A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF PF-06700841 TO EVALUATE THE EFFICACY AT 16 WEEKS AND TO EVALUATE THE SAFETY AND EFFICACY UP TO 1 YEAR IN SUBJECTS WITH ACTIVE PSORIATIC ARTHRITIS

Investigational Product Number:	PF-06700841
Investigational Product Name:	Tyk2/Jak1
United States (US) Investigational New Drug (IND) Number:	Not applicable
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Protocol Number:	B7931030
Phase:	2b

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 2	22 October 2019	Schedule of Activities (SOA) and Section 7.2.8 Electrocardiogram (ECG) were updated to include the additional ECGs, and the requirements for centrally read ECG, alongside the locally read ECG. CCI [redacted] [redacted] Section 4.4.1. Contraception. Sexually active male subjects with female partners of child-bearing potential are no longer required to use a condom to prevent potential transfer to and exposure of partner(s) to drug through ejaculate. Rationale: Based on availability of new nonclinical developmental toxicity data that enabled assessment of the PF-06700841 systemic exposure risk of females resulting from male ejaculate, the requirements for condom use have been removed. Section 7.2.10. Events for Adjudication/Review Committee Submission, and Section 9.9. Safety Adjudication Committees (AC) were added to evaluate opportunistic infections, malignancy and cardiovascular events. Rationale: Based on emerging safety data across the Janus kinase (JAK) inhibitor class and regulatory feedback, a program level

Document	Version Date	Summary of Changes and Rationale
		decision has been made to include AC to more thoroughly investigate and interpret major safety events of interest. Appendix 6. Discontinuation Criteria. Additional discontinuation criterion added to clarify that study drug will be discontinued and the subject withdrawn from the study treatment in the event of any of the following: serious thromboembolic events, including venous thrombosis (including but not limited to deep vein thrombosis [DVT], pulmonary embolism [PE]), arterial thrombosis, and cerebrovascular events (thromboembolic stroke, transient ischemic attack [TIA], etc.) requiring hospitalization for treatment, or meeting other criteria that require the thromboembolic event to be classified as a serious adverse event (SAE). Rationale: The additional discontinuation criterion has been added based on regulatory feedback surrounding the emerging safety concerns across the JAK inhibitor product class. Appendix 6. Discontinuation Criteria. Additional discontinuation criteria added to clarify that study drug will be discontinued and the subject withdrawn from the study treatment in the event of any of the following: Two sequential AST or ALT elevation ≥3 times the upper limit of normal with at least one total bilirubin value ≥2 times the upper limit of normal; Two sequential AST or ALT elevation ≥3 times the upper limit of normal accompanied by signs or symptoms consistent with hepatic injury; Two sequential AST or ALT elevation ≥5 times the upper limit of normal, regardless of total bilirubin or accompanying signs or symptoms. Rationale: The additional clarification of

Document	Version Date	Summary of Changes and Rationale
		discontinuation criteria is similar to other ongoing studies with PF-06700841, and consistent with the laboratory changes expected at baseline and over time in subjects using background methotrexate.
Amendment 1	29 April 2019	Section 4.4.1 Contraception was updated to include an instruction that male subjects should refrain from sperm donation during the study and for a period of at least 90 days after completion of active treatment. Rationale: to align with Regulatory request. Section 9. Data Analysis/Statistical Methods, on the timing of SAP finalization. It is stated that the SAP will be finalized prior to the study unblinding. Section 9.7. Interim Analysis, clarification added that the interim analysis, if performed, will not be used to drive any decisions for the current study. Rationale: to align with Regulatory request.
Original protocol	31 October 2018	Not applicable (N/A)

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

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PROTOCOL SUMMARY

Background and Rationale:

Psoriatic arthritis (PsA) is a chronic inflammatory disease with heterogeneous manifestations affecting the skin, enthesis, synovium, and characterized by peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis, and nail disease.

PF-06700841 is a potent dual inhibitor of human tyrosine kinase (TYK)2 and Janus kinase (JAK)1 with a good selectivity profile over the other human kinases including JAK2 and JAK3 (PF-06700841 inhibited the in vitro activities of TYK2, JAK1, JAK2 and JAK3 with 50% inhibitory concentration (IC_{50}) of 22.7, 16.8 nM, 76.6 nM and 6490 nM, respectively). PF-06700841 is capable of inhibiting many cytokines involved in the pathogenesis of psoriasis and PsA with signaling pathways mediated by JAK1 and/or TYK2. Given the recent United States (US) and European Union (EU) approvals of tofacitinib (a JAK1/3 inhibitor) for PsA, subjects who will receive PF-06700841 in this study are expected to experience improvement in their disease. Compared to other JAK inhibitors, PF-06700841 will inhibit a similar mix of cytokines, but with relatively deeper inhibition of interleukin (IL)-12 and IL-23, due to TYK2 inhibitory activity. PF-06700841 has demonstrated efficacy in a 4-week Phase 1 psoriasis trial and a 12-week Phase 2 psoriasis study completed recently. PF-06700841 appears to be generally safe and well tolerated in clinical studies to date.

This is a 52 week Phase 2b study designed to evaluate the efficacy at 16 weeks and to evaluate the safety and efficacy up to 1 year in subjects with active psoriatic arthritis.

Objectives:

1. To evaluate the efficacy of PF-06700841 compared to placebo in subjects with active psoriatic arthritis (PsA), and in subjects with active PsA who are Tumour Necrosis Factor (TNF) α inhibitor naïve.

2. To evaluate the improvement in signs and symptoms related PsA Core Domain Set in PF-06700841 treated subjects.

3. To evaluate the improvement in patient reported outcome measures and composite outcome measures in PF-06700841 treated subjects.

4. To evaluate the safety and tolerability of PF-06700841.

Study Design:

This is a Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging, parallel treatment group, efficacy and safety study designed to characterize the dose response of PF-06700841 in subjects with active PsA. A total of approximately 196 subjects will be randomized in a 4:4:1:1:2:2 ratio to one of the six parallel treatment sequences as shown below. For the comparison of each of three active treatment regimens (60 mg once daily

[QD], 30 mg QD and 10 mg QD) versus placebo in the primary endpoint of American College of Rheumatology (ACR)20 at Week 16, this results in a 2:2:1:2 allocation ratio (in the order of 60 mg QD, 30 mg QD, 10 mg QD and placebo).

The study consists of a screening period of up to 5 weeks, a double-blind treatment period of 52 weeks (ie, one year), including a placebo controlled phase from Day 1 to Week 16 visits and an extended active treatment phase from Week 17 through Week 52, and a safety follow-up period of 4 weeks from last dose of study drug to last study visit. The total duration of study subject participation will be approximately up to 61 weeks, from the screening period through the follow-up period.

All eligible subjects must have active PsA despite previous or current treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), and/or non-biologic disease-modifying antirheumatic drugs (DMARDs), or apremilast. Some subjects (up to 30% of study population) may also have been previously treated with no more than one TNF inhibitor (TNFi). Randomization will be stratified by prior TNFi exposure.

All subjects will be randomly assigned to one of the six treatment sequences (A-F) shown in the table below. Starting after the Week 16 visit, subjects receiving the 60 mg QD dose (sequence A) or the 30 mg QD dose (sequence B) will continue on their initial dose; while all other subjects, including those from the 10 mg QD dose arm (sequences C and D) or the placebo arm (sequences E and F), will be randomly assigned to receive either the 60 mg QD dose or 30 mg QD dose until Week 52 as predetermined at randomization. All subjects will receive blinded dosing throughout the 52 weeks study treatment period in order to maintain the study blind.

Treatment Sequence	Treatment	Subject Size
A	PF-06700841 60 mg QD	56
B	PF-06700841 30 mg QD	56
C[1]	PF-06700841 10 mg QD first & advance to 60 mg QD after Week 16 visit[1]	14
D[2]	PF-06700841 10 mg QD first & advance to 30 mg QD after Week 16 visit[2]	14
E[1]	Placebo QD first & advance to PF-06700841 60 mg QD after Week 16 visit[1]	28
F[2]	Placebo QD first & advance to PF-06700841 30 mg QD after Week 16 visit[2]	28

1. Starting after Week 16 visit, subjects randomized to treatment sequences C or E will receive PF-06700841 60 mg QD in a blinded fashion for the remainder of the study.
2. Starting after Week 16 visit, subjects randomized to treatment sequences D or F will receive PF-06700841 30 mg QD in a blinded fashion for the remainder of the study.

Statistical Methods:

The primary endpoint in this study is the ACR20 response rate at Week 16. Assuming an ACR20 response rate of 25% for the placebo group and 1-sided type-I error rate of 5% and using the normal approximation method, the study will have over 90% power under a sample size of 50 per arm and 80% power under a sample size of 25 per arm, to detect a treatment difference of 30% or greater without multiplicity adjustment. With the 2:2:1:2 allocation ratio (in the order of 60 mg QD, 30 mg QD, 10 mg QD and placebo), and accounting for a 10% chance of drop out, approximately a total of 196 subjects will be enrolled in this study, with 56 subjects per treatment group (with the exception of 28 subjects for the 10 mg QD treatment group).

Each of the three PF-06700841 dose regimens (60 mg QD, 30 mg QD and 10 mg QD) will be compared with placebo. In order to control for type-I error, the Dunnett's method will be used for the primary endpoint of ACR20 response rate at Week 16 to adjust for multiplicity and serve as a gatekeeper for further testing of secondary endpoints. Specifically, if any PF-06700841 dose regimen is superior to placebo under the Dunnett's test, selected secondary endpoints at Week 16 for that dose regimen will be formally tested for superiority against placebo hierarchically in the order of Psoriasis Area and Severity Index (PASI)75→ACR50→PASI90→PASI100→Health Assessment Questionnaire (HAQ) - Disability Index (DI). This testing strategy will control the family-wise type-I error rate at an overall 1-sided 5% level. The normal approximation method will be used for binary endpoints in the superiority testing. The change from baseline in the HAQ-DI score will be analyzed using a repeated measure model that includes the fixed effects of treatment group, study visit (at or prior to Week 16), treatment by visit interaction, prior TNFi exposure and baseline HAQ-DI score, with an unstructured variance-covariance matrix. Regardless of formal testing results, treatment difference between each PF-06700841 dose regimen and placebo will be summarized using descriptive statistics (ie, point estimates and two-sided 90% confidence intervals [CI]).

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Identifier[1]	**Screening**[2]	**Baseline Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 28, 36, 44**	**Week 52/ Early Termination (EOT/ET)**	**Follow-up**[21] **(EOS; 4 weeks after EOT/ET)**
Visit Window	**-35 to -1 day**	**N/A**	**±3 days**	**±3 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**+7 days**
Informed Consent	X										
Register Subject Using IRT System	X										
Demography	X										
Contraception Check[3]	X	X	X	X	X	X	X	X	X	X	X
Clinical Rheumatology Assessments											
Psoriatic Arthritis (PsA) Diagnosis[4]	X										
Tender/painful joint count, Swollen joint count[5]	X	X	X	X	X	X	X	X	X	X	
Physician's Global Assessment of Arthritis		X	X	X	X	X	X	X	X	X	
Physician's Global Assessment of Psoriatic Arthritis		X	X	X	X	X	X	X	X	X	
Dactylitis Assessment		X	X	X	X	X	X	X	X	X	
Enthesitis Assessment (Spondyloarthritis Research Consortium of Canada [SPARCC]), Leeds Enthesitis Index)		X	X	X	X	X	X	X	X	X	
Clinical Dermatology Assessments											
Evaluation of Plaque Psoriasis[6]	X	X									
Physician's Global Assessment of Psoriasis		X	X	X	X	X	X	X	X	X	
Psoriasis Area and Severity Index (PASI), Body Surface Area (BSA)		X	X	X	X	X	X	X	X	X	
Nail Psoriasis Severity Index (NAPSI)		X	X	X	X	X	X	X	X	X	

Visit Identifier[1]	Screening[2]	Baseline Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 28, 36, 44	Week 52/ Early Termination (EOT/ET)	Follow-up[21] (EOS; 4 weeks after EOT/ET)
Visit Window	**-35 to -1 day**	**N/A**	**±3 days**	**±3 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**+7 days**
Other Medical Procedures											
Concomitant/Prior Treatments[7]	X	X	X	X	X	X	X	X	X	X	X
Rescue Therapy		X	X	X	X	X	X	X	X	X	
Medical History[8]	X	X									
Vital Signs[9]	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination[10]	X	X					X			X	
Targeted Physical Examination[10]			X	X	X	X		X	X		X
12-Lead ECG[11]	X	X	X				X	X	X	X	
Chest Radiographs[12]	X										
Laboratory											
Serum FSH (WONCBP only) or Serum Pregnancy test[13]	X										
Urine Pregnancy test (conducted at study site)[14]		X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X
Rheumatoid Factor (RF)	X										
Cyclic Citrullinated Peptide (CCP) Antibodies	X										
Fasting Lipid Panel (total cholesterol, LDL, HDL, triglycerides)		X			X		X		X	X	X
Serum Cystatin C		X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X
HIV Testing	X										
HBsAg, HBcAb, HBsAb and HCV Ab, HCV RNA PCR if HCV Ab positive	X										
Tuberculosis Test	X										
Urine Myoglobin[15]	X	X									
High-Sensitivity C-Reactive Protein (hsCRP)	X	X	X	X	X	X	X	X	X	X	
CCI [redacted]											

Visit Identifier[1]	**Screening**[2]	**Baseline Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 28, 36, 44**	**Week 52/ Early Termination (EOT/ET)**	**Follow-up**[21] **(EOS; 4 weeks after EOT/ET)**
Visit Window	**-35 to -1 day**	**N/A**	**±3 days**	**±3 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**+7 days**
Viral Surveillance: EBV, CMV, HSV1, HSV2, and VZV		X									
CCI [redacted]											
Patient Report Outcomes[17]											
Patient's Assessment of Arthritis Pain		X	X	X	X	X	X	X	X	X	
Patient's Global Assessment of Arthritis		X	X	X	X	X	X	X	X	X	
Health Assessment Questionnaire (HAQ) disability index (DI)		X	X	X	X	X	X	X	X	X	
Patient's Global Joint and Skin Assessment-Visual Analog Scale (PGJS-VAS)		X	X	X	X	X	X	X	X	X	
CCI [redacted]											
Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)		X	X	X	X	X	X	X	X	X	
Short-Form-36 Health Survey (SF-36) Version 2, Acute		X		X	X	X	X	X	X	X	
CCI [redacted]											
CCI [redacted]											
Other Trial Activities											
Inclusion/Exclusion review	X	X									
Randomization		X									
Investigational Product Dispensing		X	X	X	X	X	X	X	X		
Investigational Product Accountability			X	X	X	X	X	X	X	X	
Investigational Product Administration[19]		X	→	→	→	→	→	→	→	X	

Visit Identifier[1]	Screening[2]	Baseline Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 28, 36, 44	Week 52/ Early Termination (EOT/ET)	Follow-up[21] (EOS; 4 weeks after EOT/ET)
Visit Window	**-35 to -1 day**	**N/A**	**±3 days**	**±3 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**+7 days**
Serious and Non-serious Adverse Event Monitoring	X	→	→	→	→	→	→	→	→	→	X
CCI [redacted]											
[redacted]											
[redacted]											
[redacted]											
[redacted]											

Abbreviations: → = ongoing/continuous event; CMV = Cytomegalovirus; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; ET= early termination; EBV = Epstein–Barr virus; CCI [redacted]
FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C antibody; HCV RNA PCR = hepatitis C virus ribonucleic acid polymerase chain reaction; HIV = human immunodeficiency virus; HSV = herpes simplex virus; IRT = interactive response technology; LDL = low density lipoprotein; HDL = high density lipoprotein; N/A = not applicable; WONCBP = women of non-childbearing potential; VZV = Varicella-zoster virus.

1. Day relative to start of study treatment (Day 1).
2. Screening visit occurs within 35 days prior to Baseline (Day 1) visit.
3. Contraception Check: Male subjects able to father children and female subjects of childbearing potential must agree to use two effective methods (one of which is highly effective method) of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.
4. PsA Diagnosis: Subject must have signs and symptoms consistent with the diagnosis of PsA for at least 6 months and fulfills CASPAR Criteria at Screening. Note all subsequent clinical rheumatology and dermatology assessments will be performed by a qualified assessor who is blinded to the subject's safety data, previous efficacy data and treatment randomization.
5. Tender/painful Joint Count, Swollen Joint Count: Subject must have evidence of active arthritis as defined by having at least 3 tender/painful joints on motion (out of 68 joints assessed) and at least 3 swollen joints (out of 66 joints assessed) at both Screening and Baseline (Day 1/Randomization) visits.
6. Evaluation of Plaque Psoriasis: Subject must have active plaque psoriasis, with at least one psoriatic plaque or nail changes consistent with psoriasis, at both Screening and Baseline (Day 1/Randomization) which has been diagnosed or confirmed by a dermatologist or a sponsor approved rheumatologist.
7. Concomitant/Prior Treatments: Subject must have active PsA despite previous or current nonsteroidal anti-inflammatory drug (NSAID) treatment of at least 4 weeks or intolerance, and/or non-biologic disease-modifying antirheumatic drugs (DMARD) treatment of at least 3 months or intolerance. Ongoing treatment with a single non-biologic DMARD (limited to methotrexate, leflunomide or sulfasalazine) during the study is allowed but is not required.
8. Medical History: Medical history includes herpes zoster details.
9. Vital Signs: Vital Signs include sitting blood pressure, pulse rate and temperature measured after at least 5 minutes of rest.

10. Physical Examination: Physical examination must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines. Complete Physical Exam includes height (at Screening Visit only), weight, general appearance, skin, HEENT (head, eyes, ears, nose and throat), heart, lungs, abdomen, lower extremities, neurologic function and lymph nodes. Weight and height will be measured without shoes. Targeted Physical Examinations should include skin, heart, lungs, and abdomen and examination of body systems where there are symptom complaints by the subject.
11. ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position. At the Screening Visit, a single ECG will be collected. On Day 1 only, triplicate ECGs will be obtained, and the average of the triplicate ECG measurements will serve as each subject's baseline value. At the Week 2 visit only, a single ECG will be collected between 2-4 hours postdose. At all the other visits specified, a single ECG will be collected pre-dose or post-dose.
12. Chest X-ray or other appropriate diagnostic image (ie, CT or MRI) may be performed up to 12 weeks prior to Screening. Official reading must be located and available in the source documentation.
13. Serum FSH (WONCBP only) or Serum Pregnancy test: For Women of Non-Childbearing Potential (WONCBP), serum follicle stimulating hormone (FSH) test to be performed at Screening to confirm postmenopausal status in female subjects who have been amenorrheic for at least 12 consecutive months. Serum Pregnancy test is required for all Women of Childbearing Potential (WOCBP).
14. Urine Pregnancy Tests must be performed prior to dosing with the investigational product for female subjects of childbearing potential. Two negative pregnancy tests are required before receiving investigational product (1 negative Serum Pregnancy Test at screening and 1 negative Urine Pregnancy Tests at the baseline visit before investigational product administration). Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study.
15. At Screening, Baseline (Day 1/Randomization) and in case of creatine kinase (CK) >3x upper limit normal (ULN).

CCI [redacted]

17. All patient reported outcomes (PROs) should be completed prior to any other assessments made at each visit.

CCI [redacted]

19. Investigational Product Administration: Subjects should take the medication from study Days 1 through Week 52. Subjects will be encouraged to take the medication in the morning whenever possible. At Week 2 visit only, subjects are to be instructed to refrain from dosing at home, and are to bring the Investigational Product with them and take the dose in the clinic when instructed to do so.

CCI [redacted]

21. A Follow-up Visit will be completed 4 weeks after the last administration of the investigational product for all subjects who complete the Week 52 Visit or Early Termination Visit. Additional follow-up visit(s) may be warranted (see Section 6.2.6 and Appendix 6 for more details).

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-06700841 is a potent tyrosine kinase (TYK)2/Janus kinase (JAK)1 inhibitor that is highly selective over the other human kinases and is being developed for the treatment of patients with active psoriatic arthritis (PsA).

