. Safety Analysis

The primary focus of this study is the long term safety and tolerability of tofacitinib in adult subjects with PsA.

9.2.1. Analysis of Safety Endpoints

All the safety data will be summarized descriptively through appropriate data tabulations, and descriptive statistics. To help better understand and interpret the observed safety results, registry databases will be utilized to construct an appropriate contemporaneous and/or historical control group.

- Incidence and severity of adverse events during treatment.
- Incidence of clinical abnormalities and change from baseline (in this and/or prior study) in clinical laboratory values during treatment. 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.
- Incidence of vital sign (blood pressure and pulse rate) abnormalities and changes from baseline (in this and/or prior study) in vital sign measurements during treatment.

- Incidence of adjudicated safety events.

9.3. Efficacy Analysis

The measures of efficacy will be summarized using descriptive statistics, such as number and percent, mean, standard deviation and quartiles at each visit where measured. Displays using stratification by participation in qualifying studies will also be included. Exploratory analyses may also be performed.

Complete details will be specified in the statistical analysis plan.

9.4. Interim Analysis

Interim analyses to review safety data along with some efficacy data may be performed. As this is an open-label study with no formal hypothesis testing, there are no issues of protecting the Type I error rate.

Data-cuts will be performed as needed to support tofacitinib registration. Additional data reviews may be performed as needed by the study team for safety evaluations or for administrative purposes.

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 Event Adjudication/Review Committees

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 Committee (OIRC), Malignancy Adjudication Committee (MAC), Hepatic Event Review Committee (HERC) and Gastrointestinal Perforation Review Committee (GIPRC). In addition to these external committees, an internal committee of medically qualified Pfizer personnel with expertise in the assessment and diagnosis of respiratory disease will review and categorize potential events of interstitial lung disease (Interstitial Lung Disease Review Committee, ILDRC). Further information about these committees can be found in 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 adjudication or review committees described above, all biopsies of potentially malignant tumors, suspicious lymphadenopathy, or possible extranodal lymphoproliferative disorder (LPD), should be submitted to the central laboratory for review by central laboratory pathologists. In some instances, additional expert pathology review of submitted samples may be performed. Description of the scope of review and the processes used to obtain and assess biopsies is described in the Histopathology Review for Potential Malignancy charters. Further details on central laboratory review of biopsies of suspected malignancies are found in Appendix 8.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. 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 Institutional Review Board/Ethics Committee (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 is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital 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 as well as at Pfizer that clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), 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 to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with 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.

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.

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 or his or her legally acceptable representative 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.

Tofacitinib will be provided to subjects during the study and upon study completion, the subject should be assessed for appropriate treatment with approved products for the PsA indication. In limited situations, in accordance with country regulatory requirements, the IP may be available for continued treatment.

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 which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

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

13.2. End of Trial in all Other Participating Countries

End of Trial in all other participating countries is defined as Last Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, 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 or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within one week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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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.

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15.2. Publications by Investigators

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

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

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

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

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for

Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

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

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

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Appendix 1. Abbreviations

Abbreviation	Term
Ab	Antibody
AE	Adverse Event
ACR	American College of Rheumatology
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
Anti-CCP	Anti-cyclic citrullinated protein antibody
ASQoL	Ankylosing Spondylitis Quality of Life
AST	Aspartate Aminotransferase
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BID	Twice daily
BP	Blood Pressure
BSA	Body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CCP	Cyclic Citrullinated Peptide
CHD	Coronary Heart Disease
CI	Confidence Interval
CK	Creatine Kinase
CL/F	Oral Clearance
COX-2	Cyclooxygenase-2
CPDAI	Composite Psoriasis Disease Activity Index
CRF	Case Report Form
CRP	C-reactive Protein
CSA	Clinical Study Agreement
csDMARD	Conventional synthetic Disease-Modifying Anti-Rheumatic Drugs
CTA	Clinical Trial Application
CV	Cardiovascular
CV-SEAC	Cardiovascular Safety Endpoint Adjudication Committee
CYP	Cytochrome P
CXR	Chest X-ray
DAPSA	Disease Activity Index for Psoriatic Arthritis
DAREA	Disease Activity Index for Reactive Arthritis
DAS	Disease Activity Score
DIP	Distal interphalangeal
DLQI	Dermatology Life Quality Index
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
eDMC	External Data Monitoring Committee
EDP	Exposure During Pregnancy
EIU	Exposure in Utero

Abbreviation	Term
EQ-5D	The EuroQol EQ-5D Health State Profile
EU	European Union
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACS	Fluorescence Activated Cell Sorting
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
gm	gram
HAQ-DI	Health Assessment Questionnaire-Disability Index
HbA1c	Hemoglobin A1c
HBcAb	Hepatitis B core Antibody
HBsAb	Hepatitis B surface Antibody
HBsAg	Hepatitis B surface antigen
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
ID	Identification
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
ILDRC	Interstitial Lung Disease Review Committee
IP	Interphalangeal
IRB	Institutional Review Board
IRC	Internal Review Committee
IRT	Interactive Response Technology
ISI	Itch Severity Index
IUD	Intrauterine Device
IUS	Intrauterine System
IWR	Interactive Web-based Response
JAK	Janus kinase
LDA	Low Disease Activity
LDL	Low density Lipoprotein
LEI	Leeds Enthesitis Index
LPD	Lymphoproliferative Disease
LSLV	Last Subject Last Visit
LTE	Long-Term Extension

Abbreviation	Term
LTFU	Long-Term Follow-Up
MCP	Metacarpophalangeals
MCS	Mental Component Summary
MCTD	Mixed Connective Tissue Disease
MDA	Minimal Disease Activity
mg	Milligrams
MMRM	Mixed Model for Repeated Measures
MR=NR	Missing Response=Non Response
MTP	Metatarsophalangeal
MTX	Methotrexate
NAPSI	Nail Psoriasis Severity Score
NRI	Non-responder imputation
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area Severity Index
PASI75	Psoriasis Area and Severity Index 75
PCD	Primary Completion Date
PCS	Physical Component Summary
PGA-PsO	Physician's Global Assessment of Psoriasis
PGJS-VAS	Patient's Global Joint and Skin Assessment
PI	Principal Investigator
PIP	Proximal Interphalangeals
PK	Pharmacokinetics
PPD	Purified Protein Derivative
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
PsARC	Psoriatic Arthritis Response Criteria
PsA-HCRU	Psoriatic Arthritis Healthcare Resource Utilization Questionnaire
PsAJAI	Psoriatic Arthritis Joint Activity Index
PtGA	Patient's Global Assessment of Arthritis
PT-INR	Prothrombin Time- International Normalized Rate
QFT-G	Quantiferon Gold
RA	Rheumatoid Arthritis
RBC	Red Blood Cell
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-36	36-Item Short-Form Health Survey
SLE	Systemic Lupus Erythematosus
SPARCC	Spondyloarthritis Research Consortium of Canada

Abbreviation	Term
SPC	Summary of Product Characteristics
SRSD	Single Reference Safety Document
TB	Tuberculosis
TNF	Tumor Necrosis Factor
TNFi	Tumor Necrosis Factor Inhibitor
TU	Tuberculin Units
ULN	Upper Limit of Normal
US	United States
UVB	Ultraviolet B
VAS	Visual Analog Scale
WBC	White Blood Cell
WHO	World Health Organization
WLQ	Work Limitation Questionnaire

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

Subjects taking certain medications for PsA, and deriving inadequate benefit from them, may enter the study after a sufficient washout period for that medication. Subjects receiving certain medications for psoriasis may enter the study after a sufficient washout period for that medication (Section 4.1.2, criterion #3).

All **biologic DMARDs** are prohibited and require a specific washout period (as listed in the protocol or based upon Sponsor review) prior to first dose of study treatment. Subjects on TNF inhibitors must discontinue according to the following criteria:

- Etanercept (Enbrel®): 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 the first dose of study drug.

Patients entering from studies in which adalimumab (Humira®) was administered in a double-blind manner must have a minimum of 1 week washout after their last injection (placebo or adalimumab) and prior to their first dose of tofacitinib in this study.

Subjects receiving biologic agents for the treatment of psoriasis must discontinue according to the following criteria:

- Ustekinumab (Stelara®) must be discontinued for at least 12 weeks prior to first dose of study drug;
- Alefacept (Amevive®) must be discontinued for at least 8 weeks prior to first dose of study drug;
- Efalizumab (Raptiva®) is prohibited per exclusion criterion #12.

Other biologic agents used as DMARDs or used for the treatment of psoriasis are prohibited and require a 6 month washout period unless otherwise specified above.

The following traditional non-biologic DMARDs are prohibited: azathioprine, cyclosporine, mizoribin, tacrolimus and tetracycline (used as a DMARD). In the sub-study, sulfasalazine and leflunomide are considered prohibited medications.

All of these prohibited non-biologic DMARDs require a 4 week washout period prior to first dose of study drug.

Injectable (intravenous, intramuscular) corticosteroids are prohibited during the study (Section 4.1.1); intra-articular injections of corticosteroids are only permitted as rescue medication (Appendix 6).

Medications used to treat psoriasis are prohibited (Section 4.1.2). This also includes 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. Also prohibited is ultraviolet B (UVB) (narrowband or broadband) phototherapy that must be discontinued at least 2 weeks prior to first dose of study drug. Psoralens + ultraviolet A (UVA) phototherapy (PUVA) must be discontinued at least 4 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.

All non-biologic Investigational Drugs or marketed treatments for PsA or psoriasis not otherwise specified are prohibited (unless otherwise approved by the Sponsor) and require a 4 week (≥5 half-lives) washout period prior to first dose of study treatment (Section 4.1.2).

