A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, PLACEBO-CONTROLLED, MULTI-CENTER STUDY TO ASSESS THE EFFICACY AND SAFETY PROFILE OF PF-06651600 IN SUBJECTS WITH MODERATE TO SEVERE ACTIVE RHEUMATOID ARTHRITIS WITH AN INADEQUATE RESPONSE TO METHOTREXATE

Investigational Product Number:	PF-06651600
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	131274
European Clinical Trials Database (EudraCT) Number:	2016-002862-30
Protocol Number:	B7981006
Phase:	2a

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 1	26 October 2016	In the Schedule of Activities, and Section 7.2.12, added audiogram testing • Rationale: To monitor for potential changes in hearing between baseline [between Visit 1 and Visit 2 (inclusive)] and at the end of the study [between Visit 7 and Visit 9 (inclusive)]. The following exclusion criteria has been added in Section 4.2: *Have current or recent history of clinically significant severe or progressive hearing loss or auditory disease. Subjects with hearing aids will be allowed to enter the study provided their hearing impairment is considered controlled/ clinically stable.* • Rationale: This has been added to ensure that subject hearing for safety is fully evaluated prior to study entry. Several additional minor changes were made to protocol language for the purposes of clarification.
Original protocol	31 August 2016	Not applicable (N/A)

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

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PROTOCOL SUMMARY

Background and Rationale:

PF-06651600 is a potent, Janus kinase (JAK) 3 selective, covalent inhibitor. It is an orally bioavailable small molecule that selectively inhibits JAK3 by irreversibly blocking the adenosine triphosphate (ATP) binding site without significantly inhibiting the other three JAK isoforms (JAK1, JAK2, and TYK2). The molecule also has a high specificity against the broad human kinome.

This JAK3-selective inhibition will lead to modulation of γ-common chain cytokine pathways, such as IL-7, IL-9, IL-15 and IL-21, some of which have been implicated in the pathophysiology of Rheumatoid Arthritis (RA). PF-06651600 will spare inhibition of key immuno-regulatory cytokines, such as IL-10, IL-35 which play a protective role in RA. Inhibition of JAK2 cytokine signaling, implicated to be associated with adverse effects such as neutropenia, thrombocytopenia and anemia[14] will also be spared, thus making JAK3-selective inhibitors an attractive therapeutic modality. JAK3 is also expressed only in the hematopoietic cells and thus the rationale for improved therapeutic index of PF-06651600 in RA over pan-JAK inhibition. This multicenter, placebo controlled study will be the first determination of safety and efficacy of PF-06651600 in subjects with moderate to severe active RA who have had an inadequate response to methotrexate (up to approximately 50% of subjects may also have had an inadequate response to 1 anti-TNFα biologic DMARD).

Objectives and Endpoints:

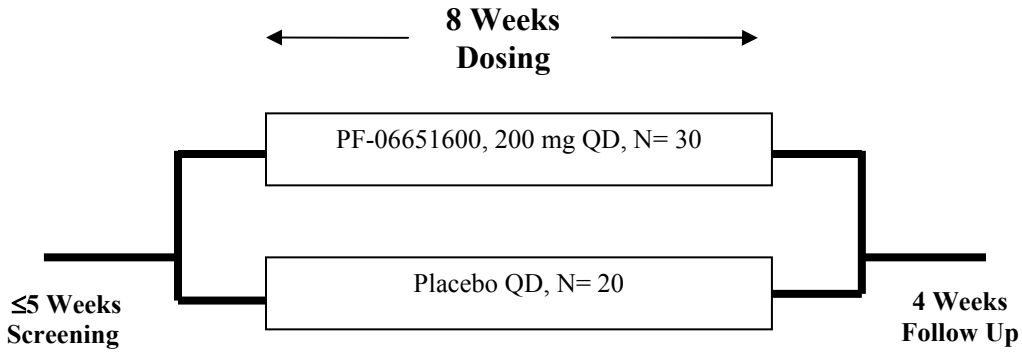
Primary Objectives:	**Primary Endpoints:**
• To evaluate the efficacy of PF-06651600 at 8 weeks in subjects with moderate to severe active RA.	• Change from baseline in Simple Disease Activity Index (SDAI) at Week 8.
Secondary Objectives:	**Secondary Endpoints:**
• To evaluate the safety of PF-06651600.	• Safety and tolerability of PF-06651600 versus placebo; vital signs, laboratory tests, adverse events (AEs) including infections and Serious Adverse Events (SAEs).
• To assess other signs of clinical efficacy over 8 weeks.	• Change from baseline in SDAI at Weeks 1, 2, 4 and 6. • Change from baseline in SDAI low disease activity scale (LDAS) and remission rates at Week 4, Week 6 and Week 8. • Change from baseline in DAS28 LDAS and remission rates at Week 4, Week 6 and Week 8. The following will also be calculated at Weeks 1, 2,4, 6 and 8: • Change from baseline in DAS28-3 (ESR), DAS28-3 (CRP), DAS28 -4 (ESR), and DAS28-4 (CRP).

	• Change from baseline in hsCRP. • Change from baseline in the Tender/Painful and Swollen Joint Count (28). • Change from baseline in the Physician Global Assessment of Arthritis.
• To assess the effect of PF-06651600 on patient reported outcome measurements.	• Change from baseline in the Patient's Assessment of Arthritis Pain (VAS) and Patient Global Assessment of Arthritis (VAS) at Weeks 1, 2, 4, 6 and 8. • Change from baseline in the HAQ-DI at Weeks 1, 2, 4, 6 and 8.
[redacted] CCI [redacted]	[redacted]
[redacted] • CCI [redacted] • CCI [redacted]	[redacted] • Change from baseline in ACR 20, ACR 50 and ACR 70 responder rates. • CCI [redacted]

*Note: (Analysis of exploratory endpoints may be further detailed in the statistical analysis plan (SAP) or exploratory analysis plan (EAP). Samples collected for exploratory endpoints may or may not be analyzed and, if analyzed, may or may not be reported in the CSR.)

Study Design and Treatments:

Study Design Schematic



Note: N indicates the total number of completers.

This is a Phase 2a, 8 week randomized double-blind, parallel group, placebo controlled, multi-center study to assess the efficacy and safety profile of PF-06651600 in seropositive subjects with moderate to severe active rheumatoid arthritis with an inadequate response to methotrexate (up to approximately 50% of subjects may also have had an inadequate response to 1 anti-TNFα biologic DMARD).

Up to approximately 60 subjects may be randomized globally into the study to ensure at least approximately 50 subjects complete 8 weeks of active dosing (assuming a dropout rate of approximately 15%). Subjects will participate in this study for approximately 17 weeks. This includes an up to 5-week screening period, an 8 week treatment period, and a 4 week follow-up period.

After an up to 5 week screening period, eligible subjects will be randomized to receive 200 mg QD of PF-06651600 or placebo (matching tablets for PF-06651600 QD) every day for 8 weeks in a blinded fashion.

Statistical Methods:

Analysis of Primary Endpoint

The primary efficacy analysis will be conducted on Simple Disease Activity Index (SDAI) change from baseline at 8 weeks.

Analysis will include data on PF-06651600 and placebo arms.

Analysis details will be outlined in statistical analysis plan (SAP). The analysis will include: Analysis of Covariance (ANCOVA) models adjusting for SDAI baseline value; Bayesian

analysis of posterior distributions of the SDAI scores and placebo adjusted change from baseline; Advanced data visualization techniques for statistical result presentation.

The primary analysis will be conducted on intention-to-treat (ITT) population (randomized subjects with at least one post baseline value). Sensitivity analysis and handling of the missing values will be outlined in the SAP.

Analysis of Secondary Endpoints

Analyses of the secondary endpoints will be outlined in the SAP. Continuous and discrete modeling techniques will be applied whenever applicable. The statistical summaries will be presented by dose groups. The correlations between the endpoints will be analyzed.

Analysis of Other Endpoints

Analysis of other endpoints will be conducted as deemed appropriate. Continuous and discrete modelling techniques will be applied whenever applicable. Distribution summaries will be presented by means of summary tables data visualization methods.

Safety Analysis

All clinical Adverse Events (AEs), Serious Adverse Events (SAEs), Treatment Emergent Adverse Events (TEAEs), withdrawal due to AEs, electrocardiograms (ECGs), vital signs and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects.

The safety analysis set will include all subjects who have received at least one dose of IP. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. All safety endpoints will be listed and summarized in accordance with Pfizer Standards. Categorical outcomes (eg, AEs) will be summarized by subject counts and percentage. Continuous outcome (eg, blood pressure (BP), pulse rate, etc) will be summarized using N, mean, median, standard deviation, etc. Change from baseline in laboratory data, ECGs and vital signs will also be summarized. Subject listings will be produced for these safety endpoints accordingly.

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.

Protocol Activity	**Screening**	**Treatment Period**						**Follow Up/End of Study**		**Early Withdrawal[b]**
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[s]**	**9**	
Week[a]		**Week 0**	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	
Study Day	**Days -35 to Day 0**	**Day 1[x]**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	
Visit Window			**±2 Days based on Week 0/Day 1 visit**							
Informed consent	X									
Inclusion/Exclusion Criteria	X	X								
Demographics and RA history	X									
Prior RA medications check[c]	X	X								
Smoking History	X									
Medical history and Non RA medications	X									
History of Alcohol and Drug Abuse	X									
Height[v]	X									
Weight[v]	X								X	X
Contraception Check[r]	X	X	X	X	X	X	X	X[s]	X	X
Vital Signs (pulse rate, blood pressure), temperature[d]	X	X	X	X	X	X	X		X	X
Complete Physical Examination[e]	X	X							X	X
Targeted Physical Examination[e]			X	X	X	X	X			
Rash assessment	X	X	X	X	X	X	X	X[s]	X	X
ECG (12 lead)[f]	X	X					X		X	X
Chest X-ray[g]	X									
Audiogram[y]	X						X			X
Laboratory Evaluations										
Blood Chemistry[h]	X	X			X		X		X	X
Hematology	X	X	X	X	X	X	X		X	X
Rheumatoid Factor (RF)	X	X			X		X		X	X
C-Reactive Protein (hsCRP)	X	X	X	X	X	X	X		X	X

Protocol Activity	Screening	Treatment Period						Follow Up/End of Study		Early Withdrawal[b]
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[s]**	**9**	
Week[a]		**Week 0**	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	
Study Day	**Days -35 to Day 0**	**Day 1[x]**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	
Visit Window			**±2 Days based on Week 0/Day 1 visit**							
Anti CCP Antibodies (ACPA)	X	X			X		X		X	X
Erythrocyte Sedimentation Rate (ESR)		X	X	X	X	X	X		X	X
Serum Ig (IgA, IgM, IgG)		X					X			X
Serum IgE		X					X			X
Sample for IP-10		X					X		X	X
Urinalysis	X	X	X	X	X	X	X		X	X
Pregnancy test[i]	X	X	X	X	X	X	X		X	X
FSH test (if applicable)[t]	X									
HBsAg, HBcAb, HBsAb and HCVAb antibody[j]	X									
HIV testing[k]	X									
HbA1c	X									
Tuberculosis test[l]	X									
Viral Surveillance[u]	X	X	X	X	X	X	X		X	X
Sample for flow cytometry		X					X		X	
Banked RNA biospecimen (Prep R1)[m]	X	X					X		X	
Banked plasma biospecimens (Prep B1)[m]		X			X		X		X	
Banked serum biospecimens (Prep B2)[m]		X			X		X		X	
Genomic banked biospecimen (Prep D1)[q,m]		X								
Study Treatment										
Randomization (after all screening procedures are complete and reviewed)		X								
Administration and Dispensing of PF-06651600 or Placebo[o]		X	X	X	X	X	X			
Investigational Product Accountability			X	X	X	X	X			X

Protocol Activity	Screening	Treatment Period						Follow Up/End of Study		Early Withdrawal[b]
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[s]**	**9**	
Week[a]		**Week 0**	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	
Study Day	**Days -35 to Day 0**	**Day 1[x]**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	
Visit Window			**±2 Days based on Week 0/Day 1 visit**							
Review of subject diary (review of subjects dosing record), IP accountability and compliance check throughout the study[p]		X	X	X	X	X	X			X
Pharmacokinetic										
Pre-dose (0hr) blood sample for PK analysis of PF-06651600		X	X	X	X	X	X			X[w]
Blood sample for PK analysis of PF-06651600 (0.5 hr) post dose				X	X	X	X			
Blood sample for PK analysis of PF-06651600 at 1 hr post dose				X		X	X			
Blood sample for PK analysis of PF-06651600 at 2 and 4 hr post dose							X			
Efficacy assessments										
Tender/Painful Joint Count (68)	X	X	X	X	X	X	X		X	X
Swollen Joint Count (66)	X	X	X	X	X	X	X		X	X
Patient Assessment of Arthritis Pain (PAAP) VAS	X	X	X	X	X	X	X		X	X
Patient's Global Assessment (PtGA) of Arthritis VAS	X	X	X	X	X	X	X		X	X
Physician's Global Assessment (PhGA) of Arthritis[n]	X	X	X	X	X	X	X		X	X
Health Assessment Questionnaire – Disability Index (HAQ-DI)	X	X	X	X	X	X	X		X	X
Serious and Non-Serious Adverse Event Assessment	X	→	→	→	→	→	→	X	X	X
Concomitant Medication & Treatments		X	→	→	→	→	→	X	X	X
Discharge from the study									X	X

Abbreviations: → = ongoing/continuous event; CRP = C-Reactive Protein; DNA = deoxyribonucleic acid ; ECG = electrocardiogram; EOS = end of study; ESR = Erythrocyte Sedimentation Rate; FACS = fluorescence-activated cell sorting; FSH = follicle stimulating hormone; HAQ-DI = Health Assessment Questionnaire – Disability Index; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBsAb= hepatitis B surface antibody;

HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; IgA, IgG, IgM, IgE = Immunoglobulin of the A, G, M, E isotypes; IGRA = Interferon Gamma Release Assay; IP = investigational product; IP-10 = IFN-gamma-inducible protein 10; IRB = institutional review board; PK = pharmacokinetic; PAAP = Patient Assessment of Arthritis Pain; PtGA = patient's global assessment; PhGA = Physician's Global Assessment; PK=Pharmacokinetics; RNA = Ribonucleic Acid; VAS = Visual Analog Scale; WONCBP = women of non-childbearing potential.

a. Visits should occur when scheduled, within the time window indicated in the column headings. The screening visit is up to 5 weeks prior to Visit 2. On all clinic visit days, PtGA and PAAP VAS measures and HAQ-DI questionnaires, should be performed prior to any other assessments. Vital signs, ECG and blood draws should be performed as specified in Section 7. Assessments including joint counts, physician questionnaire, and pre-dose blood collections are to be performed prior to dosing unless otherwise stated. Physician's assessment should be performed without knowledge of patient reported VAS assessments Additional unscheduled assessments should be performed as clinically indicated.
b. See Section 6.4 for guidelines on subject withdrawal/early withdrawal from the study. Any subject who prematurely withdraws from the treatment period should undergo the procedures for an early withdrawal visit and return for follow up visits if medically needed in the opinion of the PI. Document reasons for Early Withdrawal.
c. Check and verify prior and current RA medications taken after informed consent is signed to ensure compliance with protocol eligibility criteria. Written informed consent must be obtained prior to performing any washout of prohibited medication.
d. See Section 7.2.5 for guidelines on measurement of vital signs. The same measurement method should be used consistently throughout the study.
e. All subjects will have a dermatological full body exam at Screening Visit. Additional Physical Exams (PEs) may be performed during the study at the investigator's discretion. See Section 7.2.2 for guidelines on collecting PEs.
f. An ECG may be performed at other times, at the discretion of the investigator if there were findings during a previous examination or in the case of a new/open adverse event (AE). See Section 7.2.6 for guidelines on ECGs.
g. See Section 7.2.8 for guidelines on Chest X-rays.
h. A minimum of 8-hour fasting is required for lipid profile evaluation at Day 1, Week 4, Week 8, and EOS. Laboratory tests may be repeated once during the screening period; the last value will be used to determine eligibility. See Section 7.2.1 for additional information on blood chemistry collection.
i. Required for women of childbearing potential who do not meet the definition of non-childbearing potential as per the inclusion/exclusion criteria. Serum pregnancy test must be performed at screening. Pregnancy tests (serum/urine) may also be repeated more frequently as per request of IRBs/ECs or if required by local regulations. See Section 7.2.4.
j. See Section 4 for subject eligibility criteria.
k. HIV testing per local regulations. See Section 4 for subject eligibility criteria.
l. IGRA official reading and method, or test as per country specific guidelines, must be located in source documentation. See Section 4 for subject eligibility criteria.
m. These samples must be collected before administration of the investigational product. See Section 7.5 for details.
n. Physician's assessment should be performed without knowledge of patient reported VAS assessments.
o. At the baseline visit, (Visit 2) the first dose of investigational product will be taken in the clinic. Additionally, at Weeks 1, 2, 4, 6 and 8 subjects should be given their dose for that day in the clinic. All other doses will be taken by the subject outside of the clinic.
p. Subject diary dispensed and/or collected. Subject diary, study compliance and investigational product administration entries are reviewed. See Section 5.3.

q. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit.

r. Except for women of non-child bearing potential. See Section 4.3.1 and Section 7.2.4.

s. Telephone follow up. Adverse Event and rash assessments (if needed) will be conducted verbally over the phone and if needed subject will be asked to come in for AE assessment. Use of contraception will be confirmed and concomitant medication check will be done over the phone with the subject.

t. To confirm postmenopausal status (if applicable).

u. In addition to time points specified, a plasma sample for viral surveillance sample may also be taken at the time of an adverse event. See Section 7.2.10 for details.

v. Height and Weight will be measured without shoes.

w. At the time of the visit, a blood sample will be collected for PK analysis. As with all PK assessments, date and time of last dose and date and time of sample collection should be captured and reported.

x. Baseline Visit.

y. Audiogram testing at screening must be completed and results available by the baseline visit (Visit 2) and audiogram testing at Week 8 (Visit 7) must be completed and results available by the Week 12 visit (Visit 9). For subjects that terminate early from the study, if possible, efforts must be made to complete the audiology testing and obtain the results. See Section 7.2.12 for details.

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, autoimmune disease characterized by joint inflammation and destruction, progressive disability and adverse psychological effects. The prevalence of RA is approximately 0.5-1% of the population in developed regions with a 4-fold higher frequency in women than in men.[16] There is considerable evidence for both genetic and environmental contributions to RA. A growing body of evidence has implicated anti-citrullinated protein antibodies (ACPA) in more severe manifestations of RA. ACPA positive (ACPA+) RA subjects tend to have more rapidly progressing disease and are less likely to respond to current therapy.[20]

There are multiple therapeutic options for managing the pain and slowing the progression of rheumatoid arthritis, but none completely cure the disease. The current goal of treatment (as stipulated in the 2010 European League Against Rheumatism (EULAR) recommendations for the treatment of RA) aims toward achieving the lowest possible level of arthritis disease activity (ideally, remission), minimizing joint damage, and enhancing physical function and quality of life.[17] Disease-modifying antirheumatic drugs (DMARDs) are the standard treatments for RA. Conventional synthetic DMARDs (csDMARDs), such as methotrexate, are used either alone or in combination with newer biologic DMARDs. They work to decrease pain and inflammation, to reduce or prevent joint damage, and to preserve the structure and function of the joints but rarely induce remission. Use of biologic DMARDs, most commonly TNFα inhibitors, is indicated when symptoms are not adequately controlled with csDMARDs. Additional approved therapeutics include tocilizumab (interleukin (IL)-6 receptor neutralizing antibody) and tofacitinib (a small molecule pan-Janus kinase (JAK) inhibitor). Despite the considerable list of approved treatments for RA, there are significant numbers of subjects who do not achieve remission or achieve adequate reduction in disease activity.[5]

Tofacitinib, approved by the Food and Drug Administration (FDA) in 2012 is the first JAK inhibitor for the treatment of moderate-to-severe RA. It is a pan-JAK inhibitor with inhibitory activity ranked in the order JAK3 > JAK1 > JAK2 > TYK2. The broad inhibitory effect on JAK3, JAK1, JAK2 and TYK2 impacts a broad panel of cytokine signaling pathways including cytokines with anti-inflammatory roles such as IL-10. Tofacitinib blockade of JAK2, also results in some of the treatment-associated adverse effects such as anemia and neutropenia.[14] Thus, the rationale for selective JAK3 inhibition. This rationale is additionally supported by the fact that JAK3 deficiency in mice and humans results in immunodeficiency due to lack of circulating NK and T cells. Selectively expression of JAK3 in hematopoietic cells and its essential role in lymphocyte development lends support for JAK3 as a target for immune suppression.[9,3,12,18]

The JAK family of kinases mediates signal transduction via interactions with type I and type II cytokine receptors. Several JAK3 cytokines such as IL-15, IL-7, IL-9 and IL-21 have been implicated in RA.[21,6,19] Roles for IL-15 and IL-7 in the pathogenesis of RA have been demonstrated in mouse models. Furthermore, levels of these cytokines are also reported to be elevated in blood/serum and synovial fluid in RA subjects and IL-7 and IL-21 cytokines also promote osteoclastogenesis. Hence the rationale to target JAK3-mediated cytokine signaling pathways. Additional support for the rationale for JAK3 inhibition in RA comes

from several human clinical studies with HuMax-IL-15 (AMG714), a neutralizing antibody against IL-15 and decernotinib (VX-509, a JAK3-selective inhibitor).[2,4,16,11,10,8] Therefore blocking signaling downstream of JAK3 may be beneficial in RA.

1.1. Mechanism of Action/Indication

PF-06651600 is a potent and selective covalent inhibitor of JAK3 that is currently under development for the treatment of RA and Ulcerative Colitis (UC).

1.2. Background and Rationale

PF-06651600 is a potent, Janus kinase (JAK)3 selective, covalent inhibitor. It is an orally bioavailable small molecule that selectively inhibits JAK3 by irreversibly blocking the adenosine triphosphate (ATP) binding site without significantly inhibiting the other three JAK isoforms (JAK1, JAK2, and TYK2). The molecule also has a high specificity against the broad human kinome.

This JAK3-selective inhibition will lead to modulation of γ-common chain cytokine pathways, such as IL-7, IL-9, IL-15 and IL-21, some of which have been implicated in the pathophysiology of RA. PF-06651600 will spare inhibition of key immuno-regulatory cytokines, such as IL-10, IL-35 which play a protective role in RA. Inhibition of JAK2 cytokine signaling, implicated to be associated with adverse effects such as neutropenia, thrombocytopenia and anemia[14] will also be spared, thus making JAK3-selective inhibitors an attractive therapeutic modality. JAK3 is also expressed only in the hematopoietic cells and thus the rationale for improved therapeutic index of PF-06651600 in RA over pan-JAK inhibition.

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1.5.1. Summary of Clinical Safety of PF-06651600

Eighty (80) subjects were enrolled into the FIH study. Single doses up to 800 mg and multiple doses up to 400 mg daily, as both 400 mg QD and 200 mg BID were administered. PF-06651600 appears to be generally safe and well-tolerated. No clinically-significant changes in vital signs, electrocardiogram or laboratory data were observed. No dose-limiting adverse events were reported and no subjects met the protocol prescribed individual stopping rules. There were no deaths in the study.

The most commonly reported all causality treatment-emergent AEs across both Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) PF-06651600 cohorts were GI disorders, including diarrhea (9 subjects), abdominal pain (6 subjects), abdominal discomfort (2 subjects), and flatulence (3 subjects). Change of bowel habit, constipation, fecal volume increased, discolored feces, nausea, paraesthesia oral, and vomiting have each also been reported (1 subject each event). All cases were mild in severity with the exception of 1 moderate TEAE each of abdominal pain, dysphagia, and vomiting.

Skin and subcutaneous tissue disorders including, but not limited to rash, maculopapular rash, dermatitis acneiform, and erythema of mild to severe intensity were reported in the PF-06651600 cohorts and are summarized in Table 1 below. There were no skin and subcutaneous tissue disorders reported in the 5, 20, 50, 200, 400, and 800 single dose cohorts; nor were there any skin and subcutaneous tissue disorders reported in the 50 mg QD multiple dose cohort.

Table 1. Skin and Subcutaneous Tissue Disorder Occurrence

N= # of subjects	SAD 50 mg N=8		SAD 100 mg N=8		MAD 100 mg BID N=8		MAD 200 mg QD N=8		SAD 400 mg N=16		MAD 400 mg QD N=24		MAD 200 mg BID N=8	
Adverse Event	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**
Acne	0	0	0	0	0	0	0	0	0	0	2*	1*	0	0
Dermatitis acneiform	0	0	0	0	2*	0	0	0	0	0	0	0	1*	0
Dry Skin	0	1**	0	0	0	0	0	0	0	0	2*	1*	0	0
Eczema	0	0	0	0	0	0	0	0	0	0	0	1*	0	0
Erythema	0	0	0	0	1*	0	2*	1*	0	1*	1*	0	1**	0
Rash	0	0	1*	0	0	0	0	0	0	0	1*	0	0	0
Rash macular	0	0	1*	0	0	0	0	0	0	0	3*	0	0	0
Rash maculopapular	0	0	1**	0	1**	0	0	0	0	0	0	0	2 (1**/ 1***)	0
Rash pruritic	0	0	0	0	0	0	0	0	0	0	0	0	1**	0
Seborrhoeic dermatitis	0	0	0	0	1*	0	0	0	0	0	0	0	0	0
Skin induration	0	0	0	0	0	0	0	0	0	0	0	0	0	1*

Abbreviations: A = active, P = placebo.

*- Mild **- Moderate ***- Severe

Three (3) serious adverse events (SAEs) were reported in the FIH trial.

The first event was a cutaneous abscess on the left buttock during the 200 mg single dose period in a subject who entered the study with a pre-existing boil on the left buttock. This was assessed 19 days after the single dose was administered and was considered related to the study drug. The subject was discontinued from treatment. The SAE criterion was met as the incision and drainage procedure was performed in a hospital setting.

The second SAE was a sacrococcygeal cyst/pilonidal sinus abscess during the 400 mg single dose period. This was assessed 19 days after the single dose was administered and was considered related to the study drug. The SAE criterion was met as the incision and drainage procedure was performed in a hospital setting.

The third SAE was a varicella infection during the 400 mg QD MAD dose period. The start date was 11 days after the last dose and was considered related to the study drug. The source of the infection is unknown; however, a second subject, who had a reactivation of varicella zoster, may be the source as the subjects were confined during the same time. The varicella infection resolved in 51 days.

Please refer to the Investigator's Brochure for more details on the clinical safety information with PF-06651600.

1.5.2. Pharmacokinetics of PF-06651600

The pharmacokinetic (PK) parameters from the 5, 20, 50, 100, 200, 400 and 800 mg single dose levels are summarized below in Table 2. In general, PF-06651600 AUC_{inf} increased in a dose related manner over the 5 to 800 mg dose range with a slightly greater than proportional increase observed over the 200 mg to 400 mg dose range. C_{max} increased with dose in an apparent dose proportional manner.