1.2. Background and Rationale

1.2.1. Drug Development Rationale

Role of proinflammatory cytokines in PsA

PsA is a chronic inflammatory disease with heterogeneous manifestations affecting the skin, enthesis, synovium, and characterized by peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis, and nail disease. There is currently no cure for PsA. The treatment goals are to achieve remission/minimum disease activity in all disease domains, to optimize functional status, improve quality of life, prevent structural damage, and to minimize complications.[1,2] Current treatment of PsA typically involves the use of nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoid, disease-modifying antirheumatic drugs (DMARDs), and subsequently biologics such as tumor necrosis factor (TNF) inhibitors.[3]

Psoriatic arthritis occurs in about 30% of patients with psoriasis. Similar to psoriasis, accumulating evidence support a central role of the IL-23-IL-17 axis in pathogenesis of PsA.[3] Several monoclonal antibodies that target the IL-23-IL-17 axis have been or are being, studied in psoriasis and PsA. Clinical trials using monoclonal antibodies that target the p40 subunit of IL-12 and IL-23 (ustekinumab) or the p19 subunit of IL-23 (guselkumab, risankizumab), IL-17A (secukinumab, ixekizumab) and IL-17RA (brodalumab) have been conducted in patients with active PsA. These biologics have been shown to be effective for the treatment of psoriasis and PsA in clinical trials.[4,5] Evidence-based treatment recommendations for PsA have been updated in 2016 by the European League Against Rheumatism (EULAR)[6] and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).[1] IL-17 inhibitors and IL-12/23 inhibitors are recommended for use alongside TNF inhibitors (with or without TNF inhibitors being preferred as the first-line biological DMARD) for PsA after failure of NSAIDs and/or methotrexate.[7] A JAK1/3 inhibitor, tofacitinib (XELJANZ®/XELJANZ® XR), has been approved in the United States and European Union (EU) for the treatment of adult patients with active PsA who have had an inadequate response or intolerance to methotrexate or other DMARDs.

Description of Investigational Product

The Janus kinase (JAK) family, including JAK1, JAK2, JAK3 and tyrosine kinase (TYK) 2, is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with Type 1 and Type 2 cytokine receptors critical for leukocyte activation, proliferation, survival and function.[8] Cytokine receptors demonstrate restricted association with JAKs such that different receptors or receptor classes preferentially utilize a given JAK pair combination to transduce their signal. Following cytokine activation, receptor-associated

JAKs are phosphorylated and in turn phosphorylate specific sites on the receptor intracellular domain. Phosphorylation of specific sites on the intracellular domain of the receptor allows for the recruitment of signal transducers and activators of transcription (STATs) that can subsequently be phosphorylated by JAKs. Phosphorylated STAT molecules are released from the receptor, dimerize and translocate to the nucleus where they bind to specific sites on the deoxyribonucleic acid (DNA) and regulate gene transcription. JAK1 pairs with JAK3 to mediate γ-common cytokine signaling and also with JAK2 and or TYK2 to transmit the signals of additional cytokines important in inflammation and immune responses including interleukin (IL)-6, interferon (IFN)γ, and IFNα. JAK2 homodimers are critical for the signaling of hematopoietic cytokines and hormones including erythropoietin (EPO), IL-3, granulocyte-macrophage colony-stimulating factor (GM-CSF) and prolactin. IL-12 and IL-23 are dependent on TYK2 and JAK2 for transmitting their signal.

IL-23 induces the differentiation of naïve cluster of differentiation (CD)4^+ T cells into highly pathogenic Th17 cells, and type I IFNs exacerbate this Th17 disease by directly stimulating granulocytes to release tissue destructive proteases and cytokines. IL-22 is highly expressed in the affected skin of patients suffering from psoriasis. IL-22 prevents cellular differentiation of keratinocytes, and induces the production of chemokines that mediate inflammatory skin disorders. Type I IFNs, IL-22 and IL-23 signal via JAK1 and/or TYK2. TNFα and IL-17 do not signal via JAKs but are regulated by upstream cytokines such as IL-6 and IL-23, which are JAK-dependent.[8]

Genome-wide association studies (GWAS) have identified TYK2 as a psoriasis susceptibility gene in 2010. Subsequently, genetic variation in TYK2 has also been associated with several other seronegative auto-inflammatory conditions, including ankylosing spondylitis, ulcerative colitis, and Crohn's disease.[9]

PF-06700841 is a potent dual inhibitor of human TYK2 and JAK1 with a good selectivity profile over the other human kinases including JAK2 and JAK3. PF-06700841 inhibited the in vitro activities of TYK2, JAK1, JAK2 and JAK3 with IC50 of 22.7, 16.8 nM, 76.6 nM and 6490 nM, respectively. PF-06700841 is capable of inhibiting the cytokines with signaling pathways mediated by JAK1 and/or TYK2, including type I IFNs, IL-6, IL-12, IL-15, IL-21, IL-22, IL-23, and IFNγ. Many of these cytokines are involved in the pathogenesis of psoriasis and PsA.

Based on the signaling paradigm and the clinical efficacy of IL-23/IL-17 pathway blockers in psoriasis, PF-06700841 may provide a new therapeutic opportunity. PF-06700841 has demonstrated efficacy in a 4-week Phase 1 psoriasis trial (B7931001)[10] and a 12-week Phase 2 psoriasis study (B7931004).

Given the recent reports of clinical response to JAK inhibitors in PsA[11,12] and US/EU approval of tofacitinib (JAK1/3 inhibitor) for treatment of adult patients with PsA, PF-06700841 is expected to provide therapeutic effects in the treatment of psoriatic arthritis. Compared to other JAK inhibitors, PF-06700841 will inhibit a similar mix of cytokines, but with relatively deeper inhibition of IL-12 and IL-23 due to the TYK2 inhibitory activity. It is anticipated that the greater inhibition of IL-12 and IL-23 signaling by PF-06700841 compared to previous JAK inhibitors, may lead to better anti-inflammatory efficacy in PsA.

1.2.2. Study Rationale

The purpose of this study is to evaluate at Week 16 the efficacy in subjects with active PsA. The 36 weeks built-in extension period will provide an opportunity for all subjects to receive additional active study treatment up to 1 year.

This study is being conducted to explore the clinical efficacy of PF-06700841 in the Core Domain Set of PsA, including musculoskeletal disease activity (peripheral joint activity, enthesitis, dactylitis, and spondylitis), skin/nail disease activity, pain, patient global (assessment of disease-related health status), physical function, health-related quality of life (HRQoL), fatigue and systemic inflammation.[13,14] The efficacy of PF-06700841 will be assessed on all the PsA Core Domain Set utilizing outcome measure instruments tested and validated in recently published randomized controlled trials (RCTs) including the tofacitinib PsA studies[11,12] and systematic reviews.[15-17]

The assessments include American College of Rheumatology response criteria components (tender/swollen joint count, Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis, health assessment questionnaire disability index [HAQ-DI], C-reactive protein [CRP]), Psoriasis Area and Severity Index (PASI), Leeds Enthesitis Index, Dactylitis severity score, CCI [redacted] Nail Psoriasis Severity Index (NAPSI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), Short-Form-36 Health Survey (SF-36), CCI [redacted] and several other assessments. Based on the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis/Outcome Measures in Rheumatology (GRAPPA-OMERACT) recent consensus, the treatment target of minimal disease activity (MDA)/very low disease activity (VLDA) will also be assessed.[2]

The outcome measure instruments selected in this Phase 2 study B7931030 should adequately assess the impact of PF-06700841 on these core PsA disease domains within the current Phase 2 study timeframe. The study is also intended to enable selection of dosing regimen for the future clinical development of PF-06700841 in PsA, and provide additional PF-06700841 safety and tolerability information. An assessment of inhibition of PsA related structural progression will not be interpretable in the absence of a placebo control beyond 16 weeks and therefore not conducted in this study.

Rationale for Population

The population selected for this study is adult subjects with active PsA.

The study population will consist of active PsA subjects at least 18 years of age, fulfilling the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria,[18] and having active disease despite previous or current NSAID, or corticosteroids, or DMARD and/or TNF inhibitors therapy. The study is incorporating subjects who are DMARD-naïve, and/or subjects who have failed non-biological DMARDs, and/or subjects who have inadequate response to (no more than one) previous TNFi therapy.

Rationale for Placebo Treatment

In this study, placebo treatment is used as comparator which is considered the gold-standard for assessing efficacy in short-term PsA studies.

The study design allows, but does not mandate, concomitant therapy with non-biologic DMARDs (limited to methotrexate, leflunomide or sulfasalazine), corticosteroids or NSAIDs. A subject taking placebo can also be treated with a non-biologic DMARD concomitantly, if the subject has been on the non-biologic DMARDs for minimum duration of therapy of 2-3 months and dose stable for 4 weeks prior to first dose of study drug.

The placebo control period will be 16 weeks in duration which should be adequate time to see effects of active treatment on signs/symptoms of PsA without those subjects who receive placebo incurring structural damage. All subjects including placebo arm will be on active treatment after 16 weeks upon entry in the study. Given the recent reports of clinical response to JAK inhibitors in PsA[11,12] and US/EU approval of tofacitinib (JAK1/3 inhibitor) for treatment of adult subjects with PsA, PF-06700841 (Tyk2/Jak1 inhibitor) is expected to provide therapeutic effects in the treatment of psoriatic arthritis in this 52-week treatment period study.

All subjects may be offered an appropriate rescue medication (eg, acetaminophen/paracetamol, non-prohibited opioids) during the study if there is an increase in pain. In addition, if subjects do experience an increased or persistent clinical disease activity, they will have the option to withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator.

1.2.3. Preclinical Safety Data

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In summary, the nonclinical studies adequately support the planned clinical trials with PF-06700841.

1.2.4. Clinical Experience with PF-06700841

PF-06700841 has been evaluated in 3 completed Phase 1 studies in healthy subjects and psoriasis subjects (B7931001, B7931009, and B7931010), 1 complete Phase 2 study in psoriasis (B7931004). Two (2) Phase 1 studies in healthy volunteers are clinically complete and preparation of the clinical study reports are in progress: assessment of the effect of PF-06700841 on interval corrected for heart rate (QTc) interval (B7931019) and of PF-06700841 absorption, distribution, metabolism and excretion (ADME) properties and absolute oral bioavailability (B7931014). PF-06700841 is currently under assessment in 6 ongoing Phase 2 studies in alopecia areata (B7931005), ulcerative colitis (B7981005), Crohn's Disease (B7981007), systemic lupus erythematosus (SLE) (B7931028), vitiligo (B7981019), and PsA (this study, B7931030), and 1 planned Phase 2 study in hidradenitis suppurativa (C2501007). The PF-06700841 topical development program consists of 1

completed Phase 1 study in adult Japanese healthy subjects (B7931029), and 2 ongoing Phase 2 studies in atopic dermatitis (B7931022) and psoriasis (B7931023).

PF-06700841 was administered to 74 subjects (53 healthy volunteers and 21 subjects with psoriasis) in Phase 1 study B7931001 up to 200 mg in single-ascending doses, up to 175 mg daily (QD) and 50 mg twice daily (BID) for 10 days in multiple ascending doses and up to 100 mg QD for 28 days in psoriasis subjects.[10]

PF-06700841 was administered to 6 healthy Japanese subjects in the Phase 1 study B7931009 at a daily dose of 100 mg. In the clinically complete Phase 2 psoriasis study, PF-06700841 was administered at doses up to 60 mg QD for 4 weeks.

In the completed Phase 2 study B7931004, 212 psoriasis subjects were randomized and received at least one dose of study treatment. Subjects were randomized from 39 sites in 3 countries (26 United States, 8 Canada, and 5 Poland). The randomization ratio was 7:1, active: placebo. During the first 4 week treatment period, 2 oral daily dose levels (30 mg and 60 mg) of PF-06700841, plus matching placebo, were investigated. During the 8 week maintenance treatment period (Weeks 5 through 12), subjects received either 10 mg or 30 mg PF-06700841 once daily (QD), or a 100 mg once weekly (QW) regimen of PF-06700841, or matching placebo.

In the ongoing Phase 2 studies, PF-06700841 is being administered at doses up to 60 mg QD for 4 weeks (alopecia areata), 8 weeks (ulcerative colitis) or 12 weeks (Crohn's disease).

1.2.4.1. Summary of Clinical Safety with PF-06700841

Study B7931001: The first-in human study (B7931001) was a Phase 1 combination, within cohort, randomized, double blind, third-party open, placebo-controlled, parallel group study with single- and multiple-dose escalation in healthy adult subjects, and multiple dosing in subjects with plaque psoriasis. In addition, the bioavailability of a tablet formulation relative to the solution/suspension formulation as well as the effect of a high fat meal on the bioavailability of the tablet formulation was determined. During the single ascending dose (SAD) period, healthy subjects received single doses of 1, 3, 10, 30, 100 and 200 mg of PF-06700841 or placebo. In the multiple ascending dose (MAD) period, healthy subjects received doses of 10, 30, 100 or 175 mg QD, or 50 mg BID of PF-06700841 or placebo for 10 days. Psoriasis subjects received either 30 mg or 100 mg PF-06700841 or placebo (QD) for 28 days.[10]

PF-06700841 demonstrated acceptable safety and tolerability in the Phase 1 clinical study B7931001, which included both healthy subjects (n=66 randomized) and subjects with plaque psoriasis (n=30 randomized). Subjects reported 11 treatment-emergent adverse events (TEAEs) in the SAD period, 22 TEAEs in the MAD period, 39 TEAEs in the psoriasis period, and 3 TEAEs in the bioavailability (BA) period. There were no deaths or serious adverse events during this study. All adverse events (AEs) were mild or moderate in severity. Dose escalation stopping rules were not triggered at any dose level.

In Study B7931001, serum creatinine (SCr) increases were observed in the study and 6 of these AEs led to discontinuation of dosing per protocol. No cases were accompanied by clinical signs or symptoms. The proposed mechanism for the observed serum creatinine increases in study B7931001 is inhibition of creatinine transport (ie, transporter-mediated rather than direct nephrotoxicity), and is based on PF-06700841 potential to inhibit OCT2 creatinine transporter (IC_{50}=1.1 μM; unbound I_{max}/IC_{50} ratio=0.25). To differentiate from direct nephrotoxicity, the B7931001 protocol was amended (Protocol Amendment 2) to include collection of serum cystatin C. Elevated serum creatinine in the absence of clinically meaningful changes in serum cystatin C-based estimates of estimated glomerular filtration rate (eGFR) during study B7931001 supports the transporter inhibition hypothesis. Following the implementation of cystatin C-based kidney safety monitoring, no subjects were discontinued from treatment/study due to renal concerns. The lack of clinically meaningful decline in serum cystatin C based eGFR indicated that inhibition of renal transporters is the likely mechanism for the elevated SCr in PF-06700841-treated subjects showing increases in SCr levels.

Neutropenia (Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 occurred at the 175 mg QD and 50 mg BID dose levels during the MAD period. All laboratory abnormalities reported as AEs were mild in severity, except for one case of neutropenia which was reported as moderate in severity (Grade 3 neutropenia). No neutrophil counts reached or fell below 500 cells/mm^3. The AE of herpes zoster occurred in a single subject after completing 28-day treatment with PF-06700841 at the 100 mg QD dose level. The subject had non-disseminated, herpetiform rash on the upper left back and left arm that was reported to have presented on Study Day 30 (2 days after the last dose of PF-06700841). The AE was mild in severity and was treated with acyclovir and Vicodin by the Investigator. Please refer to the Investigator's Brochure (IB) for further details from the B7931001 study.

Study B7931009: PF-06700841 demonstrated acceptable safety and tolerability in healthy Japanese subjects investigated in study B7931009, in which multiple doses of 100 mg QD or placebo was administered for 10 days. There were no deaths, serious adverse events (SAEs), severe AE, discontinuations due to AEs, or dose reductions or temporary discontinuations due to AEs during this study. All AEs were mild or moderate in severity. An AE of palpitations was observed in a placebo subject during the treatment period. There were no clinically significant findings observed in laboratory parameters, vital signs, ECG parameters, and physical examinations. Please refer to the IB for further details from the B7931009 study.

Study B7931010: This was an open-label, single dose, 2-period, 2-sequence crossover study in 8 healthy subjects to characterize the PF-06700841 pharmacokinetic (PK) profile and bioavailability following single oral dose formulation of immediate release (IR) tablets and modified release (MR) tablets each administered as a 30 mg dose in the fasted state. All AEs were mild in severity. There were no deaths, SAEs, severe AEs, discontinuations due to AEs, or dose reductions or temporary discontinuations due to AEs during this study.

Study B7931014: This study was a Phase 1, open-label, non-randomized, 2-period, fixed sequence, single-dose study of PF-06700841 in healthy male subjects to characterize the absorption, distribution, metabolism, and excretion (ADME) of 14^C PF-06700841; and to evaluate the absolute oral bioavailability (F) and fraction absorbed (Fa) of PF-06700841 following oral administration of unlabeled PF-06700841 and IV and oral administration of ^{14}C-PF-06700841 to healthy male subjects. All AEs were mild or moderate in severity. There were no deaths, SAEs, severe AEs, discontinuations due to AEs, or dose reductions or temporary discontinuations due to AEs during this study. There were no clinically significant findings observed in laboratory parameters, vital signs, ECG parameters. Please refer to the IB for further details from the B7931014 study.

Study B7931019: This was a definitive QT study to determine the effect of PF-06700841 on QTc interval in healthy subjects. This was a phase 1, 3-way crossover, 3-treatment, 6-sequence, sponsor-open study, in which, each subject received single oral doses of PF-06700841 200 mg, placebo and moxifloxacin 400 mg, according to one of the treatment sequences they were randomly assigned. Treatment assignments to PF-06700841 and placebo were blinded to the subjects and investigator but moxifloxacin treatment was unblinded.

Study B7931004: This was a Phase 2, randomized, double--blind, placebo--controlled, parallel group, multicenter study in adult subjects with moderate to severe plaque psoriasis. PF-06700841 demonstrated acceptable safety and tolerability in subjects with active psoriasis, in which multiple doses were administered over 12 weeks. During the first 4 week treatment period, 2 oral daily dose levels (30 mg and 60 mg) of PF-06700841, plus matching placebo, were investigated. During the 8 week maintenance treatment period (Weeks 5 through 12), subjects received either 10 mg or 30 mg PF-06700841 once daily (QD), or a 100 mg once weekly (QW) regimen of PF-06700841, or matching placebo. A total of 212 subjects were randomized and received at least one dose of study treatment.

The incidence of TEAEs by all causalities were comparable across all treatment groups but numerically higher in the active treatment groups (64% - 77%) than the placebo group (57%): 19 subjects (76%) in 60 mg → 30 mg QD, 23 subjects (72.4%) in 60 mg → 10 mg QD, 18 subjects (69.2%) in 60 mg → 100 mg QW, 18 subjects (72.0%) in 60 mg → placebo, 21 subjects (72.4%) in 30 mg QD, 16 subjects (64.0%) in the 30 mg → 10 mg QD, 23 subjects (76.7%) in the 30 mg → 100 mg QW, and 13 subjects (56.5%) in the placebo group. The majority of the TEAEs were mild.Eleven subjects experienced severe AEs during the study: 3 in the 60 mg → 30 mg QD, 2 each in the 60 mg → placebo QD and 30 mg →100 mg QW groups, and 1 each in the 60 mg → 10 mg QD, 60 mg → 100 mg QW, 30 mg → 10 mg QD and placebo groups. There was no severe AE reported in the PF-06700841 30 mg QD group. There were 2 serious infections in 1 subject in the 60 → 30 mg QD group.

Five subjects in the PF-06700841 groups experienced 6 SAEs (angina pectoris, gunshot wound, anemia, pneumonia, sepsis, and non-cardiac chest pain), only anemia was a study drug-related SAE as evaluated by the investigator.

For AEs of special interest, one unrelated death due to gunshot wound occurred after the subject was discontinued from the study due to noncompliance with study drug. There was 1 case of squamous cell carcinoma in the 30 mg QD → 100 mg QW group during the Induction phase of the study. The event was not related to the study drug as evaluated by the Principal Investigator (PI). No cases of herpes zoster were reported during the study. 6 cases of herpes simplex were reported, all were mild except for 1 moderate case in the 60 → 100 mg QW group. There were 2 Suspected Unexpected Serious Adverse Reactions (SUSARs) in the study, including the SAE event of anemia, and a birth defect of 'fetus cleft lip' that occurred in a fetus after a female subject became pregnant while on the study drug for 6 weeks.

A total of 13 subjects discontinued from the study due to AEs, 2 in the 60 mg → 30 mg QD, 4 in the 60 mg → 10 mg QD, 1 in the 60 mg → 100 mg QW, 2 in the 60 mg → placebo, 2 in the 30 mg → 10 mg QD, and 2 in the 30 mg → 100 mg QW group. One subject in the 60 mg → placebo discontinued the study drug treatment, but remained in the study. There were 5 subjects with dose reduced or temporary discontinued due to AEs, 1 each in the 60 mg → 30 mg QD, 60 mg → 100 mg QW, 60 mg → placebo, 30 mg → 10 mg QD, and placebo groups.

