

Tofacitinib (CP-690,550)
A3921120
Final Protocol Amendment 3, 03 April 2020



**A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, STUDY
OF THE EFFICACY AND SAFETY OF TOFACITINIB IN SUBJECTS WITH
ACTIVE ANKYLOSING SPONDYLITIS (AS)**

Investigational Product Number:	CP-690,550
Investigational Product Name:	Tofacitinib
United States (US) Investigational New Drug (IND) Number:	CCI [REDACTED]
European Clinical Trials Database (EudraCT) Number:	2018-000226-58
Protocol Number:	A3921120
Phase:	3

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Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 3	03-April-2020	<p>This global amendment incorporates venous thromboembolism (VTE) risk factor checks. Pfizer has determined that VTE is identified as an important identified risk/dose dependent adverse drug reaction for tofacitinib.</p> <p>The following sections have been updated to reflect these changes:</p> <p>Protocol Summary, Schedule of Activities, Section 3 (Study Design), Section 5.5 (Administration), Section 6.2 (Study Period), Section 6.3 (Follow-up Visit), Section 6.4 (Subjects Discontinuation from the Investigational Product), Section 6.4.2 (Discontinuation from Investigational Product), Section 7.1.14 (Risk Factor Check for VTE), References Section and Appendix 1.</p>
Amendment 2	10-April-2019	<ol style="list-style-type: none"> 1. Summary of Changes: Corrected a typographical error under Amendment 1 (bullet #8). 2. Protocol Summary, Section 1.2, Section 1.2.3.2, Section 1.2.6, Section 2, Section 4.1, Section 5.8, Section 6.1, Section 6.3, Section 6.4, Section 7.2.5.5, Section 7.2.9.7, Section 9.6 and Appendix 2, Appendix 4: Made clarifications and corrected typographical or formatting errors. 3. Protocol Summary, Section 3, Section 5.1, Section 5.2, Section 7.2.3, Section 9.2 and Section 9.4: Added new analysis conducted at Week 16 when all applicable subjects have completed their Week 16 visits and clarified information about blinding due to the addition of the Week 16 analysis. CCI

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Document	Version Date	Summary of Changes and Rationale
		<p style="color: red;">CCI</p> <ol style="list-style-type: none"> 4. Protocol Summary, Section 2 and Section 16: removed reference 63 as it is no longer applicable. 5. Schedule of Activities and Section 6.2.4: Removed reference to allowing the subject a light snack as this is a non-fasting visit. 6. Protocol Summary, Section 3, Section 4.2, Section 5.1, and Section 5.8.1: Changed to not exclude subjects with prior bDMARD use (non-IR) based on the available population to improve the recruitment in the study. 7. Protocol Summary, Section 2 and Section 9.2: Moved the ASQoL in sequence for global type 1 error control before the SF-36v2 PCS. Added the FACIT-F Total score to the global type I error control scheme. Disease specific ASQoL score was moved before generic SF-36v2 PCS score and FACIT-F total score was added to the type I error control scheme because of the importance of fatigue to patients and as a key core domain to measure in AS clinical studies. Also, updated the related objective. 8. Schedule of Activities, Section 4.4, Section 5.5, Section 6 and Section 7.5: Edited language to accommodate visits that may occur in the afternoon or evening. 9. Schedule of Activities and Section 6.2.6: Edited language to clarify in-clinic dosing for Week 16 visit is from the newly dispensed open-label supply. Rearranged visit procedures to ensure relevant data is collected prior to patient being dosed with open-label IP supply. 10. Section 1.2 and Section 1.2.2: Updated protocol with the most recent information of

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		<p>the tofacitinib program.</p> <p>11. Section 3: Replaced the schema with a picture to address formatting issues.</p> <p>12. Section 4.1: Removed the requirement for prior approval of sponsor for inclusion of subjects being treated for latent TB. Due to the removal of potential Sponsor waiver for the requirement of the protocol, in addition to consistency with other tofacitinib studies.</p> <p>13. Section 4.2 (exclusion criteria #26) and Section 4.4.6: Updated contraception language to include 1 highly effective method of contraception to be consistent with the updated investigator's brochure, other tofacitinib programs as well as aligning with new protocol template requirements for contraception. Male subjects are no longer required to use contraception. The risk of the partner due to drug exposure in the ejaculate was low. Also, contraception language specific for subjects from Canada requiring WOCBP to use two contraceptive methods at the same time as per agreement with the Health Authority of Canada and Canada Guidance document.</p> <p>14. Section 6.2.6: Revised the study procedures to ensure all data was collected before subjects begin administration of the open-label IP.</p> <p>15. Section 8.1: Removed optional protocol template language regarding the efficacy endpoint adjudication committee as the efficacy endpoints will not be adjudicated.</p> <p>16. Section 8.2.5: Changed discontinuation from study to discontinuation from the investigational product to align with changes made in Amendment 1.</p> <p>17. Section 9.2.3: Clarified some language to be</p>

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		<p>more precise.</p> <p>18. Appendix 1: Added or clarified relevant abbreviations.</p> <p>19. Appendix 8: Added country specific appendix required by France.</p>
Amendment 1	06-September-2018	<ol style="list-style-type: none"> 1. Protocol Summary, Sections 2, 9.2.1 and Section 9.2.3: Clarified the role of ASAS40 response at 16 weeks as a key secondary endpoint. Replaced ΔSF-36v2 Physical Functioning domain by ΔSF-36v2 PCS as a Type I error controlled endpoint. Added ΔAnkylosing Spondylitis Quality of Life (ASQoL) as an additional Type I error controlled endpoint. Moved AS-HCRU from a secondary to tertiary endpoint as it is supportive data. 2. Protocol Summary and Section 2: Added Inflammation, Patients Assessment of Spinal Pain and PGA to the secondary endpoints as these were not included in the original protocol. Clarified the BASMI secondary endpoint includes the 5 components. Realigned secondary endpoints to be consistent with the statistical testing (ie, Type I error control). 3. Protocol Summary and Section 3: Administrative changes to clarify blinding. Removed mention of last treatment visit per FDA feedback for subject discontinuation of investigational product and withdrawal from study. 4. Protocol Summary, SOA, Section 2, Section 6, Section 7.2.9.6 and 7.2.9.7: Updated names of the SF-36v2 and EQ-5D-3L. 5. Schedule of Activities, Section 6.1 and Section 7.1.12: Added clarification that SI joint radiographs will be performed at screening if previous radiographs cannot be interpreted by the central reader. 6. Schedule of Activities, Section 6 and Section 7:

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		<p>Added waist circumference at the Baseline visit, CV risk at the Screening visit and a check of the skin for the presence of rash to the targeted physical exam. These assessments were missing from the original protocol.</p> <p>7. Schedule of Activities: Corrected the definition of TNFi-IR in the abbreviations list.</p> <p>8. Schedule of Activities (footnote 11, removal of ET visit), Sections 4.4.1, 5.5, 6.2.11, 6.3, 6.4, 6.4.2, 7.1.4, 7.1.7, 7.2.4, 8.1.3, and 8.2.2: Updated sections based upon FDA feedback for subject discontinuation of investigational product and withdrawal from study.</p> <p>9. Schedule of Activities, Sections 5.3, 5.5, 5.1, 6.3, 6.4, 6.4.2, 8.1.3, 8.2, and Appendix 6: Updated the term study drug or study treatment to investigational product to maintain consistency throughout the protocol.</p> <p>10. Schedule of Activities and Sections 7.2.9, 7.2.9.3 and 7.2.9.4: Administrative update, removed quotations marks from PROs.</p> <p>11. Sections 1.2 and 1.2.1.3: Added approval information for tofacitinib for UC.</p> <p>12. Section 1.2.1.2: Corrected a typographical error and added date of approval and the approved dose for PsA.</p> <p>13. Section 1.2.6: Included UC as an approved indication for the 5 mg dose.</p> <p>14. Section 3: Corrected an error in the study design schematic figure.</p> <p>15. Section 4.1, 8.1.2: Updated by removing reference to a legally acceptable representative (all subjects are required to comprehend all pertinent aspects of the study).</p> <p>16. Section 4.1: Updated inclusion criteria #3 to</p>

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		<p>address countries whose majority age is ≥ 18 years.</p> <p>17. Section 4.1: Updated Inclusion Criteria #5 to clarify that radiographs would be obtained during the screening period, instead of at the Screening visit.</p> <p>18. Section 4.1: Inclusion criteria #7 updated the definition of inadequate response and clarified the definition of intolerance. Corrected a typographical error in inclusion criteria #7 and #8.</p> <p>19. Section 4.1: Updated inclusion criteria #9 to align with section 5.8.1 (Subject must be on a stable dose of corticosteroids for 1 week prior to first dose of investigational product).</p> <p>20. Section 4.1; Updated inclusion criteria #13 to remove subjects that have been or are being treated for an active TB infection.</p> <p>21. Section 4.2: Updated Exclusion criteria #1 for clarity.</p> <p>22. Section 4.2 Updated exclusion criteria #4 to correct an administrative error in the protocol.</p> <p>23. Section 4.2: Updated exclusion criteria #5 to exclude targeted synthetic DMARDs (including tofacitinib) and subjects that have been previously exposed to conventional synthetic, targeted synthetic, or biological DMARDs to provide further clarification.</p> <p>24. Section 4.2: Updated exclusion criteria #6 to add the exclusion of subjects with a history of allergies or hypersensitivity to lactose or tofacitinib which was missing from the original protocol.</p> <p>25. Section 4.2: Removed the following sentence: "Documentation in the source of the typical results to allow a repeat lab is required" from</p>

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		<p>Exclusion criteria #9 for clarity.</p> <p>26. Section 4.2: Removed exclusion criteria #26 as it is now covered by updated exclusion criteria #5.</p> <p>27. Sections 4.2, 4.4.6 and 6.4.1: Corrected typographical errors.</p> <p>28. Section 4.3: Clarified the randomization criteria for participation in the study with addition that subjects should not meet any of the exclusion criteria.</p> <p>29. Sections 4.1 and 5.8.1.1: Updated methotrexate use to ≤ 25 mg/week. The 20 mg maximum MTX dose was carried over from the A3921119 Phase 2 study of AS, which originally had a higher dose of tofacitinib that was later removed from the protocol. Since many investigators use 25 mg/week MTX, and the A3921120 protocol has only a tofacitinib 5 mg BID dose, it is deemed safe to allow the combination. This observation is based on sponsor's tofacitinib RA clinical studies, which did allow 25 mg/week MTX.</p> <p>30. Section 5.1: Added rationale on stratification which was missing in the original protocol.</p> <p>31. Sections 5.8.2, 5.8.1.2 and Appendix 4: Corrected language to clear up inconsistencies.</p> <p>32. Sections 6.2.1, 6.2.6, 6.2.10: Administrative change to provide clarity for the investigators that the EQ-5D-3L and the EQ-VAS are on the same questionnaire.</p> <p>33. Section 7.1: Approximate total blood volume revised to be consistent with updated total blood volumes received from Central Laboratory.</p> <p>34. Section 7.2.9.8: Clarified FACIT fatigue scale.</p> <p>35. Section 7.4: Clarified rater qualifications per new</p>

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		<p>protocol template guidance.</p> <p>36. Sections 8.2.4 and 8.2.6: Removed Treated Infections Section. Final tables and listings will describe safety data using industry wide standard terms: MedDRA(Infections and Infestations) and serious infection events (SIE). These will be compared with other tofacitinib studies (eg, RA, PsA, UC) as well as external databases which include the same standardized terms. There is no industry standard definition of a "treated infection" nor a consistent internal definition that could be used for comparison.</p> <p>37. Sections 11.1, 11.2 and 12.3: Corrected a typographical error (Section 11.1) and updated to revise sponsor's protocol template language to comply with new EU general data protection regulation (GDPR) guidelines.</p> <p>38. Section 13.1: Edited to reflect sponsor's updated protocol template language.</p> <p>39. Section 16: Corrected page numbers for reference #18. Added reference #63.</p> <p>40. Appendix 1: Added abbreviations used in updated protocol text (oz, PBO, CHD and tsDMARD). Updated abbreviations for consistency (bDMARD, csDMARD, DMARD, HBsAB, HBsAG).</p>
Original protocol	22 February 2018	Not applicable (N/A).

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

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PROTOCOL SUMMARY

Background and Rationale

Ankylosing Spondylitis (AS) is prevalent among spondyloarthropathies, a group of arthritic conditions affecting the spine. This under recognized disease is often not diagnosed for many years and typically presents in people between 20 and 40 years of age leading to progressive disability and adverse effects on quality of life. Tofacitinib inhibits signaling of cytokines that are integral to lymphocyte activation, proliferation, and function and may thus result in suppression of multiple aspects of the immune response. This forms the basis of the rationale to investigate the effect of tofacitinib in active AS.

This study is a follow-up to the A3921119 Phase 2b study of tofacitinib in active AS.

Objectives and Endpoints

Primary Objectives:	Primary Endpoint:
<ul style="list-style-type: none"> To compare the efficacy of tofacitinib 5 mg BID versus placebo on the ASAS20 response rate at Week 16 in subjects with active AS that have had an inadequate response to previous treatment. 	<ul style="list-style-type: none"> ASAS20 response at Week 16.
Key Secondary Objective:	Key Secondary Endpoint:
<ul style="list-style-type: none"> To compare the efficacy of tofacitinib 5 mg BID versus placebo on the ASAS40 response rate at Week 16 in subjects with active AS that have had an inadequate response to previous treatment. 	<ul style="list-style-type: none"> ASAS40 response at Week 16.
Other Secondary Objectives:	Other Secondary Endpoints:
<ul style="list-style-type: none"> To compare the safety and tolerability of tofacitinib 5 mg BID versus placebo in subjects with active AS that have had an inadequate response to previous treatment. To compare the efficacy (including health-related quality of life, function, pain, and fatigue) of tofacitinib 5 mg BID versus placebo at all time points in subjects with active AS that have had an inadequate response to previous treatment. 	<ul style="list-style-type: none"> Incidence and severity of Adverse Events (AE). Clinical laboratory tests, vital signs, physical examination and 12-lead ECG parameters. ASAS20 response at all other time points. ASAS40 response at all other time points. Change from baseline in Ankylosing Spondylitis Disease Activity Score using C-Reactive Protein (ASDAS_{CRP}) at all time points. Change from baseline in hsCRP at all time points. Change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) at all time points collected. Change from baseline in Short-Form-36 Health Survey-Version 2 Acute (SF-36v2) at all time points collected. Change from baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) including the 5 components (lateral spine flexion, tragus-to-wall distance, lumbar flexion, maximal intermalleolar distance and cervical rotation) at all time points. Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (3 endpoints: total score, experience domain and impact domain scores) at all time points Change from baseline in Patients Global Assessment of Disease (PGA) at all time points collected.

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	<ul style="list-style-type: none"> • Change from baseline in Patient’s Assessment of Spinal Pain (Total Back Pain, Nocturnal Spinal Pain) at all time points collected. • Change in from baseline Bath Ankylosing Spondylitis Functional Index (BASFI) at all time points. • Change from baseline in inflammation (mean of the answers to questions 5 and 6 of the BASDAI) at all time points collected. • ASAS 5/6 response at all time points. • ASAS partial remission criteria at all time points. • Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at all time points. • BASDAI50 response at all time points. • ASDAS clinically important improvement, ASDAS major improvement and ASDAS inactive disease at all time points. • Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) at all time points collected. • Change from baseline in extra-articular Involvement (Specific Medical History and peripheral articular involvement [as assessed by change from baseline in swollen joint count]) at all time points collected. • Change from baseline in spinal mobility at all time points collected. • Change from baseline in EuroQol EQ-5D Health State Profile 3 level (EQ-5D-3L) and Your own health state today (EQ-VAS), at all time points collected. • Change from baseline in Work Productivity and Activity Impairment (WPAI) Questionnaire: Spondyloarthritis at all time points collected.
<p>Tertiary/Exploratory Objectives:</p>	<p>Tertiary/Exploratory Endpoints:</p>
<ul style="list-style-type: none"> • [REDACTED] • To evaluate the effect of tofacitinib 5 mg BID on lymphocyte subsets using FACS analysis. • To measure the effect of tofacitinib 5 mg BID on healthcare resource utilization at all collected time points. 	<ul style="list-style-type: none"> • [REDACTED] • Fluorescence Activated Cell Sorting (FACS) analysis of lymphocyte subsets. • AS HealthCare Resource Utilization Questionnaire (AS-HCRU) at all time points collected.

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Study Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled efficacy and safety study designed to compare tofacitinib to placebo in subjects with active AS. An estimate of approximately 480 AS subjects will be screened globally in order that approximately 240 eligible subjects (120 per arm) will be randomized in a 1:1 ratio to tofacitinib 5 mg BID (twice daily) or matching placebo BID. Active disease is required for entry into this study and is defined as: Modified New York Criteria for Ankylosing Spondylitis (1984), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4 and back pain score (BASDAI Question 2) of ≥ 4 despite an adequate therapeutic trial with 2 or more non-steroidal anti-inflammatory drugs (NSAIDs) (or intolerance to NSAIDs).

Eligible subjects will be treated with one of the two sequences for 16 weeks followed by treatment with tofacitinib 5 mg BID for an additional 32 weeks.

The duration of participation for eligible subjects will be approximately 56 weeks. This will include a screening period of approximately 30 days, a 16-week double-blind treatment period, a 32-week open-label treatment period and a 28 day follow-up period. During the 16-week treatment period subjects will visit the clinic every two weeks (± 3 days) until the Week 4 visit and then every 4 weeks (± 7 days) until completion of Week 16. At the Week 16 visit all subjects will be assigned to open-label tofacitinib and will visit the clinic every two months (± 7 days) until week 48. Subjects will then return to the clinic for a Follow-up visit approximately 28 days after the week 48 visit. The investigators, subjects and sponsor study team will remain blinded to the first 16 weeks of treatment assignment through the entire duration of the trial until database release.

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All subjects in the study will be evaluated for risk factors for venous thromboembolism (VTE) (2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the ERS. *European Heart Journal* (2020) 41;543-603).

The study investigator or designee will need to review each subject's medical history and study records, including their concomitant medications, to determine whether he/she is at high risk for developing VTE.

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

- has heart failure or prior myocardial infarction within the past 3 months;
- has inherited coagulation disorders;
- has had VTE, either deep venous thrombosis or pulmonary embolism;
- is taking combined hormonal contraceptives or hormone replacement therapy;

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- has a malignancy (association is strongest with cancers other than non-melanoma skin cancers);
- is undergoing major surgery or is immobilized.

Additional risk factors for VTE, such as age, diabetes, obesity (body mass index [BMI] ≥ 30 kg/m²), smoking status, hypertension, and first degree family history of VTE should also be taken into consideration by the investigator and the sponsor medical monitor when evaluating the benefit:risk for each individual subject whether to discontinue from open-label 5 mg BID dose of tofacitinib.

See Risk Factor Check for VTE in Section 7.1.14 for tofacitinib dosing guidance when a risk factor is identified.

If a subject has 1 or more of the risk factors for VTE listed above and is receiving tofacitinib 5 mg BID, they may remain on tofacitinib 5 mg BID after careful investigator assessment of benefit: risk. For subjects who do not have any of the risk factors for VTE listed above, he/she will remain on their open-label tofacitinib dose of 5 mg BID.

Study Treatments

Subjects will be randomized at the Baseline visit in a 1:1 ratio to one of the following two treatment sequences for a total of 16 weeks of treatment. Randomization will be stratified by prior treatment history: (1) Biological disease-modifying anti-rheumatic drug-naïve (bDMARD-naïve) and (2) Tumor Necrosis Factor inhibitor inadequate responders (TNFi-IR) or bDMARD use (non-IR).