Table 2. Summary of Plasma PF-06651600 Pharmacokinetic Parameters Following Single Oral Doses, Study B7981001

	PF-06651600 Parameter Summary Statistics[a] by Treatment						
Parameter, units	5 mg	20 mg	50 mg	100 mg	200 mg	400 mg	800 mg
N, n	6,6	6,6	6,6	6,6	6,6	12,12	6,6
AUC_{inf}, ng.hr/mL	43.86 (26)	211.7 (39)	384.1 (47)	1085 (23)	2464 (42)	7824 (34)	16760 (18)
AUC_{last}, ng.hr/mL	42.42 (26)	209.3 (40)	382.6 (47)	1081 (23)	2461 (42)	7821 (34)	16760 (18)
C_{max}, ng/mL	27.02 (29)	120.9 (54)	253. 3 (45)	647.7 (24)	1039 (40))	2691 (26)	4992 (11)
T_{max}, hr	0.5 (0.5-0.5	0.5 (0.5-1)	0.5 (0.5-1	0.5 (0.5-0.6)	0.75 (0.5-2)	1(0.5-2)	1.5 (1-2)
t½, hr	1.20 (0.107)	1.2 (0.174)	1.13 (0.166)	1.48 (0.176)	1.75 (0.434)	2.18 (0.337)	2.48 (0.460)

[a] Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for t½.

N = Number of subjects in the treatment group and contributing to the mean; n= number of subjects where t½, AUC_{inf} were determined.

PF-06651600 was absorbed rapidly following single doses of 5 mg to 200 mg with median T_{max} values ≤0.750 hours, and more slowly at the higher doses with a median T_{max} of 1.0 and 1.5 hours for the 400 mg and 800 mg doses, respectively. Following attainment of C_{max}, the disposition of PF-06651600 generally showed a monophasic decline at the lower doses of 5 to 200 mg (mean t½ of 1.2 to 1.8 hours) while a biphasic decline observed at doses of 400 to 800 mg (mean t½ of 2.2 to 2.5 hours). An apparent trend toward longer t½ values at higher doses (400 and 800 mg) is probably due to concentrations remaining above the quantifiable limit for a longer period of time at the higher doses and defining a later terminal phase.

The PK parameters following administration of 50, 200 and 400 QD and 100 mg and 200 mg BID for 14 days are summarized below in Table 3.

On Day 14 of multiple-dose administration, PF-06651600 was absorbed rapidly with median T_{max} values of 1 hour or less across the entire range of doses, from a total daily dose of 50 mg (50 mg QD) up to 400 mg (200 mg BID or 400 mg QD). Following attainment of C_{max}, the disposition of PF-06651600 was consistent with that observed following single-dose administration, showing a monophasic decline for the lowest doses and a biphasic decline following the 200 mg BID and 400 mg QD dosing regimens and a mean terminal t½ of about approximately 1.3 to 2.3 hours. In general, plasma PF-06651600 AUC_{τ} and C_{max} increased with dose across the 50 mg to 400 mg total daily dose range in a dose related manner based on visual comparison of individual and dose normalized geometric mean C_{max} and AUC_{τ} values. Steady-state generally appears to have been reached by Day 4 for the QD regimens and Day 6 for the BID regimens based on similar median trough (predose) concentrations on Days 6, 8, 10, 12 and 14.

Table 3. Summary of Plasma and Urine PF-06651600 Pharmacokinetic Parameters Following Multiple Dose Administration for 14 days, Study B7981001

	PF-06651600 Parameter Summary Statistics[a] by Treatment				
Parameter, units	50 mg (QD)	100 mg (BID)	200 mg (QD)	400 mg (QD)	200 mg (BID)
N, n	6, 6	4,4	5, 5	15, 14	5, 5
AUC_{τ}, ng.hr/mL	540.1(38)	1984 (15)	4069 (22)	10040 (19)	5207 (24)
C_{max}, ng/mL	315.2 (38)	663.0 (35)	1422 (28)	3136 (26)	1903 (27)
T_{max}, hr	0.5 (0.5- 1)	0.75 (0.5- 2)	1 (0.5- 1)	1 (0.5- 2)	1 (0.5- 1)
CL/F, L/hr	92.56 (38)	50.43 (15)	49.14 (22)	39.85 (19)	30.41 (24)
t½, hr	1.3 (0.241)	2.11 (0.341)	1.84 (0.409)	2.16 (0.100)	2.27 (0.212)
V_z/F, L	170.6 (26)	151.4 (27)	128.0 (29)	126.1 (18)	125.3(18)
Ae_{τ}%	4.09 (23)	6.46 (4)	5.47 (31)	6.46 (19)	7.04 (20)
CLr, mL/min	63.06 (28)	54.33 (12)	44.76 (38)	42.90 (18)	45.46 (17)

Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for t½; N = Number of subjects in the treatment group and contributing to the mean; n= number of subjects where t½ was determined.

AUC_{τ}, = Area under the concentration-time curve from zero to 24 hours (QD) or zero to 12 hours (BID) postdose at steady state; QD = Once daily; BID = Twice daily; C_{max} = Peak plasma concentration; CL/F = apparent total body clearance; V_z/F = apparent volume of distribution; Ae_{τ}% = Percent of dose recovered unchanged in urine over the dosing interval τ; CLr = Renal clearance.

Urinary recovery of PF-06651600 was low, with approximately <8% of the dose recovered unchanged in urine on Day 14 across all doses (geometric mean Ae_{τ}% of 4.1% to 7.0%). Renal clearance ranged from 42.9 mL/min to 63.1 mL/min.

The relative bioavailability (B7981003) of 50 mg PF-06651600 tablets was compared to 50 mg oral suspension. The ratio (90% CI) of adjusted geometric mean was 93.49% (87.8, 100) for AUC_{inf} and 90.4% (72.2, 113) for C_{max} under fasted conditions. When the 50 mg tablets were administered under fed conditions, T_{max} was slightly delayed with a median value of 1.0 hours, compared to a median T_{max} 0.5 hours under fasted conditions. For the 50 mg tablets fed vs. fasted, the ratio of adjusted geometric means for AUC_{inf} and C_{max} was 102% (95.2, 109) and 61.5% (48.5, 77.8), respectively.

1.6. Summary

1.6.1. Study Rationale

This multicenter, placebo controlled study will be the first determination of safety and efficacy of PF-06651600 in subjects with moderate to severe active RA who have had an inadequate response to methotrexate (up to approximately 50% of subjects may also have had an inadequate response to 1 anti-TNFα biologic DMARD).

The subject population in this study is methotrexate non-responders. These subjects could potentially also have failed one TNFα inhibitor. The inclusion of subjects who have failed one TNFα inhibitor is driven by the fact that anti-TNFα therapy is widely used in the US (which is planned to be one of the countries participating in this study) in subjects who have failed methotrexate. The decision to limit the number of TNFα non responders in B7981006 (up to 50% of study subjects) is based on the American College of Rheumatology (ACR) recommendations to reserve anti-TNFα agents for RA subjects for whom prior methotrexate monotherapy led to an inadequate response, RA subjects with moderate disease activity and features of a poor prognosis, and for RA subjects with high disease activity, irrespective of prognostic features.[15]

In addition, although anti-TNFα therapy is very effective in controlling disease activity and slowing down radiological damage, prolonged response is only seen in approximately 60-70% of the subjects,[7] which indicates that there is an un-met need for RA subjects who fail anti-TNFα therapy.

An 8 week study was determined of an appropriate duration to assess disease activity and provide safety information for PF-06651600 in subjects with RA. SDAI was selected as the primary endpoint since this assessment is the best predictor for transformational efficacy defined in terms of 6 month SDAI remission rate.

1.6.2. Dose Rationale

The dose selection strategy was designed to balance pharmacology and safety for an 8 week study) in this subject population.

CCI [redacted]

The predicted PK parameters for PF-06651600 based on simulations using the global PK model are provided in Table 4.

Table 4. Summary of Predicted Steady State Plasma Pharmacokinetic and Pharmacodynamic Parameters Following Multiple Dose Administration of PF-06651600

Dose mg QD	C_{max} ng/mL	Predicted Margins[a]	AUC_{tau} ng.hr/mL	Predicted Margins[a]	IP-10 %CFB
200	1254 (2.1)	11	3712 (14)	14	42 (19)

AUC_{tau} = Area under the concentration-time curve from zero to 24 hours postdose at steady state; C_{max} = Peak plasma concentration; QD = Once daily; %CFB= percent change from baseline; human unbound fraction (fu) = 0.86; 1 ng/mL= 3.504 nM.

a. NOAEL-highest dose in dogs, 45 mg/kg/day; Week 8 mean male and female C_{max} (free) = 12,000 ng/mL; C_{max} (total) = 14,634 ng/mL; AUC_{tau} (free) = 44,100 ng•h/mL; AUC_{tau} (total) = 53,780 ng•h/mL. dog (fu) = 0.82.

The predicted exposure during the treatment period at a dose of 200 mg QD for 8 weeks is projected to maintain 12- and 14-fold safety margins for C_{max} and AUC_{tau}, respectively. The selective inhibition of JAK3 will lead to modulation of γ-common chain cytokine pathways, such as IL-7, IL-15 and IL-21 which have been implicated in the pathophysiology of RA. In lymphocytes, PF-06651600 inhibited JAK1/JAK3 dependent STAT5 and STAT3 phosphorylation by IL-15 and IL-21 respectively, with IC_{50}s of 56.5 ng/mL and 103 ng/mL, respectively. All other pathways were inhibited at IC_{50}s >5708 ng/mL. The predicted average percent IL-15 and IL-21 in-vitro signaling inhibition in human whole blood based on human PK are provided in Table 5.

Table 5. Summary of the Predicted Average Percent In Vitro Signaling Inhibition Based on Steady State PK from 200 mg PF-06651600

Cytokine	Average Percent Signaling Inhibition
	200 mg
IL-15	81
IL-21	71

Pharmacological modulation of the target can be inferred from the results.

1.6.3. Summary of Benefits and Risks

Overall, the safety profile observed during the Phase I program for PF-06651600 appears to be acceptable at dosages CCI [redacted] administered orally.

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

1.6.4. Additional Information

Banked biospecimens will be collected for the purpose of conducting research; specific uses are described in the Banked Biospecimens section. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/genomic/biomarker analyses and retaining them in the Biospecimen Banking System (BBS) make it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

Banked biospecimens retained in the BBS also can be used in research on diseases of inflammation.

Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited by local regulations or ethics committee (EC) decision.

2. STUDY OBJECTIVES AND ENDPOINTS

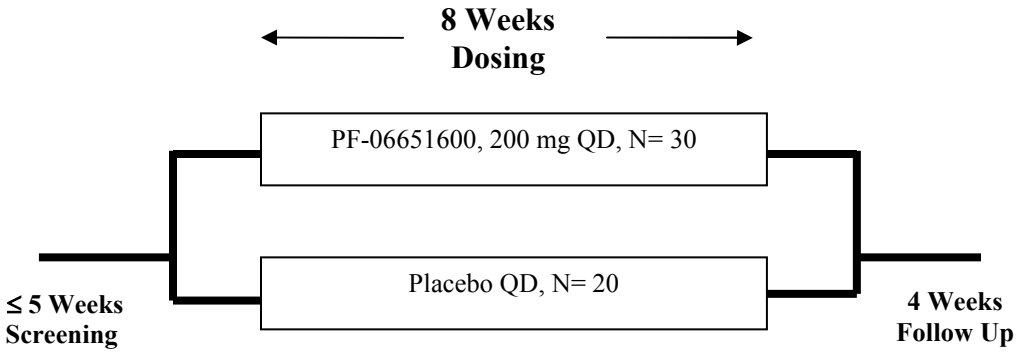
Primary Objectives:	**Primary Endpoints:**
• To evaluate the efficacy of PF-06651600 at 8 weeks in subjects with moderate to severe active RA.	• Change from baseline in simple disease activity index (SDAI) at Week 8.
Secondary Objectives:	**Secondary Endpoints:**
• To evaluate the safety of PF-06651600.	• Safety and tolerability of PF-06651600 versus placebo; vital signs, laboratory tests, adverse events (AEs) including infections, and Serious Adverse Events (SAEs).
• To assess other signs of clinical efficacy over 8 weeks.	• Change from baseline in SDAI at Weeks 1, 2, 4 and 6. • Change from baseline in SDAI low disease activity scale (LDAS) and remission rates at Week 4, Week 6 and Week 8 • Change from baseline in DAS28 LDAS and remission rates at Week 4, Week 6 and Week 8. The following will also be calculated at Weeks 1, 2,4, 6 and 8:

	• Change from baseline in DAS28-3 (ESR), DAS28-3 (CRP), DAS28 -4 (ESR), and DAS28-4 (CRP). • Change from baseline in hsCRP. • Change from baseline in the Tender/Painful and Swollen Joint Count (28). • Change from baseline in the Physician's Global Assessment of Arthritis.
• To assess the effect of PF-06651600 on patient reported outcome measurements.	• Change from baseline in the Patient's Assessment of Arthritis Pain (VAS) and Patient's Global Assessment of Arthritis (VAS) at Weeks 1, 2, 4, 6 and 8. • Change from baseline in the HAQ-DI at Weeks 1, 2, 4, 6 and 8.
[redacted] CCI	[redacted]
[redacted]	[redacted]

[redacted]

3. STUDY DESIGN

Figure 1. Study Design Schematic



Note: N indicates the total number of completers.

This is a Phase 2a, 8 week randomized double-blind, parallel group, placebo controlled, multi-center study to assess the efficacy and safety profile of PF-06651600 in seropositive subjects with moderate to severe active rheumatoid arthritis with an inadequate response to methotrexate (up to approximately 50% of subjects may also have had an inadequate response to 1 anti-TNFα biologic DMARD).

Up to approximately 60 subjects may be randomized globally into the study to ensure at least approximately 50 subjects complete 8 weeks of active dosing (assuming a dropout rate of approximately 15%). Subjects will participate in this study for approximately 17 weeks. This includes an up to 5-week screening period, an 8 week treatment period, and a 4 week follow-up period.

After an up to 5 week screening period, eligible subjects will be randomized to receive 200 mg QD of PF-06651600 or placebo (matching tablets for PF-06651600 QD) every day for 8 weeks in a blinded fashion.