There were no clinically meaningful observable dose dependent neutropenia, lymphopenia, thrombocytopenia, and anemia among the active treatment groups, except for 1 SAE of anemia in the 60 mg → 10 mg QD group. During the Induction Phase, there was a decrease in reticulocyte count in the active treatment groups (-12.0% in the 60 mg QD, -7.18% in the 30 mg QD) compared to placebo (3.77%). The observed decreases appear to improve during the Maintenance phase, with all active treatment groups approaching 10% change from baseline (CFB) at Week 12. Platelet counts were quite stable during the Induction and Maintenance periods. Small increases were observed in lymphocytes in all treatment groups during the Induction and Maintenance periods. There were no clinically meaningful changes

from baseline over time in mean or median values in hepatic transaminases in all active treatment groups compared to the placebo. There was no subject withdrawn due to elevation of hepatic enzymes. There were no meaningful changes in cystatin C in all treatment groups and placebo, except for the subject who was discontinued because of decline of eGFR >30% from the baseline at Week 4 (see above in the discontinuation section). Elevations of creatine kinase (CK) at least 3 times the upper limited of normal (ULN) were observed in 17 subjects out of 189 (8.9%) who received PF-06700841 during the study, 4 of these 17 subjects had CK>3x ULN at baseline. Five subjects had at least one CK elevation greater than 10 x ULN. One adverse event of CK elevation was deemed to be study drug related by the investigator. No subject was discontinued from the study due to CK elevation. All increased CKs were in the creatine kinase MM (CK-MM) subunits. No subjects with increased CK had rhabdomyolysis or cardiovascular events.

Please refer to the IB for further details from the B7931004 study.

There is no evidence to date, of a cardiovascular safety signal associated with PF-06700841 treatment from the completed and ongoing clinical trials. In the Phase 1 PF-06700841 clinical program, no clinically significant changes in ECG parameters have been observed, including no changes in QTcF >60 msec or an absolute value >500 msec. In the Phase 2 PF-06700841 program, no clinically significant changes in ECG parameters have been observed. In addition, there have been no adverse events of ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation or flutter, torsade de pointes, syncope, seizures, sudden death, or QT prolongation.

Phase 2 studies in alopecia areata (B7931005), ulcerative colitis (B7981005), Crohn's disease (B7981007), SLE (B7931028) and vitiligo (B7981019) are ongoing and the study teams remain blinded. Blinded data from these studies have not revealed any concerning safety signals or signals that alter the overall risk/benefit profile, including exposure to PF-06700841 at doses up to 60 mg QD for 4-12 weeks.

In summary, PF-06700841 has demonstrated an acceptable safety and tolerability profile, and is consistent across clinical studies to date. Please refer to the IB for more details on the clinical safety information with PF-06700841.

1.2.4.2. Summary of Pharmacokinetics (PK)

In Study B7931001, following single oral doses of 1 mg to 200 mg under fasted conditions, PF-06700841 was absorbed rapidly with median T_{max} of 1 hour or less. Mean terminal half-life ($t_{½}$) ranged from 3.8 to 7.5 hours. In general, both the area under the plasma concentration-time curve from time 0 extrapolated to infinity (AUC_{inf}) and maximum plasma concentration (C_{max}) appeared to increase proportionally with dose from 1 mg to 100 mg. Increases from 100 mg to 200 mg appear more than dose proportional, especially for AUC_{inf}.

On Day 10 of multiple-dose administration, PF-06700841 was absorbed rapidly with median T_{max} of 1.5 hours or less across the entire range of doses, from a total daily dose of 10 mg up to 175 mg. Following attainment of C_{max}, the disposition of PF-06700841 was similar with that observed following single-dose administration. Mean terminal half-life ($t_{½}$) ranged from 4.9 to 10.7 hours. Both area under the concentration-time curve from time 0 to time τ

(AUC_τ) and C_{max} generally appeared to increase proportionally with dose from 10 mg to 100 mg QD, with a trend towards greater than proportional increase from 100 mg to 175 mg QD. Accumulations, following once daily dosing, ranged from 1.1 to 1.4 for AUC_τ and 0.8 to 1.1 for C_{max}. The urinary recovery of unchanged (Aeτ%) PF-06700841 on Day 10 across all doses ranged from 8.9% to 15.5%. Following multiple dose administration of PF-06700841 to subjects with psoriasis for 28 days, the overall exposure observed was comparable to that in healthy subjects at same dose level.

The relative bioavailability of a solid dose formulation of PF-06700841 relative to a solution and the food effect on the solid dosage formulation was also evaluated. Following single oral 100 mg doses under fasting conditions, median T_{max} was 0.5 hours for the tablet formulation and 1.0 hours for the solution. The ratios of adjusted geometric means between tablet versus solution formulation were 96.2% for AUC_{inf} and 94.3% for C_{max}. When the tablet was administered following a high fat meal, T_{max} was delayed with median of 4.0 hours and the AUC_{inf} and C_{max} were 82.3% and 64.3%, respectively of those observed when tablets were given fasted.

In B7931009 study, higher exposure in Japanese subjects (n=6) observed compared to that in non-Japanese subjects from B7931001 study: The mean steady state C_{max} (CV) were 1114 (14%) vs 734.1 (29%) ng/mL and steady state mean AUC_{24} (CV) were 9888 (33%) vs 6089 (38%) ng•h/mL for Japanese subjects and non-Japanese subject respectively after multiple doses of 100 mg QD.

B7931004 study was recently completed. In this study, PK samples were collected at pre-dose and/or 0.5 hours post-dose at each visit over 12-week treatment. Post-dose samples were also collected up to 4 hours at Weeks 4 and 12. Plasma concentrations of PF-06700841 observed were as expected based on PK in healthy subjects.

1.2.5. Dose Selection Rationale

A QD regimen (utilizing three doses of PF-06700841 of 10 mg, 30 mg and 60 mg QD) will be evaluated in this dose-ranging Phase 2 study in PsA. The 30 and 60 mg QD dose levels of PF-06700841 have demonstrated clinical efficacy in psoriasis subjects in Phase 1 (B7931001) and/or Phase 2 (B7931004) studies, with the 30 mg dose being studied in both studies. The 60 mg QD demonstrated slightly higher clinical effect compared to 30 mg QD at Week 4 as measured by PASI in the B7931004 study, however only the 30 mg dose was studied for an additional 8 weeks. The preliminary exposure response analysis based on PASI data in B7931004 trial suggested the predicted PASI responder rates (PASI75 and PASI90) at Week 16 could be 15% to 20% greater after 60 mg QD compared to 30 mg QD treatment in patients with moderate to severe psoriasis.

Both 30 mg and 60 mg QD dose levels have demonstrated acceptable safety profiles to date. The expected steady state exposures following 60 mg QD, the top dose in this study (C_{max}=264 ng/mL and AUC_{24}=2320 ng•h/mL) are 4.6x to 30x below the exposures at the no observed adverse effect levels (NOAELs) observed in the 6-month rat (45 mg/kg/day) and 9-month monkey (20 mg/kg/day) studies (Section 1.2.3). The 30 mg and 60 mg QD doses are also being investigated in ongoing Phase 2 studies in subjects with alopecia areata

(B7931005), ulcerative colitis (UC) (B7981005) and Crohn's disease (CD) (B7981007). Since 60 mg QD provided increased efficacy over 30 mg QD in psoriasis over a four week dosing period while maintaining an acceptable safety profile, 60 mg QD is selected as the highest dose for the current study. This study will enable assessment of the safety and efficacy of this higher dose level of PF-06700841 over 52 weeks. As doses lower than 30 mg QD provided lower efficacy in psoriasis in the B7931004 study, inclusion of a sub-optimal dose regimen of 10 mg QD will allow a more thorough characterization of the dose response curve. The three QD doses, 10 mg, 30 mg and 60 mg QD are expected to provide sufficient information to derive optimal dose(s) for the planned PF-06700841 Phase 3 program in PsA.

1.2.6. Summary of Benefit Risk Assessment

As previously noted, in view of the reports of clinical response to JAK inhibitors in PsA[11,12] and US/EU approval of tofacitinib (JAK1/3 inhibitor) for treatment of adult patients with PsA, PF-06700841, a TYK2/JAK1 inhibitor, is expected to offer therapeutic benefit in the treatment of psoriatic arthritis. Indeed, compared with other JAK inhibitors, a more profound inhibition of IL-12 and IL-23 signaling mediated by TYK2 inhibitory activity may provide a new and improved therapeutic benefit. This study will enable a thorough assessment of the safety and efficacy of PF-06700841 in PsA over 52 weeks, including the assessment of efficacy endpoints that typically require greater than 16 weeks to achieve (including but not limited to ACR50/70, PASI90/100 and Minimal Disease Activity (MDA) and Very Low Disease Activity (VLDA) responses). All subjects entering the study will have the opportunity to receive one of the two higher doses of active treatment starting at week 16, including placebo subjects and those on the lowest dose. Study participants could benefit from the potential achievement of disease control, improvement of signs and symptoms, as well as improvements in quality of life.

Based on the clinical and nonclinical experience with PF-06700841 and/or other JAK inhibitors (eg, Xeljanz® [tofacitinib], Jakafi® [ruxolitinib], Olumiant® [baricitinib], and Rinvoq® [upadacitinib]), anticipated potential risks with PF-06700841 include: (1) an increase in susceptibility to infection, (2) viral reactivation, (3) malignancy and lymphoproliferative disorders, (4) alterations in laboratory parameters: decreased neutrophil counts, decreased lymphocyte counts, decreased hemoglobin level, decreased platelet counts, elevation of hepatic transaminases, alterations in the hepatic transaminases and serum creatinine, alterations in the lipid profile, increases in creatine phosphokinase, and (5) QT prolongation. There was one AE of herpes zoster infection in a psoriasis subject treated with 100 mg PF-6700841 for 4 weeks. Laboratory changes can be managed by monitoring criteria as well as adjustment of the inclusion/exclusion criteria.

There have been events of pulmonary embolism reported with other JAK inhibitor products CCI [redacted] Suspected thrombotic and embolic events will be subject to review by an external blinded adjudication committee.

In conclusion, the sponsor considers that the available information from the nonclinical and clinical studies completed to date with PF-06700841 provide a favorable benefit-risk for subjects with PsA and support its continued investigation as a potential treatment for PsA.

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

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2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the efficacy of PF-06700841 compared to placebo in subjects with active psoriatic arthritis (PsA).	• The proportion of subjects achieving an American College of Rheumatology 20 (ACR20) response at Week 16.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the efficacy of PF-06700841 compared to placebo in subjects with active PsA who are TNFα inhibitor naïve.	• The proportion of subjects achieving an ACR20 response at Week 16 in the subgroup of subjects who are TNFα inhibitor naïve.
• To evaluate the improvement in signs and symptoms related PsA Core Domain Set[13] in PF-06700841 treated subjects.	*Assessed at all treatment timepoints:* • The proportion of subjects achieving an ACR20 response at all treatment timepoints (other than Week 16), and proportion of subjects achieving an ACR50 and ACR70 response; • Change from baseline in the ACR response criteria components (Tender/painful joint count, Swollen joint count, Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis, Health Assessment Questionnaire [HAQ] disability index [DI], and hsCRP); • The proportion of subjects achieving a Psoriasis Area and Severity Index 75/90/100 (PASI75/90/100) response; • Change from baseline in the enthesitis score (using the Spondyloarthritis Research Consortium of Canada [SPARCC] Enthesitis Index and Leeds Enthesitis Index); • Change from baseline in the Dactylitis Severity Score; • Change from baseline in the Nail Psoriasis Severity Index (NAPSI) Score.

• To evaluate the improvement in patient reported outcome measures related PsA Core Domain Set[13] in PF-06700841 treated subjects.	*Assessed at all treatment timepoints:* • Change from baseline in the Patient's Global Joint and Skin Assessment-Visual Analog Scale (PGJS-VAS); • Change from baseline in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue); *Assessed at all treatment timepoints except Week 2:* • Change from baseline in the Short-Form-36 Health Survey (SF-36) Version 2, Acute.
• To evaluate the improvement in additional composite outcome measures in PF-06700841 treated subjects.	Assessed at all treatment timepoints except Week 2: • The proportion of subjects achieving Minimal Disease Activity (MDA) and Very Low Disease Activity (VLDA) response; • Change from baseline in the Disease Activity Index for Reactive Arthritis/PsA (DAREA/DAPSA); • The proportion of subjects achieving the Psoriatic Arthritis Response Criteria (PsARC); • Change from baseline in the Psoriatic Arthritis Disease Activity Score (PASDAS).
• To evaluate the safety and tolerability of PF-06700841.	• Incidence of adverse events (AEs), serious adverse events (SAEs) and serious infectious events (SIEs), withdrawals due to AEs and SAEs, and laboratory abnormalities, changes in vital signs, and electrocardiogram (ECG) findings throughout the study.
CCI [redacted]	[redacted]
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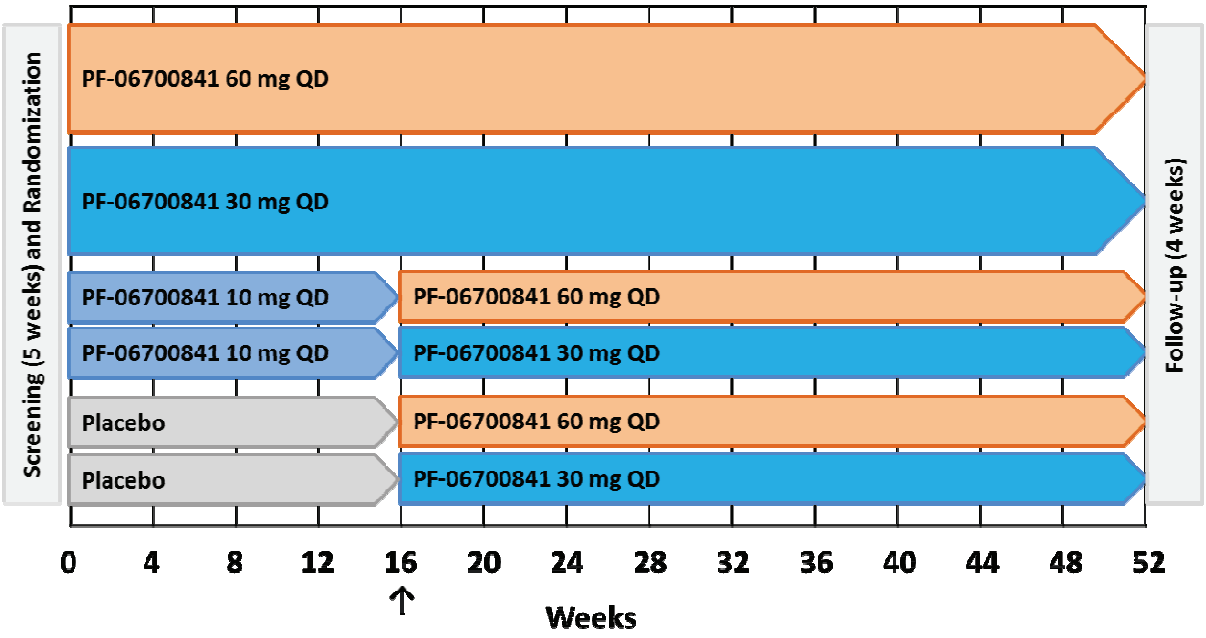
3. STUDY DESIGN

This is a Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging, parallel treatment group, efficacy and safety study designed to characterize the dose response of PF-06700841 in subjects with active PsA. A total of approximately 196 subjects will be randomized in a 4:4:1:1:2:2 ratio to one of the six parallel treatment sequences as shown below. The primary efficacy endpoint is the ACR20 response rate at Week 16. For the treatment comparison of each of three active treatment regimens (60 mg QD, 30 mg QD and 10 mg QD) versus placebo in the primary endpoint, this results in a 2:2:1:2 allocation ratio (in the order of 60 mg QD, 30 mg QD, 10 mg QD and placebo).

A schematic of the study design is shown below:

Figure 1. Schematic of Study Design



↑ Primary study endpoints of ACR20 will be obtained at Week 16 visit. All subjects randomized to placebo will receive PF-06700841 in a blinded manner after Week 16 visit.

The study consists of a screening period of up to 5 weeks, a double-blind treatment period of 52 weeks (ie, one year), including a placebo controlled phase from Day 1 to Week 16 visits and an extended active treatment phase from Week 17 through Week 52, and a safety follow-up period of 4 weeks from last dose of study drug to last study visit. The total duration of study subject participation will be approximately 61 weeks, including the screening period and follow-up period.

All eligible subjects must have active PsA despite previous or current treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), and/or non-biologic disease-modifying antirheumatic drugs (DMARDs), or apremilast. Some subjects (up to 30% of study population) may also have been previously treated with no more than one TNF inhibitor (TNFi). Randomization will be stratified by prior TNFi exposure.

All subjects will randomly be assigned to one of the six treatment sequences (A-F) shown in Table 1. Starting after the Week 16 visit, subjects receiving the 60 mg QD dose (sequence A) or the 30 mg QD dose (sequence B) will continue on their initial dose; while all other subjects, including those from the 10 mg QD dose arm (sequences C and D) and placebo arm (sequences E and F), will start to randomly receive either the 60 mg QD dose or 30 mg QD dose until Week 52, as predetermined at randomization. All subjects will receive blinded dosing throughout the 52 weeks study treatment period in order to maintain the study blind.

Table 1. Treatment Sequence

Treatment Sequence	Treatment	Subject Size
A	PF-06700841 60 mg QD	56
B	PF-06700841 30 mg QD	56
C[1]	PF-06700841 10 mg QD first & advance to 60 mg QD after the Week 16 visit	14
D[2]	PF-06700841 10 mg QD first & advance to 30 mg QD after the Week 16 visit	14
E[1]	Placebo QD first & advance to PF-06700841 60 mg QD after the Week 16 visit	28
F[2]	Placebo QD first & advance to PF-06700841 30 mg QD after the Week 16 visit	28

1. Starting after the Week 16 visit, subjects randomized to treatment sequences C or E will receive PF-06700841 60 mg QD in a blinded fashion for the remainder of the study.
2. Starting after the Week 16 visit, subjects randomized to treatment sequences D or F will receive PF-06700841 30 mg QD in a blinded fashion for the remainder of the study.

An interim analysis may be performed for business reasons and planning for future studies when approximately 118 (60%) subjects have completed or have the opportunity to complete Week 16 of the study. Safety and efficacy data may be reviewed by an Internal Review Committee (IRC). Members of the study team will not be part of the IRC.

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 nonmedical 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 appropriate member of the investigator's study team before subjects are included in the study.

4.1. Inclusion Criteria

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

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

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

3. Male or female subjects between 18-75 years of age, inclusive, at time of informed consent.

4. Male subjects able to father children and female subjects of childbearing potential must agree to use two effective methods (one of which is highly effective method) of contraception throughout the study and for at least 28 days after the last dose of investigational product.

   Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:

   - Achieved postmenopausal 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 a 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.

Disease under study

5. The subject must have signs and symptoms consistent with the diagnosis of PsA for at least 6 months and fulfills CASPAR Criteria at Screening.

6. To meet the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria,[18] a subject must have inflammatory articular disease (joint, spine, or entheseal) with at least 3 points from the following 5 categories:

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

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

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

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

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

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

7. The subject must have evidence of active arthritis as defined by having at least 3 tender/painful joints on motion (out of 68 joints assessed) and at least 3 swollen joints (out of 66 joints assessed) at <u>both Screening and Baseline (Randomization)</u>.

8. The subject must have active plaque psoriasis, with at least one psoriatic plaque or nail changes consistent with psoriasis, at <u>both Screening and Baseline (Randomization)</u> which has been diagnosed or confirmed by a dermatologist or a sponsor-approved rheumatologist.

9. Rheumatoid factor (RF), cyclic citrullinated peptide (CCP) antibodies negative.

10. Subject must have active PsA despite previous or current nonsteroidal anti-inflammatory drug (NSAID) treatment of at least 4 weeks or intolerance, and/or non-biologic disease-modifying antirheumatic drugs (DMARD) treatment of at least 3 months or intolerance.

Prior and concomitant medication

11. Subjects who are on any non-biologic DMARD <u>other than</u> methotrexate, leflunomide or sulfasalazine must discontinue the non-biologic DMARD at least 28 days prior to randomization. Ongoing treatment with **a single non-biologic DMARD** (limited to methotrexate, leflunomide or sulfasalazine) during the study is allowed but is not required, providing the following criteria are met:

- Methotrexate: Maximum dose of 25 mg/week. Minimum duration of therapy 3 months and dose stable for 4 weeks prior to first dose of study drug, and should remain stable throughout the course of the study. Subjects on methotrexate should be on an adequate and stable dose of folate supplementation (not less than 5 mg weekly based on folic acid, unless such doses would violate the local label guidelines or standard of care) for at least 4 weeks prior to the first dose of study drug. Subject must not have had previous serious toxicity while on methotrexate and not be expected to require evaluation for possible methotrexate toxicity (eg, require a liver biopsy for methotrexate toxicity) during the study.

- Sulfasalazine: Maximum dose of 3 gm/day. Minimum duration of therapy 2 months and dose stable for 4 weeks prior to first dose of study drug, and should remain stable throughout the course of the study.

- Leflunomide: Maximum dose of 20 mg/day. Minimum duration of therapy 3 months and dose stable for 4 weeks prior to first dose of study drug, and should remain stable throughout the course of the study.

For subjects who plan to continue receiving the aforementioned permitted concomitant non-biologic DMARD treatment during the study, all local standard-of-care practices for the administration of non-biologic DMARD therapy, including laboratory testing, contraceptive requirements, follow-up care and contraindications should be performed according to local standards of care throughout the study.