Strata (Patient Population)	Sequence	Treatment Sequence and Description	Planned Number of Randomized Subjects
bDMARD-naïve	1	Blinded Tofacitinib 5 mg BID for 16 weeks followed by open-label tofacitinib for 32 weeks <i>One-tofacitinib 5 mg tablet in AM & PM</i>	96
bDMARD-naïve	2	Placebo BID for 16 weeks followed by open-label 5 mg BID tofacitinib for 32 weeks <i>One-5 mg matching placebo tablet in AM & PM for the first 16 weeks followed by one-tofacitinib 5 mg tablet in the AM & PM for 32 weeks</i>	96
TNFi-IR or bDMARD use (non-IR)	1	Blinded Tofacitinib 5 mg BID for 16 weeks followed by open-label tofacitinib for 32 weeks <i>One-tofacitinib 5 mg tablet in AM & PM</i>	24

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Strata (Patient Population)	Sequence	Treatment Sequence and Description	Planned Number of Randomized Subjects
TNFi-IR or bDMARD use (non-IR)	2	Placebo BID for 16 weeks followed by open-label 5 mg BID tofacitinib for 32 weeks <i>One-5 mg matching placebo tablet in AM & PM for the first 16 weeks followed by One-tofacitinib 5 mg tablet in the AM & PM for 32 weeks</i>	24

Subjects will receive one tablet in the morning and one tablet in the evening for a total of two tablets per day. Placebo tablets will match the 5 mg tablets in order to maintain the blind.

At the end of the 16 week double-blinded treatment period, all subjects will be assigned to open-label tofacitinib 5 mg BID to Week 48. The investigators, subjects and sponsor study team will remain blinded to the first 16 weeks of treatment assignment through the entire duration of the trial until database release.

Statistical Methods

The Assessment of the SpondyloArthritis International Society $\geq 20\%$ improvement (ASAS20) response rate at Week 16 is the primary efficacy endpoint in this trial. The analysis of the primary endpoint will be based on the full analysis set. The normal approximation for the difference in binomial proportions adjusting for the prior treatment history at randomization (bDMARD-naïve vs TNFi-IR) via the Cochran–Mantel–Haenszel approach will be used to estimate the treatment effect (treatment difference, standard error, 95% confidence interval) and to test (Normal Z-test) the superiority of tofacitinib to placebo.

Approximately 120 subjects per arm will be randomized. A sample size of 120 per arm will yield about 89% power to detect a difference of at least 20% between tofacitinib 5 mg BID and placebo at a two-sided significance level of 5%, assuming a placebo response rate of 40% for ASAS20 response at Week 16.

The family-wise Type I error rate will be controlled at the 2-sided 5% (or equivalently 1-sided 2.5%) significance level using a step-down testing procedure for the primary endpoint of ASAS20, the key secondary endpoint of Assessment of the SpondyloArthritis International Society $\geq 40\%$ improvement (ASAS40) and a select set of secondary endpoints at Week 16 tested in the sequence below: ASAS20, ASAS40, change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS_{CRP}), change from baseline in High Sensitivity C-Reactive Protein (hsCRP), change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL), change from baseline in SF-36 Health Survey Version 2, Acute (SF-36v2) Physical-Component Summary (PCS), , and change from baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI), and change from baseline in Functional

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Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Total score (See [Section 9.2.3](#) for additional Type I error control procedures).

There will be a total of 2 planned analyses conducted when all applicable subjects have completed their Week 16 and Week 48 (including follow-up) visits, respectively. CCI

 (see [Section 9.2](#) for details).

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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.

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

Protocol Activity Visit Window (days)	Screening ¹	Treatment Period										Follow -up ¹¹
	30 days	Baseline Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40	Week 48	
			±3	±3	±7	±7	±7	±7	±7	±7	±7	±7
Informed Consent/Assent	X											
AS Diagnosis ²	X	X										
Demographics	X											
General Medical History (includes previous vaccinations, family history of AS, herpes zoster history, smoking and alcohol use, CV)	X											
Determination of “bDMARD-naïve” or “TNFi-IR” status		X										
Complete Physical Exam ³	X	X					X				X	
Targeted Physical Exam ⁴			X	X	X	X		X	X	X		X
Height, Weight ⁵ and Waist circumference ⁵	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (blood pressure, pulse rate, temperature)	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG ⁶	X						X				X	
Chest Radiograph	X											
Radiographs of SI joints ⁷	X											
Prior/Concomitant Treatments(s)	X	X	X	X	X	X	X	X	X	X	X	X

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Protocol Activity Visit Window (days)	Screening ¹	Treatment Period										Follow -up ¹¹
	30 days	Baseline Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40	Week 48	
			±3	±3	±7	±7	±7	±7	±7	±7	±7	±7
LABORATORY TESTING												
Hematology	X	X		X		X	X	X	X	X	X	X
Chemistry Panel	X	X		X		X	X	X	X	X	X	X
Lipid Panel (fasting) ⁸		X		X			X		X		X	X
Urinalysis	X	X		X		X	X	X	X	X	X	X
QuantiFERON [®] TB Gold	X											
Urine Pregnancy Test (HCG) ⁹	X ¹⁰	X	X	X	X	X	X	X	X	X	X	X
C-Reactive Protein (hsCRP) ¹²	X	X	X	X	X	X	X	X	X	X	X	X
HIV serology, HBsAg, HBcAb, HCV Ab	X											
Prothrombin Time (INR)	X											
██████████				█	█							
HLA-B27 Sample		X										
FACS Analysis: Lymphocyte Markers		X		X			X		X		X	
EVALUATION OF DISEASE ACTIVITY												
Specific Medical History: Uveitis, IBD, Psoriasis, Peripheral Articular Involvement*	X	X			X		X		X		X	X
ASAS, ASDAS _{CRP}	X	X	X	X	X	X	X	X	X	X	X	
BASMI (linear function) ^{14,15}	X	X	X	X	X	X	X	X	X	X	X	
Spinal Mobility ^{14,16}	X	X	X	X	X	X	X	X	X	X	X	

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	30 days	Baseline Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40	Week 48	
			±3	±3	±7	±7	±7	±7	±7	±7	±7	±7
Enthesitis Evaluation (MASES) ¹⁴		X		X	X	X	X	X	X	X	X	
Number of swollen joints (44 joint count) ¹⁴		X	X	X	X	X	X	X	X	X	X	
PATIENT REPORTED OUTCOMES												
Patient Global Assessment of Disease	X	X	X	X	X	X	X	X	X	X	X	
Patient Assessment of Spinal Pain ¹⁷	X	X	X	X	X	X	X	X	X	X	X	
BASDAI, BASFI	X	X	X	X	X	X	X	X	X	X	X	
ASQoL, SF-36v2, EQ-5D-3L including EQ-VAS		X					X				X	
FACIT-F		X	X	X	X	X	X	X	X	X	X	
Work Productivity & Activity Impairment Questionnaire (WPAI):		X					X				X	
AS HealthCare Resource Utilization Questionnaire (AS-HCRU)		X					X				X	
OTHER ACTIVITIES												
Randomization		X										
Assignment to Open-label Treatment							X					
Dosing in Clinic ¹⁸		X	X	X	X	X	X	X	X	X	X	
Drug Dispensing		X		X	X	X	X ¹⁹	X	X	X		
Dosing Instructions ²⁰		X	X	X ¹³	X ¹³	X	X	X	X	X		
Drug Accountability			X	X	X	X	X	X	X	X	X	

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	30 days	Baseline Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40	Week 48	
			±3	±3	±7	±7	±7	±7	±7	±7	±7	±7
Serious and non-serious adverse Event Reporting	X	X	X	X	X	X	X	X	X	X	X	X
Contraception Check ²¹	X	X	X	X	X	X	X	X	X	X	X	X
Risk Factor Check for Venous Thromboembolism ²²									X	X	X	X

AS=Ankylosing Spondylitis; bDMARD= Biological Disease-modifying anti-rheumatic drugs, TNFi-IR= Tumor Necrosis Factor inhibitor-Inadequate Responder, IBD=Inflammatory Bowel Disease; HCG=Human Chorionic Gonadotrophins; hsCRP= High-Sensitivity C-Reactive Protein; FACS=Fluorescence-Activated Cell Sorting; FSH=Follicle Stimulating Hormone; ASAS=Assessment in Ankylosing Spondylitis; ASDAS=Ankylosing Spondylitis Disease Activity Score; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; MASES=Maastricht Ankylosing Spondylitis Enthesitis Score; ASQoL=Ankylosing Spondylitis Quality of Life; SF-36v2=Short Form 36; EQ-5D-3L=EuroQol Health State Profile; EQ-VAS="Your own health state today"; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; SI=Sacroiliac; WOCBP = women of childbearing potential*as assessed by swollen joint count.

1. Screening visit occurs within 30 days prior to administration of the investigational product at the Baseline (Day 1) visit.
2. Prior to randomization confirm diagnosis of active AS: Modified New York Criteria for Ankylosing Spondylitis (1984), BASDAI score of ≥ 4 and back pain score (BASDAI Question 2) of ≥ 4 .
3. The following parameters and body systems will be examined and any abnormalities described: 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), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes. Any clinically significant change(s) from Baseline/Day 1 should be recorded as an adverse event(s).
4. Targeted physical examination will be performed assessing the following: lungs, heart, abdomen, lower extremities (for peripheral edema), skin (presence of rash) and lymph nodes. Any clinically significant change(s) from Baseline (Day 1) should be recorded as an adverse event(s).
5. Height is collected at Screening visit only, waist circumference is collected at Baseline visit only. After Baseline visit, only weight is required.
6. ECG to be read centrally.
7. Radiographs to be read centrally. Previous radiographs (up to 2 years old) of the SI joints documenting the diagnosis of AS will be acceptable if they can be obtained and sent to the central reader for confirmation. If radiographs are not available or cannot be interpreted by the central reader, new radiograph (AP pelvis) should be obtained during the screening period and submitted to the central reader.
8. The lipid panel will include apolipoprotein A-1 and B, total cholesterol, HDL, LDL, and triglycerides. Other lipoprotein tests potentially include particle size measurements.
9. Urine pregnancy test is required only for WOCBP; may be repeated more frequently if required by local regulation/practice, if a menstrual cycle is missed, or if a potential pregnancy is suspected.
10. Women of non-childbearing potential must meet one of the following criteria: undergone hysterectomy and/or bilateral oophorectomy, medically confirmed

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Protocol Activity Visit Window (days)	Screening ¹	Treatment Period										Follow -up ¹¹
	30 days	Baseline Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40	Week 48	
			±3	±3	±7	±7	±7	±7	±7	±7	±7	±7

ovarian failure or confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause); status may be confirmed with/and have a central laboratory confirmation of FSH level indicative of postmenopausal state.

11. The Follow-up Visit is required of all subjects who complete the study or are withdrawn from the investigational product after the Week 40 visit. These subjects must have a Follow-up visit within 28 days (±7 days) of the Week 48 visit. Subjects who are withdrawn from the investigational product prior to the Week 40 visit are not required to have a follow-up visit after they complete the study at the Week 48 visit.

12. hsCRP will be blinded after the Screening visit.

14. Qualified blinded assessor (blinded to previous assessments both of efficacy and safety) must be used. It is recommended that the same qualified personnel be used for each visit.

15. The combined index score will be calculated by the Sponsor using the individual scores from the following measures: lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance, and cervical rotation.

16. Chest expansion will be measured for spinal mobility.

17. Spinal pain assessment includes both Total Back Pain and Nocturnal Spinal Pain.

18. At all visits, the scheduled dose of investigational product will be taken by the subject in the clinic.

19. All blinded investigational product will be collected at the start of the Week 16 visit and subjects will receive new investigational product as a part of the open-label portion of the study at the Week 16 visit and will receive the first dose of open-label investigational product in the clinic.

20. Instruct subject not to take the in-clinic dose of investigational product the day of the next study visit and to bring the drug supply with them to the visit.

21. Confirm and document that contraception, if assigned, is used consistently and correctly.

22. Per Amendment 3, all subjects will be asked at every remaining study visit if they have any newly-developed risk factors for VTE as described in Section 7.1.14

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1. INTRODUCTION

1.1. Mechanism of Action/Indication

Tofacitinib is being developed for the treatment of adult subjects with active ankylosing spondylitis (AS) who have had an inadequate response to previous non-steroidal anti-inflammatory drug (NSAID) or tumor necrosis factor inhibitor (TNFi) treatment.

Tofacitinib is a potent, selective inhibitor of the Janus Kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome. 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.^{1,2,3} This affects signaling via IL-17, IL-21 and IL-23 which have been implicated in AS pathology.³ Antibodies to IL-17 have demonstrated efficacy in AS.³

Through direct and indirect inhibition of cytokine pathways, tofacitinib can modulate immune responses and reduce or prevent inflammation.³

1.2. Background and Rationale

AS is prevalent among spondyloarthropathies, a group of arthritic conditions affecting the spine. AS causes bone erosions in the axial skeleton and chronic inflammation at the insertion of ligaments and tendons which results in new bone formation and eventual ankylosis of the joints. The diagnosis is confirmed by pelvic x-rays that meet Modified New York Criteria for Ankylosing Spondylitis (1984) (See [Appendix 2](#)). AS usually progresses from sacral inflammation initiating in the sacroiliac joints to progressive spine ankylosis over time leading to back pain, loss of mobility, fatigue, stiffness and functional impairment. AS is frequently associated with peripheral arthritis, enthesitis, osteoporosis and extraarticular manifestations such as anterior uveitis and inflammatory bowel disease (IBD). This under-recognized disease is often not diagnosed for many years and typically presents in people between 20 and 40 years of age with a slightly higher prevalence in males leading to progressive disability and adverse effects on quality of life.^{4,5} It is estimated that this condition affects approximately 0.1-1.1% of the Caucasian adult population globally.^{5,6}

The etiology of AS is currently unknown but a genetic link was noted in 90-95% of people with AS who are positive for HLA-B27 allele and risk increases with HLA-B27-positive relatives.^{5,7,8} There is currently no cure for AS. As a result patients with AS face a poor quality of life with increased rates of work disability and unemployment and an ever increasing cost to society.^{9,10}

In the past several years there has been significant progress in the management of AS. With the advent of new consensus-based criteria issued by Assessments in Ankylosing Spondylitis International Society (ASAS)/the European League Against Rheumatism (EULAR) group, the earlier identification of patients with AS is possible.¹¹ Magnetic Resonance Imaging (MRI) has proven valuable in identifying early sacroiliitis and spondylitis with detection of enthesitis and synovitis in the axial skeleton.¹²

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For many decades, the mainstay of treatment of AS has been NSAIDs and structured exercise programs including physical therapy with the aim of relieving clinical symptoms. However, gastrointestinal and other adverse effects limit the tolerability of NSAIDs including some COX-2 selective inhibitors. In addition, AS patients report insufficient control with NSAIDs alone.¹¹ Treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) that have shown efficacy in rheumatoid arthritis have not shown similar efficacy in AS.^{13,14} Sulfasalazine may provide some benefits for peripheral arthritis but does not impact axial disease.^{15,16}

TNF- α (Tumor Necrosis Factor alpha) antagonists, also known as TNF inhibitors (TNFi), have demonstrated efficacy and are approved for the reduction of clinical signs and symptoms, in patients with AS. A recent recommendation from the ASAS recommends that anti-TNF therapy is indicated for those patients with persistently high disease activity despite conventional treatment.¹⁸ However, parenteral administration of TNF inhibitors limit the use of TNFi in AS, and there is a substantial proportion of patients who have an inadequate response to TNFi.¹⁹⁻²¹ Additional biological DMARDs (bDMARDs) have been subsequently approved but these remain parenteral. There remains an unmet medical need for an effective oral treatment for AS.

Tofacitinib has previously demonstrated efficacy and safety in Phase 2²¹⁻²⁶ and Phase 3²⁵ randomized controlled clinical trials of rheumatoid arthritis (RA) with up to 24 months duration and in long-term extension studies (LTE) with up to 105 months of observation.³³⁻³⁵ Tofacitinib is approved by the FDA (Food and Drug Administration) and the European Medicines Agency (EMA) for the treatment of moderate to severe RA. In psoriatic arthritis (PsA), tofacitinib was safe and effective in phase 3^{36,37} and long-term extension studies. Tofacitinib was approved by the FDA in December 2017 and the EMA in June 2018 for the treatment of PsA. Efficacy and safety was demonstrated in phase 2 and phase 3 studies of other chronic inflammatory diseases such as psoriasis (PsO)³⁸⁻⁴¹ and was approved for the treatment of ulcerative colitis (UC) by the FDA and Japan in May 2018.⁴²

A previous Phase 2 study, A3921119, was conducted in AS patients with an inadequate response to NSAIDs.⁴ This study, A3921120, will evaluate the efficacy and safety of tofacitinib in patients with active AS in a double-blind 16-week, placebo-controlled, randomized, multicenter study in subjects that have an inadequate response to previous treatment with NSAIDs or with TNFi.

This study is a follow-up to the A3921119 Phase 2b study of tofacitinib in active AS. This trial will use placebo control in the study design. Subjects who are enrolled in this study will be allowed to remain on their concomitant NSAIDs/csDMARDs as noted in the inclusion and exclusion criteria. In addition, subjects may be offered an appropriate rescue medication (see [Appendix 6](#)) during the study if there is an increase in pain. The placebo-controlled phase of the study is of short duration (16 weeks), if some subjects do experience increased or persistent clinical disease activity, worsening or persistent high disease activity should be clinically apparent given the frequency of visits and they will have the option to withdraw from the investigational product at any time. Finally, all subjects will be advanced to open-label tofacitinib 5 mg BID after the 16-week double-blind treatment period. Subjects

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will remain blinded to the sequence whether or not they were on placebo or tofacitinib throughout the study. Given these considerations, it is appropriate to investigate tofacitinib in a bDMARD naïve population, as well as those who have had an inadequate response to TNFi.

1.2.1. Summary of Efficacy

1.2.1.1. Rheumatoid Arthritis

Tofacitinib has demonstrated efficacy in RA as both monotherapy and in combination with methotrexate in Phase 2 and 3 studies. Efficacy in relieving signs and symptoms and in restoring physical function was demonstrated by American College of Rheumatology 20% response (ACR20) primary endpoint and secondary efficacy endpoints including ACR50, ACR70, Disease Activity Score for 28 Joints (DAS 28) and the Health Assessment Questionnaire Disability Index (HAQ-DI). Additionally, radiographic assessments showed tofacitinib reduced or inhibited the progression of structural damage.

Evidence of sustained efficacy of tofacitinib treatment in RA was provided from data in open-label extension studies. In the long-term follow-up studies A3921024 (ongoing at the time of analysis) and A3921041, efficacy was maintained in these studies through at least 96 months. No additional long term safety issues were identified.

1.2.1.2. Psoriatic Arthritis

The tofacitinib Phase 3 program was designed to evaluate the safety and efficacy of tofacitinib 5 mg and 10 mg BID in subjects with active psoriatic arthritis (PsA). The 2 pivotal studies (A3921091, A3921125) compared the efficacy of both tofacitinib doses to that of the placebo over 3 months for improvements in multiple PsA domains, examined the onset of efficacy, and assessed the persistence of efficacy (over a period of greater than 3 months) of both tofacitinib doses in csDMARD inadequate responder (csDMARD-IR) TNFi-naïve and TNFi-IR populations. For both studies the ACR20 response rate and the mean Δ HAQ-DI (decrease) were statistically higher for both tofacitinib 5 mg and 10 mg BID dose treatment groups than the placebo treatment group at Month 3. For both studies, early onset of efficacy in ACR20 response was shown with both tofacitinib doses as demonstrated by a statistically significant superior response to placebo at Week 2, Month 1, and Month 2. ACR50 response rates demonstrated superiority to placebo at Month 3 for both studies. Tofacitinib 5 mg BID was approved by the FDA for the treatment of PsA as of 14 December 2017 and by the EMA as of 25 June 2018.