Subjects will remain on stable background arthritis therapy, which must include methotrexate (supplemented with folic/folinic acid per local treatment guidelines). Subjects additionally may continue stable doses of Nonsteroidal Anti-inflammatory Drugs (NSAIDs), COX-2 inhibitors, allowed opioids (at doses ≤ the potency equivalent of 30 mg of orally-administered morphine), acetaminophen/paracetamol for pain control (≤2.6 grams per day), and/or low dose oral corticosteroids (≤10 mg prednisone or equivalent per day). Methotrexate must have been dosed orally for at least 3 months, the dose must have been stable for at least 4 weeks before first dose of study drug, and the dose must remain stable during the study. Allowed methotrexate doses are 15 to 25 mg, inclusive, weekly, unless there is documented (in the source documentation) intolerance to or toxicity from these doses, in which case a dose between 10 and <15 mg, inclusive, may be used.

Folic or folinic acid must be dosed per local standards of care stably for at least 4 weeks before first dose of study drug. NSAIDs, COX-2 inhibitors, allowed opioids and/or low dose oral corticosteroids (≤10 mg prednisone or equivalent per day) must be dosed stably for at least 4 weeks prior to first dose of study drug (See Section 5.8).

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 [or a legally acceptable representative] has been informed of all pertinent aspects of the study.

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

3. Male and female subjects (including Women of Childbearing Potential (WOCBP)) between the ages of 18 and 75 years, inclusive. For subjects >70 years old, the site must discuss subject eligibility with the study team to ensure that these subjects are sufficiently healthy to participate.

4. Female subjects of childbearing potential must test negative for pregnancy at screening visit and baseline visit.

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

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

    b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    c. Have medically confirmed ovarian failure.

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

6. Diagnosis of rheumatoid arthritis (RA) and meeting the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria (see Appendix 2) for RA with a Total Score ≥6/10. The duration of time since diagnosis of RA should minimally be sufficient to meet the definition of methotrexate inadequate response (see criteria 10 below).

7. Meets Class I, II or III of the ACR 1991 Revised Criteria for the classification of Global Functional Status in RA (see Appendix 2).

8. The subject has active disease at both Screening and Baseline, as defined by both:

   - ≥6 joints tender or painful on motion; AND
   - ≥6 joints swollen;

   and

   - High sensitivity C reactive protein (hsCRP) ≥7 mg/L at screening performed by the central laboratory. Subjects who do not meet this entry criterion but satisfy all other study entry criteria may have serum hsCRP concentration re-tested and, if the repeat hsCRP concentration is ≥7 mg/L prior to the baseline visit, will be eligible to enroll into the study provided all other inclusion/exclusion criteria are met.

9. Subjects must be seropositive (rheumatoid factor positive and/or anti-citrullinated protein antibody positive) at the screening visit.

10. Subjects must have been taking oral MTX for at least 3 months at an adequate dose to determine that the subject had an inadequate response to MTX, defined, for the purpose of this study, by the investigator's and subject's opinions that the subject did not experience adequate benefit from methotrexate plus the presence of sufficient residual disease activity to meet the entry criteria. Allowed methotrexate doses are 15 to 25 mg, inclusive, weekly, unless there is documented (in the source documentation) intolerance to or toxicity from these doses, in which case a dose between 10 and <15 mg, inclusive, may be used (See Section 5.8). The dose must have been stable for at least 4 weeks before first dose of study drug, and the dose must remain stable during the study.

    - Subjects should be on an adequate and stable dose of folic acid (not less than 5 mg weekly, unless higher doses would violate the local label) for at least 4 weeks prior to the first dose of investigational product or oral folinic acid (≥5 mg once per week) supplementation for at least 4 weeks prior to the first dose of study drug. Folic acid must be dosed per local standards of care stably for at

least 4 weeks before first study dose and the dose must remain stable during the study. In countries which do not have approved folic acid 1 mg or folinic acid 5 mg presentations, a regimen of folic acid of at least ≥5 mg weekly is acceptable.

11. Up to 50% of subjects may have received one approved TNFα-inhibiting biologic agent administered in accordance with its labeling recommendations that was inadequately effective and/or not tolerated. For the purpose of this study, inadequate efficacy is defined by the investigator's and subject's opinions that the subject did not experience adequate benefit from the anti-TNFα inhibitor and the presence of sufficient residual disease activity to meet the entry criteria. The anti-TNFα inhibitor should have been discontinued for a minimum of the washout period defined as follows:

    - etanercept (Enbrel®): 4 weeks.
    - infliximab (Remicade®), adalimumab (Humira®), golimumab (Simponi®), certolizumab (Cimzia®): 10 weeks.

12. Subjects receiving non-prohibited medications (See Section 5.8) for any reason must be on a stable regimen, which is defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever is longer) prior to first study dose and the dose must remain stable during 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 studies involving investigational drug(s) within 30 days or 5 half-lives (whichever is longer) prior to study entry (screening visit) and/or during study participation.

3. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4. Any major illness/condition(s) or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary or local active infection/infectious illness) that, in the investigator's judgment will substantially increase the risk to the subject if he or she participates in the study.

5. Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and any history of cerebrovascular disease within 24 weeks before screening or in the period between the Screening Visit and the Baseline Visit.

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

7. Subjects with acute or active chronic dermatological disorders within 4 weeks prior to study entry or in the period between the Screening Visit and the Baseline Visit.

8. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who wish to become pregnant or who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.

9. History of alcohol or drug abuse with less than 6 months of abstinence prior to the Baseline Visit.

10. Subjects with any of the following acute or chronic infections or infections history:

    a. Any infection requiring treatment within 2 weeks prior to the Screening Visit or in the period between the Screening Visit and the Baseline Visit.

    b. Any infection requiring hospitalization, parenteral antimicrobial therapy within 60 days of the Baseline Visit, or as otherwise judged to be an opportunistic infection or clinically significant by the investigator, within the past 6 months of the Baseline Visit.

    c. Known active or history of recurrent bacterial, viral, fungal, mycobacterial or other infections.

    d. Recurrent (more than one episode) herpes zoster or disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.

    e. Infected joint prosthesis at any time with the prosthesis still in situ.

    f. Subjects will be screened for Human Immunodeficiency Virus (HIV). Subjects who test positive for HIV will be excluded from the study.

g. Subjects will be screened for hepatitis B virus infection and will be excluded if positive for hepatitis B surface antigen (HBsAg). Subjects with HBsAg negative testing but who test positive for hepatitis B core antibody (HBcAb) must have further testing for hepatitis B surface antibody (HBsAb). If HBsAb is positive, the subject will be excluded from the study.

h. Subjects will be screened for hepatitis C virus (HCV Ab). Subjects with positive HCV Ab tests will be reflex tested for HCV ribonucleic acid (HCV RNA). Only subjects with negative HCV Ab or HCV RNA will be allowed to enroll in the study.

11. Subjects treated with prohibited medications will be excluded unless appropriate washout has been performed (See Section 5.8).

12. Any current evidence of untreated latent or active TB infection, evidence of currently active TB by chest x-ray, residing with or frequent close contact with individual(s) with active TB. Subjects who have a positive Mantoux (PPD) tuberculin skin test or a positive Interferon Gamma Release Assay during screening or within 12 weeks prior to screening. The following are acceptable assays: QuantiFERON® - TB Gold test (QFT-G), QuantiFERON® - TB Gold In-Tube test (QFT-GIT) and T-SPOT® - TB test during screening or within 12 weeks prior to screening.

    - A positive Mantoux tuberculin skin test is defined as ≥5 mm of induration (or as defined by country specific or local standards) at 48-72 hours without consideration of prior Bacillus Calmette-Guerin (BCG) vaccination. Documentation of the dose and product used for the Mantoux tuberculin test as well as the official test reading must be obtained and available in the subject's source documentation.

    - An Interferon-Gamma Release Assay (IGRA) is preferred for subjects with a prior 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.

13. Current routine household contact with children or anyone else who have received varicella or oral polio or any other live (attenuated) vaccine within 6 weeks of first study dose, or during the course of the study (including the Follow Up period).

14. Any live (attenuated) vaccines from 30 days prior to the Baseline Visit and through the Follow Up Visit.

15. Subjects who have been in contact with people with acute infections within 2 weeks prior to the Screening Visit or in the period between the Screening Visit and the Baseline Visit.

16. History of any lymphoproliferative disorder (such as Epstein-Barr Virus (EBV)-related lymphoproliferative disorder, as reported in some subjects on immunosuppressive drugs), history of lymphoma, leukemia, myeloproliferative disorders, multiple myeloma, or signs and symptoms suggestive of current lymphatic disease.

17. Have a history of a major organ transplant (eg, heart, lung, kidney and liver) or hematopoietic stem cell/marrow transplant. Skin grafts are allowed.

18. History of severe allergic or anaphylactoid reaction to kinase inhibitors, or corticosteroid preparations.

19. Subjects with malignancy or history of malignancy (including but not limited to lymphoma, leukemia, or lymphoproliferative disease), with the exception of subjects with adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.

20. Pre-existing chronic autoimmune disease (eg, inflammatory bowel disease, Systemic Lupus Erthematosus (SLE), moderate to severe atopic dermatitis) other than RA. Secondary Sjogren's -Syndrome associated with RA may be included.

21. Major surgery within 4 weeks of the Screening Visit or if scheduled to occur during the study, excluding diagnostic surgical procedures.

22. Previous treatment with total lymphoid irradiation.

23. Subjects 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.

24. Screening 12-lead ECG that demonstrates clinically relevant abnormalities (eg, QTc >450 msec or a QRS interval >120 msec) which may affect subjects' safety or interpretation of study results. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTc or QRS values should be used to determine the subject's eligibility.

25. Have current or recent history of clinically significant severe or progressive hearing loss or auditory disease. Subjects with hearing aids will be allowed to enter the study provided their hearing impairment is considered controlled/clinically stable.

26. Subjects with an oral or tympanic temperature at the Baseline Visit of 38°C or higher.

27. Presence of any of the following laboratory abnormalities at the Screening Visit or within the 3 months prior to first study dose:

    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≥1.5 times the upper limit of normal (ULN).
    - Total bilirubin level ≥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 and other liver function assessments are normal.
    - Hemoglobin level ≤90 g/L (9.0 g/dL).
    - Platelet count ≤100 x 10^9/L (100,000 cells/mm^3) or ≥1000 x 10^9/L (1,000,000 cells/mm^3).
    - White blood cell (WBC) count ≤3.0 x 10^9/L (3000 cells/mm^3) or absolute neutrophil count (ANC) <1500 cells/mm^3 or absolute lymphocyte count of <0.5 x 10^9/L (<500 cells/mm^3).
    - Serum creatinine level ≥177 μmol/L (2 mg/dL).
    - Glycosylated hemoglobin (HbA1C) >10%.

28. In the opinion of the investigator or sponsor, have any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the subject's participation in the study.

29. Grade 3 or greater laboratory abnormality based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 toxicity scale.

Screening laboratory tests with abnormal results may be repeated once to confirm abnormal results. If results return to normal protocol acceptable limits within the 5-week screening period, the subject may enter the study.

Subjects who fail screening can be rescreened once.

4.3. Lifestyle Requirements

It is recommended that subjects avoid consumption of grapefruit juice exceeding 8 ounces (~240 ml) total in a day while in the study.

4.3.1. Contraception

In this study, fertile male subjects and female subjects who are of childbearing potential as applicable to the study will receive PF-06651600, which has been associated with suspected teratogenicity (based on the demonstrated nonclinical findings). 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 highly effective contraception throughout the study and for at least 28 days after the last dose of PF-06651600. 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 highly effective methods of 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:

- 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.

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

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

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

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

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of investigational product.

4.4. 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 manual.

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.

If the subject has a medical emergency and is unable to reach the investigator or the study staff, they need to visit the Emergency Room/Urgent Care or appropriate medical site for care by a qualified health professional per local guidelines.

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-06651600. Investigational product will be administered only to subjects who have provided informed consent. Once a subject's participation in the study has ended, investigational product will no longer be supplied to the subject by the investigative site and/or sponsor.

5.1. Allocation to Treatment

Allocation of subjects to treatment groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, 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

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

5.3. Subject Compliance

Subject compliance will be verified by the accounting of investigational product at each visit.

For self-administration of PF-06651600 at home, compliance will be captured and completed by the subject within a Subject Dosing Diary. When investigational product is administered at the research facility, it will be administered under the supervision of study personnel.

Subjects will be directed to bring Subject Dosing Diary and blister cards with any remaining study drug to each visit for review. Compliance with expected consumption of dispensed investigational product will be assessed by comparing the expected number of doses to be taken to the number of doses returned (pill count) during any given time period. Compliance will be documented in the source records.

Non-compliance is defined as taking less than 80% or more than 120% of the allowed investigational product during the study treatment period.

Subjects who are non-compliant will be counseled and the site will implement appropriate measures to secure subject compliance, as appropriate to the site and reason for non-compliance. Subjects interrupting investigational product for more than 5 days between study visits are to be discussed with the medical monitor for possible discontinuation from the study.

Upon completion of each visit, the Subject Dosing Diary should be collected from the subject at the site and stored in the site master file only. The investigator has the discretion to withdraw any subject from the study for reasons of non-compliance with the dosing regimen. Inventory control of all investigational product must be rigorously maintained throughout the duration of the study until all medication has been accounted for and/or returned to the sponsor. Any discrepancies noted between drug dispensing records and drug inventory must be reported to Pfizer.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

Blinded PF-06651600 and its matching placebo will be provided as tablets in blister cards for oral administration. The PF-06651600 50 mg tablets and their matching placebos will be supplied in separate blister cards 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 Week 0 through Week 8. Each dispensing visit will provide sufficient investigational product to complete dosing until the next scheduled dispensing visit. Visit dates are calculated such that visit windows are not cumulative and are anchored on Day 0.

Investigational product should be dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance, Only qualified personnel who are familiar with procedures that minimize undue exposure to their person and to the environment should undertake the preparation, handling, and safe disposal of agents.

The subject 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 PF-06651600 tablets and matching placebo for oral administration in blister packs. Subjects will be dispensed blister cards and given clear dosing instructions.