12. Subjects who have received an approved TNF inhibiting biologic agent that was administered in accordance with its labeling recommendations must have experienced an inadequate response due to lack of efficacy and/or intolerance as follows:

    - An inadequate response to TNF inhibitor treatment due to lack of efficacy, and prior treatment according to local label and after minimum treatment duration of at least 3 months treatment for adalimumab (Humira® or biosimilars), etanercept (Enbrel® or biosimilars), and certolizumab (Cimzia®), or at least 3 injections of golimumab (Simponi® and Simponi Aria®), or at least 4 infusions of infliximab (Remicade® or biosimilars).

    - An inadequate response to TNF inhibitor treatment due to intolerance is defined as a treatment-related adverse event (eg, infusion/injection reactions, infections, laboratory test changes, etc).

Subjects **could have failed no more than one TNF inhibiting biologic agents** that were administered in accordance with its labeling recommendations and was inadequately effective and/or not tolerated.

13. Subjects must not be receiving TNF inhibitors during the study. Subjects on TNF inhibitors must discontinue and require washout according to the following criteria:

    - Adalimumab (Humira® or biosimilars), certolizumab (Cimzia®), golimumab (Simponi® and Simponi Aria®): Discontinued at least 10 weeks prior to first dose of study drug;

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

    - Etanercept (Enbrel® or biosimilars): Discontinued at least 4 weeks prior to the first dose of study drug.

14. Subjects who are already taking nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors may participate in the study provided that the dose is stable for two weeks prior to first dose of study drug, and should remain stable throughout the course of the study.

15. Subjects who are already taking oral corticosteroids (but not injectable) may participate in the study provided that they are on a stable dose of ≤10 mg/day of prednisone or equivalent for 4 weeks prior to first dose of study drug, and the dose should remain stable throughout the course of the study.

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.

2. Participation in other interventional studies within 4 weeks or 5 half-lives, if known, whichever is longer, prior to study entry and/or during study participation. Participation in any observational studies during study participation. *Note any investigational or experimental therapy or procedure for psoriasis, PsA or rheumatoid arthritis must be discontinued for at least 12 weeks prior to first dose of study drug.*

3. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use two effective methods (one of which is highly effective) of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product. Women of childbearing potential must test negative for pregnancy prior to enrollment in this study.

4. 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.

5. Subjects with ANY of the following abnormalities in clinical laboratory tests at Screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:

   - Hemoglobin <10 g/dL (<100 g/L) or hematocrit <30%;
   - White blood cell count <3.0 x 10^9/L (<3000 mm^3);
   - Absolute neutrophil count <1.5 x 10^9/L (<1500 mm^3);
   - Absolute lymphocyte count of <1.0 x 10^9/L (<1000/mm^3);
   - Platelet count <100 x 10^9/L (<100,000/mm^3);
   - eGFR<60 mL/min/1.73 m^2 based on the age appropriate calculation;
   - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >=2 times the ULN;
   - Total bilirubin >=1.5 times the ULN; subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is <ULN;
   - Creatine kinase (CK) >3 times the ULN and positive urine myoglobin.

6. Current or recent history of uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, or neurologic disease. Known history of pulmonary embolism or recurrent deep vein thrombosis (DVT).

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

Infection related exclusion criteria

8. History of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 6 months prior to the first dose of study medication; or history of infection requiring oral antimicrobial therapy within 2 weeks prior to the first dose of study medication.

History of an infected joint prosthesis at any time, with the prosthesis still in situ. Any known current chronic infection or recurrent infection.

9. History of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized, dermatomal herpes zoster.

10. Known infection with hepatitis B viruses. All subjects will undergo testing for Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb). Subjects who are HBsAg positive are not eligible for the study. Subjects who are HBsAg negative and HBcAb positive will be reflex tested for Hepatitis B Surface Antibody (HBsAb) and if HBsAb is positive, may be enrolled in the study; if HBsAb is negative, the subject is not eligible for the study.

11. Known infection with hepatitis C viruses. Subjects who are hepatitis C antibody (HCV Ab) positive require further testing with HCV RNA PCR and are allowed to enroll if negative.

12. Known infection with human immunodeficiency virus (HIV) or positive HIV serology at screening.

13. Infected with Mycobacterium tuberculosis (TB) as defined by the following:

    a. A positive Interferon Gamma Release Assay (IGRA) test performed at Screening or within the 12 weeks prior to Day 1 is exclusionary; a negative test is required for eligibility (except adequately treated latent or active TB infection as defined below). The following are acceptable IGRA assays: QuantiFERON®-TB Gold Plus test, QuantiFERON® - TB Gold test (QFT-G), QuantiFERON® - TB Gold In-Tube test (QFT-GIT), and T-SPOT® TB test (T-Spot).

        - If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary.

        - Subjects with repeat indeterminate IGRA results may be enrolled after consultation with pulmonary or infectious disease specialist that determines low risk of infection (ie, subject would be acceptable for immunosuppressant treatment without additional action).

        - Subjects who test positive for QFT-G/QFT-GIT test, but in the opinion of the Investigator are at low risk of TB infection may be referred to pulmonary or infectious disease specialist for consultation and potential IGRA test repeated once. Subjects will be eligible if the repeat test is negative before the randomization.

- If a subject has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug resistant TB infection are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, no IGRA test need be obtained, but a chest radiograph must still be obtained if not done so within the prior 12 weeks.

b. Chest radiograph taken at screening with changes suggestive of active TB infection, unless previously performed normal and documented chest radiograph within 12 weeks prior to Screening.

c. A history of either untreated or inadequately treated latent or active TB infection.

d. A subject who is currently being treated for active or latent TB infection is to be excluded.

14. Have been vaccinated with live or attenuated live vaccine within the 6 weeks prior to the first dose of study drug, or expects to be vaccinated with these vaccines during study treatment, or within the 6 weeks following the last dose of study drug. (For further information regarding avoidance of household contacts who may be vaccinated see Section 5.10). Recombinant subunit vaccines (eg, Shingrix®) is permitted and it is preferably that the last dose is administered at least 4 weeks prior to Day 1.

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

Disease under study related exclusion criteria

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

17. Currently have non-plaque forms of psoriasis, eg erythrodermic, guttate or pustular, with the exception of nail psoriasis, which is allowed. Have current drug-induced psoriasis, eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, antimalarial drugs or lithium.

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

19. Functional Class IV as defined by the American College of Rheumatology revised criteria for classification of functional status in rheumatoid arthritis, ie, limited in ability to perform usual self-care, vocational, and avocational activities.

Concomitant medication related exclusion criteria

20. Cannot discontinue systemic therapies and/or topical therapies for the treatment of psoriasis and cannot discontinue phototherapy (UVB or Psoralens + UVA phototherapy [PUVA]).

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

    - Biologics: All biologic agents not otherwise mentioned in this Protocol must be discontinued for a minimum of 6 months prior to first dose of study drug.

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

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

21. Subjects who have undergone treatment with injectable corticosteroids (eg, intraarticular, intramuscular or intravenous) within 4 weeks prior to the first dose of study drug, or may require injectable corticosteroids during the study (except intra-articular corticosteroids may be given as rescue medication; See Appendix 3, Rescue Therapy).

22. Subjects who have undergone treatment with any IL-17 inhibitor, IL-12/23 inhibitor, or IL-23 inhibitor, including but not limited to secukinumab (Cosentyx®), ixekizumab (Taltz®), ustekinumab (Stelara®), brodalumab (Siliq®), guselkumab (Tremfya®), risankizumab, bimekizumab, and tildrakizumab.

23. Subjects who have undergone treatment with any Janus kinase (Jak) inhibitors, (including but not limited to tofacitinib [Xeljanz®], baricitinib [Olumiant®], upadacitinib, peficitinib, filgotinib).

24. Subjects who have undergone treatment with apremilast (Otezla®) within 4 weeks of first dose of study drug.

25. Subjects who have undergone treatment with abatacept (Orencia®) within 10 weeks prior to first dose of study drug.

26. Subjects currently taking high potency opioid analgesics (Appendix 2, Prohibited Prior and Concomitant Medications).

27. Any prior treatment with non B cell-specific lymphocyte depleting agents/therapies (eg, alemtuzumab [Lemtrada®, CamPath®], alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation, etc); subjects who have received rituximab or other selective B-lymphocyte depleting agents (including experimental agents) within 6 months of first dose of study drug or 5 half-lives (if known), whichever is longer, or until lymphocyte count returns to normal, whichever is longer.

28. Have previously been treated with efalizumab (Raptiva®).

29. Require treatment with prohibited concomitant medication(s) (Appendix 2, Prohibited Prior and Concomitant Medications) or have received a prohibited concomitant medication within 7 days or 5 half-lives (whichever is longer) prior to first dose of study drug.

Other exclusionary conditions

30. 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.

31. History of alcohol or drug abuse in investigator's opinion unless in full remission for greater than 12 months prior to first dose of study medication.

32. Screening 12-lead electrocardiogram (ECG) that demonstrates clinically significant abnormalities requiring treatment (eg, acute myocardial infarction, serious tachy- or brady-arrhythmias) or that are indicative of serious underlying heart disease (eg, cardiomyopathy, major congenital heart disease, low voltage in all leads, Wolff-Parkinson-White syndrome) and other clinically relevant abnormalities which may affect subject safety or interpretation of study results. Specifically, subject with screening or Day 1/Baseline QTcF >450 milliseconds (msec) should be excluded. If QTcF exceeds 450 msec, the ECG should be repeated two more times and the average of the three QTcF should be used to determine the subject eligibility.

33. A history of additional risk factors for torsade de pointes (TdP) (eg, heart failure [New York Heart Association status of class III or IV], hypokalemia, family history of Long QT Syndrome).

34. Use of concomitant medications that prolong the QT interval.

35. A subject with a malignancy or 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 with no evidence of recurrence.

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

37. 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 meets all Subject Eligibility Criteria for participation in the study at the baseline visit, may be randomized into this study. Subjects will be randomized in a 4:4:1:1:2:2 ratio to one of the six parallel treatment sequences in Table 1. Randomization will be stratified by prior TNFi exposure. A centralized computer-generated randomization schedule will be used to assign subjects to the treatment sequences. Subjects will be assigned a subject identification number in the order of their screening for the study. The identifying number will be retained throughout the study.

4.4. Lifestyle Requirements

4.4.1. Contraception

In this study, fertile male subjects and female subjects who are of childbearing potential as applicable to the study will receive PF-06700841, which has been associated with demonstrated teratogenicity/fetotoxicity in animals (more details in the IB). Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of effective contraception (one must be highly effective contraception) throughout the study and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected 2 appropriate methods of contraception for the individual subject and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the subject has been instructed in their 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 2 effective methods of contraception (one must be highly effective contraception) consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or designee will instruct the subject to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the subject or partner.

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

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male sterilization with absence of sperm in the postvasectomy ejaculate.

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

Examples of effective, but not highly effective methods of contraception can be found in Appendix 8.

Male subjects should refrain from donating sperm during the study and for at least 90 days after the last administration of the investigational product.

4.4.2. Fasting Visit Requirements

On visit days when fasting lipid panels are scheduled to be collected, all subjects should refrain from all food and liquids (water and medications permitted, if appropriate) for at least 8 hours prior to scheduled safety laboratory tests. Visits that require fasting are indicated in the Schedule of Activities.

4.4.3. Other Requirements

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

- Agree to avoid strenuous exercise during the study, especially within one week prior to the scheduled study visits and maintain adequate hydration, if possible.

- 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.

- Refrain from consumption of grapefruit or grapefruit juice or citrus fruits eg, Seville oranges, pomelos within 7 days prior to the first dose of study medication until the end of treatment (Week 52).

- On study visit days, showering or bathing is permitted prior to attending the study visit, but do not moisturize.

- As needed, subjects may use the permitted psoriasis treatments as listed in Section 5.8.1 for the specified body sites described. On clinic visit days, do not use any of these treatments until after the clinic visit is completed.

- On study visit days, take prescribed permitted concomitant medication, as needed, prior to the study visit, if it can be administered with water only.

- Must agree to avoid prolonged exposure to the sun and avoid use of tanning booths or other ultraviolet light sources during the study.

- Discontinue and avoid using certain medications and treatments used to treat PsA or psoriasis (see Section 5 and Appendix 2). Discontinue and avoid using certain other prohibited medications and treatments (see Section 5 and Appendix 2) not used to treat PsA or psoriasis. For a medical condition where it is important for the subject's safety to continue using the prohibited drug, and where there is no study-permitted alternative, the subject must not participate in this study.

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

- Avoid having elective surgery.

- 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 Week 16 visit, but preferably after Week 52 visit.

4.5. Sponsor's Qualified Medical Personnel

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

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

For this study, the investigational product is PF-06700841.

5.1. Allocation to Treatment

Subjects will be randomized in a 4:4:1:1:2:2 ratio to one of the six parallel treatment sequences in Table 1. 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, 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.

5.2. Breaking the Blind

The study will be subject and investigator blinded. 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 (but not required) 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 case report form (CRF).

At all times, treatment and randomization information will be kept confidential and will not be released to the investigator/study stuff until the conclusion of the study.

5.3. Subject Compliance

For self-administration of study medication at home, compliance will be captured and completed by the subject.

Subject compliance with dosing administration will be verified by accounting of returned study medication at each clinic visit. When study medication is administered at the research facility, it will be administered under the supervision of study personnel.

Compliance of the study drug will be monitored by the accounting of unused medication returned by the subject and will be documented. Subjects will be directed to bring any used and unused blister cards to each visit after randomization. The number of tablets dispensed minus the number of tablets returned will be used to calculate the number of tablets taken and compliance.

- Subjects who demonstrate <80% compliance should be counseled by the investigator or designee and ensure steps are taken to improve compliance. Subjects who are <80% compliant with dosage regimen for any two consecutive visit periods should be withdrawn from the study.

- If the subject is over-compliant (>120%) with study drug (intentional or accidental) the investigator or designee is to counsel the subject and ensure correct understanding of the study drug dosing regimen. The investigator should contact the Pfizer Study Clinician promptly with any over-compliance that may potentially impact the safe use of study drug or that may result in a serious adverse event (SAE; See Section 8 for SAE reporting).

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

Blinded PF-06700841 tablets and matching placebo will be provided as tablets for oral administration. The PF-06700841, 5 mg and 25 mg tablets and their matching placebos will be supplied in blisters and labeled according to local regulatory requirements.

5.4.2. Preparation and Dispensing

The investigational product will be dispensed using an IRT drug management system at each visit from Day 1 to Week 44. A qualified staff member will dispense the investigational product via unique container numbers in the blister cards provided, in quantities appropriate for the study visit schedule. The subject/caregiver should be instructed to maintain the product in the blister cards provided throughout the course of dosing and return the blister cards to the site at the next study visit.

5.5. Administration

Subjects will receive investigational product (IP) as outpatients. PF-06700841 tablets and matching placebo for oral administration will be dispensed in blisters. Subjects will be provided dosing instructions.

All subjects, regardless of assigned treatment regimen will receive blinded QD dosing throughout the study treatment period to maintain the study blind.

Sites will be trained on how subjects should take tablets at home through an IP manual and/or other vehicle(s). Sites are responsible for communicating this information.

Subjects should take the medication orally for 52 weeks from study Days 1 through Week 52 during the trial; Subjects will be encouraged to take the medication in the morning whenever possible; Subjects should swallow the tablets with ambient temperature water to a total volume of approximately 240 mL; Subjects will swallow the investigational product whole, and will not manipulate or chew the medication prior to swallowing; IP may be taken with or without food; however, for the Week 2 study visit day only, subjects are to be instructed to refrain from dosing at home and are to bring the investigational product with them, and are to

take the dose in the clinic from their previous blister card and dose from the newly dispensed blister card on the next day at home.

If a dose is missed and the interval to the next dose is less than 8 hours, the missed dose should not be administered.

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 SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt 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.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

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

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 blister cards of study drug must be returned to the investigator by the subject at every applicable 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 Treatments

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

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

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

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

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

5.8.1. Permitted Background Pain or Other Psoriatic Arthritis Therapy

Subjects taking permitted traditional non-biologic DMARDs (eg, methotrexate (≤25 mg/week), sulfasalazine (≤3 gm/day), leflunomide (≤20 mg/day)), nonsteroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), acetaminophen/paracetamol, and/or corticosteroids (≤10 mg prednisone mg/day) should remain on the same dose regimen throughout the study except if adjustment is needed to protect the subject's safety (See Appendix 5, Oral Corticosteroid Equivalents).

Daily dosage of NSAIDs/COX-2 inhibitors, corticosteroids, permitted 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.

As needed (PRN) dosage of NSAIDs/COX-2 inhibitors, permitted opioids, or paracetamol/acetaminophen within the 2 weeks before randomization can continue after randomization, however, subject have to refrain from any intake within the 24 hours prior to any study visit.

The total daily dose of acetaminophen may not exceed 2.6 grams per day, and the total daily dose of opioid may not exceed the potency equivalent of 30 mg of orally-administered morphine (See Appendix 4, Maximum Allowed Total Daily Dose of Opioid Analgesics).

Intravenous or intramuscular corticosteroids are not allowed during this study either as a stable concomitant medication or as rescue medication.

Concomitant psoriasis therapies are not permitted during the study, with the exception of:

Table 2. Permitted Topical Concomitant Psoriasis Treatment

Body Region	Permitted Topical Treatments
Palms, soles, face, and intertriginous areas	Hydrocortisone ≤1% and hydrocortisone acetate ≤1% are the only topical corticosteroids permitted
Scalp	Tar preparations Salicylic acid preparations, Shampoos free of corticosteroids
All body regions	Study supplied non-medicated emollient, Cetaphil® moisturizing cream

5.8.2. Prohibited Concomitant Medications

Prohibited drugs must be discontinued according to protocol guidelines; a list of prohibited drugs with specific discontinuation recommendations is listed in Appendix (See Appendix 2, Prohibited Prior and Concomitant Medications).

Subjects taking certain medications for PsA, and deriving inadequate benefit from them, may enter the study after a sufficient washout period for that medication. Subjects receiving certain medications for psoriasis may enter the study after a sufficient washout period for that medication. All biologic DMARDs are prohibited. Non-biologic DMARD other than methotrexate, leflunomide or sulfasalazine are prohibited. Injectable corticosteroids are

prohibited except for use as rescue medication (Appendix 3, Rescue Therapy). High potency opioid analgesics (eg, methadone, hydromorphone, buprenorphine, and fentanyl) are prohibited.

5.8.3. 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 significant CYP3A inhibition or induction. Otherwise, herbals with pharmaceutical properties must be discontinued for at least 4 weeks prior to first dose of study drug, unless there is sufficient data available regarding the duration of an herbal medication's [redacted] All other prohibited drugs require at least a 7 day or 5 half-life (whichever is longer) washout period prior to the first dose of study treatment.

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

5.9. Rescue Medications

The only medications that are allowed for rescue are listed and detailed in Appendix (Appendix 3, Rescue Therapy). Briefly, acetaminophen/paracetamol (dosed no more than 2.6 gm/day) and/or opioid (not exceeding the potency equivalent of 30 mg of orally-administered morphine) are allowable as rescue medication throughout the study if dosed for no more than 10 consecutive days (See Section 5.8.1 for stable background usage of acetaminophen/paracetamol and permitted opioids).

- Subjects who require rescue for more than 10 consecutive days should be discontinued from the study.
- Subjects must not be dosed with rescue medication on the preceding day or the same day of a study visit (including Day 1/Randomization, Week 16 and any study visit where efficacy assessments are being collected), except if adjustment is needed because subject is experiencing intolerable pain.
- Baseline stable use acetaminophen/paracetamol or opioids should NOT be discontinued in advance of study visits.

In addition, intra-articular corticosteroids or hyaluronate sodium will be allowed as rescue medication and may be given at or after the Week 16 visit only. If performed at the Week 16 visit, intra-articular injections must be given after all assessments are completed. Injected joints will also be considered as having their pre-injection status (swollen and/or painful/tender) and should not be counted for the remainder of the trial.

5.10. Vaccination

Vaccination with live virus, attenuated live virus, or any live viral components is prohibited within the 6 weeks prior to the first dose of study drug, during the study, and for 6 weeks after the last dose of investigational product. Similarly, current routine household contact with individuals who have been vaccinated with live vaccine components should be avoided during treatment and for 6 weeks following completion of treatment. Such vaccines include but are not limited to: FluMist® (intranasal influenza vaccine), attenuated rotavirus vaccine, varicella (chickenpox) vaccine, attenuated typhoid fever vaccine, oral polio vaccine, MMR (measles, mumps, rubella) vaccine and vaccinia (smallpox) 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.

Recombinant subunit vaccines (eg, Shingrix®) is permitted and it is preferably that the last dose is administered at least 4 weeks prior to Day 1.