1.2.1.3. Ulcerative Colitis

Efficacy in UC was shown in Phase 2 and 3 studies. In Phase 3 induction studies (A3921094 and A3921095) the proportion of subjects showing remission by Week 8 was statistically significantly greater in the tofacitinib 10 mg BID group as compared with the placebo group. Mucosal healing at Week 8 also showed statistically significant improvement over the placebo. In maintenance study A3921096, efficacy of tofacitinib 5 mg BID and 10 mg BID was demonstrated with statistically significant greater treatment effects for both treatment groups versus placebo at Week 52 for remission, mucosal healing and sustained

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corticosteroid-free remission. Tofacitinib 5 and 10 mg BID was approved for the treatment of UC in the US as of 30 May 2018 and in Japan as of 25 May 2018.

1.2.1.4. AS

A dose-ranging Phase 2 study, A3921119, evaluated the efficacy and safety of tofacitinib in AS subjects with an inadequate response to NSAIDs. The primary endpoint estimated the dose-response relationship using the Emax model for the ASAS20 response rate at Week 12. Tofacitinib 5 mg and 10 mg BID had response rates with model based estimated differences from placebo of 22.9% and 27.3% respectively. Normal approximation analysis of the ASAS20 at Week 12 demonstrated tofacitinib 5 mg BID was the only dose statistically superior to the placebo. Secondary endpoints generally demonstrated greater improvements with tofacitinib 5 and 10 mg BID than the placebo.

1.2.2. Summary of Safety

The clinical development program for tofacitinib (oral administration) has included patients with RA, juvenile idiopathic arthritis (JIA), PsA, UC, PsO, renal transplant rejection, Crohn's disease (CD) and AS, enrolled in 48 Phase 2, Phase 3 and LTE studies.

Cumulatively through 05 May 2018, it is estimated that 23,038 subjects have participated in tofacitinib clinical trials worldwide, with more than 14,473 subjects receiving at least 1 study dose of oral tofacitinib, in either a randomized clinical study or LTE study. Of these subjects, approximately 8700 subjects continue to receive tofacitinib by participating in LTE or other types of continuation studies.

Potential safety risks for subjects treated with tofacitinib are based on the totality of the data including nonclinical observations, clinical observations, as well as safety risks reported for other therapies that may share common pathways with tofacitinib. These risks are discussed briefly in the following section.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure.

1.2.3. Overall Risk-Benefit

1.2.3.1. 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 AS. In addition, patients may have an inadequate response to available treatment options such as TNFi.

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

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1.2.3.2. Potential Risks

The risks associated with tofacitinib are similar to the risks associated with the use of other bDMARDs, including a potential risk for development of serious and other infections, eg, tuberculosis and viral reactivation such as herpes zoster (HZ). In the RA program, the serious infection rate in the tofacitinib-treated subjects was consistent with the rates of serious infections in patients treated with other therapeutic interventions including bDMARDs. Serious infections were more frequent among the elderly (>65 years), subjects with diabetes mellitus and subjects treated previously with biological agents. Rates of HZ infections in tofacitinib-treated subjects with RA were increased compared with placebo-treated RA subjects and historical controls; this included an increased risk of HZ infections in Asian RA subjects compared with non-Asian RA subjects. 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 decreased hemoglobin have been observed. These effects are 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 treatment, and reversible on 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 Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL) cholesterol, with the ratios of mean LDL/HDL cholesterol unchanged. In the previous controlled trials, elevation of LDL cholesterol generally returned to pre-treatment levels after discontinuation of tofacitinib. In light of the association of RA and accelerated atherosclerosis, cardiovascular (CV) mortality and morbidity CV events were evaluated by an independent adjudication committee. Review of cardiovascular events by the committee reported in RA and PsO studies suggest that tofacitinib was not associated with an increase in major adverse cardiovascular events.

Also observed 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 the subject recovered following treatment with prednisone and azathioprine. The time course of the subject's biochemical abnormalities were atypical for DILI, however investigation 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).

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

Cases of gastrointestinal (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 (NSAIDs) and/or corticosteroids that have been associated with an increased risk of GI tract injury.^{43,44} Isolated events of GI perforation have also been reported in clinical trials in other tofacitinib indications including one (preferred term: appendicitis) in the PsA program, 8 in the UC program, 3 in the CD program and 2 in the renal transplant program.

Interstitial lung disease (ILD), a complex co-morbidity in RA subjects, has also been reported in RA subjects 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 subjects as compared to non-Asian subjects 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.

1.2.4. 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 Cytochrome P450 enzyme 3A4 (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

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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 renal 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 Investigator's Brochure.

1.2.5. Drug Development and Study Rationale

The effects of tofacitinib on cytokines (including the cross over to JAK1 which may result in some attenuation of signaling by additional cytokines, such as IL-6 and IFN- γ) that 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. Cytokines IL-17, IL-21 and IL-23 have been implicated in AS pathology and antibodies to IL-17 have demonstrated efficacy in AS.³ This forms the basis of the rationale to investigate the effect of tofacitinib in active AS.

Ankylosing Spondylitis as a chronic inflammatory disease shares many characteristics with RA and PsA such as inflammation and bone erosions. The axial inflammation that is specific to AS, is the inflammation in the spine. This can lead to bone erosions, new bone formation and ankylosis of the spine. In addition, RA, PsA, and AS share many similar circulating pro inflammatory cytokines, including IL-6, IL-17, IL-23, TNF- α and TNF- γ .⁴⁵ Increased concentrations of IL-6 have been observed in patients with chronic inflammatory conditions such AS.⁴⁵⁻⁴⁸

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Phase 2 study A3921119 assessed the safety and efficacy of tofacitinib in subjects with active AS at 2 mg BID, 5 mg BID and 10 mg BID. Approximately 200 subjects (~50 per arm) were randomized in a 1:1:1:1 ratio to one of 4 treatment sequences for a total of 12 weeks of treatment. At Week 12 the primary endpoint E_{\max} model ASAS20 response rates for the tofacitinib 2 mg BID, 5 mg BID and 10 mg BID treatment groups and placebo treatment group were 56.0%, 63.0%, 67.4% and 40.1%, respectively. The tofacitinib 5 mg and 10 mg BID treatment groups had numerically greater ASAS20 response rates than the placebo treated group at Week 12, and greater mean improvement from Baseline in Patient Global Assessment (PGA) of disease score, total back pain, inflammation score, and nocturnal spinal pain than the placebo group. There was statistically significant greater improvement in ASAS40 rates, ASDAS_{CRP} values, ASDAS_{CRP} clinically important improvement, improvement in mean BASDAI values, and BASDAI50 response rate at Week 12 for all tofacitinib treatment groups compared to the placebo.

Secondary endpoints such as BASDAI50 and Bath Ankylosing Spondylitis Functional Index (BASFI), as well as patient-reported outcomes such as AS Quality of Life (ASQoL) were also met. Efficacy was also demonstrated through objective measures such as the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI index of disease activity scores. There was statistically significant greater improvement from Baseline for LS mean SPARCC MRI index of disease activity score of the SI joints compared to placebo for the tofacitinib 5 mg BID and 10 mg BID treatment groups. There was also statistically significant greater improvement from Baseline for LS mean SPARCC MRI index of disease activity score of the spine compared to placebo for the tofacitinib 2 mg BID, 5 mg BID and 10 mg BID treatment groups, with the 5 and 10 mg doses showing statistical significance. The safety profiles for both the tofacitinib treated and placebo treated groups were similar. The totality of these results forms the basis of our decision to move to Phase 3.

1.2.6. Dose Selection Rationale

Tofacitinib 5 mg BID will be evaluated in this Phase 3 study in AS.

Tofacitinib doses of 5 and 10 mg BID were demonstrated to be efficacious in RA and PsA subjects in those respective clinical development programs. The primary endpoint E_{\max} model analysis estimated an ASAS20 response rate of 63.0% after tofacitinib 5 mg BID, a 22.9% rate higher than placebo. Supportive normal approximation analysis demonstrated an ASAS20 response rate after tofacitinib 5 mg BID significantly higher than placebo (80.8% vs 41.2%; $p < 0.001$); tofacitinib 2 mg and 10 mg BID demonstrated greater response rate than placebo but were not significant (51.9% and 55.8%, respectively). A consistent magnitude of efficacy was not observed after the lowest dose (2 mg BID) of tofacitinib, especially with more objective endpoints such as MRI. Compared to 5 mg BID, the 10 mg tofacitinib dose did not demonstrate consistent or clinically meaningful additional improvements in efficacy across study endpoints. No new safety concerns were identified in the Phase 2 AS study at any dose of tofacitinib.

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Tofacitinib 5 mg BID is the currently approved dose in the United States Prescribing Information (USPI) for use in RA, PsA, and UC. Given the results of the Phase 2 study of tofacitinib in AS subjects as well as taking into consideration the current BID posology for tofacitinib in other rheumatologic diseases, 5 mg BID of tofacitinib was selected to be evaluated in this Phase 3 study in AS subjects.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objectives:	Primary Endpoint:
<ul style="list-style-type: none"> To compare the efficacy of tofacitinib 5 mg BID versus placebo on the ASAS20 response rate at Week 16 in subjects with active AS that have had an inadequate response to previous treatment. 	<ul style="list-style-type: none"> ASAS20 response at Week 16.
Key Secondary Objective:	Key Secondary Endpoint:
<ul style="list-style-type: none"> To compare the efficacy of tofacitinib 5 mg BID versus placebo on the ASAS40 response rate at Week 16 in subjects with active AS that have had an inadequate response to previous treatment. 	<ul style="list-style-type: none"> ASAS40 response at Week 16.
Other Secondary Objectives:	Other Secondary Endpoints:
<ul style="list-style-type: none"> To compare the safety and tolerability of tofacitinib 5 mg BID versus placebo in subjects with active AS that have had an inadequate response to previous treatment. To compare the efficacy (including health-related quality of life, function, pain, and fatigue) of tofacitinib 5 mg BID versus placebo at all time points in subjects with active AS that have had an inadequate response to previous treatment. 	<ul style="list-style-type: none"> Incidence and severity of Adverse Events (AE). Clinical laboratory tests, vital signs, physical examination and 12-lead ECG parameters. ASAS20 response at all other time points. ASAS40 response at all other time points. Change from baseline in Ankylosing Spondylitis Disease Activity Score using C-Reactive Protein (ASDAS_{CRP}) at all time points. Change from baseline in hsCRP at all time points. Change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) at all time points collected. Change from baseline in Short-Form-36 Health Survey-Version 2 Acute (SF-36v2) at all time points collected. Change from baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) including the 5 components (lateral spine flexion, tragus-to-wall distance, lumbar flexion, maximal intermalleolar distance and cervical rotation) at all time points. Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (3 endpoints: total score, experience domain and impact domain scores) at all time points. Change from baseline in Patients Global Assessment of Disease (PGA) at all time points collected. Change from baseline in Patient's Assessment of Spinal Pain (Total Back Pain, Nocturnal Spinal Pain) at all time points collected. Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at all time points. Change from baseline in inflammation (mean of the answers to questions 5 and 6 of the BASDAI) at all time points collected.

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	<ul style="list-style-type: none"> ASAS 5/6 response at all time points. ASAS partial remission criteria at all time points. Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at all time points. BASDAI50 response at all time points. ASDAS clinically important improvement, ASDAS major improvement and ASDAS inactive disease at all time points. Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) at all time points collected. Change from baseline in extra-articular Involvement (Specific Medical History and peripheral articular involvement [as assessed by change from baseline in swollen joint count]) at all time points collected. Change from baseline in spinal mobility at all time points collected. Change from baseline in EuroQol EQ-5D Health State Profile 3 level (EQ-5D-3L) and Your own health state today (EQ-VAS), at all time points collected. Change from baseline in Work Productivity and Activity Impairment (WPAI) Questionnaire: Spondyloarthritis at all time points collected.
Tertiary/Exploratory Objectives:	Tertiary/Exploratory Endpoints:
<ul style="list-style-type: none"> [REDACTED] To evaluate the effect of tofacitinib 5 mg BID on lymphocyte subsets using FACS analysis. To measure the effect of tofacitinib 5 mg BID on healthcare resource utilization at all collected time points. 	<ul style="list-style-type: none"> [REDACTED] Fluorescence Activated Cell Sorting (FACS) analysis of lymphocyte subsets. AS HealthCare Resource Utilization Questionnaire (AS-HCRU) at all time points collected.

3. STUDY DESIGN

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of tofacitinib in subjects with active AS. Approximately 480 AS subjects will be screened globally in order that approximately 240 eligible subjects (120 per arm) will be randomized in a 1:1 ratio to tofacitinib 5 mg BID or matching placebo BID for a total of 16 weeks of blinded treatment. During the 16-week treatment period subjects will visit the clinic every two weeks (± 3 days) until the Week 4 visit and then every 4 weeks (± 7 days) until the completion of Week 16. At the Week 16 visit all subjects will be assigned to open-label tofacitinib and will visit the clinic every two months (± 7 days) until Week 48. Subjects will then return to the clinic for a Follow-up visit approximately 28 days after the Week 48 visit. There will be a total of 2 planned analyses conducted when all applicable subjects have completed their Week 16 and Week 48 (including follow-up) visits, respectively. CCI [REDACTED]

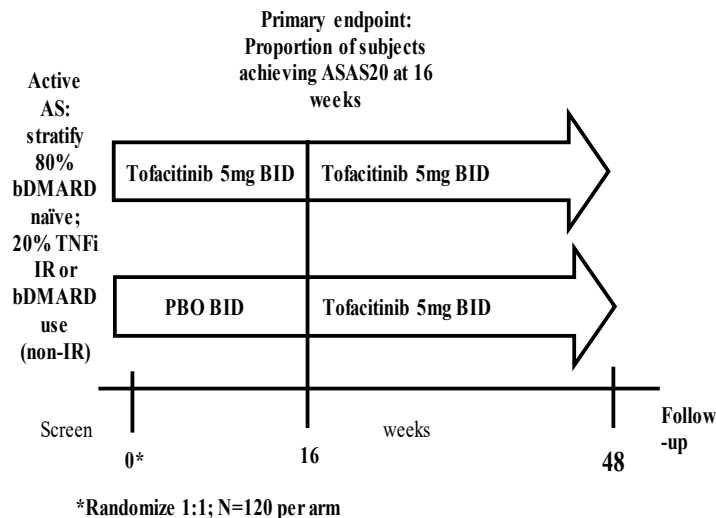
[REDACTED] The first analysis will be conducted when all applicable subjects

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have completed their Week 16 visit (see [Section 9.2](#)). The investigators, subjects and sponsor study team will remain blinded to the first 16 weeks of treatment assignment through the entire duration of the trial until database release.

Randomization will be stratified by prior treatment history: (1) bDMARD-naïve and (2) Tumor Necrosis Factor inhibitor-inadequate responder (TNFi-IR) or bDMARD use (non-IR). Approximately 80% of the subjects will be bDMARD-naïve and have an inadequate response to at least 2 NSAIDs (designed as Stratum bDMARD-naïve), and the other approximately 20% of subjects who had an inadequate response to at least one but not more than 2 TNFi and have an inadequate response to at least 2 NSAIDs or bDMARD use (non-IR) [designed as Stratum TNFi-IR or bDMARD use (non-IR)]. Subjects who had prior bDMARD use (non-IR) will be eligible to participate in the study and will be included in the TNFi-IR or bDMARD use (non-IR) stratum. An inadequate response to NSAID or TNFi treatment is defined as having a treatment related adverse event or lack of response to NSAID or TNFi treatment that was administered in accordance with its labeling recommendations. The sponsor may limit enrollment of subjects with baseline hsCRP below 0.287 mg/dl to match their estimated prevalence in AS. See Figure 1.

Figure 1. Study Design Schematic



Active disease is required for entry into this study and is defined as: Modified New York Criteria for Ankylosing Spondylitis (1984), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4 and back pain score (BASDAI Question 2) of ≥ 4 . If subjects have fulfilled entry criteria, they will be randomized to receive either tofacitinib 5 mg BID or placebo.

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Including the Screening visit, subjects will return to the clinic site at above noted intervals for a total of 12 visits. If the subject completes the Follow-up visit, the minimum duration of participation will be approximately 56 weeks (Screening: 30 days, 16 week double blind treatment period, 32 week open-label treatment period, Follow-up visit: 28 days \pm 7 days) without inclusion of any alterations in the visit schedule according to the protocol.

Selected assessments during the study will need to be completed by a qualified blinded assessor. This blinded assessor should be blinded to subject's baseline treatment assignment, all previously completed efficacy assessments (including patient's global assessment) and all safety data (eg, laboratory results, adverse events) in order that the current assessments are completed in an objective manner throughout the study.

Amendment 3

All subjects in the study will be evaluated for risk factors for VTE⁵⁰.

The study investigator or designee will need to review each subject's medical history and study records, including their concomitant medications, to determine whether he/she is at high risk for developing VTE.

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

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

Additional risk factors for VTE, such as age, diabetes, obesity (BMI \geq 30 kg/m²), smoking status, hypertension, and first degree family history of VTE should also be taken into consideration by the investigator and the sponsor medical monitor when evaluating the benefit:risk for each individual subject whether to discontinue from open-label 5 mg BID dose of tofacitinib.

See Risk Factor Check for VTE in Section 7.1.14 for tofacitinib dosing guidance when a risk factor is identified.

If a subject has one or more of the risk factors for VTE listed above under Amendment 3 and is receiving tofacitinib 5 mg BID, they may remain on tofacitinib 5 mg BID after careful investigator assessment of benefit: risk. For subjects who do not have any of the risk factors

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for VTE listed above under Amendment 3, he/she will remain on their open-label tofacitinib dose of 5 mg BID.

4. SUBJECT ELIGIBILITY CRITERIA

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

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

4.1. Inclusion Criteria

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

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of and is capable of comprehending all pertinent aspects of the study.
2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Subject is at least 18 years old (*or* the minimum country-specific age of consent if >18) at the screening visit.
4. The subject has a diagnosis of AS based on the Modified New York Criteria for Ankylosing Spondylitis (1984). See [Appendix 2](#).
5. The subject must have a radiograph of the SI joints (AP Pelvis) documenting diagnosis of AS. Previous radiographs (up to 2 years old) can be used if they are accepted by the central reader. Otherwise, a new radiograph will be obtained during the screening period.
6. Subject has active AS Screening and Baseline (Day 1) visits defined as:
 - BASDAI score of ≥ 4 ; and
 - Back pain score (BASDAI Question 2) of ≥ 4 .
7. Subject has active disease despite nonsteroidal anti-inflammatory drug (NSAID) therapy or is intolerant to NSAIDs as defined by:

Subject must have had at least a total of 2 occurrences of an inadequate clinical response (minimum of 4 week trial) or intolerance to at least 2 different oral NSAIDs. An inadequate response to a previous NSAID or TNFi is defined as a lack of sufficient clinical response based on a clinical judgment or based on a related adverse

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event (eg an adverse drug reaction requiring discontinuation) to the subject's previous treatment for AS. This will be documented on the relevant case report form (CRF).

Intolerance is defined as having discontinued NSAID treatment due to a related adverse event (eg, allergic reaction, gastrointestinal symptoms or signs, hypertension, etc).

8. Subjects who are designated as TNFi-IR must have received at least 1, but not more than 2 approved TNF inhibiting biologic agent that was administered in accordance with its labeling recommendations and was inadequately effective after the minimum treatment times listed below and/or not tolerated after one or more doses.
 - At least 3 months of adalimumab treatment;
 - At least 3 months of etanercept treatment;
 - At least 4 infusions of infliximab;
 - At least 3 injections of golimumab;
 - At least 3 months of certolizumab treatment.

Intolerance is defined as having experienced a treatment-related AE (eg, infusion/injection reactions, infections, laboratory test changes, etc). Discontinuation for economic reasons is not considered intolerance.

NOTE: The washout period required for study entry for TNFi at Baseline (Day 1) is discussed in [Section 5.8.1](#).