Investigational product tablets will be administered to the subject in the clinic on the morning of clinic visits and all other dosing will be performed by the subject outside of the clinic. Subjects will record their study drug dosing information within a Subject Dosing Diary which should be brought to each clinic visit.

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

If a dose is missed and the interval to the next dose is less than 6 hours, the missed dose should not be administered. At the baseline visit, (Visit 2) the first dose of investigational product will be taken in the clinic. Additionally, at Weeks 1, 2, 4, 6 and 8 subjects should take their dose for that day in the clinic. All other doses will be taken by the subject outside of the clinic.

The investigational product may be administered with or without food. Subjects will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing with a glass of water.

Subjects who experience AEs that require treatment may have their study drug temporarily discontinued during treatment at the investigator's discretion. Subjects interrupting investigational product for more than 5 days are to be discussed with the medical monitor for possible discontinuation from the study.

Temporary discontinuation of study drug should be recorded in the CRF.

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 visit and at the end of the trial.

5.7.1. Destruction of Investigational Product Supplies

Returned investigational product can be destroyed only after the sponsor monitor has verified the accuracy of the dispensing and inventory record.

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. Background and Concomitant Treatment(s)

All concomitant medication(s) and treatment(s) administered/taken during the study must be recorded with indication, daily dose, and start and stop dates of administration.

All subjects will be questioned about concomitant medication at each site visit.

Medications that are taken after informed consent is obtained, but before the first dose of investigational product, will be documented as prior medications. Medications taken after the first dose of investigational product has been administered will be documented as concomitant medications.

5.8.1. Permitted Background Arthritis Therapy

Methotrexate (MTX) (Required Background RA Treatment).

Subjects will continue on their pre-study dose of MTX (supplemented with folic/folinic acid). Subjects must have been taking oral MTX for at least 3 months at an adequate dose to determine that the subject had an inadequate response to MTX, defined, for the purpose of this study, by the investigator's and subject's opinions that the subject did not experience adequate benefit from MTX plus the presence of sufficient residual disease activity to meet the entry criteria. The dose must have been stable for at least 4 weeks before first dose of study drug, and the dose must remain stable during the study. Allowed MTX doses are 15 to 25 mg, inclusive, weekly, unless there is documented (in the source documentation) intolerance to or toxicity from these doses, in which case a dose between 10 and <15 mg, inclusive, may be used.

Other background RA Treatments

The following concomitant medications may be continued during the study as background RA treatments, provided the dosage(s) do not change for the entire period from Screening through Discharge from the study (except for Rescue Medication. See Section 5.9) and have been stable for the stipulated interval before Randomization and dosing with the investigational product.

- Anti-malarials (eg, chloroquine,hydroxychloroquine).

- Nonsteroidal Anti-inflammatory Drugs (NSAIDs), selective Cyclooxygenase-2 inhibitors ("COX-2 inhibitors") at a stable dose in accordance with local label/standard of care beginning at least 4 weeks prior to first study dose.

- Opioids at doses ≤ the potency equivalent of 30 mg of orally-administered morphine at a stable dose beginning at least 4 weeks prior to first study dose (See Appendix 11).

- Acetaminophen/paracetamol at doses ≤2.6 grams per day

- Low dose oral corticosteroids (≤10 mg prednisone or equivalent per day) at a stable dose beginning at least 4 weeks prior to first study dose (See Appendix 10).

- Subjects should be on an adequate and stable dose of folic acid (not less than 5 mg weekly, unless higher doses would violate the local label) for at least 4 weeks prior to the first dose of investigational product or oral folinic acid (≥5 mg once per week) supplementation for at least 4 weeks prior to the first dose of study drug. Folic acid must be dosed per local standards of care stably for at least 4 weeks before first study dose and the dose must remain stable during the study. In countries which do not have approved folic acid 1 mg or folinic acid 5 mg presentations, a regimen of folic acid of at least ≥5 mg weekly is acceptable.

Other Permitted Concomitant Medications

A subject who is receiving an allowed concomitant medication for any reason must be on a locally-approved medication and dose that is considered standard-of-care for the treated indication and be documented in the case report form with indication, daily dose, and start and stop dates of administration.

It is recommended that subjects receiving non-prohibited concomitant medications, vitamins, and dietary supplements must be on a **stable regimen**, which is defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever is longer) prior to first dose of investigational product and the dose must remain stable during the study.

5.8.2. Prohibited Background Arthritis Therapy

Disease Modifying Antirheumatic Drugs (DMARDs)

- Subjects who have received the following treatment regimens are eligible to participate in the study, providing the following discontinuation periods are observed prior to the first dose of investigational product. (Biosimilars of the below agents should be considered the same as the originators).

Biologics

- TNF inhibitors
  - Up to 50% of subjects may have received one approved TNFα-inhibiting biologic agent administered in accordance with its labeling recommendations that was inadequately effective and/or not tolerated. For the purpose of this study, inadequate efficacy is defined by the investigator's and subject's opinions that the subject did not experience adequate benefit from the anti-TNFα and the presence of sufficient residual disease activity to meet the entry criteria. The anti-TNFα should have been discontinued for a minimum of the washout period defined as follows: [27]
    - etanercept (Enbrel®): 4 weeks.
    - infliximab (Remicade®), adalimumab (Humira®), golimumab (Simponi®), certolizumab (Cimzia®): 10 weeks.
- Other Biologic Agents/DMARDs
  - Subjects who have previously been treated with other, non-TNFα inhibiting biologic DMARDs (including, abatacept (Orencia®), tocilizumab (Actemra®), anakinra (Kineret®), rituximab (Rituxan®) or other selective B lymphocyte-depleting agents (both marketed and investigational)) or other lymphocyte-depleting agents/therapies (such as CamPath® [alemtuzab], alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation) are excluded from participation in the current study.
  - Subjects who have been previously treated with tofacitinib (Xeljanz®) should have a washout treatment of 3 months prior to screening.
- Intra-articular, intravenous or intramuscular corticosteroids, DMARDs including methotrexate and biologic response modifiers are not allowed during this study.

Other RA Drugs

The following drugs are excluded during the study and for the prescribed washout period prior to the start of the study:

- Auranofin (oral gold), aurothioglucose (injectable gold), aurothiomalate (injectable gold) must be discontinued for 8 weeks prior to the first dose of the investigational product.
- Sulfasalazine, d-penicillamine, bucillamine, mizoribin, azathioprine, cyclosporine, tacrolimus, and staphylococcal protein A immuno-absorbant pheresis columns

(eg, PROSORBA® device/column) must be discontinued for 4 weeks prior to the first dose of investigational product.

- Subjects on Leflunomide (Arava®) must undergo the following drug elimination procedure at least 4 weeks prior to the first dose of investigational product:

  - Cholestyramine at a dosage of 8 grams three times daily for at least 11 days, or activated charcoal at a dosage of 50 grams 4 times a day for at least 11 days to achieve non-detectable plasma levels (less than 0.02 mg/L or 0.02 μg/mL) after stopping treatment with Arava® [22,23] Verify plasma levels less than 0.02 mg/L (0.02 μg/mL) by two separate tests at least 14 days apart. If plasma levels are higher than 0.02 mg/L, additional cholestyramine treatment should be considered.

- Tetracyclines and minocycline, unless prescribed for the treatment of acne or other dermatologic disorders, must be discontinued for 4 weeks prior to the first dose of investigational product.

Other Prohibited Concomitant Medications

- Interferon therapy within 8 weeks prior to the Baseline Visit and through the Follow up Visit.

- Lymphocyte-depleting agents/therapies.

- Leukocyte apheresis including selective lymphocyte, monocyte, or granulocyte apheresis, or plasma exchange within 6 months of baseline and through the Follow up Visit.

- Other marketed immunosuppressants or biologics with immunomodulatory properties within 3 months prior to the Baseline Visit and through the Follow up Visit.

- Use of immunosupressants used in transplantation (eg, mycophenolate mofetil, cyclosporine, rapamycin, or tacrolimus) within 30 days prior to the Baseline Visit and through the Follow up Visit.

- Any live (attenuated) vaccines from 30 days prior to the Baseline Visit and through the Follow up Visit.

- No investigational compounds, other than PF-06651600, may be taken during participation in this study.

- Herbal medications with pharmaceutical properties must be discontinued at least 4 weeks before the first dose of investigational product.

- Subjects receiving prohibited concomitant medications, including moderate to potent CYP3A inducers or inhibitors (See Appendix 4) in the time periods described below:

- For moderate to potent CYP3A inducers, within 28 days or 5 half-lives, whichever is longer, prior to the Baseline Visit.

- For moderate to potent CYP3A inhibitors, within 7 days or 5 half-lives, whichever is longer, prior to the Baseline Visit.

Subjects who are treated with any prohibited medication during the course of the study will be discontinued.

5.9. Rescue Medication

Rescue therapy for RA is not permitted except for transient (up to 10 consecutive days) addition or increased dose of acetaminophen/paracetamol (dosed no more than 2.6 grams per day) or an opioid (not exceeding the potency equivalent of 30 mg of orally-administered morphine) If a subject is already taking stable background doses of acetaminophen/paracetamol, s/he may increase the dose up to 2.6 grams per day for up to 10 consecutive days for rescue purposes. **Subjects who require rescue for more than 10 consecutive days should be discontinued from the trial.** Acetaminophen/paracetamol may be taken for up to 5 days/week for headache, fever, or other acute, non-arthritis pain, provided the total dose (including background dose) does not exceed 2.6 grams per day.

Subjects should not be dosed with rescue treatments during the 24 hours prior to interval study visits and 7 days prior to the last day of the active dosing period (Week 8). (Note: baseline stable doses of acetaminophen/ paracetamol or opioids should NOT be discontinued in advance of study visits) (See Appendix 11).

6. STUDY PROCEDURES

Visits should occur when scheduled, within the time window indicated in the Schedule of Activities. Written informed consent must be obtained prior to performing any protocol-specific procedures, including washout of prohibited medications. On study drug dosing days, PtGA and PAAP VAS measures and HAQ-DI questionnaires, should be performed prior to any other assessments. Assessments including joint counts, physician questionnaire, and pre-dose blood collections are to be performed prior to dosing unless otherwise stated.

Where possible the following order of activities should be followed during the clinic visits

1. Patient's Assessment of Arthritis Pain (VAS) and Patient Global Assessment of Arthritis (VAS)

2. ECGs

3. Vital signs

4. Physician's Global Assessment (PhGA) of Arthritis (Physician's assessment should be performed without knowledge of patient reported VAS assessments)

5. Blood and Urine Sample Collection

6. Investigational Product Dosing

6.1. Screening

For screening procedures, see Schedule of Activities and ASSESSMENTS section.

6.2. Treatment Period

For treatment period procedures, see Schedule of Activities and ASSESSMENTS section.

6.3. Follow-up/End of Study

For follow-up and end of study procedures, see Schedule of Activities and ASSESSMENTS section.

6.4. Subject Withdrawal/Early 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 (See Schedule of Activities for procedures to be followed at the Early Withdrawal Visit). Subjects who require rescue medication for more than 10 consecutive days should be discontinued from the trial. (See Section 5.9)

Subjects who are discontinued from study treatment will enter into the Follow-up Period **with the follow-up visit occurring 1 week after the last dose whenever possible** and protocol specified follow-up procedures should be performed.

See Appendix 4 for Guidelines for Monitoring and Discontinuations. The Early Withdrawal Visit applies to subjects who are randomized, received at least one dosing and then are prematurely withdrawn from the study treatment.

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

6.4.1. 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 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 post-treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status

(whether the subject is alive or dead) is being assessed, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

6.4.2. Lost to Follow-up

Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 phone calls (documented in the source documents), faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. 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.

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. American College of Rheumatology (ACR) Assessments

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

1. Tender/Painful Joint count (TJC) (68).
2. Swollen Joint Count (SJC) (66).
3. Patient's Assessment of Arthritis Pain.

4. Patient's Global Assessment of Arthritis.

5. Physician's Global Assessment of Arthritis.

6. C-Reactive Protein (CRP), measured by high sensitivity methodology (hsCRP).

7. Erythrocyte Sedimentation Rate (ESR)

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

Components of the ACR Core Dataset will be collected at the visits indicated in the Schedule of Activities.

7.1.2. Tender/Painful Joint Count (68)

Sixty-eight (68) joints will be assessed by a joint assessor to determine the number of joints that are considered tender or painful. The response to pressure/motion on each joint will be assessed using the following scale: Present/Absent/Not Done/Not Applicable (to be used for artificial or missing joints). Artificial joints will not be assessed.

The 68 joints to be assessed are:

- Upper Body: temporomandibular, sternoclavicular, acromioclavicular;

- Upper Extremity: shoulder, elbow, wrist (includes radiocarpal, carpal and carpometacarpal considered as one unit), metacarpophalangeals (MCP I, II, III, IV, V), thumb interphalangeal (IP), proximal interphalangeals (PIP II, III, IV, V), distal interphalangeals (DIP II, III, IV, V);

- Lower Extremity: hip, knee, ankle, tarsus (includes subtalar, transverse tarsal and tarsometatarsal considered as one unit), metatarsophalangeals (MTP I, II, III, IV, V), great toe interphalangeal (IP), proximal and distal interphalangeals combined (PIP II, III, IV, V).

7.1.3. Swollen Joint Count (66)

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

Sixty-six (66) joints will be assessed for swelling, the same as those listed above for tenderness/pain, except that the right and left hip joints are not included in the swollen joint count. Artificial joints will not be assessed. Physician assessment should be performed without the knowledge of patient reported outcome measures.

7.1.3.1. Tender and Swollen Joint Counts (28)

The twenty-eight tender/painful joint count includes the following joints: shoulders, elbows, wrists, metacarpophalangeal joints (MCP), proximal interphalangeal joints (PIP), and knees. Artificial joints will not be assessed. This count will be calculated by Pfizer from the 68 tender/painful joint count assessed by the joint assessor as described in Section 7.1.2.