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. **For a medical condition (other than PsA) where it is important for the subject's safety to continue a prohibited drug, and where there is no study-permitted alternative, the subject must not participate in this study. Note that the list of prohibited medications includes, for example, anti-seizure and antiviral drugs for chronic use.**

- 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 the 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	

Appendix 4. Guidelines for Safety Monitoring, Dose Adjustments and Discontinuation

The following protocol-specified guidelines for safety monitoring and discontinuation are to be implemented.

For guidelines that reference changes from baseline, the baseline reference value is the baseline value from the qualifying study for all subjects who enter A3921092 within 2 weeks of the EOS visit of the qualifying study. For any subject who has >14 days between the EOS visit of the qualifying study and entry into A3921092, the baseline reference value is the value from the baseline visit of the A3921092 study.

Appendix 4.1. Safety Monitoring

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, if indicated after review by the Pfizer Study Clinician or Investigator. Factors that will be considered include stability of hemoglobin values, and their relationship to the standard reference range.
- Absolute neutrophil count $<1.2 \times 10^9$/L ($<1200/mm^3$).
- Absolute lymphocyte count $<0.5 \times 10^9$/L ($<500/mm^3$).
- Platelet count $<100 \times 10^9$/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 screening and baseline values, if indicated after review by the Pfizer Study Clinician or Investigator. Factors that will be considered include stability of the serum creatinine values, and their relationship to the standard reference range.
- Any single AST and/or ALT elevation >3 times the upper limit of normal (repeat laboratory testing must also include CK, total bilirubin, direct and indirect bilirubin, GGT, PT [prothrombin time], and alkaline phosphatase), regardless of the total bilirubin.
- Any creatine kinase (CK) >5x ULN (repeat laboratory testing should also include cardiac troponin).

Additional individual subject safety monitoring in addition to these guidelines is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled laboratory testing through the central laboratory may be obtained at any time during the study to assess such concerns, and a subject may be withdrawn at any time at the discretion of the investigator. Changes in values from the qualifying study should be considered.

Appendix 4.2. Guidelines for Dose Adjustments of Tofacitinib

The maximum tofacitinib dose allowed is 10 mg BID. All subjects will receive tofacitinib 5 mg BID upon entry into study. Tofacitinib dose may be increased from 5 mg BID to 10 mg BID based upon investigator discretion and should be modified during the study in the following manner:

- Subjects taking tofacitinib 5 mg BID may have their dose increased to 10 mg BID if the investigator feels that the subject's PsA symptoms are not adequately controlled and the subject is not experiencing any tofacitinib-related adverse events, including abnormalities in laboratory parameters that are judged to be related to tofacitinib.

- Dose increases may only occur at scheduled study visits.

Other dosage adjustments that may occur at any time may include:

- Subjects receiving tofacitinib 10 mg BID may reduce dose to 5 mg BID in response to mild to moderate AEs at the discretion of the investigator, either temporarily or for the duration of the study. If the dose has already been decreased to 5 mg BID, the dose may be temporarily discontinued for up to 28 days.

- Subjects receiving tofacitinib 10 mg BID may reduce dose to 5 mg BID either temporarily or for the duration of the study, after laboratory abnormalities specified in Appendix 4.1 are repeated and confirmed. If the dose has already been decreased to 5 mg BID, the dose may be temporarily discontinued for up to 28 days.

- Dosage of tofacitinib (5 mg or 10 mg BID) may be temporarily discontinued for up to 28 consecutive days, for laboratory abnormalities, for infections which do not meet criteria for serious infections (those requiring parenteral antimicrobial therapy or hospitalization), for surgical procedures or other moderately severe AEs. If treatment must be discontinued for more than 28 days, the subject should be withdrawn from the study.

- If a subject is temporarily discontinued from study drug for up to 28 days due to laboratory abnormalities, safety labs need to be repeated prior to resumption of treatment.

- If a subject taking tofacitinib 10 mg BID is temporarily discontinued from study drug for up to 28 days due to laboratory abnormalities, mild to moderate AEs or for infections that do not meet criteria for serious infections (those requiring parenteral antimicrobial therapy or hospitalization), their study drug should be restarted at 5 mg BID.

Appendix 4.3. Discontinuation Criteria

Study drug will be discontinued and the subject withdrawn from the study for:

- Requirement of rescue medication for more than 10 consecutive days.
- Serious infections, defined as any infection (viral, bacterial, and 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 8.7).
- Two sequential absolute neutrophil counts <1.0 x 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 platelet counts <75 x 10^9/L (<75,000/mm^3).
- Two sequential absolute lymphocyte counts <0.5x10^9/L (<500/mm^3).
- Two sequential AST or ALT elevations ≥3 times the upper limit of normal with at least one total bilirubin value ≥2 times the upper limit of normal.[a]
- Two sequential AST or ALT elevations ≥3 times the upper limit of normal accompanied by signs or symptoms consistent with hepatic injury (eg, new onset elevated PT/INR).[a]
- Two sequential AST or ALT elevations >5 times the upper limit of normal, 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 screening and baseline values.
- Two sequential creatine kinase (CK) elevations >10 times the upper limit of normal, 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.
- 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.

[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.

Appendix 4.4. Discontinuation/End of Treatment Follow-up Safety Monitoring

If a subject discontinues from the study due to abnormalities in hematology or clinical chemistry parameters which meet criteria as defined in Appendix 4.3, a follow-up visit must be performed within 28 days (±7 days) of last dose of study treatment.

All abnormal laboratory events of clinical significance should be followed until the laboratory values have returned to normal or baseline levels or are deemed clinically stable. 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.

Appendix 5. Approximate Equivalent Morphine Doses of Opioid Analgesics

Common Opioid Analgesics

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

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

References:

1. Twycross R, Wilcock A, Thorp S. Palliative Care Formulary. Abingdon: Radcliffe Medical Press, 1998.
2. Twycross R. Pain relief in advanced cancer. Edinburgh: Churchill Livingstone, 1994.

Appendix 6. 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 5) opioid that is not one of those listed above, they may increase the dosage for up to 10 consecutive days (up to a total daily dose which must not exceed the potency equivalent of 30 mg of orally-administered morphine [Appendix 5]) for rescue purposes;

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

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

Intravenous or intramuscular corticosteroids, biologic response modifiers and DMARDs, other than methotrexate, sulfasalazine and leflunomide, are not allowed during this study. Intra-articular corticosteroids may be given in no more than two joints, in a cumulative dose of no more than 80 mg methylprednisolone or its equivalent in any 6 month study period. Intra-articular hyaluronate sodium injections may be administered for indications in accordance with the local label at least 6 months from the last hyaluronate injection in no more than two joints in any 6 month study period. Injections should be avoided for 6 weeks before any study visit. Injected joints will also be considered as having their pre-injection status (swollen and/or painful/tender) and should not be counted for the remainder of the trial.

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. There is no limit to the duration of nonconsecutive use of rescue medications. In addition, subjects must not be dosed with rescue acetaminophen/paracetamol or opioids within 24 hours prior to a study visit except if adjustment is needed because subject is experiencing intolerable pain. Baseline stable acetaminophen/paracetamol or opioids should NOT be discontinued in advance of study visits.

Subjects must not be dosed with any rescue intervention within 24 hours prior to a study visit except if adjustment is needed because subject is experiencing intolerable pain.

Appendix 7. Composite Psoriatic Disease Activity Index (CPDAI)[22] score 0-15

	Not involved (0)	Mild (1)	Moderate (2)	Severe (3)
Peripheral arthritis		≤4 Joints (swollen/tender); normal function (HAQ <0.5)*	≤4 Joints but function impaired; or >4 joints, normal function	>4 Joints and function impaired
Skin disease		PASI ≤10 and DLQI ≤10	PASI ≤10 but DLQI >10; or PASI >10 but DLQI ≤10	PASI >10 and DLQI >10
Enthesitis		≤3 Sites; normal function (HAQ <0.5)*	≤3 Sites but function impaired; or >3 sites but normal function	>3 Sites and function impaired
Dactylitis		≤3 Digits; normal function (HAQ <0.5)*	≤3 Digits but function impaired; or >3 digits but normal function	>3 Digits and has function impaired
Spinal disease		BASDAI <4; normal function (ASQoL <6)	BASDAI >4 but normal function; BASDAI <4 but function impaired	BASDAI >4 and function impaired

*Health assessment questionnaire (HAQ) only counted if clinical involvement of domain (joint/enthesitis/dactylitis) present.

ASQoL, ankylosing spondylitis quality of life; BASDAI, Bath ankylosing spondylitis disease activity index; DLQI, dermatological life quality index; PASI, psoriasis area severity index.

Appendix 8. 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, suspicious 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.

Appendix 9. Contraceptive Methods (for Canada)

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

Highly effective contraceptive methods may include hormonal contraceptives (eg, combined oral contraceptives, patch, vaginal ring, injectables, and implants), intrauterine device (IUD) or intrauterine system (IUS), vasectomy or tubal ligation (see Section 4.4.6).

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

Appendix 10. Methotrexate Withdrawal Sub-Study

The purpose of this sub-study is to assess the efficacy, safety and tolerability of tofacitinib 5 mg BID administered as monotherapy after methotrexate (MTX) withdrawal compared to tofacitinib 5 mg BID continued in combination with MTX in subjects with active PsA. Subjects who have completed at least 24 months of participation in the long term extension study A3921092 and are currently receiving methotrexate may be included. Not all countries participating in the LTE will be included in this sub-study.