6. STUDY PROCEDURES

6.1. Screening

Subjects will be screened within 35 days prior to administration of study medication to confirm that they meet the entrance criteria for the study.

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

The following procedures will be performed during Screening:

- Obtain written Informed Consent;
- Register Subject Using IRT System;
- Demography;
- Contraception Check: Male subjects able to father children and female subjects of childbearing potential must agree to use two effective methods (one of which is highly effective method) of contraception throughout the study and for at least 28 days after the last dose of assigned treatment. Appropriate contraception must be commenced from Screening;
- Confirmation of PsA diagnosis: The subject must have a diagnosis of PsA based upon the CASPAR Criteria. PsA disease subtype will be documented in CRF;
- Tender/Painful Joint Count (68), Swollen Joint Count (66): Subject must have evidence of active arthritis as defined by having at least 3 tender/painful joints on motion (out of 68 joints assessed) and at least 3 swollen joints (out of 66 joints assessed) at both Screening and Baseline (Randomization);

- Dermatological Assessment of active plaque psoriasis;

- Prior and Concomitant treatments: Include a complete history of all DMARDs ever taken with reasons for discontinuation (those taken during the 1 year prior to the first dose of study drug should include dose and duration of treatment). In addition to DMARD, complete history of steroid (oral/injectable/topical) and NSAIDs. History of all other drugs (including nonprescription drugs, vitamins, and dietary supplements), taken within 4 weeks prior to screening procedures;

- Medical history: Include history of infection such as zoster. The medical history should also include smoking status; average weekly alcohol consumption and family history of disease including premature coronary heart disease (CHD). Premature coronary heart disease is defined as CHD in a male first-degree relative first observed at <55 years or CHD in female first-degree relative first observed at <65 years;

- Vital signs: Sitting blood pressure, pulse rate and temperature;

- Complete Physical Examination (including height): Height (at Screening Visit only), weight; general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (presence of peripheral edema), abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes;

- Perform a single 12-lead ECG (read locally and centrally): If QTcF exceeds 450 ms, the ECG should be repeated two more times and the average of the three QTcF should be used to determine the subject eligibility;

- Chest radiograph. Chest X-ray or other appropriate diagnostic imaging (ie, CT or MRI) may be performed up to 12 weeks prior to Screening Visit. Official reading (by radiologist or pulmonologist per local standard of care) must be located in the source documentation;

- Central laboratory testing: Serum FSH or Serum Pregnancy test; Hematology, Chemistry, Rheumatoid Factor (RF), Cyclic Citrullinated Peptide (CCP) Antibodies, Urinalysis, High-Sensitivity C-Reactive Protein (hsCRP), HIV Testing, HBsAg, HBcAb, HBsAb and HCV Ab and HCV RNA PCR if HCV Ab is positive, Tuberculosis Tests, Urine Myoglobin. Specifically:

    - Serum Follicle stimulating hormone (FSH) test to be performed at Screening to confirm postmenopausal status in female subjects who have been amenorrheic for at least 12 consecutive months;

    - Serum Pregnancy test is required for all Women of Childbearing Potential;

  - Tuberculosis Tests: QuantiFERON-Gold (QFT-G) or other Interferon Gamma Release Assay (IGRA) test: Must be performed unless previously tested and documented within 12 weeks prior to Day 1/Randomization OR unless subject has previously received an adequate course of therapy for either latent or active TB infection;

  - Screening laboratory tests with abnormal results may be repeated once to confirm abnormal results; the last value will be used to determine eligibility. If results return to normal within the 5-week screening period, the subject may enter the study;

- Review all Inclusion and Exclusion criteria;

- Assess for occurrence of Adverse Events: The reporting period starts with the signing of the informed consent.

Sites will be permitted to re-screen subjects (with a new screening number) who initially do not meet eligibility criteria **once**. Subjects may not be rescreened unless approved by the sponsor. Rescreening of subjects will be allowed in a limited number of circumstances as determined by the Pfizer study clinician (eg, subject requires washout of prohibited medications, requires antimicrobial therapy within 2 weeks prior to the first dose of study medication, requires emergency surgery) and should be confirmed with the Pfizer study clinician when rescreening can occur.

6.2. Study Period

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

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

All rheumatological and dermatological assessments will be performed by qualified, trained assessors who are blinded to the subject's safety data, previous efficacy data and treatment randomization. Assessors performing efficacy assessments are not required to be blinded prior to treatment randomization, ie at Screening and Baseline visits. To ensure consistency and reduce intra-individual variability, the same qualified assessor should score all evaluations for a particular assessment for a given subject throughout the study (See Section 7.6 Rater (Assessor) Qualifications).

6.2.1. Baseline Day 1

Subjects are required to fast for at least 8 hours prior to the visit.

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

- These PROs include the following:
  - Patient's Assessment of Arthritis Pain;
  - Patient's Global Assessment of Arthritis;
  - Health Assessment Questionnaire (HAQ) disability index (DI);
  - Patient's Global Joint and Skin Assessment-Visual Analog Scale (PGJS-VAS);
  - [redacted]
  - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue);
  - Short-Form-36 Health Survey (SF-36) Version 2, Acute;
  - [redacted]
  - [redacted]
  - [redacted]

All clinical rheumatological and dermatological assessments will be performed by qualified, trained assessors:

- Clinical Rheumatology Assessments by qualified, trained assessors:
  - Tender/painful joint counts (68) and Swollen joint counts (66): Subject must have evidence of active arthritis as defined by having at least 3 tender/painful joints on motion (out of 68 joints assessed) and at least 3 swollen joints (out of 66 joints assessed) at both Screening and Baseline (Randomization);
  - Physician's Global Assessment of Arthritis;
  - Physician's Global Assessment of Psoriatic Arthritis;
  - Dactylitis Assessment;
  - Enthesitis Assessment (Spondyloarthritis Research Consortium of Canada [SPARCC]), Leeds Enthesitis Index).

- Clinical Dermatology Assessments by qualified, trained assessors:
  - Evaluation of Plaque Psoriasis;
  - [redacted]
  - Psoriasis Area and Severity Index (PASI);
  - Body Surface Area (BSA);
  - Nail Psoriasis Severity Index (NAPSI).

Other clinical assessment procedures that will be performed prior to randomization and the first dose of study drug on Day 1 for baseline include:

- Contraception Check: Male subjects able to father children and female subjects of childbearing potential must agree to use two effective methods (one of which is highly effective method) of contraception throughout the study and for at least 28 days after the last dose of assigned treatment;
- Medical History: Review any changes in the medical history (any AEs happened before the first dosing of Investigational Product should be reflected on the medical history);
- Complete Physical Examination: Weight, general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (presence of peripheral edema), abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes;
- Perform 12-lead ECG in triplicate approximately 2-4 minutes apart (read locally and centrally): The average of three ECG measurements will serve as baseline value. If baseline QTcF exceeds 450 ms, subjects should be excluded;
- Vital signs: Sitting blood pressure, pulse rate and temperature;
- Urine Pregnancy Tests (conducted at study site) must be performed prior to dosing with the investigational product for female subjects of childbearing potential. Two negative pregnancy tests are required before receiving investigational product (1 negative Serum Pregnancy Test at Screening and 1 negative Urine Pregnancy Tests at the Baseline Day 1 visit);
- Central laboratory testing: Hematology, Chemistry, Fasting Lipid Panel, Serum Cystatin C, Urinalysis, Urine Myoglobin, High-Sensitivity C-Reactive Protein (hsCRP), FACS-TBNK, and Viral Surveillance (EBV, CMV, HSV1, HSV2, and VZV);

- Collect banked biospecimen (Prep D1, Prep R1, Prep B2.5 and Prep B1.5);
- Review of prior and concomitant treatment;
- Review of rescue medication;
- Inclusion/Exclusion review.

If the subject is eligible for continued participation:

- Randomization;
- Investigational Product Dispensing and Administration;
- Monitoring of adverse events;
- Subjects are to be instructed not to take the study medication prior to coming to the clinic at the next (Week 2) visit but to bring the study medication with them to the visit.

6.2.2. Week 2 Visit

There is a ±3 day window for this visit.

CCI [redacted]

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

- These PRO include the following:
  - Patient's Assessment of Arthritis Pain;
  - Patient's Global Assessment of Arthritis;
  - Health Assessment Questionnaire (HAQ) disability index (DI);
  - Patient's Global Joint and Skin Assessment-Visual Analog Scale (PGJS-VAS);
  - CCI [redacted]
  - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue);
  - CCI [redacted]

[redacted]

All clinical rheumatological and dermatological assessments will be performed by blinded, qualified, trained assessors.

- Clinical Rheumatology Assessments by blinded assessor:
  - Tender/painful joint counts (68) and Swollen joint counts (66);
  - Physician's Global Assessment of Arthritis;
  - Physician's Global Assessment of Psoriatic Arthritis;
  - Dactylitis Assessment;
  - Enthesitis Assessment (Spondyloarthritis Research Consortium of Canada [SPARCC]), Leeds Enthesitis Index).
- Clinical Dermatology Assessments by blinded assessor:

  [redacted]

  - Psoriasis Area and Severity Index (PASI);
  - Body Surface Area (BSA);
  - Nail Psoriasis Severity Index (NAPSI).

Other clinical assessment procedures that will be performed include:

- Contraception Check: Male subjects able to father children and female subjects of childbearing potential must agree to use two effective methods (one of which is highly effective method) of contraception throughout the study and for at least 28 days after the last dose of assigned treatment;
- Targeted Physical Examination should include skin, heart, lungs, and abdomen and examination of body systems where there are symptom complaints by the subject;
- Perform a single 12 lead ECG (read locally and centrally): At Week 2 visit only, ECG will be collected between 2-4 hours post-dose.
- Vital signs: Sitting blood pressure, pulse rate and temperature;
- Urine Pregnancy Tests (conducted at study site) must be performed for female subjects of childbearing potential;

- Central laboratory testing: Hematology, Chemistry, Serum Cystatin C, Urinalysis, High-Sensitivity C-Reactive Protein (hsCRP), FACS-TBNK;
- Collect banked biospecimen (Prep R1, Prep B2.5 and Prep B1.5);
- CCI [redacted]
- Review of concomitant treatment;
- Review of rescue medication;
- Monitoring of adverse events;
- Investigational Product Accountability.

If the subject is eligible for continued participation:

- Investigational Product Dispensing.

6.2.3. Week 4, 8, 12, 16 Visit

There is a ±3 day window for the Week 4 Visit, and ±7 day window for the rest of the Visits.

Subjects are required to fast for at least 8 hours prior to the Week 8 and Week 16 visits only.

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

- These PROs include the following:
  - Patient's Assessment of Arthritis Pain;
  - Patient's Global Assessment of Arthritis;
  - Health Assessment Questionnaire (HAQ) disability index (DI);
  - Patient's Global Joint and Skin Assessment-Visual Analog Scale (PGJS-VAS);
  - CCI [redacted]
  - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue);
  - Short-Form-36 Health Survey (SF-36) Version 2, Acute;
  - CCI [redacted]

- [redacted]
- [redacted]

All clinical rheumatological and dermatological assessments will be performed by qualified, trained assessors.

- Clinical Rheumatology Assessments by blinded assessor:
  - Tender/painful joint counts (68) and Swollen joint counts (66);
  - Physician's Global Assessment of Arthritis;
  - Physician's Global Assessment of Psoriatic Arthritis;
  - Dactylitis Assessment;
  - Enthesitis Assessment (Spondyloarthritis Research Consortium of Canada [SPARCC]), Leeds Enthesitis Index).
- Clinical Dermatology Assessments by blinded assessor:
  - [redacted]
  - Psoriasis Area and Severity Index (PASI);
  - Body Surface Area (BSA);
  - Nail Psoriasis Severity Index (NAPSI).

Other clinical assessment procedures that will be performed include:

- Contraception Check: Male subjects able to father children and female subjects of childbearing potential must agree to use two effective methods (one of which is highly effective method) of contraception throughout the study and for at least 28 days after the last dose of assigned treatment;
- Complete Physical Examination (Week 16 Visit only): Weight, general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (presence of peripheral edema), abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes;
- Targeted Physical Examination (Week 4, 8, 12 Visits only) should include skin, heart, lungs, and abdomen and examination of body systems where there are symptom complaints by the subject;

- Perform a single 12-lead ECG (read locally and centrally; Week 16 only);
- Vital signs: Sitting blood pressure, pulse rate and temperature;
- Urine Pregnancy Tests (conducted at study site) must be performed for female subjects of childbearing potential;
- Central laboratory testing: Hematology, Chemistry, Fasting Lipid Panel (Week 8 and Week 16 visits only), Serum Cystatin C, Urinalysis, High-Sensitivity C-Reactive Protein (hsCRP), FACS-TBNK;
- Collect banked biospecimen (Prep R1, Prep B2.5 and Prep B1.5) at Week 4, 16 only;
- [redacted]
- Review of concomitant treatment;
- Review of rescue medication;
- Monitoring of adverse events;
- Investigational Product Accountability.

If the subject is eligible for continued participation:

- Investigational Product Dispensing.

6.2.4. Week 20, 28, 36, 44 Visit

There is a ±7 day window for these Visits.

Subjects are required to fast for at least 8 hours prior to the Week 28, 36, 44 visits.

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

- These PROs include the following:
  - Patient's Assessment of Arthritis Pain;
  - Patient's Global Assessment of Arthritis;
  - Health Assessment Questionnaire (HAQ) disability index (DI);
  - Patient's Global Joint and Skin Assessment-Visual Analog Scale (PGJS-VAS);
  - [redacted]

- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue);
- Short-Form-36 Health Survey (SF-36) Version 2, Acute;
- [redacted]

All clinical rheumatological and dermatological assessments will be performed by qualified, trained assessors.

- Clinical Rheumatology Assessments by blinded assessor:
  - Tender/painful joint counts (68) and Swollen joint counts (66);
  - Physician's Global Assessment of Arthritis;
  - Physician's Global Assessment of Psoriatic Arthritis;
  - Dactylitis Assessment;
  - Enthesitis Assessment (Spondyloarthritis Research Consortium of Canada [SPARCC]), Leeds Enthesitis Index).
- Clinical Dermatology Assessments by blinded assessor:
  - [redacted]
  - Psoriasis Area and Severity Index (PASI);
  - Body Surface Area (BSA);
  - Nail Psoriasis Severity Index (NAPSI).

Other clinical assessment procedures that will be performed include:

- Contraception Check: Male subjects able to father children and female subjects of childbearing potential must agree to use two effective methods (one of which is highly effective method) of contraception throughout the study and for at least 28 days after the last dose of assigned treatment;
- Targeted Physical Examination should include skin, heart, lungs, and abdomen and examination of body systems where there are symptom complaints by the subject;
- Perform a single 12 lead ECG (read locally and centrally);

- Vital signs: Sitting blood pressure, pulse rate and temperature;
- Urine Pregnancy Tests (conducted at study site) must be performed for female subjects of childbearing potential;
- Central laboratory testing: Hematology, Chemistry, Fasting Lipid Panel (Week 28, 36, 44 visits only), Serum Cystatin C, Urinalysis, High-Sensitivity C-Reactive Protein (hsCRP), FACS-TBNK;
- [redacted]
- Review of concomitant treatment;
- Review of rescue medication;
- Monitoring of adverse events;
- Investigational Product Accountability.

If the subject is eligible for continued participation:

- Investigational Product Dispensing.

6.2.5. Week 52 Visit or Early Termination Visit

There is a ±7 day window for the Week 52 Visit.

Subjects are required to fast for at least 8 hours prior to the visit.

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

- These PROs include the following:
  - Patient's Assessment of Arthritis Pain;
  - Patient's Global Assessment of Arthritis;
  - Health Assessment Questionnaire (HAQ) disability index (DI);
  - Patient's Global Joint and Skin Assessment-Visual Analog Scale (PGJS-VAS);
  - [redacted]
  - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue);
  - Short-Form-36 Health Survey (SF-36) Version 2, Acute;

[redacted]

All clinical rheumatological and dermatological assessments will be performed by qualified, trained assessors.

- Clinical Rheumatology Assessments by blinded assessor:
  - Tender/painful joint counts (68) and Swollen joint counts (66);
  - Physician's Global Assessment of Arthritis;
  - Physician's Global Assessment of Psoriatic Arthritis;
  - Dactylitis Assessment;
  - Enthesitis Assessment (Spondyloarthritis Research Consortium of Canada [SPARCC]), Leeds Enthesitis Index).
- Clinical Dermatology Assessments by blinded assessor:

  [redacted]

  - Psoriasis Area and Severity Index (PASI);
  - Body Surface Area (BSA);
  - Nail Psoriasis Severity Index (NAPSI).

Other clinical assessment procedures that will be performed include:

- Contraception Check: Male subjects able to father children and female subjects of childbearing potential must agree to use two effective methods (one of which is highly effective method) of contraception throughout the study and for at least 28 days after the last dose of assigned treatment;
- Complete Physical Examination: Weight, general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (presence of peripheral edema), abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes;
- Perform a single 12-lead ECG (read locally and centrally);

- Vital signs: Sitting blood pressure, pulse rate and temperature;
- Urine Pregnancy Tests (conducted at study site) must be performed for female subjects of childbearing potential;
- Central laboratory testing: Hematology, Chemistry, Fasting Lipid Panel, Serum Cystatin C, Urinalysis, High-Sensitivity C-Reactive Protein (hsCRP), FACS-TBNK;
- Collect banked biospecimen (Prep R1, Prep B2.5 and Prep B1.5);
- [redacted]
- Review of concomitant treatment;
- Review of rescue medication;
- Monitoring of adverse events;
- Investigational Product Accountability.

6.2.6. Follow-up Visit

A Follow-up Visit will be completed 4 weeks after the last administration of the investigational product for all subjects who complete the Week 52 Visit or Early Termination Visit.

There is a +7 days window for the Follow-up Visit.

Subjects are required to fast for at least 8 hours prior to the visit.

The following procedures will be performed:

- Contraception Check: Male subjects able to father children and female subjects of childbearing potential must agree to use two effective methods (one of which is highly effective method) of contraception throughout the study and for at least 28 days after the last dose of assigned treatment;
- Targeted Physical Examination should include skin, heart, lungs, and abdomen and examination of body systems where there are symptom complaints by the subject;
- Vital signs: Sitting blood pressure, pulse rate and temperature;
- Urine Pregnancy Tests (conducted at study site) must be performed for female subjects of childbearing potential;
- Central laboratory testing: Hematology, Chemistry, Fasting Lipid Panel, Serum Cystatin C, Urinalysis;

- Review of concomitant treatment;
- Monitoring of adverse events.

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

In the event that a Follow-up Visit is not possible, at the bare minimum, a follow-up phone contact must be completed 4 weeks (+7 days window) after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section).

Any subject meeting discontinuation criteria for adverse events, laboratory, or ECG (Appendix 6, Discontinuation Criteria) must enter into the Follow up Period with additional follow up visit occurring 1 week after their last dose or Early Termination Visit whenever possible, and follow up until any clinically relevant abnormalities or adverse events have resolved, returned to a baseline state, or are deemed clinically stable. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her.

6.3. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

The investigator may withdraw/early terminate a subject from the study treatment based on the Discontinuation Criteria described in Appendix 6, Discontinuation Criteria. An Early Termination Visit and subsequent Follow-up Visit should be completed in the case where a subject is withdrawn from the study treatment by the investigator.

Withdrawal of consent:

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

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures, ie, Early Termination Visit and Follow-up Visit as specified in Section 6.2. 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. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible.

The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page.

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response according to the definition of adverse event noted in Protocol Section 8 ADVERSE EVENT REPORTING. 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".

Lost to follow-up (LTFU):

If a subject does not return for a scheduled visit, every effort should be made to contact the subject who is potentially LTFU. In any circumstance, every effort should be made to document subject outcome, if possible.

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. A subject should not be considered a withdrawal due to LTFU until at least 3 attempts to contact the subject by multiple methods have been unsuccessful. All methods of attempted contact with the subject must be clearly documented (dated and initialed) in the subject's source documents and recorded on appropriate case report form (CRF) page.

If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

All potential LTFU subjects must be discussed with the Pfizer study team or designee prior to assigning LTFU status.

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. Efficacy Assessments

7.1.1. Clinical Rheumatology Assessments

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

7.1.1.1. Tender/Painful and Swollen Joint Count

Tender/Painful and swollen joints will be assessed by a blinded assessor to determine the number of joints that are considered tender/painful and/or swollen using the following scale: Present/Absent/Not Done/Not Applicable (to be used for artificial or missing joints). Artificial joints will not be assessed. Injected joints will be counted according to their pre-injection status for the remainder of the study.