The twenty-eight swollen joint count measurement will include the same joints as described above for 28 tender/painful joint count, and will be calculated by Pfizer from the 66 swollen joint count assessed for swelling by the joint assessor as described in Section 7.1.3. Artificial joints will not be assessed. Physician assessment should be performed without the knowledge of patient reported outcome measures.

7.1.4. Patient's Assessment of Arthritis Pain (PAAP)

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 (See Appendix 7). This assessment must be performed early in the clinic visit and before the subject has extensive contact with site personnel and/or investigator (and ideally should be performed before the TJC and SJC measurements) and prior to dosing.

7.1.4.1. Patient's Global Assessment (PtGA) 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) (See Appendix 8). This assessment must be performed early in the clinic visit and before the subject has extensive contact with site personnel and/or investigator and prior to dosing.

7.1.4.2. Physician's Global Assessment (PhGA) of Arthritis

The investigator will assess how the subject's overall arthritis appears at the time of the visit. This is an evaluation based on the subject's disease signs, functional capacity and physical examination, and should be independent of the Patient's Global Assessment of Arthritis. The investigator's response will be recorded using a 100 mm visual analog scale (VAS) (See Appendix 9). Physician assessment should be performed without the knowledge of patient reported outcome measures.

7.1.4.3. High Sensitivity C-Reactive Protein (CRP)

Samples for analysis of high sensitivity CRP (hsCRP) will be collected at the visits specified in the Schedule of Activities. The samples will be shipped to and analyzed by a central laboratory. After randomization, the investigator and Pfizer study personnel directly involved in the conduct of the trial will be kept blinded of the results of this test.

7.1.4.4. Erythrocyte Sedimentation Rate (ESR)

Samples for analysis of ESR will be collected at the visits specified in the Schedule of Activities. ESR will be analyzed by a local laboratory using the Westergren method. The results from the local laboratory will be captured in a central database.

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

The HAQ-DI assesses the degree of difficulty a subject has experienced during the past week in 8 domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities. 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 "without any 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. This questionnaire must be performed early in the clinic visit and before the subject has extensive contact with site personnel and/or investigator. The form should then be checked by the site staff for completeness. A copy of the questionnaire can be found in Appendix 13. This must be performed early in the clinic visit and before the subject has extensive contact with site personnel and/or investigator and prior to dosing.

7.1.5. Composite Efficacy Assessments Derived from the ACR Core Dataset

Composite endpoints in this study will be calculated by Pfizer using individual components.

7.1.5.1. Simple Disease Activity Index (SDAI) Assessment

The SDAI is a continuous composite measure derived components of the ACR Core Dataset. The **SDAI** will be calculated using the following formula:

SDAI = TJC (using 28 joints) + SJC (using 28 joints) + PtGA (0–10 cm scale) + PhGA (0-10 cm scale) + and hsCRP (mg/dL).[1]

7.1.5.2. ACR Responder Analysis

The American College of Rheumatology's definition for calculating improvement in RA (ACR20) is calculated as a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR-core set measures: patient's and physician's global assessments, pain, disability, and an acute-phase reactant. Similarly, ACR50 and ACR70 are calculated with the respective percent improvement. Components of the ACR Responder Index will be collected as indicated in the Schedule of Activities.

7.1.6. Disease Activity Score (DAS) Assessments

The Disease Activity Score (DAS) assessment is a continuous composite measure derived using differential weighting given to each component. DAS28 is a measure based on 28 tender and swollen joint counts. DAS28 may be calculated with 3 components (not including assessment of an acute phase reactant) (DAS28-3) or 4 components (DAS28-4 = DAS28-3 + either ESR or CRP). The formulae for calculation of DAS28-4 (CRP) and DAS28-4 (ESR) are presented in Appendix 6. Components of DAS28-3 (CRP),

DAS28-3 (ESR), DAS28-4 (CRP), and DAS28-4 (ESR) will be collected as indicated in the Schedule of Activities.

The components of the DAS 28 arthritis assessment include:

- Tender/Painful Joint Count (28).
- Swollen Joint Count (28).
- CRP or ESR.
- Patient's Global Assessment of Arthritis.

7.2. Safety and other Assessments

Safety will be assessed by the spontaneous reporting of AEs, physical examinations, ECGs, and clinical laboratory results in all subjects who received at least 1 dose of investigational product. Investigators and Pfizer clinician/medical monitor will review individual subject data throughout the conduct of the trial to ensure subjects' well-being.

7.2.1. Clinical Safety and Other Laboratory Tests

The following laboratory tests will be performed at times defined in the Schedule of Activities. Laboratory tests may be repeated once during the screening period; the last value will be used to determine eligibility. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

Table 6. Safety and other Laboratory Tests

Hematology	Blood Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs and %) Eosinophils (Abs and %) Basophils (Abs and %) Lymphocytes (Abs and %) Monocytes (Abs and %) Reticulocyte count (Abs and %) PT/INR/PTT	BUN/Urea & Creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (Bicarbonate) AST, ALT Total bilirubin Direct bilirubin[g] Alkaline phosphatase Uric acid Albumin Total protein Lipid profiles [c] Creatine kinase (CK) CK fractionation[h]	pH Glucose Protein Blood Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[d]	FSH[a] Pregnancy Tests[b] HbA1c HIV[i], HBsAg, HBc Ab, HBsAb and HCVAb, HCV RNA IGRA[k] Viral surveillance[e] Ig subtypes Herpitiform rash evaluation (HSV and HZV swab) Skin biopsies/swabs[f] IP-10[j] Anti CCP antibodies[j] Rheumatoid Factor[j] C-Reactive Protein (hsCRP)[j] T cell, B cell and NK cell subsets ESR Exploratory samples (serum, plasma, RNA, DNA)

a. In females who are amenorrheic for at least 12 consecutive months to confirm post-menopausal status.

b. Pregnancy tests (serum/urine) for women of childbearing potential. Serum pregnancy test must be performed at screening.

c. Lipid profile panel will include total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides. A minimum of 8-hour fasting is required for lipid profile evaluation at Day 1, Week 4, Week 8, and EOS.
d. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
e. Blood sample will be collected for potential exploratory viral load analyses including but not limited to CMV, EBV, HSV1, HSV2, and VZV, if applicable.
f. When required in cases of skin rash adverse events. Skin swabs for herpetiform rash and skin swab for potential drug-related rash
g. Only if total bilirubin is elevated.
h. Only if CK is elevated.
i. HIV testing per local regulations.
j. After randomization, the investigator and Pfizer study personnel directly involved in the conduct of the trial will be kept blinded of the results of this test.
k. Complete at screening.

7.2.2. Physical Examination

Complete Physical Examination:

Complete physical examinations must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines and will be performed at the visits identified in Schedule of Activities. Complete physical examinations consist of assessments of general appearance which includes but is not limited to:general appearance, head, eyes, ears, nose and throat (HEENT), mouth, heart; lungs; breast (optional); abdomen; external genitalia (optional); extremities; neurologic function, back, lymph nodes and skin (including presence of rash). In addition, a **dermatological full body exam** must be performed at the Screening Visit by the investigator, sub-investigator or a qualified health professional per local guidelines.

Targeted Examination

At all other visits, as defined in the Schedule of Activities, a targeted physical examination will be performed by the investigator, sub-investigator or a qualified health professional per local guidelines and should include skin (including presence of rash), lungs, heart, abdomen and lymph nodes and examination of body systems where there are symptom complaints by the subject. Any clinically significant changes from the baseline examination should be recorded as AEs.

Additional physical examinations may be performed at the investigator's discretion.

7.2.3. Medical History, Height and Weight

Medical history in addition to RA history including history of drug, alcohol, tobacco use, skin rash, skin infection, and any dermal abnormalities that may predispose to infection will be collected at Screening.

Complete RA disease history includes RA diagnosis and collection of details of RA at Screening. This includes but is not limited to background, RA history including disease duration and extent of disease.

Height and weight will be measured without the subject wearing shoes. Height (inches or centimeters) and weight (lbs or kg) will be measured and recorded in the source document as indicated in the Schedule of Activities.

7.2.4. Pregnancy Testing

Pregnancy tests are required to be done (if applicable) as specified in the Schedule of Activities.

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 (1 negative pregnancy test at screening and 1 at the baseline visit immediately before investigational product 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. 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 but will remain in the study for further follow-up..

7.2.5. Vital Signs (Blood Pressure, Pulse Rate and Temperature)

Sitting BP, pulse rate, and temperature will be measured after approximately 5 minutes of rest at times specified in the Schedule of Activities. It is preferred that the same measurement method be used consistently throughout the study. Additional collection times or changes to collection times will be permitted, as necessary to ensure appropriate collection of safety data. When the timing of these measurements coincides with a blood collection, it is preferred that vital signs be obtained prior to the nominal time of blood collection.

Sitting blood pressure will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mmHg. It is preferred that the same arm (preferably the dominant arm) be used throughout the study.

A properly sized and calibrated Blood Pressure (BP) cuff, will be used to measure BP each time. The use of automated devices for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

It is preferred that body temperature be collected (either oral or tympanic) and that the same method be used consistently throughout the study.

7.2.6. Electrocardiogram

Single twelve (12) lead ECGs will be obtained on all subjects. All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes.

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.

If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTc or QRS values should be used to determine the subject's eligibility.

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.

An ECG may also be performed at other times, at the discretion of the investigator if there were findings during a previous examination or in the case of a new/open adverse event (AE).

7.2.7. Interferon-Gamma Release Assay

IGRA will be tested during screening or within 12 weeks prior to screening. The following are acceptable assays: QuantiFERON®-TB Gold test (QFT-G), QuantiFERON®-TB Gold In-Tube test (QFT-GIT) and T-SPOT® TB test. Blood sampling may include 3 mL up to 10 mL of blood. Site personnel should follow the processing and analyses steps based on the assay chosen. Ensure incubation steps are followed as appropriate.

A documented IGRA test performed within 12 weeks prior to screening is acceptable. IGRA product used, official reading and method, or test as per country specific guidelines, must be located in the subjects source documentation.

7.2.8. Chest X-Ray

Chest radiograph (posterior-anterior and lateral views are recommended, however local guidelines should be followed) or other appropriate diagnostic image (ie, Computerised Tomography (CT) or Magnetic Resonance Imaging (MRI)) with no evidence of current, active TB or previous inactive TB, general infections, heart failure or malignancy taken at Screening or within 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.

7.2.9. Infection Monitoring

Subjects will be monitored for development of any infection (viral, bacterial, and fungal). Infections will be classified as either treated or non-treated infections. All treated infections occurring during the study should be cultured if feasible and the results (eg, any identified organisms or absence of growth) recorded in the CRF.

Treated infections are infections that:

- Require antimicrobial therapy by any route of administration or;
- Require any surgical intervention (eg, incision and drainage).

Treated infections will be further classified as serious or non-serious. Serious infections are treated infections that:

- Require parenteral antimicrobial therapy or;
- Required hospitalization for treatment or;
- Meet other criteria that require the infection to be classified as a SAE.

A subject who experiences a serious infection should be **discontinued** from the study. A serious infection should be reported as a SAE and should be listed as the reason for discontinuation in the CRF. All serious infections occurring during the study should undergo appropriate laboratory investigations, including culture, and the results (eg, any identified organisms or absence of growth) be recorded in the CRF.

Subjects who experience non-serious infections that require treatment may have their study drug temporarily discontinued during treatment at the investigator's discretion. Consultation with the Pfizer medical monitor is available. Temporary discontinuation of study drug should be recorded in the CRF.

7.2.10. Viral Surveillance

Blood samples will be collected according to the times outlined in the Schedule of Activities and may be used to test viral load that may include Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Varicella Zoster Virus (VZV) and Herpes Simplex Virus Type 1 (HSV1) and Herpes Simplex Virus Type 2 (HSV2).

Due to delayed reporting times for these assays, the results might not be available along with the other study tests.

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

7.2.11. Dermatological Assessments

All subjects will have a dermatological full body exam at Screening Visit. Skin lesions will be evaluated as defined in the National Cancer Institute Common Toxicity Criteria for Adverse Events v4.03 (See Appendix 12, for Dermatology/Skin Category) and managed as shown below.

Table 7. Management of Dermatological Events

Dermatologic Event (CTCAE v 4.03)*	Course of Management
Acne/Acneiform Rash/Maculopapular Rash	
Grade 1/2	1. Investigator's discretion for withdrawing investigational product. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 3	1. Discontinue investigational product. 2. Monitor to resolution (defined as a Return to Baseline status). 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Pruritus	
Grade 1 Mild or localized	1. Investigator's discretion for withdrawing investigational product. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 2 Intense or widespread	1. Discontinuation of the investigational product may not be required unless condition is sustained >4 days or at the investigator's discretion. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 3 Intense or widespread and interfering with activities of daily living	1. Permanently discontinue investigational product. 2. Monitor to resolution (Return to Baseline). 3. Consider treatment with topical agents such as clindamycin or corticosteroids.

* Refer to Appendix 12 for clarification.

Herpetiform Rash

For any occurrence of a suspected herpetiform rash (eg, herpes zoster and herpes simplex), specimens for viral DNA analysis will be obtained: A swab of the affected area will be collected for confirmation; a blood sample for viral surveillance will be collected for the analysis of viral load. Details for these collections will be provided in the laboratory manual.

Drug-Related Rash

All potential drug related reports of rash will be followed up until resolution or clinically stable or in agreement with Pfizer.

All events of rash should be treated according to international and local guidelines for the treatment of rash, eg, where appropriate, topical corticosteroids and/or agents such as antibiotics or antivirals could be prescribed.

All subjects reporting an unexplained skin rash should be referred to a local dermatologist or appropriately qualified physician according to local guidelines for formal comprehensive dermatologic evaluation. A 4 mm punch biopsy will be taken unless there is a clear, non-drug related etiology (eg, infection, pre-existing condition) or other clinical rationale (eg, if the rash is present on the face it may not be appropriate to take a biopsy) or if a subject refuses to have biopsy performed. The biopsy will be sent to the local laboratory for histological investigation of the rash in order to gain insight into potential etiology of the rash. Note: For herpetiform rash, no biopsy is required.