Subjects will be randomized to the 2 treatment arms in a 1:1 ratio, one in which they will receive open label tofacitinib 5 mg tablets BID and blinded methotrexate capsules (oral dose range from 7.5 mg to 20 mg per week) and the second in which they will receive open label tofacitinib 5 mg tablets BID and blinded MTX placebo capsules. The sub-study will be approximately 12 (standardized 4-week) months in duration and visits will occur at Baseline, Months 1, 3, 6, 9 and 12. The sub-study baseline will occur at the same time as a scheduled study visit at or after Month 24 of A3921092. This visit will be referred to as Sub-study Switch visit or Baseline visit (Sub-study Switch/Baseline visit).

Throughout this Appendix, Sections 4.5, 7, 8, 9.5 to 15.2 will be referenced to the main LTE protocol to avoid duplication.

SUB-STUDY TABLE 1. SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the sub-study visits and procedures. Refer to Sub-study Procedures (Section 6) and Assessments (Section 7) 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.

Protocol Activity	Combined A3921092 Sub-study Switch/Baseline[1]	Sub-study Month 1 (±7 days)	Sub-study Month 3 (±7 days)	Sub-study Month 6 (±7 days)	Sub-study Month 9 (±7 days)	Sub-study Month 12 Or Early Termination (±7 days)	Follow-up Visit (28 days ±7)[2]
Informed Consent	X						
Register for subject identification number and Randomization	X						
Complete Physical Exam[4]	X					X	
Targeted Physical Exam[4]		X	X	X	X		
Vital signs, temperature		X	X	X	X	X	
Waist and hips circumference			X	X	X	X	
Cardiovascular Risk Assessment[3]	X					X	
12-Lead ECG[5]	X					X	
QuantiFERON or Mantoux PPD /Chest Radiograph, if Necessary[6]	X	X	X	X	X	X	
LABORATORY TESTING							
Hematology, Chemistry Panel[7]		X	X	X	X	X	X
CRP[7]		X	X	X	X	X	
Lipid panel (fasting)[8]	X[8]			X		X	X
CBC with Differential and Chemistry Labs[7,9]	As per standard of Care						
Lymphocyte subset analysis (FACS)			X	X	X	X	
Urinalysis[10]		X	X	X	X	X	
Urine pregnancy test (hCG)[11]		X	X	X	X	X	X

Protocol Activity	Combined A3921092 Sub-study Switch/Baseline[1]	Sub-study Month 1 (±7 days)	Sub-study Month 3 (±7 days)	Sub-study Month 6 (±7 days)	Sub-study Month 9 (±7 days)	Sub-study Month 12 Or Early Termination (±7 days)	Follow-up Visit (28 days ±7)[2]
CLINICAL EVALUATION OF RHEUMATOLOGY ENDPOINTS							
Tender/Painful Joint Count (68), Swollen Joint Count (66)		X	X	X	X	X	X
Physician's Global Assessment of Arthritis (VAS)		X	X	X	X	X	
Dactylitis Assessment		X	X	X	X	X	
Enthesitis Assessment (Leeds Index)[12]		X	X	X	X	X	
CLINICAL EVALUATION OF RHEUMATOLOGY/DERMATOLOGY ENDPOINTS							
Physician's Global Assessment of Psoriatic Arthritis (VAS)		X	X	X	X	X	
CLINICAL EVALUATION OF DERMATOLOGY ENDPOINTS							
Physician's Global Assessment of Psoriasis (PGA-PsO)		X	X	X	X	X	X
Body Surface Area (BSA)		X	X	X	X	X	
PATIENT REPORTED OUTCOMES[13]							
Patient's Assessment of Arthritis Pain (VAS); Patient's Global Assessment of Arthritis (VAS); HAQ-DI[14]		X	X	X	X	X	
Patient's Global Joint and Skin Assessment (PGJS-VAS)		X	X	X	X	X	
SF-36v2, FACIT-F, EQ-5D[14]		X	X	X	X	X	
OTHER ACTIVITIES							
Adverse Event Assessment		X	X	X	X	X	X
Prior/Concomitant Treatment		X	X	X	X	X	X
Dispense study medication/Accountability[15]	X[16]	X[15]	X	X	X	X[15]	

1. Subjects who are qualified to enter into the MTX withdrawal sub-study, the combined A3921092 Sub-study Switch/Baseline visit will occur at a scheduled study visit at Month 24, Month 27, Month 30, Month 33 or Month 36 of the long term extension study A3921092. Any study procedure required for the sub-study baseline visit that was not included as part of the A3921092 study must be completed during this visit. There will be no separate Baseline visit for the sub-study.
2. If a subject discontinues from the study due to abnormal hematology or clinical chemistry results which meet criteria as described in Appendix 4, or discontinues due to an adverse event, a follow-up visit must be performed after the Early Termination visit within 28 days (±7 days) of last dose of study treatment.
3. Cardiovascular (CV) Risk Factor Assessment includes multiple assessments such as smoking status, average weekly alcohol consumption, and family history of premature coronary heart disease (CHD) (See Section 7.4 of LTE for complete list). This should be done as part of the Month 24 visit in study A3921092.
4. Complete physical exam should be performed annually (Baseline and Month 12 or Early Termination) and includes: height, weight, general appearance, skin, HEENT (head, eyes, ears, nose and throat), heart, lungs, abdomen, lower extremities, neurologic and lymph nodes. Targeted physical exam should be performed at other scheduled visits except Follow-Up and includes: weight, examination of heart, lungs, abdomen, lower extremities (for peripheral edema) and lymph nodes.
5. 12-lead ECG will be taken at sub-study baseline and Month 12 or Early Termination (ET) visit only. ECG will be evaluated by a central reader.
6. Tuberculosis annual screening procedures must be performed if not completed during the Month 24 LTE study visit in appropriate subjects. Annual TB screening will be conducted using Quantiferon-TB® Gold In-Tube test (QFT) for subjects in those countries in which TB incidence has been reported at a rate of >50 cases per 100,000 persons (see Section 7.6.3). All subjects with positive results (and who tested negative at their last QFT) must have chest radiograph performed and reviewed by a radiologist or pulmonologist as per local standard of care. Subjects who must have a PPD administered must return within 48-72 hours for evaluation.
7. Hematology includes: white blood cell (WBC) count/differential, hemoglobin, hematocrit, red blood cell (RBC) count and morphology, reticulocyte and platelet counts. Serum chemistry 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). All hematology, clinical chemistry tests and HbA1C will be performed by the central laboratory; C-reactive Protein (CRP) will also be measured by central laboratory (results will be blinded).
8. A fasting lipid panel (total cholesterol, LDL, HDL, triglycerides, apolipoprotein A-1 and B) and other lipoprotein tests potentially including particle size measurements per Sub-Study Table 7 in Section 7.6.7 will be collected at the sub-study combined/baseline visit; Month 6, and Month 12, Early Termination or Follow-up visits.
9. Clinical chemistry as appropriate for standard of care in subjects receiving background non-biologic DMARDs may include creatinine, albumin and liver function tests.
10. 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).
11. Urine pregnancy testing (human chorionic gonadotropin; β-hCG) is required only for women of childbearing potential.
12. Enthesitis will be assessed using only the Leeds Enthesitis Index per Section 7.2.8 of the LTE.
13. All Patient Reported Outcomes should be completed prior to any other assessments made at each visit.

14. Subject completed questionnaires include: Health Assessment Questionnaire-Disability Index (HAQ-DI), Short-Form-36 Health Survey (Version 2, Acute) (SF-36), Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F), EQ-5D.
15. Study medication will not be dispensed at Month 1 or End of Treatment or Early Termination visit; however, drug accountability and compliance assessment will be performed.
16. At the Switch/Baseline visit, all investigational product from the main A3921092 LTE study will be collected for accountability under the main protocol. New tofacitinib supplies will be dispensed under the sub-study.

1. INTRODUCTION

1.1. Indication

Tofacitinib is being developed for the treatment of adult subjects with active Psoriatic Arthritis (PsA).

1.2. 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.[1,2] Treatment recommendations for the cardinal clinical manifestations of the disease have been developed in recent years by a consensus of rheumatologists and dermatologists.[41] Treatment of subjects with PsA is frequently influenced by the severity of each domain and treatment recommendations vary depending on what disease domain is more severely affected.[43,44] Some of the agents recommended for the treatment of PsA include non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular glucocorticoid injections, conventional synthetic (cs) DMARDs and TNF inhibitors.[42,44] The csDMARDs are either prescribed as monotherapy or in combination with other agents.[43] Methotrexate (MTX) is a widely used csDMARD for the treatment PsA and commonly one of the first agents administered to patients.[42,43,44] Despite its popular use, there are only a few randomized placebo controlled trials comparing MTX to placebo in the treatment of PsA and none of them have clearly demonstrated efficacy of this therapy.[44] One of the few placebo-controlled trials of MTX in psoriatic arthritis failed to find evidence for MTX improving synovitis and showed no advantage of MTX over placebo with respect to rheumatology related global responses.[45] MTX is frequently used in combination with other therapies also recommended for the treatment of PsA, such as biologics or other csDMARDs.[42,43,44] Liver toxicity and other secondary effects related to the long term use of MTX continue to be a concern for treating physicians and patients.[42] Understanding the disease activity of subjects that discontinue one of the agents in their combination treatment will help the medical community determine the usefulness of a step down process of treatment.

The majority of subjects who participated in the tofacitinib PsA development program continue therapy on a stable dose of one background DMARD for the duration of their participation in the long term extension study.

