A 12 WEEK RANDOMIZED, DOUBLE-BLIND, DOUBLE DUMMY, PARALLEL GROUP, ACTIVE AND PLACEBO-CONTROLLED, MULTICENTER STUDY TO ASSESS THE EFFICACY AND SAFETY PROFILE OF PF-06650833 IN SUBJECTS WITH ACTIVE RHEUMATOID ARTHRITIS WITH AN INADEQUATE RESPONSE TO METHOTREXATE

Investigational Product Number:	PF-06650833
Investigational Product Name:	
United States (US) Investigational New Drug (IND) Number:	131,052
European Clinical Trials Database (EudraCT) Number:	2016-002337-30
Protocol Number:	B7921005
Phase:	2b

[redacted]

[redacted]

Document History

Document	Version Date	Summary of Changes
Amendment 4	08 August 2017	• Protocol summary and section 3 is being updated to clarify that methotrexate must have been dosed for at least 3 months to establish "inadequate response" not "lack of inadequate response. • CCI [redacted]
Amendment 3	12 July 2017	• Protocol summary and sections 3, 4.1 and 5.7.1 are being updated to clarify that prior use of parenteral metoteraxate (intramuscular or subcutaneous, only, not intravenous administration) is permitted. • Protocol summary and sections 4.1, 5.7.1 are being updated to change prior metotrexate exposure duration from 3 months prior to screening to 3 months prior to baseline (randomization). • The SOA is being updated to clarify that sites have +/- 2 days flexibility to schedule follow up or EOS visits. • The SOA is being updated to clarify that urinalysis includes creatinine test. • The SOA is being updated to correct the spelling "antibody" from the text. • The SOA, footnote "s" is being updated to allow a delay in randomization (ie, date of Visit 2) up to 14 days beyond the 28 day Screening window (total interval between Screening and Visit 2 must be ≤42 days) solely due to IP unavailability (the delay will not be considered a protocol deviation (PD)).

Document	Version Date	Summary of Changes
		• Section 4.1, inclusion 3, is being updated to increase the recruitment age from 70 to 75 years old. 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. • Section 4.2, exclusion 7 is being updated to clarify TB exclusion criteria. • Section 4.2, exclusion 8 is being updated to clarify vaccination exclusion criteria. • Section 4.2, exclusion 15 and 16 are being updated to exclude recruitment of subjects with dermatomyositis and fibromyalgia. • Section 4.2, exclusion 22 is being updated to define the exclusion based on urine albumin creatinine ratio. • CCI [redacted] • Section 4.4.1 and exclusion 3 are being updated to allow the use of 1 highly effective method of contraception instead of 2 methods. The use of contraception methods must be consistent with local medical, Ethics Committee, and Regulatory Authority guidelines. • Section 5.7.1 is being updated to clarify that bisphosphonates (oral or parenteral) should ideally be administered after the baseline/randomization (Visit 2) and Week 12 (Visit 8) visits, and under any circumstances, must not to be administered within 1 week preceding these visits. • Sections 6.2.4, 6.2.6 and 6.2.8 are being updated to correct a discrepancy that patients are not required to fast for at least 6 hours prior to the visit" at visits 5, 7, and 9.

Document	Version Date	Summary of Changes
		• Section 7.3.1, Table 9 is being updated to clarify that urinalysis includes creatinine test. • Section 7.7 is being updated to clarify serum creatinine (SCr) values to define potential cases of acute kidney injury: Triggered responses for assessing possible cases of Acute Kidney Injury described in Section 7.6.2 will supersede those in Section 7.7. Therefore, serum creatinine (SCr) values in Section 7.6.2 (rather than in Section 7.7) will be used to trigger actions needed to assess potential cases of acute kidney injury. Relevant SCr values are updated in Section 7.7 to match those in Section 7.6.2.
Amendment 2	28 November 2016	• The SOA was updated to add the missing abbreviation for HBsAb = hepatitis B surface antibody. • Footnote "m" and exclusion #6 are being updated to clarify that HIV testing is mandatory unless local regulations prohibit mandatory testing. • Footnote "u" is being updated to clarify that subject compliance will be checked throughout the study. • The protocol is being updated to allow prior (single) TNF experience after appropriate washout irrespective of inadequate response or due to lack of continued access. • Section 4.4.1 is being updated to remove the double barrier method from the list of highly effective methods of contraception. • Exclusion criteria # 4 is being updated to clarify exclusion of subjects with alcohol or substance abuse. • Exclusion criteria #7 is being updated to clarify exclusion of subjects with prior active tuberculosis.