9. Subjects may be receiving the following csDMARDs at the time of the screening visit. These medications should be continued throughout the entire study and doses should remain unchanged. Any other Disease-Modifying Anti-Rheumatic Drugs (DMARDs) require discussion prior to enrollment with the sponsor for washout timeframe.

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- Methotrexate (MTX): Maximum dose of 25 mg/week. Minimum duration of therapy 4 months and dose stable for 4 weeks prior to first dose of investigational product. Subjects on MTX should be on an adequate and stable dose of folate supplementation per local standards/regulatory approval (eg, 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 investigational product. Subject must not have had previous serious toxicity while on MTX and not be expected to require evaluation for possible methotrexate toxicity (eg, require a liver biopsy for methotrexate toxicity) during the study;
 - Sulfasalazine (Azulfidine[®], Salazopyrin[®]): Maximum dose of 3 gm/day. Minimum duration of therapy 2 months and dose stable for 4 weeks prior to first dose of investigational product.
10. Subjects who are already taking oral corticosteroids (not injectables) 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 1 week prior to the first dose of investigational product;
 - Injected (eg, intraarticular, intramuscular, epidural or intravenous) corticosteroids must be discontinued 4 weeks prior to the first dose of investigational product;
 - Topical and intra-rectal corticosteroids will be allowed during the study.
11. Subject has discontinued all disallowed concomitant medication for the required time prior to the first dose of investigational product.
12. Subjects who are receiving any investigational or marketed treatment for AS, arthritis or back pain not mentioned elsewhere must have that treatment discontinued for 4 weeks or 5 half-lives, whichever is longer.
13. Subjects receiving non-prohibited concomitant medications for any reason must be willing to stay on a stable regimen (doses and frequency) as defined in the protocol.
14. No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined by **all** of the following:
- A negative QuantiFERON[®]-TB Gold (QFT G) In Tube test performed at or within 3 months prior to the Screening visit. Subjects with a history of Bacille Calmette Guérin (BCG) vaccination will be tested with the QFT G test;
 - No local QTF G testing will be accepted for meeting this inclusion criterion;

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- A chest radiograph taken at or 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 of suggestive active TB infection;
- No history of either untreated or inadequately treated latent or active TB infection.

NOTE: If a subject has previously received an adequate course of therapy for latent (eg, 9 months of isoniazid in a locale where rates of primary multi drug resistant TB infection are <5% or an acceptable alternative regimen) TB infection, a QuantiFERON®-TB Gold In Tube (QFT Gold test) need not 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 latent TB infection can only be enrolled with confirmation of current incidence rates of multi drug resistant TB infection and documentation of an adequate treatment regimen.

15. Women of childbearing potential must test negative for pregnancy prior to enrollment in this study.
16. Female subjects of non-childbearing potential must meet at least 1 of the following criteria:
 - Achieved post-menopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with/and have a central laboratory confirmation of serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
 - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
 - Have medically confirmed ovarian failure.

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

4.2. Exclusion Criteria

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

1. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study. Persons who are dependent upon the sponsor, investigator or the study site are excluded.

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2. Participation in other studies involving investigational drug(s) within 4 weeks prior to study entry and/or during study participation (excluding non-interventional follow-up during the screening period).
3. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
4. History of known or suspected complete ankylosis of the spine.
5. Subjects that have been **exposed** to or are currently receiving targeted synthetic DMARDS (including JAK inhibitors) or those currently on biological DMARDS (ie, washout from any current bDMARD required per [Section 5.8.1](#)), thalidomide (including previous use) and other prohibited concomitant medications noted in [Appendix 4](#).
6. History of allergies, intolerance or hypersensitivity to lactose or tofacitinib (CP-690,550). This includes subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. The investigators of potential subjects with acquired lactose intolerance should consider whether this is sufficiently concerning so as to preclude participation.
7. Blood dyscrasias at screening or within 3 months prior to the first dose of investigational product including confirmed:
 - Hemoglobin <10 g/dL;
 - Absolute white blood cell count (WBC) <3.0 x 10⁹/L (<3000 mm³);
 - Absolute neutrophil count (ANC) <1.5 x 10⁹/L (<1500 mm³);
 - Absolute lymphocyte count <1.0 x 10⁹/L (<1000/mm³);
 - Platelet count <100 x 10⁹/L (<100,000/mm³).
8. Estimated Creatinine Clearance <40 mL/min based on Cockcroft Gault equation at Screening visit (see [Appendix 3](#)).
9. Total bilirubin, AST or ALT more than 1.5 times the upper limit of normal (ULN) at screening visit.

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One re-testing of a laboratory-acceptable specimen (eg, appropriately labeled, within stability parameters, not hemolyzed, appropriate type (tube and reagent) and volume) is allowed of any above parameters if the abnormal lab(s) was an uncharacteristic result(s).

Re-test must be completed within the screening period.

10. History of any other autoimmune rheumatic disease.
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 related lymphoproliferative disease (EBV-LPD), 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/multi-dermatomal (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.
14. History of 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 investigational product.
15. History of infection requiring antimicrobial therapy within 2 weeks prior to the first dose of investigational product.
16. Any prior treatment with non-B cell specific lymphocyte depleting agents/therapies (eg, alemtuzamab, efalizumab), alkylating agents (eg, cyclophosphamide or chlorambucil), or total lymphoid irradiation.
17. Any subject who has been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of investigational product or is to be vaccinated with these vaccines at any time during treatment or within 6 weeks after last dose of investigational product.
18. A subject with any condition possibly affecting oral drug absorption, eg, gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass. Procedures such as gastric banding, that simply divide the stomach into separate chambers, are NOT exclusionary.
19. A subject that is considered at risk for GI perforation by the investigator or Sponsor.
20. History of alcohol or drug abuse unless in full remission for greater than 6 months prior to first dose of investigational product. Subjects currently using marijuana.

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21. Screening 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities 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).
22. A subject with a known immunodeficiency disorder or a first degree relative with a hereditary immunodeficiency.
23. 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.
24. Significant trauma or surgery procedure within 1 month prior to first dose of study medication, or any planned elective surgery during the study period.
25. A subject known to be infected with human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus or any chronic infection.
 - Hepatitis B Surface Antigen positive (HBsAg+) is exclusionary; subjects who are HBsAg- but Hepatitis B core antibody positive (HBcAb+) must undergo further testing for HBsAb to be considered for enrollment. If HBsAb+, subject may enroll; if HBsAb-, subject is excluded.
 - Subjects who are Hepatitis C Virus Antibody Positive (HCV Ab+) must undergo further testing for Hepatitis C Virus Ribonucleic Acid (HCV RNA). Subjects who are HCV RNA- may enroll.
26. Pregnant female subjects; breastfeeding female subjects; female subjects of childbearing potential, who are unwilling or unable to use 1 highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after last dose of investigational product. *Note: This is 2 methods of contraception for female subjects of childbearing potential from Canada.*
27. A subject who, in the opinion of the investigator or Pfizer (or designee), will be uncooperative or unable to comply with study procedures.

4.3. Randomization Criteria

A subject who has signed an informed consent document to participate in the study, has undergone all screening procedures, and has met all inclusion and none of the exclusion criteria for participation in the study at the Baseline visit.

4.4. Lifestyle Requirements

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

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- On designated study visit days, comply with fasting requirements for at least 9 hours prior to visit (See [Section 6](#)). On study visit days, subject should not take the in-clinic dose of study medication before the clinic visit.
- 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, take prescribed permitted concomitant medication, as needed, prior to the study visit, if it can be administered with water only.
- Avoid vaccinations with live or attenuated live vaccines and contact with individuals who have recently received live or attenuated live vaccines (See [Section 4.4.4](#)).
- Discontinue and avoid using certain medications and treatments (see [Inclusion Criteria](#) and list of prohibited medications in [Section 5.8.4](#) and [Appendix 4](#)).
- 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. 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 regular medications permitted; [REDACTED]) for at least 9 hours prior to scheduled safety laboratory tests. Visits that require fasting are Baseline/Day 1, Weeks 4, 16, 32, 48 and Follow-up.

4.4.2. Non-Pharmacologic Interventions

The subject should continue all non-pharmacological therapies, such as physical therapy, as indicated. However, the subject should avoid changing the type or intensity of therapy, or initiating new therapy, until after the Week 16 visit.

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 investigational product, unless there is sufficient data

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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 subjects should be on a stable dose for 1 week prior to first dose of investigational product and throughout the study.

4.4.4. Vaccine Guidelines

Vaccination with live or live attenuated components is prohibited during the study and for 6 weeks after last dose of investigational product. Similarly, current routine household contact with children and others vaccinated with live vaccine components should be avoided during treatment and for 6 weeks following completion of the study. Some of these vaccines include varicella ("chickenpox or shingles") 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 a potential risk that the virus may be transmitted. General guidelines suggest that exposure should be avoided following vaccination with these vaccines for the stated time period:

- Varicella or attenuated typhoid fever vaccination for 4 weeks following vaccination;
- Oral polio vaccination for 6 weeks following vaccination;
- Attenuated rotavirus vaccine for 10 days following vaccination;
- FluMist® (inhaled flu vaccine) for 1 week following vaccination.

4.4.5. Elective Surgery

During the course of this study, elective surgery should be delayed until the end of the placebo-controlled period. No elective surgery should be scheduled without first consulting with the Pfizer Medical Monitor.

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

4.4.6. Contraception

The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his/her partner(s) from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the [Schedule of Activities](#), the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the

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conversation, and the subject's affirmation, in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner. Subjects in Canada who are women of childbearing potential (WOCBP) and sexually active are required to use two contraceptive methods at the same time, one highly effective contraceptive method and one additional effective contraceptive method.

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

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

OR

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

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

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

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
 2. Intrauterine device (IUD).
 3. Intrauterine hormone-releasing system (IUS).
 4. Bilateral tubal occlusion.
 5. Vasectomized partner.
- Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

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Highly Effective Methods That Are User Dependent

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
 - Oral;
 - Intravaginal;
 - Transdermal;
 - Injectable.
2. Progestogen-only hormone contraception associated with inhibition of ovulation:
 - Oral;
 - Injectable.
3. Sexual abstinence:
 - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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.

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

4.4.7. Sponsor's Qualified Medical Personnel

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

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

5. STUDY TREATMENTS

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

For this study, the investigational products are tofacitinib and placebo.

5.1. Allocation to Treatment

Allocation of subjects to treatment groups 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, patient population (bDMARD-naïve or TNFi-IR or bDMARD use [non-IR]) and the subject number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number 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 DU or container number assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

Subjects will be randomized at the Baseline visit in a 1:1 ratio to one of the following two parallel blinded treatment sequences for a total of 16 weeks of treatment. Eligible subjects will be treated with one of the two sequences for 16 weeks followed by treatment with tofacitinib 5 mg BID for an additional 32 weeks.

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Randomization will be stratified by prior treatment history: (1) bDMARD-naïve and (2) TNFi-IR or bDMARD use (non-IR). During the feasibility phase of clinical trial preparation, the sponsor conducted a survey of the countries and sites likely to participate in the study. While there was country-to-country variability, the overall proportion of bDMARD-naïve and TNFi-IR or bDMARD use (non-IR) was approximately 80%/20% respectively. The clinical trial was thus designed to reflect this prevalence. Subjects with more than 2 TNFi failures were excluded due to the higher likelihood that they could be refractory to tofacitinib therapy, an observation noted in other tofacitinib trials in RA and PsA.

Strata (Patient Population)	Sequence	Treatment Sequence and Description	Planned Number of Randomized Subjects
bDMARD-naïve	1	Blinded Tofacitinib 5 mg BID for 16 weeks followed by open-label tofacitinib for 32 weeks <i>One-tofacitinib 5 mg tablet in AM & PM</i>	96
bDMARD-naïve	2	Placebo BID for 16 weeks followed by open-label 5 mg BID tofacitinib for 32 weeks <i>One- 5 mg matching placebo tablet in AM & PM for the first 16 weeks followed by one-tofacitinib 5 mg tablet in the AM & PM for 32 weeks</i>	96
TNFi-IR or bDMARD use (non-IR)	1	Blinded Tofacitinib 5 mg BID for 16 weeks followed by open-label tofacitinib for 32 weeks <i>One-tofacitinib 5 mg tablet in AM & PM</i>	24
TNFi-IR or bDMARD use (non-IR)	2	Placebo BID for 16 weeks followed by open-label 5 mg BID tofacitinib for 32 weeks <i>One- 5 mg matching placebo tablet in AM & PM for the first 16 weeks followed by one-tofacitinib 5 mg tablet in the AM & PM for 32 weeks</i>	24

At the end of the 16 week double-blinded treatment period, all subjects will be assigned to open-label tofacitinib 5 mg BID to Week 48. The investigators, subjects and sponsor study team will remain blinded to the first 16 weeks of treatment assignment through the entire duration of the trial until database release.

5.2. Breaking the Blind

This study will be subject-, investigator-, and sponsor-blinded. For the open-label treatment period, subjects, investigator and sponsor study team will remain blinded to the double-blind treatment period study sequence.

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At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. 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 and entered on the electronic case report form (eCRF).

5.3. Subject Compliance

Subject compliance with dosing administration will be verified by accounting of returned containers and investigational product at each visit. Compliance for the tablets will be calculated by each bottle and documented. If compliance is <80%, the investigator or designee is to counsel the subject and ensure steps are taken to improve compliance. Subjects, who are less than 80% compliant with the dosage regimen for any two consecutive visit periods, should be withdrawn from the investigational product. In the event that the investigational product is held due to an AE, infection or elective surgery, in accordance with the protocol-specified time frames, compliance should still be calculated for the visit period, but withdrawal from the investigational product would be assessed. If the subject is over-compliant with the investigational product (intentional or accidental) the investigator or designee is to counsel the subject and ensure correct understanding of the investigational product dosing regimen. The investigator should contact the Pfizer Medical Monitor or designee promptly with any over-compliance (>120%) that may potentially impact the safe use of the investigational product or that may result in a serious adverse event.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

During the double-blind treatment period, blinded tofacitinib and matched placebo will be provided as tablets for oral administration. The tofacitinib 5 mg tablets or placebo tablets will be supplied in bottles and labeled according to local regulatory requirements. The investigational product will be labeled in such a manner that the subject and study staff will be unable to determine from the dispensed packaging to which treatment sequence the subject is assigned. All blinded investigational product will be collected at the Week 16 visit and subjects will receive new investigational product as part of the open-label portion of the study at the Week 16 visit and will receive the first dose of open-label investigational product in the clinic. At the Week 16 visit, all subjects will receive tofacitinib 5 mg tablets supplied in containers and labeled according to local regulatory requirements. Supplies will be labeled as appropriate for this two-arm placebo-controlled, double-blind trial and the open-label treatment period.

5.4.2. Preparation and Dispensing

The investigational product will be dispensed using an IRT drug management system at each visit from Baseline to Week 40 (excluding Week 2). A qualified staff member will dispense the investigational product via unique container numbers in the bottles provided, in quantities appropriate for the study visit schedule. The subject/caregiver should be instructed to

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maintain the product in the bottle provided throughout the course of dosing and return the bottle to the site at the next study visit.

The investigational product will be packaged and labeled in such a manner that the subject and study staff will be unable to determine from the dispensed packaging to which treatment arm the subject is assigned during the double-blind treatment period. At study visits sufficient investigational product will be dispensed to complete dosing until the next scheduled visit. The amount of investigational product dispensed at each visit must be recorded. At study visits the subject must return all investigational product and the amount of investigational product returned will be recorded to account for all dispensed investigational product.

5.5. Administration

Investigational product will be dispensed to subjects to self-administer after appropriate training and specific instructions are provided. Instructions on dosing will be provided on the Subject Dosing Card. At all visits, the scheduled dose of investigational product will be taken by the subject in the clinic. At the end of each visit, sites will instruct subjects, when to take their investigational product prior to their next study visit. [REDACTED]

[REDACTED] Subjects should receive open-label investigational product at the Week 16 visit and should receive the first dose of the open-label investigational product at the clinic.

Tofacitinib tablets or matching placebo for oral administration may be taken with or without food. Subjects will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing.

Subjects will be instructed to take their tablet investigational product twice daily (once in the morning and once in the evening approximately 12 hours apart) for a total of two tablets per day. Placebo tablets will match the 5 mg tablets in order to maintain the blind.

During the double-blind treatment period, if the investigator deems it necessary to withhold the investigational product to treat a non-serious infection or other medical condition, temporary withholding is permitted for up to 5 days. If temporary withholding of the investigational product exceeding 5 days is required for a medical reason (eg, elective surgery), the investigator must contact the Pfizer Medical Monitor for approval.

Temporary withholding of the investigational product, as described above, is permitted once during the study without obtaining prior approval from the Pfizer Medical Monitor. Any additional request(s) for temporary withholding of the investigational product during the double blind period require(s) documented approval by the Pfizer Medical Monitor.

Per Amendment 3, for subjects with suspected VTE, treatment with tofacitinib should be temporarily withheld while the subject is evaluated. If VTE is confirmed, discontinue treatment with tofacitinib (see Section 6.4: Subjects Discontinuation from the Investigational Product).

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During the open-label period of the study, tofacitinib 5 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 investigational product permanently (see [Section 6.4.2](#)).

5.6. Investigational Product Storage

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

Investigational products should be stored in their original containers and in accordance with the labels.

Any storage conditions stated in the Investigator's Brochure will be superseded by the storage conditions stated on the product label.

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

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

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

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

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5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record. All containers of the investigational product must be returned to the investigator by the subject at every visit and at the end of the trial.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the 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.

5.8. Concomitant Treatment(s)

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

All local standard-of-care practices for the administration of permitted therapy (ie, background DMARD, contraceptives, rescue medication) including laboratory testing, follow-up care and contraindications should be performed according to local standards of care throughout the study. 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. 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 investigational product and prior to study visits unless otherwise noted below, throughout the study.

Medications that are taken during the screening period (after informed consent is obtained and before the first dose of investigational product) will be documented as prior medications. Medications taken after the first dose of investigational product has been administered will be documented as concomitant medications. All concomitant medications taken during the study must be recorded in the study records with indication (as appropriate), daily dose and start and stop dates of administration. Subjects will be queried about concomitant medications at each study visit. Minimum guidelines for folate supplementation during study: Subjects on methotrexate must receive folate supplementation according to local methotrexate label guidelines and standard of care. A minimum of 5 mg weekly based on folic acid should be given unless local guidelines or standard of care state otherwise.

5.8.1. Biologic Medications

Prior treatment with bDMARDs including TNF inhibitors is permitted if they have been discontinued for at least five half-lives before randomization. See also [Section 4.1](#) for definition of a TNF inhibitor nonresponder. Subjects on bDMARDs including TNF inhibitors must be discontinued according to the following criteria:

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- Etanercept (Enbrel[®]): Discontinued at least 4 weeks prior to the first dose of investigational product;
- Adalimumab (Humira[®]): Discontinued at least 10 weeks prior to the first dose of investigational product;
- Infliximab (Remicade[®]): Discontinued at least 8 weeks prior to the first dose of investigational product;
- Golimumab (Simponi[®]): Discontinued at least 10 weeks prior to the first dose of investigational product;
- Certolizumab (Cimzia[®]): Discontinued at least 10 weeks prior to the first dose of investigational product;
- Other bDMARDs: Discontinued at least 4 weeks or 5 half-lives (whichever is longer) washout period prior to first dose of study treatment after discussion with Sponsor.

5.8.2. Stable Background Pain or Other AS Therapy

Subjects taking permitted csDMARDs (eg, methotrexate (≤ 25 mg/week) or sulfasalazine (≤ 3 gm/day)), nonsteroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), and/or corticosteroids (≤ 10 mg prednisone mg/day) must remain on the same dose regimen throughout the study. Daily dosages of NSAIDs/COX-2 inhibitors, corticosteroids, opioids, and acetaminophen/paracetamol must be stable for 1 week prior to first study dose and must remain so during the study treatment period (Week 48) except if adjustment is needed to protect a subject's safety. Daily dosage of NSAIDs/COX-2 inhibitors, corticosteroids, opioids and acetaminophen/paracetamol must not be modified within the 24 hours prior to any study visit, except if adjustment is needed to protect a subject's safety.