This sub-study is designed to assess the efficacy of tofacitinib 5 mg BID as monotherapy after MTX withdrawal compared to tofacitinib 5 mg BID in combination with concomitant MTX. In addition, the sub-study will assess the safety and tolerability of tofacitinib 5 mg BID as a treatment for PsA in a MTX withdrawal population.

1.2.1. Single Reference Safety Document (SRSD)

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- To assess the efficacy of tofacitinib 5 mg BID monotherapy as compared to tofacitinib 5 mg BID with background MTX in subjects who have received prior treatment of tofacitinib in combination with MTX.

2.1.2. Secondary Objective

- To assess the safety and tolerability of tofacitinib 5 mg BID monotherapy as compared to tofacitinib 5 mg BID with background MTX in subjects who had received prior treatment of tofacitinib in combination with MTX.

2.2. Endpoints

2.2.1. Primary Endpoints

- Change from baseline (Δ) in HAQ-DI at 6 months.
- ΔPASDAS at 6 months.

2.2.2. Secondary Endpoints

- ΔHAQ-DI score at all time points except Month 6.
- ΔPASDAS at all time points except Month 6.
- Psoriatic Arthritis Response Criteria (PsARC) response at all time points.
- Δ in Physician's Global Assessment of Psoriasis (PGA-PsO) at all time points.
- %Δ in BSA at all time points.
- Δ in Dactylitis severity score at all time points.
- Dactylitis absence at all time points.
- Δ in Enthesitis score (using Leeds Enthesitis Index, [LEI]) at all time points.
- Enthesitis absence (using LEI) at all time points.
- MDA response at all time points.

- Δ in ACR components (tender/painful joint count (68), swollen joint count (66), Physician's Global Assessment of Arthritis, Patient's Global Assessment of Arthritis, Patient's Assessment of Arthritis Pain, CRP) at all time points.

- Physical function/other patient reported outcomes to be assessed at all time points:

  - Δ in Short-Form 36 (version 2, Acute) (8 domains and Physical Component Summary [PCS] score and Mental Component Summary [MCS] score);

  - ΔFACIT-F (Total score, Experience domain and Impact domain scores);

  - ΔEuroQol-5D Health Questionnaire (EQ-5D) (Scores from the five domains and an EQ-Visual Analog Scale (VAS) score on the subject's health state today (EQ-VAS).

- Incidence and severity of adverse events.

- Incidence of clinical abnormalities and change from baseline in clinical laboratory values during treatment.

2.2.3. Other Endpoints

- ΔDAS28-3 (CRP) at all time points.

- MDA component response at all time points.

- Δ in Patient's Global Joint and Skin Assessment (PGJS-VAS) at all time points.

- Incidence of investigator-reported clinically significant changes in physical examination from baseline during treatment.

- Incidence of electrocardiogram (ECG) abnormalities and change from baseline in ECG measurements during treatment.

- Incidence of vital sign (blood pressure and pulse rate) abnormalities and changes from baseline in vital sign measurements during treatment.

3. SUB-STUDY DESIGN

This sub-study within Study A3921092 is a Phase 3, randomized, double-blind, placebo-controlled, parallel group estimation study designed to assess the efficacy, safety and tolerability of tofacitinib 5 mg BID versus tofacitinib 5 mg BID in combination with concomitant MTX in subjects with active PsA. Subjects with active PsA will have previously completed at least 24 months of treatment with tofacitinib in Study A3921092 and will be on a stable dose of tofacitinib 5 mg BID for at least 3 months prior to the first dose of sub-study drug and be on a stable dose of oral MTX at least 4 weeks prior to the first dose of sub-study drug. This sub-study will be referred to as A3921092 Sub-study. For subjects who are

qualified to enter into the sub-study, the Combined A3921092 Sub-study Switch/Baseline visit will occur at a scheduled study visit at or after Month 24 of A3921092. There will be no separate Baseline visit for the sub-study. The visit window will remain as in the LTE in which a month is considered 28 days. Once a subject enters the sub-study, they will complete their participation in the sub-study portion and be unable to re-enter the main study. Subjects may be discontinued from the sub-study at any time during the sub-study in the event of deterioration of response as determined by the investigator.

Eligible subjects from study A3921092, will be randomized into A3921092 sub-study in a 1:1 ratio to tofacitinib 5 mg BID + MTX placebo or tofacitinib 5 mg BID + MTX. MTX will be blinded to the subjects, investigators and the sponsor. The subjects in the tofacitinib 5 mg BID + MTX group will receive blinded MTX capsules (range dose of 7.5-20 mg a week based upon the pre-existing dose) and the subjects in the tofacitinib 5 mg BID group will receive the matching MTX placebo capsules. For the duration of the sub-study tofacitinib dose must remain stable at 5 mg BID. The MTX dose and oral route of administration must remain stable for the 12 month duration of the sub-study. All subjects will receive open-label tofacitinib 5 mg BID throughout the sub-study without dose increase. The total number of subjects randomized will be approximately 180 (Sub-Study Table 2).

Sub-Study Table 2

Treatment Group	Double blind placebo controlled period	Number of Subjects
B	Tofacitinib 5 mg BID + Placebo	90
C	Tofacitinib 5 mg BID + Methotrexate	90

Treatment duration for subjects participating in this sub-study is approximately 12 months.

At various time points in this trial, safety measurements, including physical examination, clinical laboratory tests, adverse event monitoring, electrocardiograms (ECGs) and vital signs will be performed. All subjects will be monitored for clinical evidence of PsA response to treatment. Health Outcomes Measures (ie, Patient Reported Outcomes assessments for pain, quality of life, physical function, fatigue and health status) will also be performed at various time points in this trial. In addition, subjects will be monitored for serious infections, lymphadenopathy and lymphoproliferative disorder (LPD).

4. SUBJECT SELECTION

This sub-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.

4.1. Sub-Study Inclusion Criteria

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

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

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

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

3. Subjects must have previously completed at least 24 months of treatment with tofacitinib for the treatment of PsA in the long term extension study A3921092.

4. Subjects must be receiving tofacitinib 5 mg BID and be on a stable dose for a minimum of 3 months before the first dose of blinded MTX. Subject receiving tofacitinib 10 mg BID must reduce the tofacitinib dose to 5 mg BID 3 months prior to randomization into the sub-study.

5. Subjects must be receiving oral MTX as their permitted traditional non-biologic background DMARDs, and must be dosed in accordance with the A3921092 requirements.

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

        - MTX administered orally: Subjects receiving non-oral forms of methotrexate in study A3921092 should switch to an oral route of administration at least 12 weeks before the sub-study entry and remain on it for the duration of the sub-study.

        - Dosing of MTX should be stable (dose range allowed from a minimum dose of 7.5 mg/week and maximum dose of 20 mg/week) 4 weeks prior to entry to the sub-study and remain stable for the duration of it.

        - All subjects 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 blinded study drug (see Section 5.6).

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

    - Oral corticosteroids: Subjects who are already receiving oral corticosteroids in study A3921092 must remain on a stable dose of ≤10 mg/day of prednisone or

equivalent. The dose must be stable for four weeks prior to sub-study entry and remain stable for the duration of the sub-study.

- Subjects who received injectable (eg, intraarticular, intramuscular or intravenous) corticosteroids in study A3921092 should have discontinued their use 12 weeks prior to the of sub-study entry.

7. Subjects who are already taking NSAIDs/COX-2 inhibitors may participate in the sub-study provided that that the dose is stable for one week prior to sub-study entry and remain stable for the duration of it.

4.2. Sub-Study Exclusion Criteria

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

1. Subjects who are receiving other concomitant non-biologic csDMARDs, eg, leflunomide, sulfasalazine.

2. Subjects receiving MTX by a route other than oral.

3. Subjects receiving MTX at a dose lower than 7.5 mg per week or >20 mg per week.

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

5. Subjects that have become pregnant during study A3921092 and breastfeeding females and females of child-bearing potential who are unwilling or unable to use a highly effective method(s) 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 or females planning pregnancy.

6. 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 4.4.6).

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

8. Subjects who have been diagnosed with any autoimmune rheumatic disease other than PsA (including systemic lupus erythematosis, mixed connective tissue disease, scleroderma, polymyositis) or 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.

9. A subject who has been diagnosed with immunodeficiency disorder during study A3921092.

10. Functional Class IV status 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.[15]

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

12. 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.

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

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

    - Requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 3 months prior to sub-study entry;

    - Requiring oral antimicrobial therapy within 2 weeks prior to enrolling in the sub-study.

15. Any subject who has been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of sub-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 4.4.2 Vaccine Guidelines of LTE study for further information regarding avoidance of household contacts who may be vaccinated).

16. 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.

17. A subject who is considered at increased risk for GI perforation (eg, patients with diverticulitis) by the Investigator or Sponsor.

18. 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.

19. A subject requiring prohibited concomitant medications (See Appendix 3). For a medical condition in which it is important for the subject's safety to continue a prohibited drug described in Appendix 3, and there is no study-permitted alternative, the subject must not participate in this study. Subjects receiving non-prohibited concomitant medications must be on a stable regimen which is defined as not starting a new drug or changing dosage within seven days or 5 half-lives (whichever is longer) prior to the baseline visit.

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

21. 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.

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

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

24. Participation in other studies involving investigational drug(s) (Phases 1-4) during sub-study participation.

4.3. Sub-Study Enrollment Criteria

Subjects will be enrolled into the sub-study provided they have signed an informed consent document to participate in the sub-study, have undergone all Sub-study Switch /Baseline visit procedures as required, and have met all inclusion and exclusion criteria for participation in the sub-study at the Combined A3921092 Sub-study Switch/Baseline visit. Subjects will be assigned a new subject identification number that will be retained throughout the sub-study.