The sixty-eight (68) joints to be assessed for tenderness are:[19]

- Upper Body: 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular;
- Upper Extremity: 2 shoulder, 2 elbow, 2 wrist (includes radiocarpal, carpal and carpometacarpal considered as one unit), 10 metacarpophalangeals (MCP I, II, III, IV, V), 2 thumb interphalangeal (IP), 8 proximal interphalangeals (PIP II, III, IV, V), 8 distal interphalangeals (DIP II, III, IV, V);
- Lower Extremity: 2 hip, 2 knee, 2 ankle, 2 tarsus (includes subtalar, transverse tarsal and tarsometatarsal considered as one unit), 10 metatarsophalangeals (MTP I, II, III, IV, V), 2 great toe interphalangeal (IP), 8 proximal and distal interphalangeals combined (PIP II, III, IV, V).

The sixty-six (66) joints to be assessed for swelling are the same as those listed above for tenderness assessment, except that the 2 hip joints are not included in the swollen joint count.

The 28 joints to be assessed for tenderness and/or swelling are: 2 shoulders, 2 elbows, 2 wrists, 10 metacarpophalangeal joints (MCP), 10 proximal interphalangeal joints (PIP), and 2 knees. The 28 joints count will be calculated by sponsor from the 68/66 tender/swollen joint count assessed as described above.

7.1.1.2. Physician's Global Assessment of Arthritis

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

THE PATIENT'S ARTHRITIS AT THIS TIME IS:

(PLEASE MAKE AN X MARK ON THE LINE BELOW.)

Very Good _____ Very Poor

[Note: Scale will be 100 mm in length]

7.1.1.3. Physician's Global Assessment of Psoriatic Arthritis

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

THE PATIENT'S OVERALL PSORIATIC ARTHRITIS AT THIS TIME IS:

(PLEASE MAKE AN X MARK ON THE LINE BELOW.)

Not active at all _____Extremely active

[Note: Scale will be 100 mm in length]

7.1.1.4. Dactylitis Assessment

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

7.1.1.5. Enthesitis Assessment (Spondyloarthritis Research Consortium of Canada [SPARCC]), Leeds Enthesitis Index)

Number of sites with enthesitis will be evaluated by a blinded assessor using the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index[20] and Leeds Enthesitis Index (LEI).[21]

The SPARCC Enthesitis Index examines tenderness at sixteen sites: medial epicondyle humerus, lateral epicondyle humerus, supraspinatus insertion into greater tuberosity of humerus, greater trochanter, quadriceps insertion into superior border of patella, patellar ligament insertion into inferior pole of patella or tibial tubercle (considered 1 site for scoring purposes), Achilles tendon insertion into calcaneum and plantar fascia insertion into calcaneum. Each site is classified on a dichotomous basis as either tender (score=1) or not tender (score=0). The SPARCC Enthesitis Index scores range from 0-16, with higher scores indicating higher disease activity.[20]

The Leeds Enthesitis Index (LEI) examines tenderness at six sites: lateral epicondyle humerus, medial femoral condyle and Achilles tendon insertion. Each site is assessed as either tender (score=1) or not tender (score=0). The LEI scores range from 0-6, with higher scores indicating higher disease activity.[21]

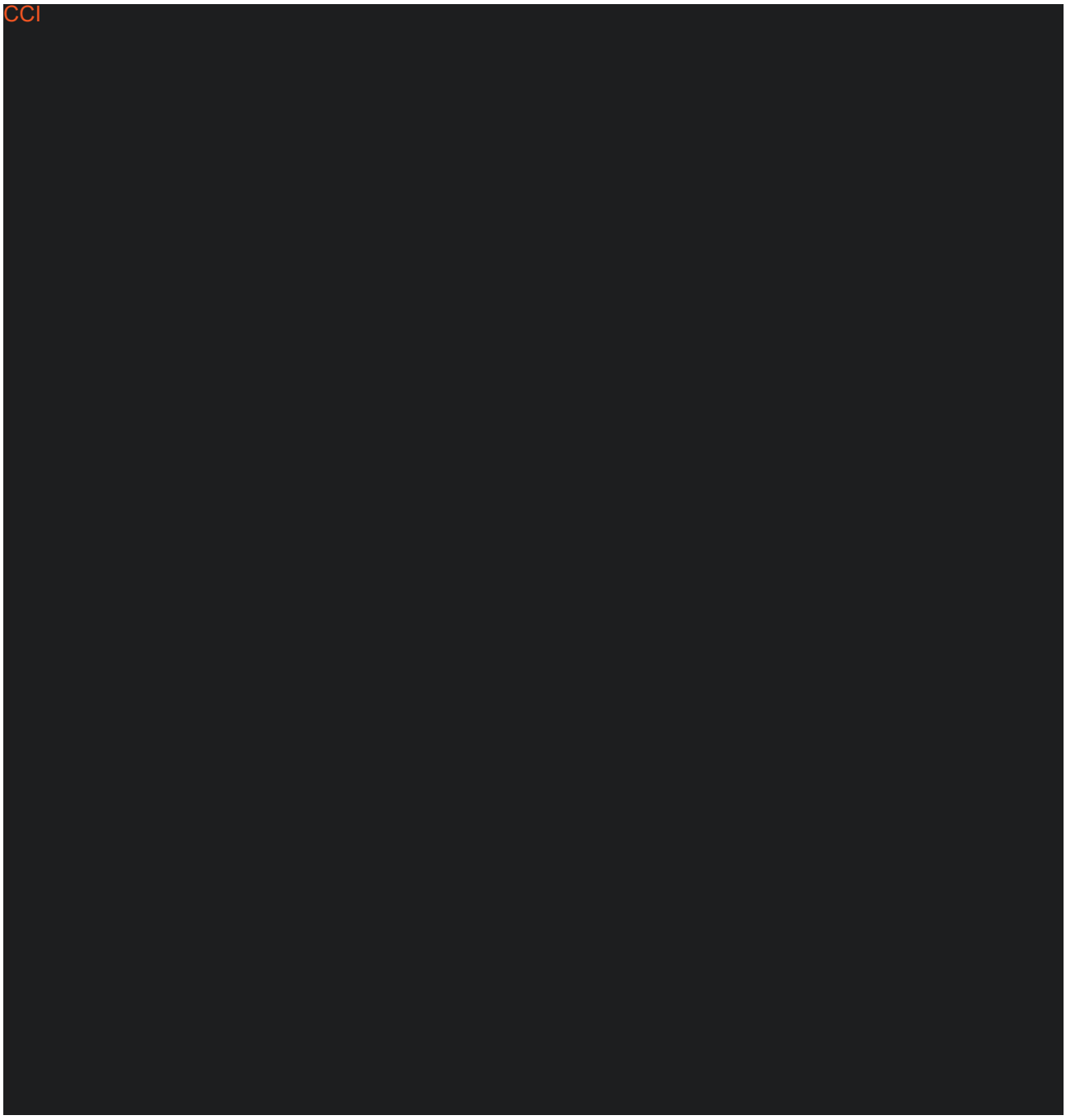
7.1.2. Clinical Dermatology Assessments

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

7.1.2.1. Evaluation of Plaque Psoriasis

Subject must have active plaque psoriasis, with at least one psoriatic plaque or nail changes consistent with psoriasis, at both Screening and Baseline (Day 1/Randomization) which has been diagnosed or confirmed by a dermatologist or a sponsor-approved rheumatologist.

CCI [redacted]



7.1.2.3. Body Surface Area (BSA)

Assessment of body surface area involved in psoriasis is performed separately for four body regions: head (including neck), upper limbs, trunk (including axillae and groin), and lower limbs (including buttocks).

The percent BSA with psoriasis is estimated by means of the handprint method,[22] where the full palmar hand of the subject (ie, the subject's fully extended palm, fingers and thumb together) represents approximately 1% of the total BSA and a set percentage of each body region:

- 1 handprint corresponds to approximately 10% of the head (including neck);
- 1 handprint corresponds to approximately 5% of the upper limbs;
- 1 handprint corresponds to approximately 3.3% of the trunk (including axillae and groin);
- 1 handprint corresponds to approximately 2.5% of the lower limbs (including buttocks).

The extent (%) to which each of the four body regions is affected by psoriasis is captured on the CRF (to 2 decimal places, as necessary).

A weighting factor is applied to each of the four body regions in calculation of the total BSA affected: head x0.1; upper limbs x0.2; trunk x0.3; lower limbs x0.4, as the four body regions correspond to approximately 10%, 20%, 30% and 40% of the total BSA, respectively. The sum of the weighted percent involvement obtained for each of the four body areas is the grand total BSA with psoriasis, as described in the following equation:

$$\text{BSA (\%)} = \frac{0.1S_h + 0.2S_u + 0.3S_t + 0.4S_l}{}$$

where S = body region surface area with psoriasis; h = head; u = upper limbs; t = trunk; l = lower limbs.

7.1.2.4. Psoriasis Area and Severity Index (PASI)

PASI assessment must be performed for PsA subject with Baseline psoriasis affecting ≥3% Body Surface Area (BSA).

The Psoriasis Area and Severity Index quantifies the severity of a subject's psoriasis based on both lesion severity and the percentage of body surface area affected.[23]

Assessments of lesion Severity Score and Area Score are performed separately for each of the four body regions: head (including neck), upper limbs, trunk (including axillae and groin), and lower limbs (including buttocks).

- Severity Score: the basic characteristics of psoriatic lesions – erythema (E), induration (I) and scaling (S) – provide a means for assessing the severity of lesions. In each body region, the severity of each sign is rated according to a 5-point scale: 0, no involvement; 1, slight; 2, moderate; 3, marked; 4, very marked.

- Area Score (A): the extent (%) to which each of the four body regions is involved with psoriasis is categorized using a non-linear scaling method to a numerical Area Score according to the following scoring criteria: 0, no involvement; 1, >0 to 9%; 2, 10 to 29%; 3, 30 to 49%; 4, 50 to 69%; 5, 70 to 89%; 6, 90 to 100% (percentage of body region, not whole body; estimated by the handprint method, ie, one handprint corresponds to approximately 10% of the head, or 5% of the upper limbs, or 3.3% of the trunk, or 2.5% of the lower limbs, as detailed in Section 7.1.2.3).

Calculating PASI

In each body region, the sum of the lesion Severity Scores for erythema, induration and scaling is multiplied by the Area Score which represents the percentage of this area involved by psoriasis, multiplied by a weighting factor (head 0.1; upper limbs 0.2; trunk 0.3; lower limbs 0.4). The sum of the numbers obtained for each of the four body region is the PASI.

$$PASI = 0.1A_h(E_h+I_h+S_h) + 0.2A_u(E_u+I_u+S_u) + 0.3A_t(E_t+I_t+S_t) + 0.4A_l(E_l+I_l+S_l)$$

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

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

Table 5. Component Scoring Criteria for the Psoriasis Area and Severity Index (PASI)

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

7.1.2.5. Nail Psoriasis Severity Index (NAPSI)

A target finger nail will be evaluated by the blinded assessor using the NAPSI scale.[24] At the baseline visit, the worst case fingernail should be chosen and the same nail evaluated consistently through the entire study. Each quadrant of the target nail is graded for nail matrix psoriasis (including any of the following parameters: pitting, leukonychia, red spots in lunula, nail plate crumbling) and nail bed psoriasis (including any of the following parameters: onycholysis, splinter hemorrhages, oil drop (salmon patch) discoloration, nail bed hyperkeratosis), giving that 1 target nail a score of 0-8.

7.1.3. Patient Report Outcomes (PROs)

All questionnaires should be completed by subjects prior to any procedures being performed at the study visit. Forms should be checked by site staff for completeness. In the unlikely event that a PRO questionnaire(s) is not able to be administered by study site staff and completed by the subject as directed at the clinic visit, the PRO questionnaire(s) should not be administered. PRO questionnaires should also be reviewed for potential adverse events. The total completion time for all the PRO questionnaires is approximately 30 minutes.

7.1.3.1. Patient's Assessment of Arthritis Pain

Subjects will assess the severity of their arthritis pain using a 100 mm visual analog scale (VAS) by placing a mark on the scale between 0 (no pain) and 100 (most severe pain), which corresponds to the magnitude of their pain.

MY PAIN AT THIS TIME IS:

(PLEASE MAKE AN X MARK ON THE LINE BELOW)

No Pain _____ Most Severe Pain

[Note: Scale will be 100 mm in length]

7.1.3.2. Patient's Global Assessment of Arthritis

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

CONSIDERING ALL THE WAYS YOUR ARTHRITIS AFFECTS YOU, HOW ARE YOU FEELING TODAY?

(PLEASE MAKE AN X MARK ON THE LINE BELOW)

Very Well _____ Very Poorly

[Note: Scale will be 100 mm in length]

7.1.3.3. Health Assessment Questionnaire (HAQ) Disability Index (DI)

The HAQ-DI assesses the degree of difficulty a subject has experienced during the past week in 8 domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities.[25] Each activity category consists of 2-3 items. For each question in the questionnaire, the level of difficulty is scored from 0 to 3 with 0 representing "no difficulty," 1 as "some difficulty," 2 as "much difficulty," and 3 as "unable to do". Any activity that requires assistance from another individual or requires the use of an assistive device adjusts to a minimum score of 2 to represent a more limited functional status. It can be completed in approximately 5 minutes.

7.1.3.4. Patient's Global Joint and Skin Assessment-Visual Analog Scale (PGJS-VAS)

Subject's perception of disease will be assessed using a 100 mm visual analog scale (VAS) by placing a mark on the scale between 0 (excellent) and 100 (poor). The rating corresponds to the way in which the subject felt over the past week in terms of how they were affected by their: 1) psoriasis and arthritis (global, PGA); 2) arthritis only (PJA) and 3) psoriasis only (PSA).[26]

- Global (PGA)

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

Excellent _____ Poor

- Joints (PJA)

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

Excellent _____ Poor

- Skin (PSA)

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

Excellent _____ Poor

[Note: Scale will be 100 mm in length]

CCI

[redacted]

7.1.3.6. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue; a 13-item FACIT Fatigue Scale)

The FACIT-Fatigue Scale is a patient completed questionnaire consisting of 13 items that assess fatigue.[28] Subjects respond to each item on a 5-point scale based on their experience of fatigue during the past 7 days (0 = not at all; 1 = a little bit; 2 =somewhat; 3 = quite a bit; 4 = very much). Instrument scoring yields a range from 0 to 52 (negatively worded items were reversed during analysis), with higher scores representing better subject status (less fatigue). It can be completed in 5 minutes.

7.1.3.7. Short-Form-36 Health Survey (SF-36) Version 2, Acute

The SF-36 v2 (Acute)[29] is a 36-item generic health status measure. It measures 8 general health domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. These domains can also be summarized as physical and mental component scores. It can be completed in 5 to 10 minutes.

CCI [redacted]

CCI [redacted]

CCI [redacted]

7.1.4. Composite Efficacy Endpoints

7.1.4.1. American College of Rheumatology (ACR) response criteria

The American College of Rheumatology's definition for calculating improvement in rheumatoid arthritis (ACR20) is calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant.[33] Similarly, ACR50, 70 and 90 are calculated with the respective percent improvement.

The specific components of the ACR Assessments that will be used in this study are:

- Tender/painful joint Count (68);
- Swollen Joint Count (66);
- Patient's Assessment of Arthritis Pain (VAS);
- Patient's Global Assessment of Arthritis (VAS);
- Physician's Global Assessment of Arthritis (VAS);
- C-Reactive Protein (CRP);
- Health Assessment Questionnaire – Disability Index (HAQ-DI).

This efficacy measurement will be calculated at every study visit during the treatment period.

7.1.4.2. Minimal Disease Activity (MDA) and Very Low Disease Activity (VLDA) Score

A psoriatic arthritis patient is defined as having Minimal Disease Activity (MDA)[34] when the subject meets ≥5 of the 7 following criteria: 1) Tender/painful joint count ≤1; 2) swollen joint count ≤1; 3) PASI score ≤1 or BSA ≤3%; 4) Patient's Assessment of Arthritis Pain (VAS) ≤15; 5) Patient's Global Assessment of Arthritis (VAS) ≤20; 6) HAQ-DI score ≤0.5; 7) tender entheseal points (using Leed's Enthesitis Index) ≤1. A patient is in Very Low Disease Activity (VLDA) when all seven criteria are met.[2] The MDA and VLDA will be calculated at every study visit during the treatment period except Week 2 visit.

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

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

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

DAREA/DAPSA will be calculated at every study visit during the treatment period except Week 2 visit.

7.1.4.4. Disease Activity Score-28 (DAS28)

The Disease Activity Score-28 (DAS28)[35] is a derived measurement with differential weighting given to each component. DAS28 (CRP) will be calculated from measurements made at study visits. The components of the DAS28 (CRP) arthritis assessment are: Tender/Painful Joint Count (28), Swollen Joint Count (28), and C-Reactive Protein (CRP). DAS28 will be calculated at every study visit during the treatment period.

7.1.4.5. Psoriatic Arthritis Response Criteria (PsARC)

The PsARC consists of 4 measurements:[36,37] Tender/painful joint count (68), Swollen joint count (66), Physician's Global Assessment of Arthritis (VAS), and Patient's Global Assessment of Arthritis (VAS). The same tender/painful joint count and swollen joint count used for ACR response criteria will be applied to the PsARC. In order to be a 'PsARC responder', subjects must achieve improvement in 2 of 4 measures, one of which must be joint pain or swelling, without worsening in any measure. PsARC will be calculated at every study visit during the treatment period except Week 2 visit.

CCI [redacted]

7.1.4.7. Psoriatic Arthritis Disease Activity Score (PASDAS)

PASDAS is a composite PsA disease activity score that includes the following components: Patient's Global Joint and Skin Assessment (VAS), Physician's Global Assessment of Psoriatic Arthritis (VAS), swollen and Tender/painful joint counts (66/68), Leeds Enthesitis Index score, tender dactylitic digit score, physical component summary (PCS) score of SF-36 and CRP. PASDAS will be calculated at every study visit during the treatment period except Week 2 visit.

7.2. Safety Assessments

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

7.2.1. Laboratory

The following safety laboratory tests will be performed at times defined in the Schedule of Activities section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood.

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns (for laboratory abnormalities require prompt re-testing, see Appendix 7, Laboratory Abnormalities Require Re-Testing).

Laboratory Tests

Hematology	Chemistry	Urinalysis[e]	Other
Hemoglobin	BUN/urea	pH	FSH[d,g]
Hematocrit	Creatinine	Glucose (qual)	Pregnancy test (β-hCG)[h]
RBC count and indices (MCH, MCHC, MCV, RBC Morphology)	Cystatin C	Protein (qual)	Hepatitis B, C and HIV[d]
	Glucose	Blood (qual)	QFT-G or other IGRA[d]
	Calcium	Ketones	
Reticulocytes count	Sodium	Nitrites	hsCRP[i]
WBC count with differential	Potassium	Leukocyte esterase	FACS-TBNK
Neutrophils (%, Abs)	Chloride	Urobilinogen	Viral Surveillance (EBV, CMV, HSV1, HSV2, VZV)[j]
Eosinophils (%, Abs)	Total CO2 (Bicarbonate)	Urine bilirubin	
Monocytes (%, Abs)	Albumin	Microscopy and/or culture[f]	
Basophils (%, Abs)	Total protein		
Lymphocytes (%, Abs)	Alanine transaminase (ALT)		
Platelet count	Aspartate transaminase (AST)		CCI [redacted]
Activated Partial Thromboplastin Time (APTT), Prothrombin Time/International Normalized Ratio (PT/INR)	Total Bilirubin		
	Direct bilirubin[a]		
	Alkaline phosphatase		
	Uric acid		
	Creatine kinase (CK)		Skin swabs for herpetiform rash[j]
	CK fractionation[b]		
	Total Cholesterol[c]		
	Triglycerides[c]		Urine Myoglobin[k]
	HDL[c]		
	LDL[c]		
	Rheumatoid Factor (RF)[d]		
	Cyclic Citrullinated Peptide (CCP) Antibodies[d]		

a. Only if total bilirubin is elevated.
b. Only if CK is elevated.
c. Fasting (water only), 8 hours prior to collection.
d. At screening only.

e. Dipstick in all cases.
f. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase. Urine culture is performed if urinalysis is positive for nitrite and/or leukocyte esterase or if clinically indicated.
g. For confirmation of postmenopausal status only, in females who are amenorrheic for at least 12 consecutive months.
h. Pregnancy tests (serum/urine) for females of childbearing potential. Serum pregnancy test must be performed at Screening.
i. Blood samples will be collected at each visit for analysis of CRP using an assay analyzed by the central laboratory. The investigator and sponsor will be kept blinded to the results of this test at all visits except the Screening Visit.
j. When required in cases of suspected herpetiform rash (eg, suspected herpes zoster and herpes simplex) a skin swab and additional blood viral surveillance sample will be collected. Blood viral surveillance sample will also be collected at Baseline Day 1.
k. At Screening, Baseline Day 1/Randomization and in case of CK >3x ULN.

7.2.2. Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory.