Subjects using topical NSAIDs or anesthetics (ie, Ben-Gay[®]) on peripheral joints are allowed if stable for 1 week prior to the first study dose and must remain so during the study treatment period.

Glucosamine sulfate and chondroitin sulfate are allowed in the study but subjects should be on a stable dose for 1 week prior to first dose of investigational product and throughout the study.

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](#)).

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5.8.3. Rescue Therapy

The only medications that are allowed for rescue are listed in [Appendix 6](#).

Increases of acetaminophen/paracetamol and opioids are allowable as rescue medication for no more than 10 consecutive days. Acetaminophen/paracetamol may be added or increased to a maximum of 2.6 gm/day. Combination products such as over-the-counter “cold remedies” or pain medications should be assessed for acetaminophen/paracetamol content so as the total dose will not exceed 2.6 gm/day. Opioids may be added or increased to a maximum potency equivalent of 30 mg of orally-administered morphine.

Subjects who require rescue for more than 10 consecutive days will be discontinued from the investigational product and be designated as discontinued from the investigational product for lack of efficacy. There is no limit to the duration of nonconsecutive use of rescue medications. In addition, subjects may not be dosed with rescue medication during the 24 hours prior to a study visit. In the judgement of the investigator, if rescue therapy has any effect on efficacy data collected during a study visit, this will constitute a protocol deviation. Baseline stable use of acetaminophen/paracetamol or opioids should NOT be discontinued in advance of study visits.

5.8.4. Prohibited Medications

Prohibited drugs and dietary supplements not otherwise specified herein or in [Appendix 4](#) must be discontinued at least 30 days or 5 half-lives (whichever is longer) before the first dose of investigational product. A list of prohibited drugs with specific discontinuation recommendations can be found in [Appendix 4](#).

- Any DMARDs (synthetic or biologic) except for methotrexate or sulfasalazine. Subjects receiving any other investigational or marketed treatment for AS, arthritis or back pain other than permitted in [Appendix 4](#). Subjects receiving any other investigational drug during the study.
- Injected (intravenous, intramuscular, intraarticular or epidural) corticosteroids are not allowed during the blinded portion of the study either as a stable concomitant medication or as rescue medication.
- Herbals with pharmaceutical properties are allowed only if there is acceptable evidence of no CYP3A inhibition or induction and must be reported as a concomitant medication. 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).
- Vaccinations with live components are prohibited during the study and for 6 weeks after last dose of investigational product.
- Currently receiving or previously used thalidomide.

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- 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.

6. STUDY PROCEDURES

6.1. Screening

Subjects will be screened within 30 days prior to administration of investigational product to confirm that they meet the entrance criteria for the study.

Rescreening of subjects will be allowed in a limited number of circumstances as determined by the Pfizer Medical Monitor (eg, requires antimicrobial therapy within 2 weeks prior to the first dose of investigational product, requires emergency surgery) and should be confirmed with the Pfizer Medical Monitor when rescreening can occur.

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

Subjects, who are on prohibited medications and are deriving a beneficial response from the medication, should not be entered into this study. However, there may be subjects taking a prohibited medication who have experienced an ineffectual/suboptimal response or side effects and wish to enter the study. These subjects may require a washout period that extends beyond the screening duration. For these subjects, written informed consent and a unique subject number obtained through the IRT system must be obtained prior to initiation of the washout period. No other screening activities should be performed at this time. These subjects should return for a Screening visit within the allowed window, at which time all screening procedures should be completed.

At all visits, subjects should complete the “Patient Reported Outcome” (PRO) questionnaires at the clinic prior to any other study procedures outside of the informed consent process.

The following procedures will be performed:

- Informed consent;
- Collect demographic information (sex, date of birth, race, and ethnicity);
- ASAS/ASDASCRP Component: “Patient Global Assessment of Disease” (NRS), “Patient Assessment of Spinal Pain” which include Total Back Pain(NRS) and Nocturnal Spinal Pain (NRS), BASDAI (NRS), BASFI (NRS);
- Confirmation of diagnosis of active AS: based on the Modified New York Criteria for Ankylosing Spondylitis (1984) and BASDAI score of ≥ 4 and back pain score (BASDAI Question 2) of ≥ 4 ;

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- General Medical History: Should include history of previous vaccinations, specifically influenza, pneumococcal and herpes zoster as well as family history of AS, herpes zoster history, CV risk factor assessment, smoking history and average weekly alcohol consumption;
- Specific Medical History: History of uveitis, psoriasis, inflammatory bowel disease and peripheral articular involvement as assessed by swollen joint count;
- Prior/Concomitant treatments: Current and prior medications (noting exclusions and required csDMARD restrictions), including a complete history of all DMARDs (synthetic/biologic) ever taken with reasons for discontinuation (those taken during the 1 year prior to the first dose of investigational product should include the dose and duration of treatment). Complete history of all drugs (including non-prescription drugs, vitamins and dietary supplements) taken within 4 weeks prior to the screening procedures;
- Vital Signs: Blood pressure (seated), pulse rate and temperature (via tympanic, oral or temporal, preferred);
- Complete Physical Examination: 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), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes;
- Height, weight (without shoes preferred);
- 12-lead electrocardiogram submitted to central reader;
- BASMI (linear function) obtained by qualified blinded assessor: Lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance and cervical rotation;
- Spinal Mobility obtained by qualified blinded assessor: chest expansion;
- Laboratory testing: Central laboratory tests include: Hematology, Urinalysis, Chemistry Panel, HIV Serology, hepatitis testing (HBsAg, HBcAb, HCV Ab), high sensitivity C-Reactive Protein (hsCRP), and Prothrombin time (PT/INR); FSH and hepatitis reflex testing, if applicable. Screening lab tests as noted in the inclusion/exclusion criteria may be repeated a single time if the initial result is inconsistent with previous subject laboratory history;
- Urine Pregnancy Test (for women of childbearing potential only);

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- QuantiFERON®-TB Gold: Must be performed unless previously tested and documented within 3 months of screening visit OR unless subject has previously received an adequate course of therapy for either latent or active TB infection;
- Radiograph of chest: Unless performed within 3 months of Screening visit and documented;
- Radiograph of SI joints (read centrally). If documentation of AS has been obtained with prior radiographs, obtain radiographs for submission to the central reader. If not, perform after all other screening procedures and only perform radiograph of SI joints if subject does not fail to meet other study criteria;
- If radiographs are not available or unable to be read by the central reader, new radiograph (AP pelvis) should be obtained at the Screening visit and submitted to the central reader;
- Monitoring for adverse events;
- Contraception check: Confirm and document that proper contraception is being used.

6.2. Study Period

Subjects who have met all the inclusion criteria and have no exclusion criteria present may participate in the study. Blood collection for laboratory testing requiring a fasting state (at least 9 hours) may be taken up to 48 hours prior to the Baseline/Day 1 visit. For post-baseline double-blind study period visits blood collection for laboratory testing requiring a fasting state (at least 9 hours) up to 48 hours prior to or following as necessary to ensure samples are collected in a fasting state. If the subject has not fasted for at least 9 hours, the visit should be rescheduled to occur within 48 hours in the fasting state.

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

6.2.1. Baseline Day 1 (Randomization)

Subjects are required to fast for at least 9 hours prior to the visit; however, blood collection for laboratory testing may be taken up to 48 hours prior to the Baseline/Day 1 visit as necessary to ensure the samples are collected in a fasting state. If the blood collection is completed in advance of the clinic visit, the PROs should not be done with the blood collection but at the clinic visit.

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- All PROs should be performed before any other study procedures at the clinic visit. These include the following: ASAS/ASDASCRP Component: “Patient Global Assessment of Disease (NRS)”, “Patient Assessment of Spinal Pain” which includes Total Back Pain (NRS) and Nocturnal Spinal Pain (NRS), BASDAI (NRS), BASFI (NRS), ASQoL, SF-36v2, EuroQol EQ-5D Health State Profile 3 Level (EQ-5D-3L) and Your own health state today (EQ-VAS), Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F), - WPAI and AS HealthCare Resource Utilization Questionnaire (AS-HCRU) Questionnaire.

Prior to the first dose the following procedures will be completed:

- Confirmation of diagnosis of active AS: based on the Modified New York Criteria for Ankylosing Spondylitis (1984) and BASDAI score of ≥ 4 and back pain score (BASDAI Question 2) of ≥ 4 ;
- Determination and confirmation of either “bDMARD-naive” or “TNFi-IR” or “bDMARD use (non-IR)” status for randomization;
- Prior/Concomitant treatments: Current and prior medications (noting exclusions and required DMARD restrictions) will be reviewed to ensure no concomitant medications (including non-prescription drugs, vitamins and dietary supplements) have been added that are prohibited;
- Vital Signs: Blood pressure (seated), pulse rate and temperature (via tympanic, oral or temporal, preferred);
- Complete Physical Examination: 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), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes;
- Weight (without shoes preferred) and waist circumference;
- Specific Medical History: History of uveitis, psoriasis, inflammatory bowel disease and peripheral articular involvement as assessed by swollen joint count;
- BASMI (linear function) obtained by qualified blinded assessor: Lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance and cervical rotation;
- Spinal mobility obtained by qualified blinded assessor: chest expansion;
- Laboratory testing: Central laboratory tests include: Hematology, Urinalysis, Chemistry Panel, Lipid Profile (fasting), Urine Pregnancy Test (for women of childbearing potential only), hsCRP;

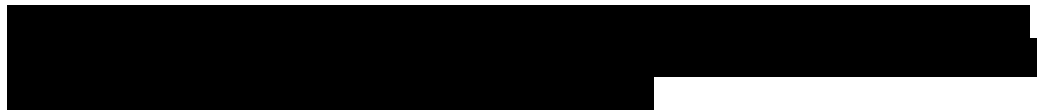
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- Blood sample for HLA-B27;
- Blood sample for Fluorescence Activated Cell Sorting (FACS) Analysis;
- Assessment of swollen joints (44-joint count) by qualified blinded assessor;
- Assessment of enthesitis using the Maastricht Ankylosing Spondylitis Enthesitis Score (MASSES) Index by qualified blinded assessor;
- Contact Interactive Web Response System (IWRS) to randomize subject;
- Dispense the investigational product to subject as described in [Section 5.5](#) and as noted in the [Administration](#) and Compliance Sections. Instruct subject on correct investigational product administration. All subsequent scheduled doses on clinic visit days will be taken in the clinic;
- Monitoring for adverse events;
- Contraception check: Confirm and document that proper contraception is being used;
- Instruct subject not to take the in-clinic dose of investigational product the day of the next study visit and to bring the drug supply with them to the visit.

6.2.2. Week 2

There is a ± 3 day window for this visit.



- All PROs should be completed prior to any other study procedures. These include the following: ASAS/ASDASCRP Component: “Patient Global Assessment of Disease (NRS)”, “Patient Assessment of Spinal Pain” which includes Total Back Pain (NRS) and Nocturnal Spinal Pain (NRS), BASDAI (NRS), BASFI (NRS), and FACIT-F.

After the PROs have been obtained, the following procedures should be completed:

- Verify morning dose of investigational product was not administered by subject. If the dose was administered, continue with visit but re-instruct subject on the requirement for in-clinic dosing;

Note: For subjects where the visit is conducted in the afternoon or evening, verify the afternoon or evening dose of investigational product was not administered by the subject.

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- Targeted physical examination (examination of heart, lungs, abdomen, lower extremities, skin (presence of rash) and lymph nodes);
- Weight (without shoes preferred);
- BASMI (linear function) obtained by qualified blinded assessor: Lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance and cervical rotation;
- Spinal mobility obtained by qualified blinded assessor: chest expansion;
- Vital signs: Blood pressure (seated), pulse rate and temperature (via tympanic, oral or temporal, preferred);
- Laboratory testing: Urine Pregnancy Test (for women of childbearing potential only), hsCRP;
- Assessment of swollen joints (44-joint count) by qualified blinded assessor;
- Administer investigational product from the previously dispensed study drug supplies unless subject had already administered dose at home;
- Complete drug accountability;
- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions;
- Contraception check: Confirm and document that proper contraception is being used;
- Instruct subject not to take the in-clinic dose of investigational product the day of the next study visit and to bring the drug supply with them to the visit.

6.2.3. Week 4

There is a ± 3 day window for this 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 hours prior to or following this visit as necessary to ensure the samples are collected in a fasting state. If the blood collection is completed in advance of the clinic visit, the PROs should not be done with the blood collection but at the clinic visit.



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- All PROs should be completed prior to any other study procedures. These include the following: ASAS/ASDAS_{CRP} Component: “Patient Global Assessment of Disease (NRS)”, “Patient Assessment of Spinal Pain” which includes Total Back Pain (NRS) and Nocturnal Spinal Pain (NRS), BASDAI (NRS), BASFI (NRS), and FACIT-F.

After the PROs are obtained, the following procedures should be completed prior to dosing:

- Verify morning dose of investigational product was not administered by the subject and previous day’s dosing was administered;

Note: For subjects where the visit is conducted in the afternoon or evening, verify the afternoon or evening dose of investigational product was not administered by the subject.

- Vital signs: Blood pressure (seated), pulse rate and temperature (via tympanic, oral or temporal, preferred);
- Laboratory testing: Central laboratory tests include: Hematology, Urinalysis, Chemistry Panel, Lipid Profile (fasting), Urine Pregnancy Test (for women of childbearing potential only), hsCRP;
- [REDACTED]
- Blood sample for FACS Analysis;
- [REDACTED]

The following procedures can be done before or after dosing depending upon the clinic’s schedule but is recommended that they be done at the same time (before or after dosing) consistently across all subsequent subject clinic visits:

- Targeted physical examination (examination of heart, lungs, abdomen, lower extremities, skin (presence of rash) and lymph nodes);
- Weight (without shoes preferred);
- BASMI (linear function) obtained by qualified blinded assessor: Lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance and cervical rotation;
- Spinal mobility obtained by qualified blinded assessor: chest expansion;
- Assessment of swollen joints (44-joint count) by qualified blinded assessor;
- Assessment of enthesitis using the MASES Index by qualified blinded assessor;
- Complete drug accountability.

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Procedures to be performed after dosing:

- [REDACTED]
- Contact IWRS and dispense new supply of investigational product to subject;
- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions;
- Contraception check: Confirm and document that proper contraception is being used;
- Instruct subject not to take the in-clinic dose of investigational product the day of the next study visit and to bring the drug supply with them to the visit.

6.2.4. Week 8

There is a ± 7 day window for this visit.

[REDACTED]

- All PROs should be completed prior to any other study procedures. These include the following: ASAS/ASDASCRP Component: “Patient Global Assessment of Disease (NRS)”, “Patient Assessment of Spinal Pain” which includes Total Back Pain (NRS) and Nocturnal Spinal Pain (NRS), BASDAI (NRS), BASFI (NRS), and FACIT-F.

After the PROs have been obtained, the following procedures should be completed:

- Verify morning dose of investigational product was not administered by the subject and previous day’s dosing was administered;
- Note: For subjects where the visit is conducted in the afternoon or evening, verify the afternoon or evening dose of investigational product was not administered by the subject.
- Vital signs: Blood pressure, pulse rate and temperature (via tympanic, oral or temporal, preferred);
 - Laboratory testing: Urine Pregnancy Test (for women of childbearing potential only), hsCRP;


- [REDACTED]
- [REDACTED]

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The following procedures can be done before or after dosing depending upon the clinic's schedule but it is recommended that they be done at the same time (before or after dosing) consistently across all subsequent subject clinic visits:

- Targeted physical examination (examination of heart, lungs, abdomen, lower extremities, skin (presence of rash) and lymph nodes);
- Weight (without shoes preferred);
- Specific Medical History: History of uveitis, psoriasis, inflammatory bowel disease and peripheral articular involvement as assessed by swollen joint count;
- BASMI (linear function) by qualified blinded assessor: Lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance and cervical rotation;
- Spinal mobility obtained by qualified blinded assessor: chest expansion;
- Assessment of swollen joints (44-joint count) by qualified blinded assessor;
- Assessment of enthesitis using the MASES Index by qualified blinded assessor;
- Complete drug accountability.

After dosing:

- 
- Monitoring of adverse events and concomitant medications. Record any modifications, deletions or additions;
- Contraception check: Confirm and document that proper contraception is being used;
- Contact IWRS and dispense new supply of investigational product to subject;
- Instruct subject not to take the in-clinic dose of investigational product the day of the next study visit and to bring the drug supply with them to the visit.

6.2.5. Week 12

There is a ± 7 day window for this visit.

- All PROs should be completed prior to any other study procedures. These include the following: ASAS/ASDASCRP Component: "Patient Global Assessment of Disease (NRS)", "Patient Assessment of Spinal Pain" which includes Total Back Pain (NRS) and Nocturnal Spinal Pain (NRS), BASDAI (NRS), BASFI (NRS), and FACIT-F.

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After the PROs are obtained, the following procedures should be completed prior to dosing:

- Verify morning dose of investigational product was not administered by subject. If the dose was administered, continue with visit but re-instruct subject on the requirement for in-clinic dosing;

Note: For subjects where the visit is conducted in the afternoon or evening, verify the afternoon or evening dose of investigational product was not administered by the subject.

- Vital signs: Blood pressure (seated), pulse rate and temperature (via tympanic, oral or temporal, preferred);
- Laboratory testing: Hematology, Chemistry Panel, Urinalysis, Urine Pregnancy Test (for women of childbearing potential only), hsCRP;
- Administer in-clinic dose of investigational product from previously dispensed study drug supplies.

The following procedures can be done before or after dosing depending upon the clinic's schedule but it is recommended that they be done at the same time (before or after dosing) consistently across all subsequent subject clinic visits:

- Targeted physical examination (examination of heart, lungs, abdomen, lower extremities, skin (presence of rash) and lymph nodes);
- Weight (without shoes preferred);
- BASMI (linear function) by qualified blinded assessor: Lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance and cervical rotation;
- Spinal mobility obtained by qualified blinded assessor: chest expansion;
- Assessment of swollen joints (44-joint count) by qualified blinded assessor;
- Assessment of enthesitis using the MASES Index by qualified blinded assessor;
- Complete drug accountability.

After dosing:

- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions;
- Contraception check: Confirm and document that proper contraception is being used;

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- Contact IWRS and dispense new supply of investigational product to subject;
- Instruct subject not to take the in-clinic dose of investigational product the day of the next study visit but to bring the drug supply with them to the visit.

6.2.6. Week 16

There is a ± 7 day window for this 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 hours prior to or following this visit as necessary to ensure the samples are collected in a fasting state. If the blood collection is completed in advance of the clinic visit, the PROs should not be done with the blood collection but at the clinic visit.

- All PROs should be performed before any other study procedures at the clinic visit. These include the following: ASAS/ASDAS_{CRP} Component: “Patient Global Assessment of Disease (NRS)”, “Patient Assessment of Spinal Pain” which includes Total Back Pain (NRS) and Nocturnal Spinal Pain (NRS), BASDAI (NRS), BASFI (NRS), ASQoL, SF-36v2, EQ-5D-3L and EQ-VAS, FACIT-F, - WPAI and AS-HCRU Questionnaire.

- Verify morning dose of investigational product was not administered by subject. If the dose was administered, continue with visit but re-instruct subject on the requirement for in-clinic dosing;

Note: For subjects where the visit is conducted in the afternoon or evening, verify the afternoon or evening dose of investigational product was not administered by the subject.