4.4. 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 Sub-Study 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.

- Avoid vaccinations with live or attenuated live vaccines and contact with individuals who have recently received live or attenuated live vaccines (See Section 4.4.2 of main LTE study).

- Discontinue and avoid using certain medications and treatments used to treat PsA or psoriasis (see Inclusion Criteria and list of prohibited medications Appendix 3). Discontinue and avoid using certain other prohibited medications and treatment (see Appendix 3) not used to treat PsA or psoriasis. For a medical condition in which it is important for the subject's safety to continue using the prohibited drug, and there is no study-permitted alternative, the subject must not participate in this study.

- Contact the study site investigator if there are any changes or additions to concomitant medications.

- Avoid having elective surgery (See Section 4.4.5).

- Agree to use highly effective contraceptive methods per Section 4.4.6.

4.4.1. Non-Pharmacologic Interventions

The subject should continue all non-pharmacological therapies, such as physical therapy, as indicated.

4.4.2. Vaccine Guidelines

For guidance on administration of vaccines to a subject and management of household contacts with others vaccinated refer to Section 4.4.2 of the main study A3921092.

4.4.3. Dietary Supplements

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

Vitamins, minerals and purified food substances are allowed in amounts not known to be associated with adverse effects (such as hypervitaminosis). Herbals with pharmaceutical properties are allowed only if there is acceptable evidence of no 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.

4.4.4. 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, Month 6 and Month 12, End of Treatment/Early Termination Visit and Follow-Up Visit (if required).

4.4.5. Elective Surgery

During the course of this trial, no elective surgery should be scheduled without first consulting the Pfizer Study Clinician.

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.

4.4.6. Contraception

4.4.6.1. Contraceptive Methods in Women of Childbearing Potential

Administration of tofacitinib in preclinical studies was shown to have teratogenic effects on the offspring of treated rats and viability of their fetuses. Due to this hypothetical risk, women of childbearing potential will not be administered tofacitinib until pregnancy is excluded and should use a highly effective method(s) of contraception during therapy with tofacitinib and for at least one ovulatory cycle after study treatment is discontinued. They must have a negative urine pregnancy test at the baseline visit prior to the first dose of study drug and at every visit during the study (or more frequently if required by local practices), if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected or if the subject has become sexually active.

In this study, male subjects who are able to father children and female subjects who are of childbearing potential will receive MTX or placebo in a blinded manner. MTX has been associated with teratogenic risk. For subjects who are sexually active and at risk for pregnancy with their partner(s) must agree to use with their partner(s) two (2) methods of highly effective contraception throughout the study and continue for at least 3 months after the last dose of sub-study drug.

For the purposes of this protocol, female subjects must either use adequate contraception or be of non-childbearing potential. The investigator, in consultation with the subject, will select an appropriate method(s) of contraception for women of child-bearing potential who are sexually active from the permitted list of contraception methods, and instruct the subject in their consistent and correct use. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the subject to call immediately if a selected birth control method(s) is discontinued or if pregnancy is

known or suspected. Subjects in the United Kingdom that are women of childbearing potential are required to use two highly effective methods of birth control.

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

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

2. Correctly placed copper containing intrauterine device (IUD) or intrauterine system (IUS).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Sterilization of male partner with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.

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

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

4.4.6.2. Women of Non-Childbearing Potential

Female subjects of non-childbearing potential must meet **at least one of the following criteria:**

- Have undergone documented hysterectomy or bilateral oophorectomy;

- Have medically confirmed ovarian failure; or

- 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 serum FSH level within the laboratory's reference range for post-menopausal females.

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

4.4.6.3. Contraceptive Methods in Male Subjects

Administration of tofacitinib in preclinical trials demonstrated no effects on male sperm or offspring in any studies conducted to date. Due to the concomitant administration of MTX in this study, male subjects need to take contraceptive precautions as described in the previous section.

4.5. Sponsor Qualified Medical Personnel

Please refer to Section 4.5 of the main Study Protocol A3921092.

5. SUB-STUDY 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 sub-study, the investigational products are tofacitinib and methotrexate.

5.1. Sub-Study Allocation to Treatment

The following medication will be supplied by Pfizer Inc:

- Tofacitinib 5 mg tablets (open-label).
- Methotrexate 2.5 mg capsules.
- Placebo capsules that match Methotrexate capsules.

Both the open-label tofacitinib 5 mg and blinded MTX will be dispensed to subjects to self-administer after appropriate training and specific written instructions are provided. Tofacitinib will be taken orally 5 mg BID (approximately every 12 hours). Methotrexate or MTX placebo will be taken orally once a week. The dose of MTX must be the same oral dose as taken prior to sub-study entry; allowed doses of MTX entry may range from 7.5 mg to a maximum of 20 mg a week but must be stable 4 weeks prior to entering the sub-study, and must not be changed with the following exception. Reductions in the dose of MTX are permitted if there is evidence of toxicity. For subjects who are on a MTX dose higher than 7.5 mg per week, the MTX dose may be reduced to 7.5 mg per week on one occasion and with Sponsor's approval. Dose re-adjustments of MTX will be allowed with Sponsor's approval. Reductions of tofacitinib dose are not permitted. Temporary withdrawals of any of the sub-study drugs (tofacitinib and methotrexate/placebo) are only permitted if required

due to safety concerns. Study treatment will continue until the subject discontinues from the study or has received approximately 12 months of treatment.

Allocation of subjects to treatment will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response (IWR). During the sub-study Baseline visit, the site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject's number. The site personnel will then be provided with a randomization number and container number(s) when investigational product is being supplied via the IRT system. The confirmation report must be stored in the site's files.

5.2. Sub-Study Breaking the Blind

This sub-study will be subject-, investigator- and Sponsor blinded.

In regards to each sub-study drug:

- Tofacitinib 5 mg BID will be open label;
- The assignment of MTX/MTX placebo will be subject-, investigator-, and Sponsor-blinded.

At the initiation of the sub-study the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process using the IRT system. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented on the case report form (CRF).

5.3. Sub-Study Drug Supplies

The Sponsor will provide tofacitinib 5 mg tablets in a bottle that will be labeled as appropriately for this sub-study. MTX 2.5 mg capsules and matching placebo will also be provided by the Sponsor. Study medication will be taken according to the instructions provided to the subject. The specific subject instructions will also direct the subject to bring the study medication bottle(s) to the clinic on study visit days. Dose increases for both tofacitinib and blinded MTX are not permitted during this sub-study. Temporary withdrawals of any study drug or MTX dose reductions due to safety concerns may occur between scheduled study visits and must be clearly documented on the subject's chart and verified for start date and dose when the subject returns for their next scheduled visit.

5.3.1. Sub-Study Preparation and Dispensing

Tofacitinib, blinded MTX and the corresponding MTX placebo will be dispensed in bottles. At each dispensing visit, subjects will receive a sufficient quantity of all study drugs to last

until their next scheduled dispensing visit. The subject should be instructed to maintain the product in the container provided throughout the course of dosing and return the containers at the next study visit. At all study visits, subjects' returned containers will be assessed for accountability and the amount of study drug returned will be recorded.

5.4. Sub-Study Administration

All investigational products will be self-administered by the subject as specified in the dosing card. Tofacitinib should be administered orally, twice daily, approximately 12 hours apart, once in the morning and once in the evening. During the sub-study all subjects will receive a dose of 5 mg BID taking 1 tablet in the morning and 1 tablet in the evening. If a tofacitinib dose is missed and the interval to the next scheduled dose is less than 6 hours, the missed dose of tofacitinib should not be administered.

At the time of enrollment (eg, the Combined A3921092 Sub-study Switch/Baseline visit), subjects must discontinue the use of their personal (commercial) supply of MTX. MTX or its matching placebo will be provided by the Sponsor and must be administered orally once a week (the same day of the week) in a predetermined dose that may range from 7.5 mg/week to 20 mg/week. Subjects will receive the corresponding number of MTX or matching placebo 2.5 mg capsules to complete their individual preselected dose of oral MTX (Sub-Study Table 3). Subjects should be instructed to document any missed doses.

Sub-Study Table 3

Assigned Dose of MTX	Corresponding number of MTX 2.5 mg capsules or matching placebo
7.5 mg/week	3 capsules
10 mg/week	4 capsules
12.5 mg/week	5 capsules
15 mg/week	6 capsules
17.5 mg/week	7 capsules
20 mg/week	8 capsules

Subjects who are randomized to tofacitinib 5 mg BID + MTX placebo will experience a full withdrawal of MTX (eg, no tapering) at the time of randomization.

Study medications may be administered with or without food, with exception of the day of the study visits that require fasting.

Medication errors may result in the sub-study from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dose. Such medication errors occurring to a study participant are to be captured on the adverse event page of the CRF and on the SAE form when appropriate. In the event of a dosing error, the sponsor should be notified immediately. Whether or not the medication error is accompanied by an AE, as determined by the investigator, it is captured on an adverse event (AE) CRF

page as well as any AEs associated with the medication error (refer to Section 8 of main LTE protocol).

5.5. Sub-Study Compliance

Subject compliance with dosing administration for both tofacitinib and MTX/placebo will be verified by accounting of returned containers and trial medication at each visit.