For female subjects of childbearing potential, 2 negative pregnancy tests are required before receiving investigational product/study treatment(s) (1 negative serum pregnancy test at screening and 1 negative urine pregnancy test at the baseline visit immediately before investigational product/study treatment administration). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy test result will then be required at the baseline visit and within 5 days after the first day of the menstrual period (counting the first day of the menstrual period as Day 1) before the subject may receive the investigational product/study treatment. In the absence of regular menstrual bleeding, the study candidate should have used 2 forms of contraception for at least 1 month before the second pregnancy test.

Pregnancy tests will also be repeated at every visit and at the end of the study to confirm that the subject has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period and when potential pregnancy is otherwise suspected, and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

7.2.3. Serum Creatinine, Serum Cystatin C and Estimated Glomerular Filtration Rate (eGFR)

Serum creatinine is the best known standard test for monitoring renal function. However, serum creatinine based estimates of glomerular filtration rate (eGFR) may be affected by factors other than renal function, including chronic and acute illness. Cystatin C is a test that can be used either as an adjunct to or a replacement for serum creatinine. The most reliable estimates of glomerular filtration rate (GFR) use both test results.[39]

Cystatin C is a low molecular weight protein that is used as an alternative to serum creatinine for monitoring of renal function. It seems to correlate more closely with GFR than does serum creatinine concentration and may be a more sensitive detector of early renal dysfunction. While use of cystatin C has been limited, its independence of demographic factors (eg, race) has made it an interesting means of determining changes in renal function in clinical settings and it is included in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[40] Estimated GFR may be calculated via the 2012 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine, cystatin C, and creatinine-cystatin C equations.[41]

Serum creatinine will be measured as part of serum chemistry at times specified in the Schedule of Activities section of the protocol and serum creatinine based eGFR will be calculated. Creatinine elevations above the ULN will be followed until resolution or baseline.

Serum cystatin C will be measured at times specified in the Schedule of Activities section of the protocol and cystatin C based eGFR will be calculated.

The eGFR will be calculated using the 2 sets of equations developed by the CKD-EPI, which utilize serum creatinine (SCr) and serum cystatin C respectively.[41,42]

- The CKD-EPI creatinine equation (2009) expressed as a single equation:[41]
  $141 \times \min(SCr/\kappa, 1)^{a} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age}$ [x 1.018 if female] [x 1.159 if black], where SCr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min is the minimum of SCr/κ or 1, and max is the maximum of SCr/κ or 1.

- The CKD-EPI cystatin C equation (2012) expressed as a single equation:[41]
  $133 \times \min(Scys/0.8, 1)^{-0.499} \times \max(Scys/0.8, 1)^{-1.328} \times 0.996^{Age}$ [× 0.932 if female], where Scys is serum cystatin C, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of Scys/κ or 1.

7.2.4. Tuberculosis Testing

Interferon-Gamma Release Assays (IGRAs) are blood tests for TB infection. Subjects may be screened for TB using an IGRA per local guidelines. IGRA will be tested at Screening or within 12 weeks prior to Day 1. The following are acceptable IGRA assays: QuantiFERON®-TB Gold Plus test, QuantiFERON®-TB Gold test (QFT-G), QuantiFERON®-TB Gold In-Tube test (QFT-GIT), and T-SPOT® TB test (T-Spot). Site personnel should follow the processing and analyses steps based on the assay chosen. Ensure incubation steps are followed as appropriate.

An IGRA is preferred for subjects with a prior Bacillus Calmette-Guerin (BCG) vaccination, but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation.

If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary.

Subjects with repeat indeterminate IGRA results may be enrolled after consultation with pulmonary or infectious disease specialist that determines low risk of infection (ie, subject would be acceptable for immunosuppressant (eg, anti-TNF) treatment without additional action).

Subjects who test positive for QFT-G/QFT-GIT test, but in the opinion of the PI are at low risk of TB infection may be referred to pulmonary or infectious disease specialist for consultation and potential IGRA test repeated once. Subjects will be eligible if the repeat test is negative before the randomization.

Refer to lab manual for any additional processing information and shipping instructions.

7.2.5. Herpetiform Skin Rash Surveillance

For any occurrence of a suspected herpetiform rash (eg, herpes zoster and herpes simplex), additional specimens for viral DNA analysis will be obtained for confirmation. An additional blood viral surveillance sample will be collected for the analysis of viral load for the relevant viruses. A swab of the affected area will also be collected and sent for the analysis of viral load for HSV1, HSV2, and VZV. Details for these collections will be provided in the laboratory manual.

7.2.6. Medical History, Physical Examination, Height and Weight

Medical history will include history of drug, alcohol and tobacco use. Medical history includes herpes zoster details. Medical history also includes collection of details on (i) Family history of diabetes mellitus, hypertension, and premature coronary heart disease (CHD), where premature CHD is defined as (a) CHD in a male first degree relative <55 years of age, or (b) CHD in a female first degree relative <65 years of age, (ii) Any prior rheumatologist confirmed diagnosis of rheumatoid arthritis, (iii) Any prior diagnosis of dry eye disease/syndrome, and (iv) Any previous history of liver biopsy. Smoking status and average weekly alcohol consumption (units/week) will also be collected, where a unit contains 12 g of pure alcohol, an amount equivalent to that contained in 5 oz (a glass) of wine, 12 oz of beer, or 1.5 oz of 90 proof of spirits. Medical History will be collected at the Screening visit, and reviewed at Baseline Day 1 visit of any changes (any AEs happened before the first dosing should be reflected on the medical history).

Complete physical examinations must be performed by the investigator, sub-investigator, or a qualified healthcare professional per local guidelines. A complete physical examination will include height (at Screening Visit only), weight, general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (presence of peripheral edema), abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes.

Targeted physical examinations must be performed by the investigator, sub-investigator, or a qualified healthcare professional per local guidelines. Targeted physical examination consists of skin, heart, lungs, abdomen, and examination of body systems where there are symptom complaints by the subject.

Complete and Targeted physical examinations are performed at specified time points (see Schedule of Activities).

Height and weight will be measured without the subject wearing shoes.

7.2.7. Vital Sign Measurements (Blood pressure, pulse rate, and temperature)

Single sitting blood pressure (BP), pulse rate, and temperature will be measured at times specified in the Schedule of Activities. Additional collection times or changes to collection times will be permitted, as necessary to ensure appropriate collection of safety data.

Sitting blood pressure will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg. It is preferred that the same arm (preferably the dominant arm) be used throughout the study. All blood pressure in this study will be measured with the subject in the sitting position after resting for at least 5 minutes. The same size BP cuff, which has been properly sized and calibrated, should be used to measure BP each time.

When the timing of the vital sign measurements coincides with a blood collection, it is preferred that vital signs be obtained prior to the nominal time of blood collection.

It is preferred that body temperature be collected using tympanic, oral, or axillary methods and that the same method be used consistently throughout the study.

7.2.8. Electrocardiogram

Twelve (12) lead ECGs should be collected at times specified in the Schedule of Activities. Additional ECG may be performed upon request by the sponsor clinician.

At the Screening Visit, a single ECG will be collected. Subjects with screening QTcF >450 milliseconds (msec) should be excluded. If the QTcF exceeds 450 msec, the ECG should be repeated two more times and the average of the three QTcF should be used to determine the subject eligibility. On Day 1 only, triplicate ECGs will be obtained approximately 2-4 minutes apart, and the average of the triplicate ECG measurements will serve as each subject's baseline value. At the Week 2 visit only, a single ECG will be collected between 2-4 hours postdose. At all the other visits specified, a single ECG will be collected pre-dose or post-dose.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position. When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, BP, and pulse rate.

ECGs will be read and interpreted locally and centrally. Locally read ECG parameters (heart rate, QT, QTcF, PR and QRS intervals) should also be recorded on the Case Report Form (CRF). A copy of the ECG should be available as source documents for review.

To ensure safety of the subjects, a qualified individual (eg, sub-investigator) at the investigator site will make comparisons to baseline measurements taken at Day 1.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

7.2.9. Chest Radiograph

Chest x-ray (posterior-anterior and lateral views are recommended however local guidelines should be followed) or other appropriate diagnostic image (ie, computed tomography [CT] or magnetic resonance imaging [MRI]) with no current evidence of untreated latent or active TB infection or evidence of currently active TB, general infections, heart failure or malignancy taken at screening or within the 12 weeks prior to Screening and read by a qualified radiologist. Documentation of the official reading must be located and available in the source documentation.

7.2.10. Events for Adjudication/Review Committee Submission

The identification of events requiring submission to external adjudication committees for review will be made by the study site and communicated to Pfizer or designee. Events requiring review, including opportunistic infections, malignancy and cardiovascular events may also be identified by the Pfizer Study Team or designee during the blinded review of subject data listings or by site monitors during routine monitoring of subject's study records. The Pfizer Study Team or designee will notify the study site of any events should they be identified.

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

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

7.3.1. High-Sensitivity C-Reactive Protein (hsCRP)

Blood samples for determination of hsCRP will be obtained at the times specified in the Schedule of Activities.

Instructions and supplies for collection, processing, and shipment of samples will be supplied under separate cover by Pfizer, the designated laboratory vendor, and the vendor laboratory manual.

CCI

[redacted]

7.3.3. Viral Surveillance

Blood sample for the analysis of CMV (cytomegalovirus), EBV, HSV-1, HSV-2 and VZV (varicella zoster virus) will be collected according to the times outlined in the Schedule of Activities. Additional sample collection instructions will be provided in the lab manual.

Note: Due to long turnaround time, the retrospective nature of these labs might make their reporting time quite delayed.

In addition to time points specified, a plasma sample for viral surveillance sample will also be taken at the time of an adverse event, as clinically appropriate.

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

- [redacted]
- [redacted]

[redacted]

7.6. Rater (Assessor) Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate subjects in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the *Assessor Qualification Requirements* provided to each participating site. The level of experience with the target population, specific scale experience (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 a waiver may be issued. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. 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.

Individuals who perform the Physician's Global Assessment of Arthritis and Physician's Global Assessment of PsA must be a physician or other healthcare professional who is competent to perform the assessments. Individuals who perform Physician's Global Assessment of Psoriasis will be similarly qualified, however, with previous psoriasis clinical

experience. The following procedures require a health care professional who is competent to perform the assessments: Tender/painful joint count; swollen joint count; assessment of dactylitis; assessment of enthesitis; PASI, BSA; NAPSI.

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

8. ADVERSE EVENT REPORTING

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

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

8.1.1. Additional Details on Recording Adverse 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 from the Study Due to Adverse Events (see also the Subject Withdrawal section)

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

8.1.5. Causality Assessment

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

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

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

8.2.2. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or

- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or

- Test result is considered to be an AE by the investigator or sponsor.

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

8.2.3. Serious Adverse Events

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

- Results in death;

- Is life-threatening (immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

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

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

8.2.4. Hospitalization

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

Hospitalization does not include the following:

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

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

8.4.3. Potential Cases of Decreased eGFR

In First in Human (FIH) study B7931001, serum creatinine elevation was reported across dose levels in healthy volunteer and psoriasis patients. The proposed mechanism for the observed serum creatinine increases in study B7931001 is inhibition of creatinine transport in the kidney (ie, transporter-mediated rather than direct nephrotoxicity).

All subjects will have serum creatinine based and serum cystatin-C based eGFR calculated at baseline upon entry into the study.

Abnormal values in serum creatinine concurrent with absence of increase in blood urea nitrogen (BUN) that meet the below criteria, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

If an individual subject demonstrates a CONCOMITANT serum creatinine based AND serum cystatin C based eGFR decline of ≥30% compared to the subject's baseline eGFR, then the subject should not be further dosed and adequate, immediate, supportive measures including **immediate evaluation by a nephrologist (preferably within 24 hours) with appropriate management** and treatment as clinically indicated. Results should be repeated as indicated by the nephrologist or weekly at a minimum until the eGFR returns to baseline ±15% or the renal parameters are deemed to be stable by the nephrologist and/or PI.

If the subject cannot be seen by a nephrologist within 24 hours (as described above), then the subject should be sent to a local emergency room for evaluation and treatment as clinically indicated.

Subjects should return to the investigational site and be evaluated as soon as possible, **preferably within 24-48 hours** from awareness of the abnormal eGFR result (CONCOMITANT serum creatinine based AND serum cystatin C based eGFR decline of ≥30% compared to the subject's baseline eGFR) for a safety follow-up visit. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating serum creatinine and serum cystatin C, laboratory tests should also include: serum BUN, serum CK, serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, calcium), in addition to urine dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities

identified should be considered as potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal serum creatinine.

All relevant test results will be forwarded to Pfizer for review immediately upon receipt by the PI.

This requirement applies to all subjects.

8.4.4. Infections

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

8.4.4.1. Serious Infections

A serious infection is any infection that requires hospitalization for treatment or requires parenteral antimicrobial therapy or meets other criteria that require it to be classified as a serious adverse event. A subject who experiences a serious infection should be discontinued from the study and the serious adverse event should be listed as the reason for discontinuation in the Case Report Form. Appropriate laboratory investigations, including but not limited to cultures should be performed to establish the etiology of any serious infection. All adverse events, including serious adverse events, should be reported as described in Section 8 on ADVERSE EVENT REPORTING.

8.4.4.2. Treated Infections

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

8.4.5. Exposure to the Investigational Product during Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.5.1. Exposure During Pregnancy

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

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

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

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

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

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

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

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

A special safety concern (SSC), fetal cleft lip, was reported in the B7931004 (investigating PF-06700841 to treat psoriasis) trial affecting a singleton pregnancy of a subject on concomitant medications including an herbal supplement which carried a pregnancy warning.

8.4.5.2. Exposure During Breastfeeding

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

8.4.5.3. Occupational Exposure

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

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

8.4.6. Medication Errors

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

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

8.4.6.1. Medication Errors

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

Medication errors include:

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

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

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

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment. The SAP will be finalized prior to the study unblinding.

9.1. Sample Size Determination

The primary endpoint in this study is the ACR20 response rate at Week 16. Assuming an ACR20 response rate of 25% for the placebo group and 1-sided type-I error rate of 5% and using the normal approximation method, the study will have over 90% power under a sample size of 50 per arm and 80% power under a sample size of 25 per arm, to detect a treatment difference of 30% or greater without multiplicity adjustment. With the 2:2:1:2 allocation ratio (in the order of 60 mg QD, 30 mg QD, 10 mg QD and placebo), and accounting for a 10% chance of drop out, approximately a total of 196 subjects will be enrolled in this study, with 56 subjects per treatment group (with the exception of 28 subjects for the 10 mg QD treatment group). Each of three PF-06700841 dose regimens (60 mg QD, 30 mg QD and 10 mg QD) will be compared with placebo for the primary endpoint. Simulations were conducted for multiple testing against placebo using the Dunnett's testing procedure for various dose-response profiles. Assuming a placebo ACR20 response rate of 20-25% and 30-35% placebo-adjusted effect for the best active dose arm and an overall one-sided type-I error rate of 5%, the study will have over 85% power to show a statistically significant effect from placebo.

9.2. Efficacy Analysis

9.2.1. Analysis of the Primary Endpoint

The primary endpoint is the ACR20 response rate at Week 16. Statistical analyses will be performed when all randomized subjects have completed Week 16 visit or have the opportunity to complete the Week 16 visit. The primary efficacy analysis population will include all randomized subjects who receive at least one dose of study medication. Each of the three PF-06700841 dose regimens (60 mg QD, 30 mg QD and 10 mg QD) will be compared with placebo. The normal approximation for the treatment difference in the ACR20 response rate at Week 16 will be used to test superiority of each PF-06700841 dose regimen against placebo. In order to control for the type-I error, the Dunnett's method will be used for the primary endpoint of ACR20 response rate at Week 16 to adjust for multiplicity and serve as a gatekeeper for further testing of secondary endpoints. Specifically, if any PF-06700841 dose regimen is superior to placebo under the Dunnett's test, selected secondary endpoints at Week 16 for that dose regimen will be formally tested for superiority against placebo hierarchically in the order of PASI75 $\rightarrow$ ACR50 $\rightarrow$ PASI90 $\rightarrow$ PASI100 $\rightarrow$ HAQ-DI. This testing strategy will control the family-wise type-I error rate at an overall 1-sided 5% level.

Treatment differences between each PF-06700841 dose regimen and placebo in the ACR20 response rate at Week 16 will be summarized by point estimates and two-sided 90% confidence intervals using the normal approximation method. To adjust for the effect of prior TNFi exposure, treatment differences in the primary endpoint will aslo be summarized using the Cochran-Mantel-Haenszel method.

Missing values due to subject dropouts from the study for any reason (eg, lack of efficacy or adverse event) will be handled by non-responder imputation for the primary analyses. Tipping-point analyses may be performed to assess the robustness of the results when necessary.

9.2.2. Analysis of Secondary Endpoints

Secondary endpoints include ACR endpoints (ACR20 at visits other than Week 16, ACR50 and ACR70 and PASI endpoints (PASI75, PASI90 and PASI100). The ACR50 and PASI75/90/100 endpoints at Week 16 will be formally tested in the testing strategy described in Section 9.2.1. Similar to the primary endpoint, the normal approximation method for the treatment differences in these binary endpoints will be used to test superiority of PF-06700841 against placebo. Regardless of formal testing results, treatment differences between each PF-06700841 dose regimen and placebo in these secondary endpoints will be summarized using descriptive statistics (ie, point estimates and two-sided 90% confidence intervals). Specifically, point estimates for the treatment differences between each PF-06700841 and placebo in all ACR and PASI endpoints and two-sided 90% confidence intervals will be generated for all visits at or prior to Week 16 using normal approximation, and Cochran-Mantel-Haenszel method adjusting for prior TNFi exposure when appropriate. For visits after Week 16, ACR and PASI response rates will be summarized using descriptive statistics by study visit and by treatment sequences, or combined when appropriate. Other analyses, including landmark logistic regression and/or generalized linear mixed model for longitudinal binary endpoints, may also be performed. Details will be documented in the SAP.

The change from baseline in the HAQ-DI score will be analyzed using a repeated measure model that includes fixed effects of treatment group, study visit (at or prior to Week 16), treatment by visit interaction, prior TNFi exposure and baseline HAQ-DI score, with an unstructured variance-covariance matrix. Details of missing data imputation method will be documented in the SAP. HAQ-DI score at visits post Week 16 will be summarized descriptively by study visit and by treatment sequences, or combined when appropriate. Other longitudinal secondary continuous endpoints will be analyzed similarly.

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9.4. Analysis of Other Endpoints

Details of analysis methods for all other endpoints will be documented in the SAP. Binary endpoints will be summarized using normal approximation method, and Cochran-Mantel-Haenszel method adjusting for prior TNFi exposure when appropriate. Longitudinal continuous endpoints will be analyzed in a repeated measure model similar to the model for HAQ-DI. For all of these endpoints, descriptive statistics will be provided by study visit and treatment sequence, or combined when appropriate.

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9.6. Safety Analysis

All subjects who receive study medication (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations. These include, but not limited to:

- Incidence and severity of adverse events;
- Summary of absolute vital signs and vital signs change from baseline;
- Summary of absolute values and changes from baseline in ECG signals;
- Serious infections, defined as infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials;

- Any safety events that trigger withdrawals of a subject;
- Safety laboratory tests.

Details will be provided in statistical analysis plan.

9.7. Interim Analysis

An administrative interim analysis may be performed when approximately 60% of subjects have completed Week 16 visit or have the opportunity to complete the Week 16 visit. If performed, this interim analysis would be conducted by an unblinded team independent of this study team and the safety and efficacy results from the interim analysis may be reviewed by an Internal Review Committee (IRC). No members of the study team will be part of the IRC. The interim analysis, if performed, will not be used to drive any decisions for the current study; however it may be used for internal business decisions regarding future study planning.

During the interim analysis, some members of the study team may be unblinded and replaced with blinded colleagues. The subjects, investigators, and individuals from the sponsor (or designee) who interact with the investigators and monitor safety will continue to be blinded to individual study treatments throughout the follow up period of the study.

Before any interim analysis is conducted, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's standard operating procedures (SOPs) will be documented and approved in an internal review committee (IRC) charter. In addition, the analysis details must be documented and approved in an interim analysis SAP or final SAP.

9.8. Data Monitoring Committee

This study will use an Internal Review Committee (IRC).

The IRC will be responsible for ongoing monitoring of the safety of subjects in the study according to the IRC charter. The IRC will review accumulating unblinded safety data and may propose changes to the protocol as needed to ensure subject safety. The IRC may also review results of the interim analyses as described in Section 9.7.

The recommendations made by the IRC to alter the design and/or conduct of the study will be forwarded to the sponsor executive team for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate. Details will be documented in the IRC charter.

9.9. Safety Adjudication Committees

To help assess the specific, complex safety events related to malignancies, cardiovascular events, and opportunistic infection in this study, Safety Adjudication Committees, consisting of external clinical experts in each of the relevant clinical areas, will be set up to harmonize and standardize assessments. Members of the safety event adjudication committees will be blinded to treatment assignment in order to allow for unbiased assessments. Further information about these committees can be found in the respective charters, including specific descriptions of the scope of their responsibilities, plans where communication timelines are defined, and the processes and definitions used to review and assess specific safety events. Other safety events for adjudication may be identified and included in the remit of the Safety Adjudication Committees as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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.