- Blood pressure (seated), pulse rate and temperature (via tympanic, oral or temporal, preferred);
- 12-lead electrocardiogram submitted to central reader;
- Laboratory testing: Central laboratory tests include: Hematology, Urinalysis, Chemistry Panel, Lipid Profile (fasting), Urine Pregnancy Test (for women of childbearing potential only), hsCRP;
- Blood sample for FACS Analysis;
- Complete Physical Examination: 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), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes;

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- Weight (without shoes preferred);
- Specific Medical History: History of uveitis, psoriasis, inflammatory bowel disease and peripheral articular involvement as assessed by swollen joint count;
- BASMI (linear function) by qualified blinded assessor: Lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance and cervical rotation;
- Spinal mobility obtained by qualified blinded assessor: chest expansion;
- Assessment of swollen joints (44-joint count) by qualified blinded assessor;
- Assessment of enthesitis using the MASES Index by qualified blinded assessor; Complete drug accountability;
- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions;
- Contraception check: Confirm and document that proper contraception is being used;

Subjects will be switched to open-label tofacitinib 5 mg BID for the remainder of the study.

- Contact IWRS and dispense new supply of open-label investigational product to subject;
- Administer in-clinic dose of investigational product from open-label study drug supply.
- Instruct subject not to take the in-clinic dose of investigational product the day of the next study visit but to bring the drug supply with them to the visit.

6.2.7. Week 24

There is a ± 7 day window for this visit.

- All PROs should be completed prior to any other study procedures. These include the following: ASAS/ASDAS_{CRP} Component: “Patient Global Assessment of Disease (NRS)”, “Patient Assessment of Spinal Pain” which includes Total Back Pain (NRS) and Nocturnal Spinal Pain (NRS), BASDAI (NRS), BASFI (NRS), and FACIT-F.

After the PROs are obtained, the following procedures should be completed prior to dosing:

- Verify morning dose of investigational product was not administered by subject. If the dose was administered, continue with visit but re-instruct subject on the requirement for in-clinic dosing;

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- Note: For subjects where the visit is conducted in the afternoon or evening, verify the afternoon or evening dose of investigational product was not administered by the subject. Vital signs: Blood pressure (seated), pulse rate and temperature (via tympanic, oral or temporal, preferred);
- Laboratory testing: Hematology, Chemistry Panel, Urinalysis, Urine Pregnancy Test (for women of childbearing potential only), hsCRP;
- Administer in-clinic dose of investigational product from previously dispensed study drug supplies.

The following procedures can be done before or after dosing depending upon the clinic's schedule but it is recommended that they be done at the same time (before or after dosing) consistently across all subsequent subject clinic visits:

- Targeted physical examination (examination of heart, lungs, abdomen, lower extremities, skin (presence of rash) and lymph nodes);
- Weight (without shoes preferred);
- BASMI (linear function) by qualified blinded assessor: Lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance and cervical rotation;
- Spinal mobility obtained by qualified blinded assessor: chest expansion;
- Assessment of swollen joints (44-joint count) by qualified blinded assessor;
- Assessment of enthesitis using the MASES Index by qualified blinded assessor;
- Complete drug accountability.

After dosing:

- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions;
- Contraception check: Confirm and document that proper contraception is being used;
- Contact IWRS and dispense new supply of investigational product to subject;
- Instruct subject not to take the in-clinic dose of investigational product the day of the next study visit but to bring the drug supply with them to the visit.

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6.2.8. Week 32

There is a ± 7 day window for this 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 hours prior to or following this visit as necessary to ensure the samples are collected in a fasting state. If the blood collection is completed in advance of the clinic visit, the PROs should not be done with the blood collection but at the clinic visit.

- All PROs should be completed prior to any other study procedures. These include the following: ASAS/ASDAS_{CRP} Component: “Patient Global Assessment of Disease (NRS)”, “Patient Assessment of Spinal Pain” which includes Total Back Pain (NRS) and Nocturnal Spinal Pain (NRS), BASDAI (NRS), BASFI (NRS), and FACIT-F.

After the PROs are obtained, the following procedures should be completed prior to dosing:

- Verify morning dose of investigational product was not administered by subject. If the dose was administered, continue with visit but re-instruct subject on the requirement for in-clinic dosing;

Note: For subjects where the visit is conducted in the afternoon or evening, verify the afternoon or evening dose of investigational product was not administered by the subject.

- Vital signs: Blood pressure (seated), pulse rate and temperature (via tympanic, oral or temporal, preferred);
- Laboratory testing: Central laboratory tests include: Hematology, Urinalysis, Chemistry Panel, Lipid Profile (fasting), Urine Pregnancy Test (for women of childbearing potential only), hsCRP;
- Blood sample for FACS Analysis;
- Administer investigational product to the subject from the previously dispensed study drug supplies.

The following procedures can be done before or after dosing depending upon the clinic’s schedule but is recommended that they be done at the same time (before or after dosing) consistently across all subsequent subject clinic visits:

- Targeted physical examination (examination of heart, lungs, abdomen, lower extremities, skin (presence of rash) and lymph nodes);
- Weight (without shoes preferred);

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- Specific Medical History: History of uveitis, psoriasis, inflammatory bowel disease and peripheral articular involvement as assessed by swollen joint count;
- BASMI (linear function) obtained by qualified blinded assessor: Lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance and cervical rotation;
- Spinal mobility obtained by qualified blinded assessor: chest expansion;
- Assessment of swollen joints (44-joint count) by qualified blinded assessor;
- Assessment of enthesitis using the MASES Index by qualified blinded assessor;
- Complete drug accountability.

Procedures to be performed after dosing:

- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions;
- Contraception check: Confirm and document that proper contraception is being used;
- Risk factor check for VTE ([Section 7.1.14](#));
- Contact IWRS and dispense new supply of study medication to subject;
- Instruct subject not to take the in-clinic dose of investigational product the day of the next study visit but to bring the drug supply with them to the visit.

6.2.9. Week 40

There is a ± 7 day window for this visit.

- All PROs should be completed prior to any other study procedures. These include the following: ASAS/ASDAS_{CRP} Component: “Patient Global Assessment of Disease (NRS)”, “Patient Assessment of Spinal Pain” which includes Total Back Pain (NRS) and Nocturnal Spinal Pain (NRS), BASDAI (NRS), BASFI (NRS), and FACIT-F.

After the PROs are obtained, the following procedures should be completed prior to dosing:

- Verify morning dose of investigational product was not administered by subject. If the dose was administered, continue with visit but re-instruct subject on the requirement for in-clinic dosing;

Note: For subjects where the visit is conducted in the afternoon or evening, verify the afternoon or evening dose of investigational product was not administered by the

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subject. Vital signs: Blood pressure (seated), pulse rate and temperature (via tympanic, oral or temporal, preferred);

- Laboratory testing: Hematology, Chemistry Panel, Urinalysis, Urine Pregnancy Test (for women of childbearing potential only), hsCRP;
- Administer in-clinic dose of investigational product from previously dispensed study drug supplies.

The following procedures can be done before or after dosing depending upon the clinic's schedule but it is recommended that they be done at the same time (before or after dosing) consistently across all subsequent subject clinic visits:

- Targeted physical examination (examination of heart, lungs, abdomen, lower extremities, skin (presence of rash) and lymph nodes);
- Weight (without shoes preferred);
- BASMI (linear function) by qualified blinded assessor: Lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance and cervical rotation;
- Spinal mobility obtained by qualified blinded assessor: chest expansion;
- Assessment of swollen joints (44-joint count) by qualified blinded assessor;
- Assessment of enthesitis using the MASES Index by qualified blinded assessor;
- Complete drug accountability.

After dosing:

- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions;
- Contraception check: Confirm and document that proper contraception is being used;
- Risk factor check for VTE ([Section 7.1.14](#));
- Contact IWRS and dispense new supply of study medication to subject;
- Instruct subject not to take the in-clinic dose of investigational product the day of the next study visit but to bring the drug supply with them to the visit.

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6.2.10. Week 48

There is a ± 7 day window for this 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 hours prior to or following this visit as necessary to ensure the samples are collected in a fasting state. If the blood collection is completed in advance of the clinic visit, the PROs should not be done with the blood collection but at the clinic visit.

- All PROs should be performed before any other study procedures at the clinic visit. These include the following: ASAS/ASDASCRP Component: “Patient Global Assessment of Disease (NRS)”, “Patient Assessment of Spinal Pain” which includes Total Back Pain (NRS) and Nocturnal Spinal Pain (NRS), BASDAI (NRS), BASFI (NRS), ASQoL, SF-36v2, EQ-5D-3L and EQ-VAS, FACIT-F, WPAI and AS-HCRU Questionnaire;
- Vital signs: Blood pressure (seated), pulse rate and temperature (via tympanic, oral or temporal, preferred);
- 12-lead electrocardiogram submitted to central reader;
- Laboratory testing: Central laboratory tests include: Hematology, Urinalysis, Chemistry Panel, Lipid Profile (fasting), Urine Pregnancy Test (for women of childbearing potential only), hsCRP;
- Blood sample for FACS Analysis;
- Complete Physical Examination: 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), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes;
- Weight (without shoes preferred);
- Specific Medical History: History of uveitis, psoriasis, inflammatory bowel disease and peripheral articular involvement as assessed by swollen joint count;
- BASMI (linear function) by qualified blinded assessor: Lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance and cervical rotation;
- Spinal mobility obtained by qualified blinded assessor: chest expansion;
- Assessment of swollen joints (44-joint count) by qualified blinded assessor;

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- Assessment of enthesitis using the MASES Index by qualified blinded assessor;
- Administer in-clinic dose of investigational product from previously dispensed study drug supplies;
- Complete drug accountability;
- Contraception check: Confirm and document that proper contraception is being used;
- Risk factor check for VTE ([Section 7.1.14](#));
- Monitoring of adverse events and concomitant treatments. Record any modifications, deletions or additions.

6.3. Follow-up Visit

The Follow-up visit is required of all subjects who complete the study or are withdrawn from the investigational product after the Week 40 visit. These subjects must have a Follow-up visit within 28 days (± 7 days) of the Week 48 visit. Subjects who are withdrawn from the investigational product prior to the Week 40 visit are not required to have a follow-up visit after they complete the study at the Week 48 visit. There is a ± 7 day window for this visit.

All subjects who complete or discontinue early from the investigational product after Week 40 must have a Follow-up visit within 28 days (± 7 days) of the Week 48 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 hours prior to or following this visit as necessary to ensure the samples are collected in a fasting state.

The following procedures will be performed:

- Targeted physical examination (examination of heart, lungs, abdomen, lower extremities, skin (presence of rash) and lymph nodes);
- Weight (without shoes preferred);
- Specific Medical History: History of uveitis, psoriasis, inflammatory bowel disease and peripheral articular involvement as assessed by swollen joint count;
- Vital Signs and temperature: Blood pressure (seated), pulse rate and temperature (via tympanic, oral or temporal, preferred);
- Laboratory testing: Central laboratory tests include: Hematology, Urinalysis, Chemistry Panel, Lipid Profile (fasting), Urine Pregnancy Test (for women of childbearing potential only), hsCRP;
- Adverse event reporting and concomitant treatment use;

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- Risk factor check for VTE ([Section 7.1.14](#));
- Contraception check: Confirm and document that proper contraception is being used.

If abnormalities in hematology or chemistry results or adverse events with a causal relationship to the study medication are still observed/ongoing at the follow-up visit, the subject must continue to be followed until the laboratory abnormality or adverse event stabilizes or returns to baseline levels as approved by the Sponsor.

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6.4. Subjects Discontinuation from the Investigational Product

Subjects may discontinue from the investigational product at any time at their own request, or they may be withdrawn from the investigational product at any time at the discretion of the investigator or sponsor for safety (see also the [Monitoring Criteria/Discontinuation Criteria \(from the Investigational Product\)](#)) or the [Withdrawal due to Adverse Events](#)) 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. Subjects who discontinue the investigational product early should continue to be followed for all regularly scheduled visits for safety and efficacy assessments. Those subjects that discontinue from the investigational product prior to Week 40 visit will not be required to have a follow-up visit.

Per Amendment 3, for subjects with suspected VTE, treatment with tofacitinib should be temporarily withheld while the subject is evaluated. If VTE is confirmed, discontinue treatment with tofacitinib [see Section 6.4.2, Discontinuation Criteria (from the Investigational Product)].

Lost to Follow-up:

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. 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 (conducted in accordance with local rules and regulations) have been unsuccessful. All methods of attempted contact with the subject must be clearly documented in the subject’s source documents and the eCRF. All potential LTFU subjects must be discussed with the study team or designee prior to assigning LTFU status.

In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, requests the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

Withdrawal of Consent:

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

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

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6.4.1. Monitoring Criteria

The following laboratory abnormalities require prompt retesting, ideally within 3- 5 days:

- Any single hemoglobin value that drops >2 g/dL (or 20 g/L) below baseline, if indicated after review by the Pfizer Medical Monitor 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 $>50\%$ over the average of screening and baseline values OR an absolute increase in serum creatinine >0.5 mg/dL (or 44 $\mu\text{mol/l}$) over the average of screening and baseline values, if indicated after review by the Pfizer Medical Monitor or investigator. Factors that will be considered include stability of the 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 8.3.2](#) Potential Cases of Drug-Induced Liver Injury.

6.4.2. Discontinuation Criteria (from the Investigational Product)

The investigational product will be discontinued in the event of any of the following:

- 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;
- Two sequential absolute neutrophil counts $<1.0 \times 10^9/L$ ($<1000/mm^3$);
- Two sequential absolute lymphocyte counts <500 lymphocytes/ mm^3 ;
- Two sequential hemoglobin values <8.0 g/dL (80 g/L) or decreases of $>30\%$ from baseline value;

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- Two sequential platelet counts $<75 \times 10^9/L$ ($<75,000/mm^3$);
- 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;¹
- 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);¹
- Two sequential AST or ALT elevations >5 times the upper limit of normal, regardless of total bilirubin or accompanying signs or symptoms;¹
- Two sequential increases in serum creatinine $>50\%$ AND an absolute increase in serum creatinine >0.5 mg/dL (44 μ mol/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;
- Requirement of rescue medication for more than 10 consecutive days;
- Subjects interrupting investigational product for more than 5 consecutive days during the double-blind portion or 28 consecutive days during the open-label treatment period or subjects who are less than 80% compliant with the dosage regimen for any two consecutive visit periods;
- 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 study team before discontinuation of the subject from the investigational product;
- If VTE is confirmed, discontinue treatment with tofacitinib.

1. 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.

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7. ASSESSMENTS

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

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Safety Assessments

Clinical Laboratory Samples

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 or for required monitoring. Any laboratory test that is not analyzable should be repeated as soon as possible, but no later than the next visit. If a subject completes the entire study without any retesting required, approximately 150 mL of blood will be taken.

Laboratory Testing Profile	Tests Included
Laboratory Tests Required at Screening Only	QuantiFERON®-TB Gold In-Tube, HIV-1/HIV-2 antibody screen, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) *HBsAb only required for reflex testing in cases of HBsAg- and HBcAb+, hepatitis C virus antibody (HCV Ab), HCV RNA reflex testing for HCV Ab+, Prothrombin time (PT/INR), ^a FSH (If applicable, 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)], platelet count.
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.

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Laboratory Testing Profile	Tests Included
Urinalysis	Specific gravity, pH, protein, glucose, ketones, blood, leukocyte esterase. Microscopy and/or culture to be performed if clinically indicated or if urinalysis results positive (blood, protein or leukocyte esterase/WBC). Urine HCG pregnancy testing for women of childbearing potential; may be repeated more frequently than indicated if required by local regulation/practices, if a menstrual cycle is missed, or if potential pregnancy is suspected.
Samples at Baseline Only	HLA-B27.
Acute Phase Reactants	High sensitivity C-reactive protein (hsCRP, tested centrally and results blinded except at Screening visit).
FACS Analysis of Lymphocyte Markers	CD3+(%, abs), CD3+CD4+ (%), abs), CD3+CD8+ (%), abs), CD19+ (%), abs), CD56+/CD16+ (%), abs).

a. All subjects will be screened for normal prothrombin time (PT/INR). PT should also be evaluated to rule out acute hepatic injury in cases of hepatic enzyme elevations (see [Section 8.3.2](#)).

7.1.1. Hepatitis B and C Virus Testing

Subjects will be excluded with a known hepatitis B infection. All subjects will be tested for HBsAg and HBcAb at the Screening visit. Any subject who is HBsAg+ is 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 be excluded with a known hepatitis C infection. At the Screening visit all subjects will be tested for HCV Ab. Subjects that are HCV Ab+ must undergo further testing for HCV RNA by the central laboratory to be considered for enrollment. HCV RNA must be negative per the central laboratory to allow entry into the study.

7.1.2. Pregnancy Testing

A woman of childbearing potential must have a negative highly sensitive pregnancy test (urine, serum) as required by local regulations within 24 hours before the first dose of investigational product. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Pregnancy tests will also be repeated at all visits and at the end of the study to confirm that the subject has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed; during the active treatment period and when potential pregnancy is otherwise suspected, and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and all the necessary follow up will be conducted.

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7.1.3. Cardiovascular (CV) Risk Factor Assessment

CV risk factor assessment will be obtained at the Screening Visit. The assessment includes:

- Smoking status;
- Average weekly alcohol consumption: units/week, where a unit contains 14 g of pure alcohol, an amount equivalent to that contained in 5 oz (a glass) of wine at 12% alcohol, 8-9 oz of malt liquor at 7% alcohol, 12 oz of beer at 5 % alcohol, or 1.5 oz of drinks containing 40% alcohol;
- Family history of premature coronary heart disease (CHD): CHD in a male first degree relative <55 years of age, CHD in a female first degree relative <65 years of age.

7.1.4. Complete Physical Examination

A standard complete physical examination will be performed at Screening, Baseline/Day 1, Week 16, and Week 48. The following parameters and body systems will be examined and any abnormalities described: 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), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes. Any clinically significant change(s) from Baseline/Day 1 should be recorded as an adverse event(s).

7.1.4.1. Targeted Physical Examination

At all other visits, an abbreviated physical examination will be performed assessing the following: lungs, heart, abdomen, lower extremities (for peripheral edema), skin (presence of rash) and lymph nodes. Any clinically significant change(s) from Baseline (Day 1) should be recorded as an adverse event(s).

7.1.5. Weight, Height and Waist Circumference

Weight will be measured at each study visit. It is preferred that weight be measured in kilograms (kg) with shoes removed. Weight should be measured to the nearest 0.1 kg.

Height will be measured at the Screening visit. It is preferred that height be measured in centimeters (cm) with shoes removed.

Waist circumference will be measured at the Baseline visit. Waist measurement 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. Waist measurement should be measured to the nearest 0.1 cm.

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7.1.6. Vital Signs

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 rate measurements coincides with a blood collection or other study procedures, BP and pulse rate should be obtained first.

7.1.7. 12-Lead Electrocardiogram (ECG)

Twelve-lead electrocardiograms (ECGs) will be obtained on all subjects at the Screening, Week 16, Week 48 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 reader for measurement. Any clinically significant changes from the Screening ECG will be recorded as adverse events and evaluated further, as clinically warranted.

7.1.8. TB Testing

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

7.1.9. 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.⁴⁹ Detection of interferon- γ by Enzyme-Linked Immunosorbent Assay is used to

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identify in vitro responses to these peptide antigens that are associated with *Mycobacterium tuberculosis* infection. QuantiFERON®-TB Gold In-Tube is an indirect test for *M. tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

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

In addition, annual screening for latent and/or active TB will be conducted using QFT for those subjects in the 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 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.

7.1.10. Chest Radiograph

A chest radiograph will be obtained at the Screening visit in all subjects unless it has been previously 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.

7.1.11. Radiograph of Sacroiliac (SI) Joints

A radiograph of the SI joints is required to meet inclusion criteria of documented AS and must meet the Modified New York criteria 1984⁵¹ for ankylosing spondylitis ([Appendix 2](#)) for a subject to be enrolled in the study. Regardless of whether the radiograph is newly obtained or historical, it must be submitted to the central reader for evaluation of suitability of quality and confirmation of diagnosis at the screening visit. Subjects should not be scheduled for Baseline visit until confirmation is received from the central reader.