Compliance for the tofacitinib tablets and MTX/placebo capsules will be monitored by the accounting of unused medication and will be documented. Subjects who demonstrate <80% compliance to either study drug should be counseled by the investigator or designee and ensure steps are taken to improve compliance. Subjects who are <80% compliant with dosage regimen for any of the 2 study medications, for two consecutive visit periods should be withdrawn from the study.

If the subject is over-compliant with either study drug (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 (>120% in a visit period) that may potentially impact the safe use of study drug or that may result in a serious adverse event.

5.6. Sub-Study Drug Storage

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

Both investigational products should be stored in its original container and in accordance with the drug label. See the drug label for storage conditions of the product.

Storage conditions stated in the single reference safety document (SRSD), tofacitinib IB and SPC for methotrexate), will be superseded by the storage conditions stated in the labeling.

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

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

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. 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.

5.7. Sub-Study Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss or other disposition of the investigational product supplies. At the Switch/Baseline visit of the sub-study, all investigational product from the main A3921092 LTE study will be collected for accountability under the main protocol. New tofacitinib supplies will be dispensed under the sub-study.

To ensure adequate records, all investigational product 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. All study drug bottles must be returned to the investigator by the subject and the investigator will return the bottles to Pfizer. 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.

5.7.1. Destruction of Investigational Product Supplies

Process for destruction will be as noted in Section 5.5.1 of the LTE protocol.

5.8. Concomitant Treatment(s)

It is important to be aware of, and document, all concomitant treatments 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 to receive 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.

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

Minimum guidelines for folate supplementation during study: All subjects 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

Adjustments for safety reasons may be done at any time, but if this leads to changes in excess of those allowed, the investigator must receive approval from the Pfizer Study Clinician to allow the subject to continue in the trial.

For subjects receiving background NSAID/COX-2 inhibitors, dose adjustments are not permitted in the first 6 months of the sub-study unless there is a safety concern. Switching to other NSAIDs/COX-2 inhibitors is not allowed during the sub-study. Oral corticosteroid dose should not exceed 10 mg prednisone or its equivalent daily. Daily dosage of corticosteroids must not be modified during the sub-study, 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 5, Appendix 6).

Daily dosage of opioids and acetaminophen/paracetamol must not be modified in the first 6 months of the sub-study, except if adjustment is needed to protect a subject's safety.

5.8.2. Other Medications

Prohibited drugs and dietary supplements must be discontinued according to protocol guidelines: a list of prohibited drugs with specific discontinuation recommendations is listed in Appendix 3. 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). All concomitant treatment taken during the study must be recorded with indication (as required), daily dose, and start and stop dates of administration.

5.9. Rescue Therapy

The only medications that are allowed for rescue are listed in Appendix 6. Subjects who require rescue medication for more than 10 consecutive days should be discontinued from the study. There is no limit to the total duration of nonconsecutive use of rescue medications. In addition, subjects must not be dosed with rescue medication during the 24 hours prior to a study visit except if adjustment is needed because subject is experiencing intolerable pain.

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

5.9.1. Dosage Reduction and Withholding

All subjects will receive open-label tofacitinib 5 mg BID and MTX or matching placebo upon entry into the sub-study. Dosage of both tofacitinib and MTX (predetermined dose as described in Sub-Study Section 5.1) must remain stable for the duration of the sub-study.

If the investigator deems it necessary to withhold any of the study medications to treat a non-serious infection or other medical condition, temporary withholding is permitted for up to 5 days of tofacitinib and 1 weekly dose of MTX. If the study drug administration is interrupted for more than 5 days or 1 weekly dose of MTX due to a medical reason, the investigator must contact the Pfizer study clinician for approval.

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

Dosage of tofacitinib and/or MTX may be temporarily discontinued for up to 14 consecutive days or 2 weekly doses, for severe cytopenias, for infections which meet criteria for serious infections (ie, those requiring parenteral antimicrobial therapy or hospitalization), for surgical procedures or other moderately severe AEs.

Treatment with tofacitinib will be discontinued and the subject withdrawn from this study due to safety issues as defined in Appendix 4.3.

6. SUB-STUDY PROCEDURES

Subjects from the long term extension study who elect to participate in the sub-study should complete a combined A3921092 Sub-study Switch/Baseline visit on the same day of the scheduled A3921092 study visit at or after Month 24.

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 sub-study. Subjects may be discontinued from the sub-study at any time during the sub-study in the event of deterioration of response as determined by the investigator.

6.1. Combined A3921092 & Sub-Study Switch/Baseline Visit

The Combined A3921092 Sub-study Switch/Baseline visit occurs at Month 24, Month 27, Month 30, Month 33, or Month 36 of A3921092. Since not all of the study procedures and assessments needed for the Baseline of the sub-study are collected at these visits of A3921092, any assessment or activity that was not completed as part of the A3921092 visit needs to be completed at this combined visit. At the Switch/Baseline visit of the sub-study, all investigational product from the main A3921092 LTE study will be collected for accountability under the main protocol. New tofacitinib supplies will be dispensed under the sub-study. Details of the required activities are listed below.

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

All Patient Reported Outcomes should be completed prior to any other study procedures.

6.1.1. Combined A3921092 & Sub-Study Switch/Baseline Visit at Month 24 or Month 36

For subjects with the Combined A3921092 Sub-study Switch/Baseline visit conducted at the scheduled A3921092 study visit of Month 24 (M24) or Month 36 (M36), subjects must complete activities as indicated from M24 or M36 visit of A3921092 in addition to the following procedures:

- Informed consent obtained.
- Collect tofacitinib LTE investigational product supplies and complete accountability for the last visit of the main LTE study.
- Register for subject identification number.
- Randomization completed.
- Dispense study medication/schedule next visit.
- Observe subject taking the study drugs (tofacitinib and MTX or placebo) and record the dosing in the dosing log CRF.

6.1.2. Combined A3921092 & Sub-Study Switch/Baseline Visit at Month 27 or Month 33

For subjects with the Combined A3921092 Sub-study Switch/Baseline visit conducted at the scheduled A3921092 study visit of Month 27 or Month 33, the subjects must complete activities as indicated from M27 or M33 visit of A3921092 in addition to the following procedures.

- Informed consent obtained.
- Collect tofacitinib LTE investigational product supplies and complete accountability for the last visit of the main LTE study.
- Register for subject identification number.
- Randomization completed.
- SF-36 Version 2 (Acute).
- FACIT-F.
- EQ-5D.

The following additional procedures will also be performed:

- Cardiovascular Risk Assessment: smoking status, average weekly alcohol consumption and family history of premature coronary heart disease (see Section 7.4 of LTE study).
- Physical Examination: Complete physical examination (height, weight, general appearance) skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), 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.
- Blood testing: Central laboratory testing of Lipid Profile (fasting).
- Yearly TB testing if applicable.
- 12-lead electrocardiogram.
- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions.

- Drug dispensing.

- Observe subject taking the study drugs (tofacitinib and MTX or placebo) and record the dosing in the dosing log CRF.

6.1.3. Combined A3921092 & Sub-Study Switch/Baseline Visit at Month 30

For subjects with the Combined A3921092 Sub-study Switch/Baseline visit conducted at the scheduled A3921092 study visit of Month 30, the subjects must complete activities as indicated from M30 visit of A3921092 in addition to the following procedures at the combined screening/baseline visit.

- Informed consent obtained;

- Collect tofacitinib LTE investigational product supplies and complete accountability for the last visit of the main LTE study.

- Register for subject identification number.

- Randomization completed.

The following additional procedures will also be performed:

- Physical Examination: Complete physical examination (height, weight, general appearance) skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), extremity exam (presence of peripheral edema), abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes.

- 12-lead electrocardiogram.

- Yearly TB testing if applicable.

- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions.

- Drug dispensing.

- Observe subject taking the study drugs (tofacitinib and MTX or placebo) and record the dosing in the dosing log CRF.

6.2. Study Period

The blood collection for laboratory testing at specified visits (ie, Month 1, Month 3, Month 6, Month 9 and Month 12) requiring a fasting state (at least 9 hours) may be taken up to 48 hours prior to or after the visit 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. Prior to attending the study visits, subjects are allowed to shower or bathe that morning but should not moisturize with topical emollient.

Subjects should complete the Patient Reported Outcome 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. 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. The visit window for this sub-study utilizes 28 days for a month.

6.2.1. Sub-Study Month 1

The window for this visit is ±7 days.

All Patient Reported Outcomes 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;
- PGJS-VAS;
- SF-36 Version 2 (Acute);
- FACIT-F;
- EQ-5D.

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).
- Blood and urine specimen testing: Central laboratory tests including: Hematology, Chemistry Panel, CRP, Urinalysis.

- Urine Pregnancy Test (for women of women of childbearing potential only).
- Yearly TB testing if applicable.
- Clinical Evaluation of Rheumatology Endpoints:
  - Tender/Painful Joint Count (68);
  - Swollen Joint Count (66);
  - Physician's Global Assessment of Arthritis (VAS);
  - Assessment of presence and severity of dactylitis;
  - Assessment of enthesitis using LEI.
- Clinical Evaluation of Dermatology Endpoints:
  - PGA-PsO;
  - BSA.
- Clinical Evaluation of Rheumatology and Dermatology Endpoint: PGA-PsA (VAS).
- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions.
- Drug accountability.

6.2.2. Sub-Study Months 3, 6 And 9

The window for the Month 3, 6 and 9 visits is ±7 days.

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

All Patient Reported Outcomes 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);
- PGJS-VAS;
- HAQ-DI;

- SF-36 Version 2 (Acute);
- FACIT-F;
- EQ-5D.