In addition to a biopsy of suspected drug-related rash, a swab (for microbiological assessment) of the affected area will also be taken for culture and sensitivity to assess for any bacterial, viral or fungal pathogens, if applicable. A blood sample for viral surveillance will be collected for the analysis of viral load, if applicable.

Subjects reporting rash should assess itch on a 10-point numeric rating scale (NRS) provided by Pfizer (Appendix 14). The investigator (and/or designee) will enter this assessment into the data collection tool.

Investigators (and /or designee) will complete required documentation and take appropriate photographs of the rash.

All de-identified biopsy results, culture results, photographs, and any additional relevant test results will be forwarded to Pfizer (and/or designee) for review within 30 days of receipt by the investigator.

An independent dermatologist contracted by Pfizer will review all relevant data and summarize the data at the end of the study

7.2.12. Audiogram

All subjects will have an audiogram at times specified in the Schedule of Activities. Audiogram testing at screening must be completed and results available by the baseline visit (Visit 2) and audiogram testing at Week 8 (Visit 7) must be completed and results available by the Week 12 visit (Visit 9). For subjects that terminate early from the study, if possible, efforts must be made to complete the audiology testing and obtain the results.

When possible the subject should have the audiogram performed at the same evaluation center during the study.

If there is a clinically meaningful, treatment related decline in hearing from baseline, the subject will be followed off treatment with appropriate testing at regular intervals, until hearing returns to baseline or is determined to be clinically stable.

The information from the audiogram will be entered into the data collection tool.

Any de-identified audiogram results/reports and any additional relevant test results (if applicable) may be requested to be forwarded to Pfizer (and/or designee) at any time during the study.

7.3. Pharmacokinetics

During all study periods, blood samples to provide plasma for pharmacokinetic analysis of PF-06651600 and for potential exploratory analysis of its metabolite(s) will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the Schedule of Activities. The date and time of last dose and date and time of sample collection should be recorded in the source documents and data collection tool (eg, CRF/DCT).

7.3.1. Shipment of Pharmacokinetic Samples

The shipment address and contact information will be provided to the investigator site prior to the initiation of the study.

7.4. Exploratory Biomarkers

All blood, serum, plasma and urine samples for assessment of biomarkers must be collected prior to investigational product administration. Any or all samples may not be analyzed, and data may or may not be included in the clinical study report. Any exploratory biomarkers assessed would be to further understand RA or the effects PF-06651600 only.

Analysis of exploratory endpoints may be further detailed in the statistical analysis plan (SAP) or exploratory analysis plan (EAP). Pooled or exploratory analyses, if conducted, utilizing the retained exploratory genomic and biomarker samples across PF-06651600 studies or across multiple programs will be documented in a separate analysis plan.

7.4.1. IFN-gamma-inducible protein 10 (IP-10)

Samples for analysis of IP-10 will be collected at the visits specified in the Schedule of Activities. The samples will be shipped to and analyzed by a contract lab. After randomization, the investigator and Pfizer study personnel directly involved in the conduct of the trial will be kept blinded of the results of this test.

7.4.2. Anti-CCP and Rheumatoid Factor

A blood sample for assaying Anti-CCP and Rheumatoid Factor will be collected according to the Schedule of Activities. After randomization, the investigator and Pfizer study personnel directly involved in the conduct of the trial will be kept blinded of the results of this test.

7.4.3. Samples for Exploratory Fluorescence Activated Cell Sorting (FACS) analysis

Whole blood samples will be collected according to the times specified in the Schedule of Activities. This blood sample will be used to run a standard T cell, B cell and NK cell subsets (TBNK) panel, and may be used to analyze additional FACS analyses.

7.5. Banked Biospecimens

Banked biospecimens will be collected from subjects for exploratory research relating to the drug response in diseases of inflammation. These collections are not typically associated with a planned assessment described in the protocol. They will be handled in a manner that protects each subject's privacy and confidentiality. Banked biospecimens will be assigned the subject's study identification code (ID) at the site. The data generated from these banked biospecimens will also be indexed by this ID. Biospecimens will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen-derived data will be stored on password-protected computer systems. The key between the subject's ID and the subject's direct personally identifying information (eg, name, address) will be held at the study site. Biospecimens will be used only for the purposes described in the protocol and informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug-development process and also postmarketing research. Subjects may withdraw their consent for the use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining biospecimens will be destroyed, but data already generated from the biospecimens will continue to be available to protect the integrity of existing analyses.

Unless prohibited by local regulations or ethics committee decision, a 4-mL blood genomic banked biospecimen **Prep D1 (dipotassium edetic acid [ethylenediaminetetraacetic acid] [K_2EDTA] whole-blood collection optimized for DNA analysis)** will be collected at the time specified in the Schedule of Activities section of the protocol to be retained for potential pharmacogenomic/genomic/biomarker analyses related to drug response in diseases of inflammation. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined. The primary purpose is to examine DNA; however, the biospecimen may also be used to study other molecules (eg, RNA, proteins, and metabolites).

If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit. These samples must be collected before administration of the investigational product.

Additional banked biospecimens to be retained for such exploratory analyses in this study include the following:

- **Prep B1 (K_2EDTA plasma collection optimized for biomarker/proteomic/ metabonomic analysis):** A 10-mL blood biospecimen will be collected at times specified in the Schedule of Activities section of the protocol.

- **Prep B2 (serum collection optimized for biomarker/proteomic/metabonomic analysis):** a 10-mL blood biospecimen will be collected at times specified in the Schedule of Activities section of the protocol.

- **Prep R1 (PAXGene whole-blood collection optimized for RNA analysis):** A 2.5-mL blood biospecimen will be collected at times specified in the Schedule of Activities section of the protocol.

The banked biospecimens will be collected from all subjects unless prohibited by local regulations or IRB/EC.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document that they will not be compensated in this event.

7.5.1. Shipment of Biomarkers Samples

The shipment address and contact information for the lab will be provided to the investigator site.

7.5.2. Additional Research

Unless prohibited by local regulations or IRB/EC decision, subjects will be asked to indicate on the consent form whether they will allow banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Banked Biospecimens section will be used. Subjects may still participate in the study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.6. Rater Qualifications

Tender and swollen joint counts will be evaluated by a designated study staff member at the clinic.

For consistency, the **same assessor** should perform all joint-count evaluations across the study for an individual subject when possible. It is especially important that the same assessor evaluate the subject at Screening, Baseline, and Week 8 to ensure integrity of the eligibility criteria and the clinical response up to the Week 8 primary endpoint. Only if the assigned joint count assessor cannot be present, the joint counts should be performed by a different study staff member.

The joint count assessor must have a background in performing RA or other clinical trials involving swollen and tender joint assessment and to have personal prior experience performing joint 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/legally acceptable representative. In addition, each study subject/legally acceptable representative 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/Early 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. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.3.1. Exposure During Pregnancy

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

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

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

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

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

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

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

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

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

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

8.4.3.2. Exposure During Breastfeeding

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

8.4.3.3. Occupational Exposure

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

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

8.4.4. Medication Errors

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

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

8.4.4.1. Medication Errors

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

Medication errors include:

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

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

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

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

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

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 information from the placebo arm will be combined with the historic database using Bayesian statistical methodology. The historic study data base will include the data obtained from Phase III tofacitinib trials available to the Sponsor. The integration details and historical data specifications will be detailed in SAP. The integration with historical data will involve application of statistical procedures attempting maximization of the commensurability between the current trial and the subgroup of the historical data used for synthesizing the prior distribution.

9.1. Sample Size Determination

The primary endpoint of the study will be the change from baseline in SDAI at 8 weeks. The study will enroll approximately 50 completers allocated as follows:

PF-06651600 (200 mg) (N)	**Placebo (N)**
30	20

Assuming a 15% dropout rate* the study will enroll approximately 60 subjects.

The study will have over 90% power to detect separation from placebo, assuming a 13 point difference in response between the placebo and 200 mg arm (standard deviation is assumed to be 14 points for both arms*) and controlling Type-I error rate at 5% level. More detailed sample size considerations will be discussed in the SAP.

**Based on information from Phase 3 tofacitinib studies.*

9.2. Efficacy Analysis

9.2.1. Analysis of the Primary Endpoint

The primary efficacy analysis will be conducted on SDAI change from baseline at 8 weeks.

Analysis will include data on PF-06651600 and placebo arms.

Analysis details will be outlined in statistical analysis plan. The analysis will include: ANCOVA models adjusting for SDAI baseline value; Bayesian analysis of posterior distributions of the SDAI scores and placebo adjusted change from baseline; Advanced data visualization techniques for statistical result presentation.

The primary analysis will be conducted on intention-to-treat (ITT) population (randomized subjects with at least one post baseline value). Sensitivity analysis and handling of the missing values will be outlined in the SAP.

9.2.2. Analysis of Secondary Endpoints

Analyses of the secondary endpoints will be outlined in the SAP. Continuous and discrete modeling techniques will be applied whenever applicable. The statistical summaries will be presented by dose groups. The correlations between the endpoints will be analyzed.

9.3. Analysis of Other Endpoints

Analysis of other endpoints will be conducted as deemed appropriate. Continuous and discrete modelling techniques will be applied whenever applicable. Distribution summaries will be presented by means of summary tables and data visualization methods.

9.4. Randomization

The indicator of prior exposure and inadequate response to anti-TNFα treatment will be used as a stratification variable for randomization. Randomization will be stratified to achieve equal proportion of anti-TNFα inadequate responders in all arms.

9.5. Safety Analysis

All clinical AEs, SAEs, TEAEs, withdrawal due to AEs, ECGs, vital signs and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects.

The safety analysis set will include all subjects who have received at least one dose of IP. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. All safety endpoints will be listed and summarized in accordance with Pfizer Standards. Categorical outcomes (eg, AEs) will be summarized by subject counts and percentage. Continuous outcome (eg, BP, pulse rate, etc) will be summarized using N, mean, median, standard deviation, etc. Change from baseline in laboratory data, ECGs and vital signs will also be summarized. Subject listings will be produced for these safety endpoints accordingly.

9.6. Data Monitoring Committee

This study will not use a data monitoring committee.

9.7. PK/PD Unblinding Plan

A PK/PD unblinding plan approved by the clinical lead, clinical pharmacology lead and statistical lead will be in place to describe the procedures to be employed in safeguarding the study blind for members of this study team. These procedures will be in accordance with applicable Pfizer SOPs for releasing randomization codes and breaking the study blind.

Under this plan a group of Statisticians, PK/PD data provider, PK/PD analyst and PK/PD support would be unblinded in order to initiate the building of statistical models of the PK, dose/response as well as exposure/response analysis models and conduct associated simulations. The aim of this work would be to facilitate a fuller interpretation of the study upon completion (at appropriate interim milestone).

This group will not serve on the study team during the period of early unblinding. The unblinding may occur after the last subject has been randomized. The details of the procedures will be described in the PK/PD Unblinding Plan for Modelling and Simulation for study B7981006 which will be finalized prior to the start of the PK/PD unblinding.

9.8. Unblinding for Biomarkers

In order to expedite the analyses of the biomarkers, an unblinded team may review the biomarker data (including exploratory biomarkers) and exposure data on an ongoing basis. This group will minimally be comprised of a bioanalyst and a statistician, but may also include clinicians/precision medicine personnel, clinical pharmacologist and PK/PD analyst/support staff as appropriate. This group will be unblinded when needed in order to conduct the analyses of the biomarkers in accordance with a biomarker data analysis plan, and will be independent of the study team. This unblinding process will be in accordance with Pfizer SOPs related to Releasing Randomization Codes and Breaking the Blind and will not have any impact on the conduct of the study.

The biomarker plan, approved by the clinical lead, clinical pharmacology lead and statistical lead, will be in place to describe the procedures to be employed in safeguarding the study blind for members of the study team. The biomarker plan will outline the range of possible analyses and provide details of the decision-making process regarding unblinding.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

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

11.2. Record Retention

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

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

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

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

12. ETHICS

12.1. Institutional Review Board/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 ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

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

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

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

The investigator must ensure that each study subject, or his or her legally acceptable representative is fully informed about the nature and objectives of the study and possible risks associated with participation.

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

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

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 a Member State

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

13.2. End of Trial in All Other Participating Countries

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

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06651600 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 1 month. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in subjects) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (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 subjects has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by 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
AE	adverse event
ACR	american college of rheumatology
ACPA	anti-citrullinated protein antibodies
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
ATP	adenosine triphosphate
BA	bioavailability
BID	twice a day
BBS	biospecimen banking system
BP	blood pressure
C_{max}	peak or maximum observed concentration
CK	creatine kinase
CMV	cytomegalovirus
CRF	case report form
CSA	clinical study agreement
CSR	clinical study report
CT	computerised tomography
CTA	clinical trial application
CTCAE	common terminology criteria for adverse events
CYP	cytochrome p
DCT	data collection tool
DILI	drug-induced liver injury
DMARD	disease-modifying antirheumatic drugs
DNA	deoxyribonucleic acid
DU	dispensable unit
EBV	epstein-barr virus
EC	ethics committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EDP	exposure during pregnancy
EOS	end of study
EU	european union
EudraCT	european clinical trials database
EULAR	european league against rheumatism
FACS	fluorescence-activated cell sorting
FDA	food and drug administration
FIH	first in human

Abbreviation	Term
FSH	follicle-stimulating hormone
FU	follow up
fu	fraction unbound
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GST	glutathione-S-transferase
HAQ-DI	health assessment questionnaire – disability index
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HIV	human immunodeficiency virus
hsCRP	high-sensitivity C-reactive protein
HSV	herpes simplex virus
IC50	50% inhibitive concentration
ICH	international conference on harmonisation
ID	identification
IgA, G, M, E	immunoglobulin of the A, G, M , E isotypes
IGRA	interferon-gamma release assay
IL	interleukin
IND	investigational new drug application
IFN	interferons
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
IV	intravenous
IWR	interactive web response
JAK	janus kinase
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test
LOAEL	lowest observed adverse effect level
LSLV	last subject last visit
MAD	multiple ascending dose
MCP	metacarpophalangeals
MRI	magnetic resonance imaging
N/A	not applicable
NOAEL	no observed adverse effect level
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drugs
PAAP	patient assessment of arthritis pain

Abbreviation	Term
PCD	primary completion date
PD	pharmacodynamics(s)
PGx	pharmacogenomics(s)
PhGA	physician's global assessment
PI	principal investigator
PK	pharmacokinetic
PO	per os (oral)
PT	prothrombin time
PtGA	patient's global assessment
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAD	single ascending dose
SAP	statistical analysis plan
SC	subcutaneous
SDAI	simple disease activity index
SJC	swollen joint count
SLE	systemic lupus erthematosus
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TEAE	treatment emergent adverse event
TJC	tender joint count
TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
TNFi	TNF inhibitors
UC	ulcerative colitis
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VZV	varicella zoster virus
WBC	white blood cells
WONCBP	women of non-childbearing potential

Appendix 2. 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis[24,25]

Presented below are the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis.