7.1.12. Historical Radiograph

Previous radiographs (up to 2 years old) of the sacroiliac (SI) joints (ideally AP view of the pelvis) documenting the diagnosis of AS will be acceptable and should be used in lieu of performing screening radiographs if they can be obtained and sent to the central reader for confirmation. The original films, or a copy, must be on site and a copy should be sent to the central reader. If the radiograph is a digital image, a copy can be sent to the central reader. If the results are considered unevaluable by the central reader, the x-ray must be repeated.

7.1.13. New Radiograph at Screening

If a historical radiograph cannot be obtained or interpreted by the central reader, x-ray of the anterior-posterior (AP) pelvis view at the screening visit must be obtained to visualize the SI joints. This should be done after all screening activities have been completed and if subject does not fail to meet other study criteria.

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7.1.14. Risk Factor Check for Venous Thromboembolism

All subjects will undergo a risk factor check at each applicable study visit to check for newly developed risk factors for VTE⁵⁰. This information is to be captured in the subject's source file.

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

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

Additional risk factors for VTE, such as age, diabetes, obesity (BMI \geq 30 kg/m²), smoking status, hypertension, and first degree family history of VTE should also be taken into consideration by the investigator and the sponsor medical monitor when evaluating the benefit:risk for each individual subject whether to discontinue from open-label 5 mg BID dose of tofacitinib.

If a subject has 1 or more of the risk factors for VTE listed above and is receiving tofacitinib 5 mg BID, they may remain on tofacitinib 5 mg BID after careful investigator assessment of benefit: risk. For subjects who do not have any of the risk factors for VTE listed above, he/she will remain on their open-label tofacitinib dose of 5 mg BID.

7.2. Efficacy Assessments

7.2.1. ASAS Improvement Criteria

The Assessment of SpondyloArthritis International Society (ASAS) has developed improvement criteria for clinical trials in AS which include the ASAS20, ASAS40, ASAS 5/6 assessments⁵² and partial remission.⁵³ These composite scores are derived from several of the "Patient Reported Outcome" measures or disease activity assessments. The composite score will be calculated by the sponsor. In order for this calculation to be completed, the investigator is responsible to ensure completeness of the PROs and appropriately conduct the assessments that comprise this endpoint.

ASAS20 and ASAS40 assess 4 domains: the "Patient Global Assessment of Disease", Spinal Pain (total back pain), Function (BASFI) and Inflammation (from the BASDAI). ASAS20 improvement is defined as \geq 20% and \geq 1 unit in at least 3 domains on a scale of 0-10 and no worsening of \geq 20% and \geq 1 unit in the remaining domain. ASAS40 improvement criteria are

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classified as $\geq 40\%$ and ≥ 2 units in at least 3 domains on a scale of 0-10 and no worsening at all in the remaining domain.

ASAS 5/6 assesses 6 domains: the domains as noted in the ASAS20 and 40, CRP and Spinal mobility, specifically lateral spinal flexion (from the BASMI). Improvement is defined as $\geq 20\%$ in at least 5 domains.

ASAS partial remission is based on the same 4 ASAS domains noted above. Partial remission is defined as a response if a score of 2 or less (on a scale of 0-10) for each of the 4 domains.

7.2.2. Ankylosing Spondylitis Disease Activity Score (ASDAS_{CRP})

The ASDAS_{CRP} endpoint is derived from several patient reported outcomes and CRP which will be calculated by the sponsor. In order for this calculation to be completed, the investigator is responsible to ensure completeness of the PROs and appropriately conduct the assessments that comprise this endpoint. Following is the formula used for calculating the ASDAS_{CRP}.⁵³

$$\text{ASDAS}_{\text{CRP}} = 0.121 \times \text{Back Pain} + 0.058 \times \text{Duration of Morning Stiffness} + 0.110 \times \text{Patient Global} + 0.073 \times \text{Peripheral Pain/Swelling} + 0.579 \times \text{Ln}(\text{CRP mg/L} + 1).^{52}$$

Question 2 of the BASDAI provides the data for Back Pain, Question 6 of the BASDAI provides the data for Duration of Morning Stiffness, the score from the Patient Global Assessment of Disease is utilized for the Patient Global and Question 3 of the BASDAI contributes the data for Peripheral Pain/Swelling.

The ASDAS clinically important improvement, major improvement and inactive disease will be calculated from the ASDAS data.⁵³

7.2.3. High Sensitivity C-Reactive Protein (hsCRP)

Blood samples will be collected at each visit for analysis of hsCRP using an assay analyzed by the central laboratory. The investigator, study site personnel and Sponsor study team will be kept blinded to the results of this test at all visits except the Screening visit.

7.2.4. Specific Medical History and Peripheral Articular Involvement

Subjects will be assessed at Screening, Baseline/Day 1, Week 8, Week 16, Week 32, Week 48, and at Follow-up to determine if they have experienced an adverse event of IBD, psoriasis or uveitis as well as any complaints suggestive of peripheral articular involvement (as assessed by swollen joint count) since the last visit.

7.2.5. Bath Ankylosing Spondylitis Metrology Index (BASMI)

The Bath Ankylosing Spondylitis Metrology Index (BASMI)⁵⁴ is used to assess the axial status and mobility (cervical, dorsal and lumbar spine, hips and pelvic soft tissue). Five clinical measures comprise this scale and in this clinical study the linear function method⁵⁵ will be used; these measures will be obtained by the qualified blinded assessor. It is

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recommended that the same qualified personnel be used for each visit. The combined index score will be calculated by the sponsor using the individual scores from the following measures: lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance, and cervical rotation.

Constricting clothing should be removed to ensure the subject can adequately move for the examinations and visualization of anatomical positions where necessary.

7.2.5.1. Lateral Spinal Flexion

The subject should stand upright and the subject's head and back should rest against the wall as close as possible with shoulders level and feet 30 cm apart and feet parallel. There should be no flexion in the knees, no bending forward. Subject's hands should be resting on his/her lateral thighs. At the tip of the middle finger, place a mark on the thigh. This is the neutral position mark. Measure and record the neutral position. Have the subject bend sideways without bending knees or lifting heels while attempting to keep the shoulders in the same position (flexion position). Place a second mark and record the lateral flexion (left or right as appropriate) using a centimeter tape measure. Measure and record two tries for the left and two tries for the right. The results of the two tries are recorded for left and right separately in cm to the nearest 0.1 cm. The difference between the neutral position and the lateral flexion for each side will be calculated by the sponsor and the better of two tries will be used in the analysis of the data.

Alternatively, measure the distance between the subject's middle fingertip and the floor before (this is the neutral position) and after bending sideways. Record the neutral position in cm to the nearest 0.1 cm. Measure and record two tries for the left and two tries for the right. The results of the two tries are recorded for the left and right separately in cm to the nearest 0.1 cm. The difference between the neutral position and the lateral flexion for each site will be calculated by the sponsor and the better of two tries will be used in the analysis. If this technique is used, it must be consistently used for the entire time this subject is participating. If marks are placed on the subject, ensure marks are not visible at the next clinic visit.

7.2.5.2. Tragus-to-Wall Distance

Place the subject standing with his/her back against the wall; knees straight; scapulae, buttocks, and heels against wall; and head in as neutral position as possible. Measure the distance between the tragus and wall in cm (to the nearest 0.1 cm) from both the right side and left side at the maximum effort to touch the head against the wall. Measure two tries on the right side and two tries on the left side. Record both tries on the appropriate eCRF.

7.2.5.3. Lumbar Flexion (Modified Schober)

With the subject standing erect and outer edges of feet 30 cm apart, place a mark in the midpoint of a line that joins the posterior superior iliac spines (baseline mark). Place a second mark (A) 10 cm above the baseline mark and a third mark (B) 5 cm below the baseline mark. Then have the subject maximally bend forward, keeping the knees fully extended. With the subject's spine in full flexion, re-measure the distance between marks

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A and B (in cm to the nearest 0.1 cm). This measurement should include the original 15 cm. Measure two tries. Record both tries on the appropriate eCRF.

7.2.5.4. Maximal Intermalleolar Distance

The subject should lie supine with the knees straight and feet/toes pointing straight up. The subject is asked to separate the legs as far as possible and the distance between the medial malleoli is measured (in cm to the nearest 0.1 cm). Measure and record two tries on the appropriate eCRF.

7.2.5.5. Cervical Rotation

Subject should be sitting straight on a chair with chin level and hands on their knees. The qualified blinded assessor places a goniometer at the top of the head in line with the nose. The qualified blinded assessor asks the subject to rotate the neck maximally to the left, follows with the goniometer and records the angle between the sagittal plane and the new plane after rotation. Ensure the subject keeps shoulders still and no neck or shoulder flexion occurs. A second reading is obtained and the both of the readings are recorded. The procedure is repeated for the right side and the both of the readings are recorded for the right side. The better of the two for each side is selected for scoring. Scoring is done by calculating the mean of the left and right measurement and is recorded in degrees (0-90°).

7.2.6. Spinal Mobility: Chest Expansion

This assessment is performed by the qualified blinded assessor. It is recommended that the same qualified personnel be used for each visit. Spinal Mobility includes the measures collected in the BASMI and Chest Expansion. For collecting chest expansion the subject should have their hands rest on or behind the head. With the subject standing and at maximal inspiration, measure the chest circumference at nipple line or at the 4th intercostal space (in cm to the nearest 0.1 cm) anteriorly. Re-measure the chest circumference at maximal expiration. The difference between maximal inspiration and expiration of the two attempts will be obtained and recorded. The better of the two attempts will be utilized for data reporting.

7.2.7. Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)

Enthesitis will be evaluated by the qualified blinded assessor using the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).⁵⁶ It is recommended that the same qualified personnel be used for each visit. Thirteen sites (right and left) will be assessed for tenderness: costochondral 1 (right and left), costochondral 7 (right and left), spina iliaca anterior superior (right and left), crista iliaca (right and left), spina iliaca posterior (right and left), processus spinosus at L5 and Achilles tendon proximal insertion (right and left).

Scoring at each site will be 0 for no tenderness or 1 for tenderness.

7.2.8. Swollen Joint Count (44)

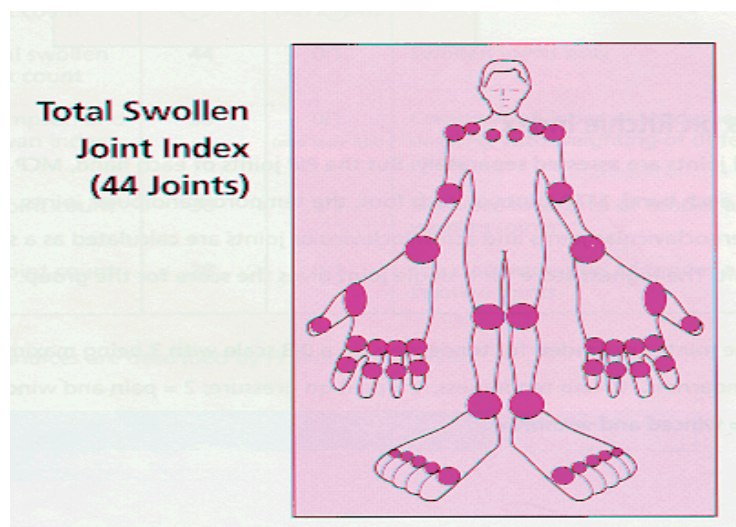
The qualified blinded assessor will also assess joints for swelling using the following scale: Present/Absent/Not Done/Not Applicable (to be used for artificial or missing joints) for

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determination of the total number of swollen joints. It is recommended that the same qualified personnel be used for each visit. Forty-four (44) joints will be assessed for swelling as noted in Figure 2¹¹ below and will include the following: sternoclaviculars, acromioclaviculars, shoulders, elbows, wrists, metacarpophalangeals (MCP I, II, III, IV, V), thumb interphalangeal (IP), proximal interphalangeals (PIP II, III, IV, V), knees, ankles, and metatarsophalangeals (MTP I, II, III, IV, V). Artificial joints will not be assessed.

Figure 2. 44 Swollen Joint Count Mannequin



7.2.9. Patient Reported Outcomes

7.2.9.1. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI is a validated questionnaire that consists of 6 questions pertaining to the 5 major symptoms of AS: fatigue; spinal pain; peripheral arthritis; enthesitis, intensity of morning stiffness and duration of morning stiffness.⁵⁷ Each question will be rated using a numerical rating scale from 0 (none) to 10 (very severe). The BASDAI score is calculated by computing the mean of questions 5 and 6 and adding it to the sum of questions (Q)1-4.

This score is then divided by 5. See following equation:

$$\text{BASDAI} = ((Q1 + Q2 + Q3 + Q4) + ((Q5 + Q6) / 2)) / 5$$

Q=Question

The total score and the response to Question 2 will be used for entry into the study. See Inclusion Criteria, [Section 4.1](#).

7.2.9.2. Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those with AS.⁵⁸ The ten questions were chosen with a major input from patients with AS.

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The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the subjects' ability to cope with everyday life. A 0-10 numerical rating scale is used to answer the questions with 0 being "Easy" and 10 being "Impossible." The score will be derived from the mean of the 10 items by the sponsor and is indicative of the subject's level of ability.

7.2.9.3. Patient Global Assessment of Disease

Subjects will assess their overall disease activity over the last week using a numerical rating scale between 0 (Not Active) and 10 (Very Active) to the question, "How active was your spondylitis on average during the last week?" Results of this assessment will be used to calculate the ASAS improvement criteria.

7.2.9.4. Patient Assessment of Spinal Pain

Two NRS scales will be used to assess the subject's spinal pain: level of nocturnal pain and total back pain on average during the last week. For each of these scales, subjects will mark their level of pain on a 0-10 NRS anchored by 0 for "No Pain" to 10 "Most Severe Pain." Results of total back pain will be used to calculate the ASAS improvement criteria.

7.2.9.5. Ankylosing Spondylitis Quality of Life

The Ankylosing Spondylitis Quality of Life (ASQoL) is an 18-item questionnaire assessing the amount of restriction the subject is experiencing in daily activities, level of pain and fatigue, and the impact on the subject's emotional state.⁵⁹ Each item is scored as 0 (no impact) or 1 (yes - impact). A total score is calculated by summing the items. The total score ranges from 0 to 18, with higher values indicating more impaired health-related quality of life.

7.2.9.6. SF-36v2 Health Survey)

The SF-36 v.2 (Acute) is a 36-item generic health status measure. It measures 8 general health domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health.⁶⁰ These domains can also be summarized as physical and mental component summary scores. This questionnaire should be completed by the subject prior to any procedures being performed at the visit. The form should be checked for completeness by the site staff.

7.2.9.7. EuroQol 5 Dimensions 3 Levels (EQ-5D-3L) Health State Profile

The EuroQol 3 Levels EQ-5D-3L Health State Profile (3 levels) is a subject completed instrument designed to assess impact on health related quality of life in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.⁶¹ 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 3 Levels EQ-5D-3L has been established in a number of disease states, including rheumatoid arthritis. In addition, "Your own health state today" (EQ-VAS) records the subject's self-rated health, a score ranging from 0 to 100 mm will be recorded, with higher scores representing better health state today.

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This questionnaire should be completed by the subject prior to any procedures being performed at the visit. The form should then be checked by site staff for completeness.

7.2.9.8. Functional Assessment of Chronic Illness Therapy – Fatigue Scale

The FACIT – Fatigue Scale is a subject completed questionnaire consisting of 13 items that assess fatigue.⁶² Instrument scoring yields a range from 0 to 52 for the total score, with higher scores representing better subject status (less fatigue). The FACIT - Fatigue Scale will also be summarized as FACIT-Fatigue experience domain score and FACIT-Fatigue impact domain score. This questionnaire should be completed by the subject prior to any procedures being performed at the visit. The form should then be checked by site staff for completeness.

7.2.9.9. Work Productivity & Activity Impairment Questionnaire: Spondyloarthritis

The Work Productivity & Activity Impairment Questionnaire (WPAI): Spondyloarthritis is a 6-item questionnaire that is specific for spondyloarthritis which yields four types of scores: absenteeism, presenteeism (impairment at work/reduced job effectiveness), work productivity loss and activity impairment.⁶³ WPAI outcomes are expressed as impairment percentages with higher numbers indicating greater impairment and less productivity. This questionnaire should be completed by the subject prior to any procedures being performed at the visit, if possible. The form should be checked for completeness by the site staff.

7.2.9.10. Ankylosing Spondylitis Healthcare Resource Utilization Questionnaire

The AS Healthcare Resource Utilization Questionnaire (AS-HCRU) is a seventeen item scale 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. This questionnaire should be completed by the subject prior to any procedures being performed at the visit, if possible. The form should be checked for completeness by the site staff.

7.3. Imaging Assessments (Chest and SI joint radiographs)

Management of incidental findings

An incidental finding is one unknown to the subject that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study, but is unrelated to the purpose and beyond the aims of the study.

Radiograph images will be reviewed by a central review facility. The purpose of this review is to evaluate images for TB screening or diagnosis of AS. Central image review is not a complete medical review of the subject and no incidental findings will be shared with the principal investigator, site staff, or the subject. All safety reviews will be the sole responsibility of site staff.

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7.4. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate subjects in this study. It is a strong preference that the same rater perform all assessments for a subject throughout the study. However, if a situation arises where this is not feasible and a back-up rater must conduct the assessments this will not be considered a protocol deviation. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the study Rater Experience Questionnaire for Blinded Assessors provided to each participating site. The level of experience with the target population (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. Proposed raters who do not meet specific criteria but who may be qualified based on unique circumstances may be individually reviewed by the study clinical team to determine whether or not they are qualified to perform the assessments. Documentation that the rater is certified to perform selected study assessments before he or she can participate in the conduct of the study is required. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

The following procedures require a health care professional who is competent to perform the assessments: swollen joint count; Bath Ankylosing Spondylitis Metrology Index (BASMI); Maastricht Ankylosing Spondylitis Enthesitis Score (MASES); spinal mobility.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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8. ADVERSE EVENT REPORTING

8.1. Requirements

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

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

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

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

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the [Serious Adverse Events](#) section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to

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the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

8.1.3. Withdrawal due to Adverse Events (see also the [Subjects Discontinuation from the Investigational Product](#) section)

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

When a subject withdraws from the investigational product because of an SAE, the SAE must be recorded on the eCRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the [Requirements](#) section above.

Subjects that are withdrawn due to an AE will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. In this case, no further evaluation 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.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each subject begins from the time the subject provides informed consent, which is obtained before the subject’s participation in the study (ie, before undergoing any

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study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

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

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

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

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

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

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

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8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

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

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8.2.2. Abnormal Test Findings

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

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

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

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

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

Or that is considered to be:

- An important medical event.

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

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

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8.2.4. Infections

Some infections may be classified as serious infections, as defined below.

8.2.5. Serious Infections

A serious infection is any infection (viral, bacterial, and fungal) that requires hospitalization for treatment or requires parenteral antimicrobial therapy or meets other criteria that require it to be classified as a serious adverse event. A subject who experiences a serious infection should be discontinued from the investigational product and the serious adverse event should be listed as the reason for discontinuation in the CRF. Appropriate laboratory investigations, including but not limited to cultures should be performed to establish the etiology of any serious infection. All adverse events, including serious adverse events, should be reported as described in [Section 8](#) on Adverse Event Reporting.

8.2.6. Hospitalization

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

Hospitalization does not include the following:

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

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);

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- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

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

Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

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

8.3. Special Situations

8.3.1. Protocol-Specified Serious Adverse Events

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

8.3.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt

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are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are “susceptible” to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (\times ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations ($>2 \times$ ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above $3 \times$ ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values $>3 \times$ ULN AND a TBili value $>2 \times$ ULN with no evidence of hemolysis and an alkaline phosphatase value $<2 \times$ ULN or not available;
- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
 - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND $>3 \times$ ULN; or $>8 \times$ ULN (whichever is smaller).
 - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least $1 \times$ ULN **or** if the value reaches $>3 \times$ ULN (whichever is smaller).