Procedures that will be performed include:

- Targeted Physical Examination: 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).
- Blood and urine specimen testing: Central laboratory tests including: Hematology, Chemistry Panel, CRP, Lipid Profile (fasting)-only Month 6, Urinalysis, Lymphocyte subset analysis (FACS).
- Urine Pregnancy Test (for women of childbearing potential only).
- Yearly TB testing if applicable.
- Waist and hips circumference.
- Clinical Evaluation of Rheumatology Endpoints:
  - Tender/Painful Joint Count (68);
  - Swollen Joint Count (66);
  - Physician's Global Assessment of Arthritis (VAS);
  - Assessment of absence/presence and severity of dactylitis;
  - Assessment of enthesitis using LEI.
- Clinical Evaluation of Dermatology Endpoints:
  - PGA-PsO;
  - BSA.
- Clinical Evaluation of Rheumatology and Dermatology Endpoint: PGA-PsA (VAS).
- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions.

- Drug Accountability;
- Drug Dispensing.

6.2.3. Sub-Study Month 12 or Early Termination Visit

The window for these visits is ±7 days.

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

All Patient Reported Outcomes 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);
- CV Risk Factor Assessment;
- PGJS-VAS;
- HAQ-DI;
- SF-36 Version 2 (Acute);
- FACIT- F;
- EQ-5D.

Procedures that will be performed include:

- Physical Examination: Complete physical examination (height, weight, general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), extremity exam (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).
- Blood and urine specimen testing: Central laboratory tests including: Hematology, Chemistry Panel, CRP, Lipid Profile (fasting), Urinalysis, Lymphocyte subset analysis (FACS).

- Urine Pregnancy Test (for women of childbearing potential only).
- Yearly TB testing if applicable;
- Waist and hips circumference.
- 12-lead electrocardiogram.
- Clinical Evaluation of Rheumatology Endpoints:
  - Tender/Painful Joint Count (68);
  - Swollen Joint Count (66);
  - Physician's Global Assessment of Arthritis (VAS);
  - Assessment of absence/presence and severity of dactylitis;
  - Assessment of enthesitis using LEI.
- Clinical Evaluation of Dermatology Endpoints:
  - PGA-PsO;
  - BSA.
- PGA-PsA (VAS).
- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions.
- Drug accountability.

6.2.4. Sub-Study Follow-Up Visit

If a subject discontinues from the study with abnormalities in hematology or clinical chemistry results which meet criteria as defined in Appendix 4, 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 within 28 days (±7 days) of last dose of study treatment.

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

The following procedures will be performed:

- Blood testing: Central laboratory tests may include: Hematology, Chemistry Panel; Lipid Panel (fasting);
- Urine Pregnancy Test (for women of childbearing potential only);
- Tender/Painful Joint Count (68);
- Swollen Joint Count (66);
- PGA-PsO;
- Adverse event reporting and concomitant treatment 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 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 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 8.3 of the LTE study A3921092. 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 case report form (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 any abnormality in hematology or clinical chemistry results which meet the criteria as defined in Appendix 4, a follow-up visit must be performed within 28 days (±7 days) of last dose of study treatment.

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.

Subjects who require rescue doses of acetaminophen/paracetamol or opioid for more than 10 consecutive days, subjects who require MTX doses higher than the permitted range, subjects interrupting study drug for more than 14 consecutive days (see Appendix 4), or subjects who are <80% compliant with the dosage regimen for any of the 2 study medications for two consecutive visit periods should be withdrawn from the study.

7. ASSESSMENTS

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

7.1. Efficacy Endpoints

All rheumatological and dermatological assessments during the sub-study 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. Please refer to the sub-study Schedule of Activities for when assessments are collected.

7.1.1. ACR Components Assessments

The specific components of the ACR Assessments utilized in the sub-study can be found in Section 7.1.2 of the main protocol. This efficacy measurement will be made at every study visit except for the Follow-up visit of the sub-study.

7.1.2. Disease Activity Score Assessment

The DAS assessment description and components are noted in Section 7.1.3 of the main protocol. This assessment will be made at all study visits except for the Follow-up visit of the sub-study.

7.1.3. PsA Response Criteria (PsARC)

Please refer to Section 7.1.4 of the main protocol. This assessment will be made at all study visits except for the Follow-up visit of the sub-study.

7.1.4. Minimal Disease Activity Score

Please refer to Section 7.1.8 of the main protocol.

7.1.5. Psoriatic Arthritis Disease Activity Score (PASDAS)

Please refer to Section 7.1.9 of the main protocol.

7.2. Clinical Evaluation of Rheumatology Endpoints

All rheumatological evaluations will be performed by blinded, qualified, trained assessors. 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. Please refer to the sub-study Schedule of Activities for when assessments are collected.

7.2.1. Tender/Painful Joint Count (68)

Please refer to Section 7.2.1 of the main protocol.

7.2.2. Tender/Painful Joint Count (28)

Please refer to Section 7.2.2 of the main protocol.

7.2.3. Swollen Joint Count (66)

Please refer to Section 7.2.3 of the main protocol.

7.2.4. Swollen Joint Count (28)

Please refer to Section 7.2.4 of the main protocol.

7.2.5. Physician's Global Assessment of Arthritis

Please refer to Section 7.2.5 of the main protocol.

7.2.6. Physician's Global Assessment of Psoriatic Arthritis

Please refer to Section 7.2.6 of the main protocol.

7.2.7. Assessment of Dactylitis

Please refer to Section 7.2.7 of the main protocol.

7.2.8. Assessment of Enthesitis

Please refer to Section 7.2.8 of the main protocol, specifically the LEI assessment. The LEI will be collected at every visit of the sub-study except for the Follow-up visit.

7.2.9. C-Reactive Protein

Blood samples will be collected at each visit for analysis of CRP using an assay analyzed by the central laboratory. The test results will be blinded.

7.3. Clinical Evaluation of Dermatology Endpoints

Please refer to the sub-study Schedule of Activities for when assessments are collected.

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

Please refer to Section 7.3.1 of the main protocol.

7.3.2. Body Surface Area (BSA)

Please refer to Section 7.3.3 of the main protocol.

7.4. Cardiovascular (CV) Risk Factor Assessment

Please refer to Section 7.4 of the main protocol. This assessment will be completed at the Combined A3921092 Sub-study Switch/Baseline visit and Month 12 or Early Termination visit.

7.5. Health Outcome Measures

7.5.1. Patient's Assessment of Arthritis Pain

Please refer to Section 7.5.1 of the main protocol.

7.5.2. Patient's Global Assessment of Arthritis

Please refer to Section 7.5.2 of the main protocol.

7.5.3. HAQ-DI

Please refer to Section 7.5.3 of the main protocol.

7.5.4. Patient's Global Joint and Skin Assessment (PGJS-VAS)

Please refer to Section 7.5.4 of the main protocol.

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

Please refer to Section 7.5.8 of the main protocol.

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

Please refer to Section 7.5.9 of the main protocol.

7.5.7. EuroQol EQ-5D Health State Profile

Please refer to Section 7.5.10 of the main protocol.

7.6. Safety

Safety will be assessed by the spontaneous reporting of adverse events (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.

7.6.1. Vital Signs and Temperature

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

Please collect vital signs and temperature as noted in Section 7.6.1 of the main protocol.

7.6.2. Electrocardiogram

Twelve-lead electrocardiograms (ECGs) will be obtained on subjects who enroll into this sub-study at a scheduled A3921092 study visit at or after Month 24. All ECGs should be performed after the subject has rested quietly for at least 10 minutes. ECG data will be submitted to a central laboratory for measurement. Any clinically significant changes from the baseline ECG, will be recorded as adverse events and evaluated further, as clinically warranted.

7.6.3. Tuberculosis Screening

Annual TB testing must continue for all applicable countries as described in Section 7.6.3 of the LTE study A3921092. TB testing will be performed using the QFT for subjects in those countries for which TB incidence has been reported at a rate of >50 cases per

100,000 persons, eg, Russian Federation and Taiwan [using China incidence rate] (World Health Organization, 2016).[42] All subjects with positive results must have a chest radiograph performed and reviewed by a radiologist or pulmonologist as per local standard of care and the radiograph must be negative for active TB infection for the subject to continue study participation. Subjects identified as having latent TB should be treated appropriately; for subjects remaining on study during their treatment, the only acceptable regimen is 9 months of isoniazid. Note: QFT should not be performed in subjects who had positive result during prior testing (screening visit or prior annual visits) and/or previously received adequate treatment for TB.

7.6.3.1. Quantiferon® TB Gold In-Tube Test

Please refer to Section 7.6.3.1 of the main protocol.

7.6.3.2. Purified Protein Derivative (PPD) Tuberculin Test

Please refer to Section 7.6.3.2 of the main protocol.

7.6.4. Complete Physical Examination

A standard complete physical examination will be performed at the Sub-study Switch/Baseline visit (for those subjects who enroll in the sub-study after A3921092 Month 24 visit, sub-study Month 12 and Early Termination visit. The following parameters and body systems will be examined and any abnormalities described: height, 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 (for peripheral edema), abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes.

Any clinically significant changes from Baseline should be recorded as adverse events (AEs). Recommendations for evaluation of emergent lymphadenopathy or other findings suggestive of lymphoproliferative disorder are provided in Appendix 8.

7.6.4.1. Targeted Examination

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

7.6.5. Weight, Waist and Hips Circumference and Height

Please refer to Section 7.6.6 of the main protocol.