Target population (Who should be tested?) must have:

1) have at least 1 joint with definite clinical synovitis (swelling)*
2) with the synovitis not better explained by another disease†

Classification criteria for RA (score-based algorithm: add score of categories A–D;
a score of _6/10 is needed for classification of a patient as having definite RA)‡

A. Joint involvement§		SCORE (A) _____
1 large joint¶	0	
2-10 large joints	1	
1-3 small joints (with or without involvement of large joints)#	2	
4-10 small joints (with or without involvement of large joints)	3	
>10 joints (at least 1 small joint)**	5	
B. Serology (at least 1 test result is needed for classification)††		SCORE (B) _____
Negative RF *and* negative ACPA	0	
Low-positive RF *or* low-positive ACPA	2	
High-positive RF *or* high-positive ACPA	3	
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡		SCORE (C) _____
Normal CRP *and* normal ESR	0	
Abnormal CRP *or* abnormal ESR	1	
D. Duration of symptoms§§		SCORE (D) _____
<6 weeks	0	
≥6 weeks	1	
		TOTAL SCORE (A+B+C+D) _____

A TOTAL Score of ≥6/10 is needed for classification of a patient as having definite RA)‡

* The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

† Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

‡ Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

§ Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

¶ "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

"Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

** In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (eg, temporomandibular, acromioclavicular, sternoclavicular, etc.).

†† Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA= anti-citrullinated protein antibody.

‡‡ Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

§§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (eg, pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Appendix 3. Criteria for Classification of Functional Status in Rheumatoid Arthritis[26]

Class I: Completely able to perform usual activities of daily living (self-care, vocational, and avocational).

Class II: Able to perform usual self-care and vocational activities, but limited in avocational activities.

Class III: Able to perform usual self-care activities, but limited in vocational and avocational activities.

Class IV: Limited in ability to perform usual self-care, vocational, and avocational activities.

Usual self-care activities including dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific.

Appendix 4. Prohibited Concomitant Medications

This is not an all-inclusive list. Study personnel should stay current and consult with their pharmacy to exclude all concomitant medications that are either moderate to potent CYP3A inhibitors or inducers.

Moderate to Potent CYP3A Inhibitors*	**Moderate to Potent CYP3A Inducers****
Amprenavir	Avasimibe#
Amiodarone	Bosentan
Aprepitant	Barbiturates
Atazanavir	Carbamazepine#
Boceprevir	Efavirenz
Casopitant	Etravirine
Cimetidine	Mitotane#
Ciprofloxacin	Modafinil
Clarithromycin#	Nafcillin
Cobicistat#	Phenobarbital#
Conivaptan#	Phenytoin#
Darunavir	Rifabutin#
Diethyldithiocarbamate	Rifampin #
Diltiazem	St. John's Wort#
Dronedarone	Talviraline
Elvitegravir#	
Erythromycin	
Fluconazole	
Fluvoxamine	
Imatinib	
Indinavir#	
Itraconazole#	
Ketoconazole#	
Lopinavir#	
Mibefradil#	
Mifepristone (RU486)	
Nefazodone#	
Nelfinavir#	
Norfloxacin	
Posaconazole#	
Ritonavir #	
Saquinavir#	
Schisandra sphenanthera	
Telaprevir	
Telithromycin#	
Tipranavir#	
Tofisopam	
Troleandomycin#	
Verapamil	
Voriconazole#	

* All prohibited drugs that are CYP3A inhibitors require at least a 7 day or 5 half-lives (whichever is longer) washout prior to the first dose of study drug. Note: Amiodarone requires discontinuation at least 290 days (~5 half-lives, half-life averages ~58 days) prior to the first dose of study drug.

** All prohibited drugs that are CYP3A inducers require at least a 28 day or 5 half-lives (whichever is longer) washout prior to the first dose of study drug.

Notated as potent inhibitors or inducers.

It is recommended that subjects avoid consumption of grapefruit juice exceeding 8 ounces (~240 ml) total in a day while in the study.

In a situation where appropriate medical care of a subject requires the use of a prohibited CYP3A inhibitor or inducer:

Moderate to potent inhibitors and inducers of CYP3A are not permitted in the study EXCEPT in emergency situations requiring no more than one day of administration. ***Note: Amiodarone and mitotane are not permitted for any duration due to their long half-lives.*** Topical (including skin or mucous membranes) application of antimicrobial and antifungal medications is permitted.

Appendix 5. Guidelines for Monitoring and Discontinuations

These guidelines for subject safety monitoring and discontinuation are to be applied to all subjects in this study. Additional individual subject monitoring is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled clinical labs may be obtained at any time during the study to assess such concerns, and a subject may be withdrawn at any time at the discretion of the investigator.

Monitoring

The following laboratory abnormalities require re-testing within 1 week:

- Absolute neutrophil count <2000/mm^3; (< 2 x 10^9/L)
- Hemoglobin <9.0 g/dL;
- Platelet count below <100,000/mm^3; (<100 x 10^9/L)
- Lymphocyte counts <500 lymphocytes/mm^3; (<0.5x10^9/L)
- Any single AST and/or ALT elevation ≥3 times the upper limit of normal (repeat laboratory testing should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, PT [prothrombin time] with INR [international normalized ratio], and alkaline phosphatase), regardless of the total bilirubin. (Please note that 3 times the upper limit of normal increases in ALT, AST need confirmation on separate blood draw before undertaking thorough evaluation for liver injury);

- All potential treatment-related reports of rash will be followed up until resolution or in agreement with Pfizer.
- Positive urine β-hCG test, the subject will have study drug interrupted and a serum sample collected on the same day (or as soon as possible) and submitted to the central laboratory for β-hCG testing.

Discontinuation

The sponsor's Clinical team should be notified as soon as possible and subject treatment will be discontinued and the subject withdrawn from this study for:

- Two sequential hemoglobin value <8.0 g/dL or one that drops 2 g/dL below baseline
- Two sequential absolute neutrophil counts <750/mm^3 ; (<0.75 x 10^9/L)
- Two sequential platelet counts <75,000/mm^3 ;(<75 x 10^9/L)
- Two sequential lymphocyte counts <500 lymphocytes/mm^3; (<0.5x10^9/L)

- 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[a]
- Two sequential AST or ALT elevation ≥3 times the upper limit of normal accompanied by signs or symptoms consistent with hepatic injury[a]
- Two sequential AST or ALT elevation ≥5 times the upper limit of normal, regardless of total bilirubin or accompanying signs or symptoms[a]
- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring parenteral antimicrobial therapy, hospitalization for treatment, or meeting other criteria that require the infection to be classified as serious adverse event
- Other serious or severe AEs, at the discretion of the investigator or sponsor
- Female subjects found to be pregnant during the study; For women of child-bearing potential with any positive urine β-hCG test, the subject will have study drug interrupted and a serum sample submitted to the central laboratory for β-hCG testing
- Subjects who are treated with any prohibited medication during the course of the study
- Serious or severe drug-related rash at the discretion of the investigator or sponsor. (See Section 7.2.11)
- Subjects who require rescue doses of acetaminophen/paracetamol or opioid for more than 10 consecutive days or within the last 7 days before the last dose should be discontinued from the trial;

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

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

Appendix 6. Disease Activity Score (DAS) Assessments[1]

DAS-28-4 (CRP) Assessment

The formula for calculation of DAS28-4 (CRP) using 4 components:

- Swollen Joints (0–28);
- Tender Joints (0–28);
- CRP
- Patient's Global Assessment of Arthritis (PtGA) (0 – 100 mm VAS).

DAS28-4 (CRP)= 0.56 sqrt (DAS 28 tender joint count) + 0.28 sqrt (DAS 28 swollen joint count) + 0.36 ln(CRP [mg/L] +1) + 0.014 (PtGA [mm]) + 0.96

DAS-28-4 (ESR) Assessment

The formula for calculation of DAS28-4 (ESR) using 4 components:

- Swollen Joints (0–28);
- Tender Joints (0–28);
- Erythrocyte Sedimentation Rate (ESR);
- Patient's Global Assessment of Arthritis (PtGA) (0 – 100 mm VAS).

DAS28-4 (ESR)= 0.56 sqrt (DAS 28 tender joint count) + 0.28 sqrt (DAS 28 swollen joint count) + 0.70 ln (ESR [mg/L] + 0.014 (PtGA [mm])

Appendix 7. Patient's Assessment of Arthritis Pain (PAAP)

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]

Appendix 8. Patient's Global Assessment (PtGA) of Arthritis

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]

Appendix 9. Physician's Global Assessment (PhGA) of Arthritis

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]

Appendix 10. Oral Corticosteroid Equivalents[28,29,30,31,32]

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.

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.

Appendix 11. Allowed Opioids and Approximate Equivalent Morphine Doses Of Opioid Analgesics[33,34]

Common opioid analgesics

Drug	Maximum Allowed Total Daily Dose	Relative potency to oral morphine	Half-Life
Morphine	30 mg	1	1.5 – 4 hrs
Hydrocodone (Vicodin, Lortab)	30 mg	1	3.8 – 4.5 hrs
Hydromorphone (Dilaudid)	7.5 mg	4	2.5 hrs
Meperidine (Demerol, Pethidine)	300 mg	0.1	3.2 – 3.7 hrs
Methadone (Dolophine, Methadose, Physeptone)	10 mg	3.0	23 hrs
Codeine (Paveral, Tylenol #2 and #3)	200 mg	0.15	2.5 – 3.5 hrs
Oxycodone [Roxicodone; Percocet, Tylox]	15 mg	~2	3.2 hrs
Tramadol [Ultram, Zydol; Zamadol, Ultracet, Tramal]	300 mg	~0.1	4.7 – 5.1 hrs
Propoxyphene HCl (Darvon, Darvocet, Doloxene) Propoxyphene napsylate (Darvon-N, Darvocet-N 100)	300 mg propoxyphene HCl 400 mg propoxyphene napsylate	~0.1	6-12 hrs; 30-36 hrs. for active metabolite (norpropoxyphene)

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

Appendix 12. Common Terminology Criteria for Adverse Events v4.03 (CTCAE)-Dermatology

The NCI Common Terminology Criteria for Adverse Events v4.03 is a descriptive terminology that can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term. One page of the Dermatology/Skin Category is presented, which contains listings for Pruritus, Rash/Desquamation, and Rash: Acne/acneiform.

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-
Definition: A disorder characterized by an intense itching sensation.					
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow color.					
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.					
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.					

Rash/desquamation and erythema multiforme progressing to Grade 2, acne/acneiform rash or pruritus progressing to Grade 3 are the severity levels for permanently discontinuing a subject from investigational product.

Pruritus progressing to Grade 2 sustained (>4 days) is cause to permanently discontinue investigational product.

Appendix 13. HAQ-DI[35]

Health Assessment Questionnaire - Disability Index (HAQ-DI)© Stanford University 1983 version:

In this section we are interested in learning how your illness affects your ability to function in daily life.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
DRESSING & GROOMING				
Are you able to:				
-Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
-Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
-Stand up from a straight chair?	☐	☐	☐	☐
-Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
-Cut your meat?	☐	☐	☐	☐
-Lift a full cup or glass to your mouth?	☐	☐	☐	☐
-Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
-Walk outdoors on flat ground?	☐	☐	☐	☐
-Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

☐ Cane	☐ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
☐ Walker	
☐ Crutches	☐ Built up or special utensils
☐ Wheelchair	☐ Special or built up chair
	☐ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and Grooming	☐ Eating
☐ Arising	☐ Walking

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty	**With SOME difficulty**	**With MUCH difficulty**	**UNABLE to do**
HYGIENE				
Are you able to:				
-Wash and dry your body?	☐	☐	☐	☐
-Take a tub bath?	☐	☐	☐	☐
-Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
-Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
-Bend down to pick up clothing from the floor?	☐	☐	☐	☐

	Without ANY <u>difficulty</u>	**With SOME <u>difficulty</u>**	**With MUCH <u>difficulty</u>**	**UNABLE <u>to do</u>**
GRIP				
Are you able to:				
-Open car doors?	☐	☐	☐	☐
-Open jars, which have been previously opened?	☐	☐	☐	☐
-Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
-Run errands and shop?	☐	☐	☐	☐
-Get in and out of a car?	☐	☐	☐	☐
-Do chores such as vacuuming or yard work?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

☐ Raised toilet seat	☐ Bathtub bar
☐ Bathtub seat	☐ Long-handled appliances for reach
☐ Jar opener (for jars previously opened)	☐ Long-handled appliances in bathroom
	☐ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene	☐ Gripping and opening things
☐ Reach	☐ Errands and chores

Appendix 14. Assessment of Itch (NRS)[36]

Severity of Pruritus

Select the number that best describes your itching over the past 24 hours (check one number only).

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No itching										Worst possible itching