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

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

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

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

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

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

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

8.3.3.1. Exposure During Pregnancy

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

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

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

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

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

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

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

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

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

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subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.3.2. Exposure During Breastfeeding

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

8.3.3.3. Occupational Exposure

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

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

8.3.4. Medication Errors

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

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

8.3.4.1. Medication Errors

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

Medication errors include:

- Medication errors involving subject exposure to the investigational product;

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- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

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

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

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

Methodology for summary and statistical analyses of the data collected in this trial are given here and further detailed in a statistical analysis plan (SAP), which will be dated and maintained by Pfizer.

This analysis plan may modify what is outlined in the protocol; however, any major modifications of the primary endpoint definition or its analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The primary efficacy analysis is to compare the ASAS20 response rate at Week 16 of the tofacitinib 5 mg BID and placebo via the normal approximation for the difference in binomial proportions. Assuming a placebo response rate of 40% for ASAS20 response at Week 16, a sample size of 120 per arm will yield about 89% power to detect a difference of at least 20% between tofacitinib 5 mg BID and placebo at a two-sided significance level of 5%. In the Phase 2 proof of concept trial A3921119, ASAS20 response rates at Week 12 were 63% and 40% for tofacitinib 5 mg BID and placebo, respectively.

9.2. Efficacy Analysis

There will be a total of 2 planned analyses conducted when all applicable subjects have completed their Week 16 and Week 48 (including follow-up) visits, respectively. The investigators, subjects and sponsor study team will remain blinded to the first 16 weeks of treatment assignment through the entire duration of the trial until database release at Week 48. The first analysis (Week 16 analysis) will include all efficacy data through Week 16 and the safety data through the data cutoff date. As the primary endpoint (ASAS20), the key secondary endpoint (ASAS40) and the other Type I error controlled secondary endpoints are at Week 16, there will be no additional adjustment made for Type I error rate at the final analysis at Week 48. The efficacy analysis results through Week 16 obtained from the Week 16 analysis will be considered final and definitive. CCI

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The Week 48 analysis will be conducted when all the applicable subjects have completed their Week 48 (including follow-up) visit and the database is released. All the Week 48 analysis results will be secondary in nature. The Week 48 analysis will contain results for earlier visits prior to or at Week 16 including those for the primary endpoint and the key secondary endpoint; however they will serve as a sensitivity analysis only to ensure there are no major changes to the definitive results for the primary endpoint and the key secondary endpoint obtained at the Week 16 analysis.

9.2.1. Analysis of Primary Endpoint

The ASAS20 response rate at Week 16 is the primary efficacy endpoint in this trial. The analysis of primary endpoint will be based on the full analysis set, which includes all randomized subjects who take at least 1 dose of investigational product. For the primary analysis, the normal approximation for the difference in binomial proportions adjusting for the stratification factor (ie, prior treatment history: bDMARD-naïve vs TNFi-IR) at randomization via the Cochran–Mantel–Haenszel approach will be used to estimate the treatment effect (treatment difference, standard error, 95% confidence interval) and to test (Normal Z-test) test the superiority of tofacitinib 5 mg BID to placebo and to generate confidence interval for the difference. Missing values for any reason will be handled by setting the ASAS20 value to nonresponsive. Note that this can be viewed as a composite endpoint in the sense that a response requires the subject completes a visit of interest eg, Week 16, and achieves a response per the defined ASAS20 response criteria (otherwise it is considered a nonresponse).

Sensitivity analyses will be performed to assess robustness of the primary analysis due to missing data and will be detailed in the SAP.

9.2.2. Analysis of Secondary and Other Endpoints

Methods for the analysis of secondary endpoints and other endpoints will be enumerated in the SAP. Briefly, binary variables will follow the analyses using the normal approximation to estimating binomial proportions as described for the ASAS20 and continuous endpoints will be analyzed as change from baseline as appropriate with a mixed model for repeated measures (MMRM) that include fixed effects of treatment group, visit, and treatment-group by visit interaction, stratification factor (ie, prior treatment history: bDMARD-naïve vs TNFi-IR) at randomization, and baseline value. An unstructured variance covariance matrix will be used, provided the model converges, otherwise an alternative covariance structure will be attempted. Descriptive statistics may also be calculated and displayed.

9.2.3. Control for Type I Error Rate

This protocol is designed to establish the superiority of tofacitinib 5 mg BID to placebo for the treatment of active AS based on the primary endpoint of ASAS20 at Week 16 in subjects who have had an inadequate response to previous treatments.

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All statistical tests will be conducted at the 2-sided 5% (or equivalently 1-sided 2.5%) significance level for comparing tofacitinib 5 mg BID to placebo. Type I error will be controlled at 2-sided 5% or equivalently 1-sided 2.5%.

For the primary endpoint of ASAS20 at Week 16, if the 2-sided p value is $\leq 5\%$, the superiority of tofacitinib 5 mg BID to placebo will be declared for this primary endpoint and the primary objective of this study is met. Hypothesis testing will continue to the global family of select set of secondary endpoints stated below (*Global Type I Error Control (for the primary endpoint and a select set of secondary endpoints)*). For each of the endpoints within this family, superiority of tofacitinib 5 mg BID to placebo will be declared if statistical significance is achieved under the step-down testing procedure. In addition, three other families of hypotheses, ASAS family endpoints (*Type I Error Control for Endpoints in the ASAS Family*), ASAS20's earlier time points (*Type I Error Control for ASAS20 at Earlier Time Points*) and ASAS40's earlier time points (*Type I Error Control for ASAS40 at Earlier Time Points*) will also be tested. For each of the endpoints or time points of ASAS20/ASAS40, superiority of tofacitinib 5 mg BID to placebo will be declared if statistical significance is achieved under its respective step-down testing procedure.

Global Type I Error Control (for the primary endpoint and a select set of secondary endpoints): The family-wise Type I error rate will be controlled at the 2-sided 5% (or equivalently 1-sided 2.5%) significance level using a step-down testing procedure for the primary endpoint of ASAS20, the key secondary endpoint of ASAS40 and a select set of secondary endpoints at Week 16 tested in the sequence below: ASAS20, ASAS40, change from baseline in ASDAS_{CRP}, change from baseline in hsCRP, change from baseline in ASQoL, change from baseline in SF-36v2 Physical Component Summary (PCS), change from baseline in BASMI, and change from baseline in the FACIT-F Total score. When an endpoint fails to declare statistical significance, this endpoint and the remaining endpoints lower in the hierarchy will be considered non-significant. The rationale for the selection and ordering of the select set of secondary endpoints are clinical importance, precedence and likelihood of statistical success based on the results of the A3921119 study.

Type I Error Control for Endpoints in the ASAS Family: Δ in Patient Global Assessment (PGA) of disease, change from baseline in total back pain, Δ BASFI, and change from baseline in inflammation (average of questions 5 and 6 of BASDAI) are the 4 ASAS components used in deriving ASAS20, thus they are considered belonging to the ASAS family of endpoints. A step-down testing procedure will be applied to them and tested in the sequence below: ASAS20, change from baseline in PGA, change from baseline in total back pain, change from baseline in BASFI, and change from baseline in inflammation (average of questions 5 and 6 of BASDAI) at Week 16. When an endpoint fails to declare statistical significance, this endpoint and the remaining endpoints lower in the hierarchy will be considered non-significant. Though this testing scheme does not protect the Type I error for the family of all possible comparisons, it will provide Type I error protection for testing the family of ASAS endpoints.

Type I Error Control for ASAS20 at Earlier Time Points: In order to be more rigorous about establishing the onset of efficacy as measured by ASAS20 at the earliest time point at which

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there is statistical separation between tofacitinib 5 mg BID and placebo, a step-down approach with the ASAS20 from Week 16 to earlier time points (order of testing: Weeks 16, 12, 8, 4, and 2) will also be used for each time point. Though this testing scheme does not protect the Type I error for the family of all possible comparisons, it will provide Type I error protection for testing the family of ASAS20 time points.

Type I Error Control for ASAS40 at Earlier Time Points: In order to be more rigorous about establishing the onset of efficacy as measured by ASAS40 at the earliest time point at which there is statistical separation between tofacitinib 5 mg BID and placebo, a step-down approach with the ASAS40 from Week 16 to earlier time points (order of testing: Weeks 16, 12, 8, 4, and 2) will also be used for each time point. Though this testing scheme does not protect the Type I error for the family of all possible comparisons, it will provide Type I error protection for testing the family of ASAS40 time points.

9.3. Safety Analysis

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

- Incidence and severity of adverse events;
- Categorical summary of absolute vital signs and vital sign changes compared to baseline by subject;
- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials, will be summarized;
- Any safety events that trigger withdrawal of a subject;
- Safety laboratory tests will be summarized according to Pfizer standards.

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

9.4. Interim Analysis

No formal interim analysis will be conducted for this study. The analysis of the primary, key secondary endpoint and the other Type I error controlled secondary endpoints conducted at Week 16 is the final analysis for these endpoints (see [Section 9.2](#)).

9.5. Data Monitoring Committee

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

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions,

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which may include summaries of aggregate analyses of safety data that 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 AS 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 trained 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 the 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 the central laboratory pathologists. In some instances, additional expert pathology review of submitted samples may be performed. Description of the scope of the 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 7](#).

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10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

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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 shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

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

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

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

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred

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to Pfizer or other authorized parties will be identified by this single, subject-specific code. 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 the Clinical Study Agreement and applicable privacy laws.

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

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

The investigator must ensure that each study subject, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject, is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all 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/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of tofacitinib at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 5 business days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

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15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

Pfizer 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, the investigator will provide Pfizer an opportunity to review any proposed

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

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

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

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

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

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

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Appendix 1. Abbreviations

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

Abbreviation	Term
AE	Adverse Event
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% improvement
ACR50	American College of Rheumatology 50% improvement
ACR70	American College of Rheumatology 70% improvement
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AS	Ankylosing Spondylitis
AP	Anterior-Posterior
ASAS	Assessment in Ankylosing Spondylitis
ASAS 20/40	Assessment in Ankylosing Spondylitis 20%/40% improvement
ASDAS _{CRP}	Ankylosing Spondylitis Disease Activity Score using CRP
AS-HCRU	AS HealthCare Resource Utilization Questionnaire
ASQoL	Ankylosing Spondylitis Quality of Life
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BCG	Bacille Calmette Guérin
bDMARD	Biological Disease-Modifying Anti-Rheumatic Drug
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CD	Crohn's Disease
CHD	Coronary heart disease
CK	Creatine Kinase
cm	centimeter
COX-2	Cyclooxygenase-2
CRF	Case Report Form
CRP	C-reactive Protein
CRO	Contract Research Organization
CSA	Clinical Study Agreement
csDMARD	Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug
CTA	Clinical Trial Application
CT SAE	Clinical Trial Serious Adverse Advent Form
CYP3A4	Cytochrome P450 enzyme 3A4

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Abbreviation	Term
CYP2C19	Cytochrome P450 enzyme 2C19
CYP450	Cytochrome P450
CV	Cardiovascular
CV EAC	Cardiovascular Endpoint Adjudication Committee
DAS	Disease Activity Score
DILI	Drug-induced liver injury
DMARD	Disease-Modifying Anti-Rheumatic Drug
DMC	Data Monitoring Committee
EBV	Epstein-Barr Virus
EBV-LPD	Epstein-Barr Virus induced lymphoproliferative disease
eCRF	Electronic case report form
ECG	Electrocardiogram
EDP	Exposure During Pregnancy
EMA	European Medicines Agency
E _{max}	Maximal effect
EIU	Exposure in Utero
EQ-5D-3L	The EuroQol 5 Dimensions 3 Level Health State Profile
EQ-VAS	Your Own Health State Today Questionnaire
ER	Exposure Response
ESRD	End stage renal disease
EC	Ethics committees
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EULAR	The European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GIPRC	Gastrointestinal Perforation Review Committee
gm	gram
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C Virus
HCVAb+	Hepatitis C Virus Antibody Positive
HDL	High Density Lipoprotein
HEENT	Head, eyes, ears, nose, throat
HERC	Hepatic Event Review Committee
HDL-c	High Density Lipoprotein cholesterol

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Abbreviation	Term
HIV	Human Immunodeficiency Virus
hsCRP	High Sensitivity C-Reactive Protein
HZ	Herpes Zoster
IB	Investigator brochure
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IND	Investigational New Drug Application
ILDRC	Interstitial Lung Disease Review Committee
IP	Interphalangeal
IRB	Institutional Review Board
IRC	Internal Review Committee
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IWR	Interactive Web-based response
IWRS	Interactive Web-based response system
JAK	Janus Kinase
JIA	Juvenile Idiopathic Arthritis
LDL	Low Density Lipoprotein
LFT	Liver function test
LPD	Lymphoproliferative Disease
LTE	Long-term Extension
LTFU	Lost to Follow-Up
MAC	Malignancy Adjudication Committee
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCP	Metacarpophalangeal
mg	Milligrams
MRI	Magnetic Resonance Imaging
MTP	Metatarsophalangeal
MTX	Methotrexate
N/A	Not Applicable
NMSC	Non-melanoma skin cancer
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OIRC	Opportunistic Infection review Committee
Oz	Ounce
PBO	Placebo
PCD	Primary Completion Date
PCS	physical component summary
PD	Pharmacodynamics

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Abbreviation	Term
PIP	Proximal Interphalangeals
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
PsO	Psoriasis
PTLD	Post-Transplant Lymphoproliferative Disorders
PT-INR	Prothrombin Time- International Normalized Rate
Q	Question
QA/QC	Quality Assurance/Quality Control
QFT-G	Quantiferon Gold
RA	Rheumatoid Arthritis
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-36v2	36-Item Short-Form Health Survey Version 2
SI	Sacroiliac
SIJ	Sacroiliac joint
SPARCC	Spondyloarthritis Research Consortium of Canada
SRSD	Single Reference Safety Document
TB	Tuberculosis
TBili	Total bilirubin
TNF- α	Tumor Necrosis Factor alpha
TNFi	Tumor Necrosis Factor Inhibitor(s)
TNFi IR	Tumor Necrosis Factor Inhibitor(s) Inadequate Responder
tsDMARD	Targeted synthetic Disease-Modifying Anti-Rheumatic Drug
UC	Ulcerative Colitis
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analog Scale
VTE	Venous thromboembolism
WHO	World Health Organization
WOCBP	Woman of childbearing potential
WPAI	Work Productivity and Activity Impairment

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Appendix 2. Modified New York Criteria for Ankylosing Spondylitis (1984)

Following describes the Modified New York Criteria for Ankylosing Spondylitis (1984)⁴⁷ that will be used in this study:

Clinical Criteria:

- Low back pain and stiffness for more than 3 months that improves with exercise but it is not relieved by rest;
- Limitation of motion of the lumbar spine in the sagittal and frontal planes;
- Limitation of chest expansion relative to normal values correlated for age and sex.

Radiological Criterion:

- Sacroiliitis grade ≥ 2 bilaterally or grade 3-4 unilaterally.

Definite AS if the radiological criterion is associated with at least one clinical criterion.

Modified New York Grading Criteria:

- Grade 0: normal SI joints within thin sharp cortical margins and normal cartilage space;
- Grade 1: non-specific “suspicious” findings;
- Grade 2: minimal sacroiliitis and consists of loss of definition of the SI joint margins. There may be minimal sclerosis and erosions. There may or may not be joint space narrowing;
- Grade 3: definite sclerosis on both sides of the joint, erosions, and loss of joint space;
- Grade 4: complete bony ankylosis of the SI joints.

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Appendix 3. Cockcroft-Gault Calculation

Creatinine Clearance (estimated) / Conventional mL/min =.

$((140 - \text{Age (years)}) \times \text{Weight (kg)} \times \text{Factor}^a) / (72 \times \text{Serum Creatinine (mg/dL)})$.

^aFactor is equal to 0.85 in females and 1.00 in males.

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Appendix 4. Prohibited Concomitant Medications

All **biologic agents and TNF inhibitors** are prohibited and subjects currently using these medications should not be enrolled in the study.

Other DMARDs

The following DMARDs are prohibited:

Auranofin (oral gold), aurothioglucose (injectable gold), aurothiomalate (injectable gold) must be discontinued for 8 weeks prior to the first dose of the study drug.

d-penicillamine, bucillamine, mizoribin, azathioprine, chloroquine, hydroxychloroquine, cyclosporine, tacrolimus, and staphylococcal protein A immuno-adsorbant pheresis columns (eg, PROSORBA[®] device/column) must be discontinued for 4 weeks prior to the first dose of study drug.

Leflunomide (Arava[®]) must be discontinued 8 weeks prior to the first dose of study drug if no elimination procedure is followed. Alternately, it should be discontinued with the following elimination procedure at least 4 weeks prior to the first dose of study drug:

- Cholestyramine at a dosage of 8 grams three times daily for at least 24 hours, or activated charcoal at a dosage of 50 grams 4 times a day for at least 24 hours (US PI, Elimination Procedure to significantly lower leflunomide drug levels).

Tetracyclines, unless prescribed for the treatment of acne or other dermatologic disorders, must be discontinued for 4 weeks prior to the first dose of study drug.

Live or attenuated live vaccines are prohibited during the study and for 6 weeks after last dose of study drug.

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

In the table below those drugs requiring washout longer than 7 days are in bold and italicized. Please note that efavirenz, nevirapine, barbiturates, carbamazepine, phenobarbital, St. John's Wort, rifabutin and rifapentine should be discontinued at least 30 days prior to first dose of study based on the 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.

All other prohibited drugs in the table below require at least a 7 day or 5 half-life (whichever is longer) washout period prior to the first dose of study treatment.

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

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

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.

Moderate CYP3A Inhibitors	Moderate CYP3A Inducers
HIV antivirals: atazanavir (Reyataz) delavirdine (Rescriptor) saquinavir (Fortovase)	<i>St. John's wort</i>
<i>amiodarone (Cordarone, Pacerone)</i>	
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	

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

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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
Propoxyphene HCl (Darvon, Darvocet, Doloxene) Propoxyphene napsylate (Darvon-N, Darvocet-N 100)	300 mg propoxyphene HCl 400 mg propoxyphene napsylate	~0.1	6-12 hrs; 30-36 hrs. for active metabolite (norpropoxyphene)

Sites should contact the study team for acceptable alternative preparations and related data. References:
 Twycross R, Wilcock A, Thorp S. Palliative Care Formulary. Abingdon: Radcliffe Medical Press, 1998.
 Twycross R. Pain relief in advanced cancer. Edinburgh: Churchill Livingstone, 1994.

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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, propoxyphene) may NOT be USED for rescue medication.

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

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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 medication for more than 10 consecutive days should be discontinued from the investigational product. In addition, subjects should not be dosed with rescue acetaminophen/paracetamol or opioids within 24 hours prior to a study visit. Baseline stable acetaminophen/paracetamol or opioids should NOT be discontinued in advance of study visits.

**SUBJECTS SHOULD NOT BE DOSED WITH ANY RESCUE INTERVENTION
WITHIN 24 HOURS PRIOR TO A STUDY VISIT.**

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Appendix 7. 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 made as soon as possible. It is recommended that a specialist with experience in the evaluation of immunosuppressed patients be consulted.

If a biopsy for the 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 aspiration 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;
- 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.

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Appendix 8. France Appendix

This appendix applies to study sites located in France.

1. GCP Training.

Prior to enrollment of any subjects, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course (“Pfizer GCP Training”) or training deemed equivalent by Pfizer. Any investigators who later join the study will complete the Pfizer GCP Training or equivalent before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Investigational Product.

No subjects or third-party payers will be charged for investigational product.

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