7.6.7. Clinical Safety Laboratory Tests

Subjects entering the sub-study will have a new baseline established at the Combined Sub-study Switch visit/Baseline visit for laboratory assessments that had previously been compared to the baseline of the qualifying study except for assays needed for Hy's law; baseline assessments from the qualifying study will be used. Blood and urine samples will be collected at the time points identified in the sub-study protocol. 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.

Sub-Study Table 7. Clinical Laboratory Testing

Laboratory Testing Profile	Tests Included
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)], platelets
Chemistry Panel	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)
Lipid Panel	Fasting total cholesterol, HDL, LDL, triglyceride; apolipoprotein A-1, B and other lipoprotein tests potentially including particle size measurements
Tuberculosis Screening	QuantiFERON®-TB Gold In-Tube[a]
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, blinded)
FACS Analysis of Lymphocyte Subsets	CD3(%, abs), CD3+CD4+ (%, abs), CD3+CD8+ (%, abs), CD19+ (%, abs), CD56+CD16+ (%, abs)

a. Performed at combined M24/M36 with Screening/Baseline Visit for those subjects in countries which have high endemic TB rates and who tested negative at their last QFT.

Abnormal test results determined to be caused from laboratory error should not be reported as AEs. Patients 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.

7.6.7.1. Pregnancy Testing

Please refer to Section 7.6.7.1 of the main protocol.

7.6.8. Events for Adjudication/Review Committee Submission

The Sponsor or designee will provide a listing of specific documents needed to support event adjudication by Adjudication/Review Committees (see LTE study A3921092 Section 9.6 Safety Event Adjudication/Review Committees). Obtaining and submitting the documentation will be the responsibility of the study site. Event documentation will vary with the event requiring adjudication and may include (but not be limited to): hospital discharge summaries, operative report, clinic notes, ECGs, diagnostic tests, pathology reports, autopsy reports and death certificate information, as applicable.

7.6.9. Triggered Requirements

7.6.9.1. 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 value of the sub-study, if indicated after review by the Pfizer Study Clinician or Investigator. Factors that will be considered include stability of hemoglobin values, and their relationship to the standard reference range.
- Absolute neutrophil count <1.2 x 10^9 cells/L (<1200 cells/ mm^3).
- Absolute lymphocyte counts <0.5 x 10^9 cells/L (<500 cells/ mm^3).
- Platelet count <100 x 10^9 cells/L (<100,000 cells/mm^3).
- Serum creatinine increase >50% over the baseline value (the first day of the sub-study) OR an absolute increase in serum creatinine >0.5 mg/dL (or 44 µmol/l), if indicated after review by the Pfizer Study Clinician or Investigator. Factors that will be considered include stability of the serum creatinine values, and their relationship to the standard reference range.
- 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.

For additional laboratory abnormalities that require prompt retesting, preferably within 48 hours from awareness of the abnormal results, see Section 8.7.2 Potential Cases of Drug-Induced Liver Injury.

7.6.9.2. Discontinuation Criteria

Both study drugs (Tofacitinib and MTX or placebo) will be discontinued and the subject withdrawn from the sub-study in the event of any of the following:

- Requirement of rescue medications for more than 10 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 8.7 of the LTE study).
- Two sequential absolute neutrophil counts <1.0 x 10^9 cells/L (<1000 cells/mm^3).
- Two sequential absolute lymphocyte counts <0.5 x 10^9 cells/L (<500 cells/mm^3).
- Two sequential hemoglobin values <8.0 g/dL (80 g/L) or decreases of >30% from baseline value (Day 1 of the sub-study).
- Two sequential platelet counts <75 x 10^9 cells/L (<75,000 cells/mm^3).
- Two sequential AST or ALT elevations ≥3 times the upper limit of normal with at least one total bilirubin value ≥2 times the upper limit of normal.[a]
- Two sequential AST or ALT elevations ≥3 times the upper limit of normal accompanied by signs or symptoms consistent with hepatic injury (eg, new onset elevated PT/INR).[a]
- Two sequential AST or ALT elevations >5 times the upper limit of normal, 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 baseline value (Day 1) in the sub-study.
- Two sequential creatine kinase (CK) elevations >10 times the upper limit of normal, 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 infection considered significant by investigator or Sponsor.

- 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 Appendix 4, 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 baseline value (Day 1) in the sub-study, 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.

7.7. Exploratory Biomarkers

7.7.1. Lymphocyte Subset Analysis

Fluorescence-activated Cell Sorting (FACS) analysis for lymphocyte subset markers will be performed to assess the effects of repeat doses of tofacitinib on T cell ($CD4^+CD3^+$, $CD8^+$), B cell ($CD19^+$) and NK cell ($CD16^+CD56^+$ cell) numbers. Whole blood samples will be collected at Baseline, Month 3, Month 6, Month 9 and Month 12.

7.8. Rater Qualifications

All rheumatological and dermatological assessments in the sub-study 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.

8. ADVERSE EVENT REPORTING

Please refer to Section 8 of the LTE A3921092 study.

9. DATA ANALYSIS/STATISTICAL METHODS

Methodology for summary and statistical analyses of the data collected in this sub-study are given here and further detailed in a statistical analysis plan (SAP), which will be dated and maintained by Pfizer. This analysis plan may modify what is outlined in the protocol; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

This is an estimation study. The primary objective will be met by estimating the effect of each treatment and their difference. A sample size of 90 subjects per group was selected such that the 2-sided 95% confidence interval (CI) half-width for the difference in ΔHAQ-DI at Month 6 between tofacitinib 5 mg BID + placebo and tofacitinib 5 mg BID + MTX would be approximately 0.18 assuming a common standard deviation (SD) of 0.6 for both groups. Similarly this sample would yield a 2-sided 95% CI half-width of approximately 0.47 for the difference in ΔPASDAS at Month 6 between the 2 treatment groups assuming a common SD of 1.6 for both groups.

No adjustment for multiple comparisons will be made in the analyses. Nominal statistical significance will be claimed if the 2-sided p value is ≤0.05.

9.2. Statistical Analyses – General

There will be 2 sets of analyses: one for the A3921092 LTE and the other for the sub-study.

For the A3921092 LTE:

- The safety analysis will include cumulative data from all the subjects and all the data (including the data collected in the sub-study).
- The efficacy analysis will include only the data collected in the A3921092 LTE (data collected in the sub-study will be excluded from the LTE analysis).

For the sub-study:

- The safety analysis will include the data collected in the sub-study only.
- The efficacy analysis will include the data collected in the sub-study only.

The analyses for the A3921092 LTE will be governed by the A3921092 LTE protocol and will not be repeated, while the analyses of the sub-study will be detailed in this sub-study protocol.

9.3. Efficacy Analysis

The Full Analysis Set (FAS) will include all subjects who were randomized to the sub-study and received at least one dose of the sub-study drug (tofacitinib, MTX or placebo). The primary efficacy population for this study is defined by the FAS.

Continuous endpoints for which change or percent change from baseline is the measure to be analyzed, would require that a subject have a baseline value and at least one post-baseline value to be included in the FAS for that endpoint.

For all the efficacy and PRO endpoint analyses, the baseline will be the latest value obtained prior to the first dose of the sub-study.

Continuous endpoints collected over multiple visits (eg, ΔHAQ-DI or ΔPASDAS) will be analyzed using a Mixed Model for Repeated Measures (MMRM) without imputation for missing values on the FAS. Treatment comparison between the 2 groups at each post-baseline time point will be generated from this model providing both 2-sided p-value and 95% CI.

Binary endpoints (eg, MDA response) will be analyzed using the normal approximation for the difference in binomial proportions with missing response as non-response (MR=NR) on the FAS. Treatment comparison between the 2 groups at each post-baseline time point will be generated providing both 2-sided p-value and 95% CI.

Efficacy will also be assessed for a subset of the subjects who had more severe PsA as defined by ≥5 swollen or tender joints at the baseline of the sub-study, if sample size permits.

Complete details will be specified in the SAP.

9.3.1. Analysis of Primary Endpoints

There are two primary endpoints in the sub-study: ΔHAQ-DI at Month 6 and ΔPASDAS at Month 6. Each primary endpoint will be analyzed using a MMRM without imputation for missing values on the FAS.

To assess the impact of missing data due to dropouts, the SAP will also specify additional analyses to assess the sensitivity of the primary analysis to departures from the assumed missing data mechanism.

9.3.2. Analysis of Secondary and Other Endpoints

Each of the continuous secondary or other efficacy/PRO endpoints listed in Sections 2.2.2 and 2.2.3 of the sub-study will be analyzed using a MMRM without imputation for missing values on the FAS.

Each of the binary secondary or other efficacy/PRO endpoints listed in Sections 2.2.2 and 2.2.3 of the sub-study will be analyzed using the normal approximation for the difference in binomial proportions with missing values handled by MR=NR on the FAS.

9.4. Safety Analysis

The safety analysis set (SAFETY) will include all subjects who received at least one dose of the sub-study drug (tofacitinib, MTX or placebo).

For the safety analyses, the baseline will be the latest value obtained prior to the first dose of the sub-study.

9.4.1. Analysis of Safety Endpoints

All safety data will be summarized descriptively through appropriate data tabulations, and descriptive statistics.

- Incidence and severity of adverse events during treatment.
- Incidence of clinical abnormalities and change from baseline in clinical laboratory values during treatment. 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.
- Incidence of vital sign (blood pressure and pulse rate) abnormalities and changes from baseline in vital sign measurements during treatment.
- Incidence of adjudicated safety events.

9.5. Interim Analysis

No formal interim analysis is planned for the sub-study. However, data-cuts may be performed as needed to support tofacitinib regulatory submission.

10. REFERENCES (Sub-Study specific)

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