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 law.

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 name 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 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.

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

12.4. 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 (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06700841 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 7 business days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

Pfizer 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 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 PI 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 following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Ab	Antibody
AC	Adjudication Committee
ACR	American College of Rheumatology
ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse Event
ALT	Alanine Aminotransferase
Anti-CCP	Anti-Cyclic Citrullinated Protein Antibody
AST	Aspartate Aminotransferase
AUC	Area under concentration-time curve
BA	Bioavailability
CCI [redacted]	[redacted]
BCG	Bacillus Calmette-Guerin
BCRP	Breast Cancer Resistance Protein
BID	Twice daily
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CASPAR	Classification Criteria for Psoriatic Arthritis
CCP	Cyclic Citrullinated Peptide
CD	Cluster Of Differentiation; Crohn's Disease
CFB	Change From Baseline
CHD	Coronary Heart Disease
CI	Confidence Interval
CK	Creatine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum Observed Concentration
CMV	Cytomegalovirus
COX-2	Cyclooxygenase-2
CRF	Case Report Form
CRP	C-reactive Protein
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P
DAPSA	Disease Activity Index for Psoriatic Arthritis
DAREA	Disease Activity Index for Reactive Arthritis
DAS28	Disease Activity Score-28
DILI	Drug-induced liver injury

Abbreviation	Term
DIP	Distal Interphalangeal
CCI	[redacted]
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DU	Dispensable Unit
DVT	Deep Vein Thrombosis
EBV	Epstein Barr Virus
EC	Ethics Committee
ECG	Electrocardiogram
EDP	Exposure During Pregnancy
EFD	Embryo-Fetal Development
eGFR	Estimated Glomerular Filtration Rate
EPO	Erythroprotein
EU	European Union
EudraCT	European Clinical Trials Database
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FACS	Fluorescence Activated Cell Sorting
FDA	Food And Drug Administration
FIH	First In Human
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
gm	Gram
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GRAPPA	Group For Research And Assessment Of Psoriasis and Psoriatic Arthritis
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 Ab	Hepatitis C Antibody
HDL	High Density Lipoprotein
HEENT	Head, Eyes, Ears, Nose, Throat
HIV	Human Immunodeficiency Virus
HRQL	Health-Related Quality Of Life
HSV	Herpes Simplex Virus
IB	Investigator's Brochure
IC50	Half maximal inhibitory concentration
ICF	Informed Consent Form

Abbreviation	Term
ICH	International Conference On Harmonisation
ID	Identification
IFN	Interferon
IGRA	Interferon-Gamma Release Assay
IL	Interleukin
IND	Investigational New Drug Application
INR	International Normalized Ratio
IP	Investigational Product; Interphalangeal
IRB	Institutional Review Board
IRC	Internal Review Committee
IRT	Interactive Response Technology
CC	[redacted]
IUD	Intrauterine Device
IV	Intravenous
IWR	Interactive Web Response
JAK	Janus kinase
KDIGO	Kidney Disease: Improving Global Outcomes
K2EDTA	Dipotassium Ethylenediaminetetraacetic Acid
LAM	Lactational Amenorrhoea Method
LDL	Low Density Lipoprotein
LEI	Leeds Enthesitis Index
LFT	Liver Function Test
LSLV	Last Subject Last Visit
LTFU	Lost To Follow-Up
MATE	Multidrug And Toxin Extrusion Protein
MCP	Metacarpophalangeal
MDA	Minimal Disease Activity
MDR	Multidrug Resistance Protein
mg	Milligrams
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
msec	Millisecond
MTX	Methotrexate
N/A	Not Applicable
NAPSI	Nail Psoriasis Severity Score
NK	Natural Killer
NOAEL	No Observed Adverse Effect Level
NSAID	Nonsteroidal Anti-Inflammatory Drug
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area Severity Index

Abbreviation	Term
PCD	Primary Completion Date
PCR	Polymerase Chain Reaction
PCS	Physical Component Summary
PD	Pharmacodynamics
PE	Pulmonary Embolism
P-gp	P-glycoprotein
CCI [redacted]	[redacted]
PGJS	Patient's Global Joint and Skin Assessment
PGx	Pharmacogenomics
PI	Principal Investigator
PIP	Proximal Interphalangeal
CCI [redacted]	[redacted]
PRN	As Needed
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
CCI [redacted] CCI [redacted]	[redacted]
PsARC	Psoriatic Arthritis Response Criteria
PsO	Psoriasis
PT	Prothrombin Time
PUVA	Psoralens + UVA phototherapy
QD	Quaque die (once daily)
QFT-G	QuantiFERON®-TB Gold test
QFT-GIT	QuantiFERON®-TB Gold In-Tube test
QTc	Corrected QT
QTcF	Corrected QT (Fridericia method)
OMERACT	Outcome Measures in Rheumatology
RBC	Red Blood Cell
RF	Rheumatoid Factor
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCr	Serum Creatinine
SF-36	36-Item Short-Form Health Survey
SJC	Swollen Joint Count
SLE	Systemic Lupus Erythematosus
SOP	Standard Operating Procedure
SPARCC	Spondyloarthritis Research Consortium of Canada
SRSD	Single Reference Safety Document
SSC	Special Safety Concern
STAT	Signal Transducer And Activator Of Transcription
SUSAR	Suspected Unexpected Serious Adverse Reaction

Abbreviation	Term
$t_{1/2}$	Terminal Phase Half-Life
TB	Tuberculosis
TBili	Total Bilirubin
TBNK	T Cell, B Cell And Natural Killer Cell
TdP	Torsade De Pointes
TEAE	Treatment Emergent Adverse Event
TIA	Transient Ischemic Attack
TJC	Tender/Painful Joint Count
T_{max}	Time to first occurrence of Cmax
TNF	Tumour Necrosis Factor
TNFi	Tumour Necrosis Factor Inhibitor
T-Spot	T-SPOT® TB test
TYK2	Tyrosine kinase 2
ULN	Upper Limit Of Normal
US	United States
UVB	Ultraviolet B
VAS	Visual Analog Scale
VLDA	Very Low Disease Activity
VZV	Varicella-Zoster Virus
WBC	White Blood Cell

Appendix 2. Prohibited Prior and Concomitant Medications

Prohibited medication and washout time prior to first dose of study drug (if applicable).

Prohibited Medication	Discontinuation and/or washout time prior to first dose of study drug	Note
Adalimumab (Humira® or biosimilars), Certolizumab (Cimzia®), Golimumab (Simponi® and Simponi Aria®)	10 weeks	
Infliximab (Remicade® or biosimilars)	8 weeks	
Etanercept (Enbrel® or biosimilars)	4 weeks	
Abatacept (Orencia®)	10 weeks	
Rituximab or other selective B-lymphocyte depleting agents (including experimental agents)	6 months or 5 half-lives (if known), whichever is longer, or until lymphocyte count returns to normal, whichever is longer	
Any IL-17 inhibitor, IL-12/23 inhibitor, or IL-23 inhibitor, including but not limited to secukinumab (Cosentyx®), ixekizumab (Taltz®), ustekinumab (Stelara®), brodalumab (Siliq®), guselkumab (Tremfya®), risankizumab, bimekizumab, and tildrakizumab		Subject is not eligible (Exclusion Criterion #22).
Non B cell-specific lymphocyte depleting agents/therapies (eg, alemtuzumab [Lemtrada® or CamPath®]), alkylating agents (eg, cyclophosphamide or chlorambucil), total lymphoid irradiation, etc.		Subject is not eligible (Exclusion Criterion #27).
Efalizumab (Raptiva®)		Subject is not eligible (Exclusion Criterion #28).
Cumulatively 2 or more TNF inhibiting biologic agents		Subject is not eligible (Inclusion Criterion #12).
Other biologic agents	6 month unless otherwise specified in this table	

Prohibited Medication	Discontinuation and/or washout time prior to first dose of study drug	Note
Any Janus kinase (Jak) inhibitors, including but not limited to tofacitinib (Xeljanz®), baricitinib (Olumiant®), upadacitinib, peficitinib, filgotinib		Subject is not eligible (Exclusion Criterion #23).
Apremilast (Otezla®)	4 weeks	
Non-biologic DMARD other than methotrexate, leflunomide or sulfasalazine, including but not limited to hydroxychloroquine, azathioprine, cyclosporine, mizoribine, tacrolimus and tetracycline (used as a DMARD)	4 weeks	
Two or more concurrent non-biologic DMARDs	4 weeks (8 weeks for leflunomide if cholestyramine washout not done)	
High potency opioid analgesics (eg, methadone, hydromorphone, buprenorphine, fentanyl)	4 weeks	
Oral corticosteroids >10 mg/day of prednisone or equivalent	4 weeks	
Injectable corticosteroids	4 weeks	Intra-articular corticosteroids may be given as rescue medication (See Appendix 3).
Intra-articular hyaluronate sodium	4 weeks	May be given as rescue medication (See Appendix 3).
Any other non-biological investigational or experimental therapy or procedure for psoriasis, PsA or rheumatoid arthritis	12 weeks unless otherwise specified in this table	
Live or attenuated live vaccine	6 weeks	
Recombinant subunit vaccines (eg, Shingrix®)	4 weeks	

Prohibited Medication	**Discontinuation and/or washout time prior to first dose of study drug**	**Note**
Topical treatments that could affect psoriasis, eg, corticosteroids (including but not limited to hydrocortisone 17 butyrate, hydrocortisone valerate, and hydrocortisone/hydrocortisone acetate with concentration higher than 1%), tars, keratolytics, anthralin, vitamin D analogs, and retinoids	2 weeks	The following topical treatments are allowed: non-medicated emollients for use over the whole body; topical steroids including hydrocortisone and hydrocortisone acetate ≤1% for the palms, soles, face and intertriginous areas only; tar and salicylic acid preparations for the scalp only and shampoos free of corticosteroid for the scalp only.
UVB (narrowband or broadband) phototherapy	2 weeks	
Psoralens + UVA phototherapy (PUVA)	4 weeks	
Medications that prolong the QT/QTc interval	7 days or 5 half-lives (whichever is longer)	Please refer to drug label.
Other prohibited medication, moderate and strong CYP3A inhibitors or inducers, strong P-gp inhibitors, P-gp substrate, and substrates of OCT2/MATE as listed in the table below	7 days or 5 half-lives (whichever is longer)	

List of prohibited CYP3A Inhibitors, CYP3A inducers, strong P-gp inhibitors, P-gp substrates, and substrates of OCT2/MATE*.

Moderate and strong CYP3A inhibitors	Moderate and strong CYP3A inducers	Strong P-gp inhibitors	P-gp substrates	Substrates of OCT2/MATE
HIV antivirals: -delavirdine (Rescriptor) -indinavir (Crixivan) -nelfinavir (Viracept) -ritonavir (Kaletra, Norvir) -saquinavir (Fortovase) amiodarone (Cordarone, Pacerone) cimetidine (Tagamet) ciprofloxacin (Cipro) clarithromycin (Biaxin, Prevpac) diethyl-dithiocarbamate diltiazem (Cardizem, Tiazac) erythromycin fluconazole (Diflucan) fluvoxamine (Luvox) gestodene (Femodene, Melodene, Minulette, Mirelle, Triodene ED) grapefruit juice and marmalade itraconazole (Sporanox) ketoconazole (Nizoral) mifepristone (Mifeprex, RU486) nefazodone (Serzone) norfloxacin (Shibroxin, Noroxin) norfluoxetine mibefradil verapamil (Calan SR, Covera HS, Isoptin SR, Tarka, Verelan)	HIV antivirals: -efavirenz (Sustiva) -nevirapine (Viramune) barbiturates carbamazepine (Carbatrol, Tegretol) modafinil (Provigil) phenobarbital phenytoin (Dilantin, Phenytek) pioglitazone (Actos) rifampin (Rifadin, Rifamate, Rifater) rifabutin (Mycobutin) St. John's wort troglitazone (Rezulin)	Quinidine	Digoxin	dofetilide

* This is not an all-inclusive list. These prohibited drugs (table above) require at least a 7 day or 5 half-life (whichever is longer) washout period prior to the first dose of study medication. Note: efavirenz, nevirapine, barbiturates, carbamazepine, phenobarbital, St. John's Wort, rifabutin should be discontinued at least 30 days prior to first dose of study drug based on half-life of these drugs, and that amiodarone should be discontinued at least 290 days prior to the first dose of study drug based on a half-life of 58 days. Topical (including skin or mucous membranes) application of antibacterial (eg, clarithromycin, erythromycin and norfloxacin) and antifungal (fluconazole, ketoconazole and itraconazole) medications is permitted. For a medical condition (other than PsA) where it is important for the subject's safety to continue a prohibited drug, and where there is no study-permitted alternative, the subject must not participate in this study.

Appendix 3. Rescue Therapy

The only medications that are allowed for rescue are listed here.

Acetaminophen/paracetamol

Acetaminophen/ paracetamol is allowable as rescue medication if dosed no more than 2.6 gm/day for no more than 10 consecutive days. There is no limit to the duration of non-consecutive use of rescue medications.

- 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.

- Acetaminophen/paracetamol is not permitted as a part of combination products such as over-the-counter "cold remedies" or in combination with opioids if the total acetaminophen/paracetamol dose will exceed 2.6 gm/day.

Opioids

Non-prohibited opioids may be added or increased to a maximum potency equivalent of 30 mg of orally-administered morphine. The following paradigm should be used to determine appropriate opioid rescue therapy:

For subjects who are NOT on 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:

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

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

- Oxycodone (with or without acetaminophen/paracetamol), not to exceed 15 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 opioid medication is 1 of the 3 listed above, they may, within the above maximum total dosage limits, increase the dosage for up to 10 consecutive days for rescue purposes.

- If their background medication is a short-acting (half-life <5 hrs, Appendix 4) opioid that is not one of those listed above, they may increase the dosage for up to 10 consecutive days (up to a total daily dose which must not exceed the potency equivalent of 30 mg of orally-administered morphine) for rescue purposes.

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

Intra-articular injection (at or after the Week 16 visit only)

Intra-articular corticosteroids or hyaluronate sodium may be given at or after the Week 16 visit. If performed at the Week 16 visit, intra-articular injections must be given **after all assessments are completed**. Injected joints will also be considered as having their pre-injection status (swollen and/or painful/tender) and should not be counted for the remainder of the trial.

- Intra-articular corticosteroids may be given at or after the Week 16 visit in no more than two joints, in a cumulative dose of no more than 40 mg methylprednisolone or its equivalent in any 6 month study period. The total allowed intra-articular corticosteroid dose may be divided into separate injections (eg, 20 mg, 20 mg). Intra-articular corticosteroids should not be administered within 4 weeks prior to a study visit.

- Intra-articular hyaluronate sodium injections may be administered for indications in accordance with the local label at or after the Week 16 visit in no more than two joints in any 6 month study period.

Note:

- Subjects who require rescue for more than 10 consecutive days should be discontinued from the study. There is no limit to the duration of non-consecutive use of rescue medications.

- Subjects must not be dosed with rescue medication during the 24 hours prior to a study visit except if adjustment is needed because subject is experiencing intolerable pain.

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

Appendix 4. Maximum Allowed Total Daily Dose of Opioid Analgesics

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

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.

Note:

- Sites should contact project team for acceptable alternative preparations and related data.
- High potency opioid analgesics (eg, methadone, hydromorphone, buprenorphine, and fentanyl) are prohibited.

Appendix 5. Oral Corticosteroid Equivalents

The following is a summary of corticosteroid equivalents.

Oral corticosteroids – subjects already taking oral corticosteroids must be on a stable dose of ≤10 mg/day of prednisone or equivalent for at least 4 weeks prior to first dose of study drug. Tapering or discontinuation of the corticosteroid treatment is only allowed after Week 52, unless required for toxicity, and should be performed slowly at the discretion of the investigator.

Compound	Equivalent Dose (mg)
Prednisone	10
Prednisolone	10
6α-methylprednisolone	8
Triamcinolone	8
Betamethasone	1.2
Dexamethasone	1.5
Hydrocortisone	40
Cortisone	50
Deflazacort	12
Cloprednol	5
Prednylidene	12

Note:

- These dose relationships apply to oral administration.
- Intravenous or intramuscular corticosteroids are not allowed during this study either as a stable concomitant medication or as rescue medication. Intra-articular corticosteroids are allowed but only as rescue therapy (See Appendix 3 Rescue Therapy).

Appendix 6. Discontinuation Criteria

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

Study Treatment:

- Requirement of rescue medication for more than 10 consecutive days;
- Interrupting study drug for more than 14 consecutive days;
- Less than 80% compliant with the dosage regimen for any two consecutive visit periods.

Adverse Events:

- Serious infections defined as any infection (viral, bacterial, or fungal) requiring parenteral antimicrobial therapy or hospitalization for treatment, or meeting other criteria that require the infection to be classified as a serious adverse event (SAE);
- Serious thromboembolic events, including venous thrombosis (including but not limited to deep vein thrombosis [DVT], pulmonary embolism [PE]), arterial thrombosis, and cerebrovascular events (thromboembolic stroke, transient ischemic attack [TIA], etc.) requiring hospitalization for treatment, or meeting other criteria that require the thromboembolic event to be classified as a serious adverse event (SAE);
- Other serious or severe adverse events, after consultation with the sponsor clinician.

Laboratory Abnormalities (repeat laboratory tests should occur within 1 week):

- Two sequential absolute neutrophil counts $<1.0 \times 10^9$/L ($<1000/mm^3$);
- Two sequential hemoglobin values <8.0 g/dL (80 g/L);
- Two sequential absolute lymphocyte counts $<0.5 \times 10^9$/L ($<500/mm^3$);
- Two sequential platelet counts $<75 \times 10^9$/L ($<75,000/mm^3$);
- Two sequential 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);
- Two sequential AST or ALT elevation ≥3 times the upper limit of normal with at least one total bilirubin value ≥2 times the upper limit of normal[†];

- Two sequential AST or ALT elevation ≥3 times the upper limit of normal accompanied by signs or symptoms consistent with hepatic injury[†];

- Two sequential AST or ALT elevation ≥5 times the upper limit of normal, regardless of total bilirubin or accompanying signs or symptoms[†];

- Two sequential total bilirubin value ≥1.5 times the upper limit of normal (subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is < upper limit of normal)[†];

  [†]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.

- Potential Cases of Decreased eGFR: If an individual subject demonstrates CONCOMITANT serum creatinine-based eGFR AND serum Cystatin C-based eGFR decline of ≥30% compared to the subject's baseline eGFR, then the subject should not be further dosed and adequate, immediate, supportive measures including immediate evaluation by a nephrologist (preferably within 24 hours) with appropriate management and treatment as clinically indicated. Results should be repeated as indicated by the nephrologist or weekly at a minimum until the eGFR returns to baseline ±15%, or the renal parameters are deemed to be stable by the nephrologist and/or PI. If the subject cannot be seen by a nephrologist within 24 hours (as described above), then the subject should be sent to a local emergency room for evaluation and treatment as clinically indicated.

ECG:

- Marked prolongation of the QTcF interval to >500 msec or >60 msec change from baseline (Day 1) ECG. If QTcF exceeds these limits, the ECG should be repeated two more times and the average of the three QTcF should be used to determine the discontinuation.

Other:

- A confirmed positive urine pregnancy test in a woman of childbearing potential.

- 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.

Note:

- Whenever possible, the investigator should consult with a member of the Pfizer study team before discontinuation of the subject.

- Discontinuation/End of Treatment Monitoring for Adverse Events, Laboratory, Vital Signs or ECG: The procedures scheduled for Week 52/Early Termination Visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. Any subject meeting discontinuation criteria must enter into the Follow up Period with additional follow up visit occurring 1 week after their last dose or Early Termination Visit whenever possible, and follow up until any clinically relevant abnormalities or adverse events have resolved, returned to a baseline state, or are deemed clinically stable. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her.

Appendix 7. Laboratory Abnormalities Require Re-Testing

The following laboratory abnormalities require prompt re-testing within 1 week until resolution or agreement with Pfizer:

- Absolute neutrophil count 1.5 $x10^9$/L (<1500/mm^3);
- Hemoglobin <9.0 g/dL;
- Platelet count below <100 $x10^9$/L (100,000/mm^3);
- Lymphocytes <0.6 $x10^9$/L (600/mm^3);
- Creatine kinase (CK) >3xULN (this also triggers urine myoglobin).

Appendix 8. Example of Effective, but Not Highly Effective Methods of Contraception

The following methods of contraception are considered effective, but not highly effective methods (failure rate of ≥1% per year):

1. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

2. Male or female condom with or without spermicide.

3. Cervical cap, diaphragm, or sponge with spermicide.

4. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (doublebarrier methods).

Note that periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

Male condom and female condom should not be used together (due to risk of failure with friction).