Document	Version Date	Summary of Changes
		• Exclusion criteria #8 is being updated to stipulate that live vaccines should not be administered for at least 30 days after the last dose of study medication. • Section 5.7.1 and Inclusion #10 are being updated to clarify allowed methotrexate doses and replace "10-25 mg, inclusive" with "15-25 mg, inclusive". 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. • Section 5.7.2.4 and 5.7.2.5.1 are being updated to add natalizumab and tacrolimus to the list of prohibited concomitant medications. • Section 6.1 and 7.3.2 are being updated to clarify and indicate what should minimally be performed during the physical examinations (complete and targeted physical exams). • Section 6.1 and 7.3.8 are being updated to clarify the requirement of a chest X-ray performed within 12 weeks prior to screening and not Day 1 (same as in footnote g). • Section 6.2.9 is being updated to delete: "Review of the diary for compliance with daily diary completion (and provide subject retraining as required), IP accountability and compliance check through the study" to beconsistent with the SoA and as stated. (Subjects do not have any IP and dairy during the follow up period (after Week 12)). • Section 6.3 is being updated to correct the "eGFR" misspelling. • Section 9.1 is being updated to clarify sample size determination. • Section 9.2 is being updated to clarify efficacy analysis.

Document	Version Date	Summary of Changes
		• Section 9.4 is being updated to clarify randomization criteria. • Section 9.5 is being updated to clarify that the study is not having an adjudication team and no safety data will be adjudicated. • Section 9.6 is being updated to provide more detail about the interim analysis. • Section 9.7 is being updated to clarify the independence and the role of the Independent Oversight Committee members. • The abbreviation list (Appendix 1) is being updated. • Appendix 7 and 10 are being updated to correct the "PtGA" abbreviation.
Amendment 1	04 October 2016	• The protocol is being amended (Amendment 1) in response to US regulatory feedback to increase the frequency of monitoring for urinary crystals and evidence of acute kidney injury by adding 3 study visits (at Weeks 6, 10 and 14). • The SoA and Section 6 are being updated to add the following at study Weeks 6, 10 and 14: assessment of adverse events, vital signs, targeted physical examinations, review of concomitant medications, clinical chemistry laboratory assessment (including blood urea nitrogen, creatinine), urinalysis, urine microscopy, urine pregnancy test, contraception check, CCI [redacted] • The SoA and Section 6 are being updated to clarify that sites will log into IRT system at screening, Weeks 0, 1, 4, 8 and 16 (and EW).

Document	Version Date	Summary of Changes
		• The SoA is being updated to capture that investigational products will be administered to subjects in the clinic on the morning of clinic visits at Weeks 6 and 10. • The SoA is being updated to clarify that "dispensing of subject diary" will be considered a separate activity and will be added as a separate row to the Schedule of Activities. Sections 6.2.1, 6.2.2, 6.2.3 and 6.2.4 will also be updated to reflect that new subject diaries are dispensed for completion between each visit. • The SoA is being updated to capture that review of subject diary (review of subject dosing record), IP accountability and compliance check is not applicable at Visit 10. • The SoA footnote "d" and Section 6 are being updated to allow for axillary method of vital sign measurement. • The SoA footnote "g", Section 6.1 and Section 7.3.8 are being updated to clarify that a chest X-ray is required at Screening, and a chest X-ray or other appropriate diagnostic chest imaging modality (ie, CT or MRI) performed within 12 weeks prior to screening and read by a qualified radiologist with no evidence of current, active TB or previous inactive TB, general infections, heart failure or malignancy may substitute for the chest X-ray taken at Screening. • The SoA footnote "h" is being updated to clarify that single repeats of laboratory tests are inclusive of Blood Chemistry, Hematology, C-Reactive Protein (hsCRP), Erythrocyte Sedimentation Rate (ESR), Anti CCP Antibodies (ACPA) and Urinalysis. Laboratory tests at Weeks 6, 10, and 14 will only include standard blood chemistry panels (not hematology).

Document	Version Date	Summary of Changes
		• The SoA footnote "i" and Section 7.1.4.4 are being updated to clarify that ESR will be tested locally using the Westergren method. ESR kits will be provided by the central laboratory and ESR results will be reported to the 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. • The SoA footnote "k" is being updated to clarify that a delay in randomization for WOCBP in order to collect the second pregnancy test within 5 days after the first day of the menstrual period will not be considered a protocol deviation (PD). • The SoA footnote "m" is being updated to clarify that human immunodeficiency virus (HIV) testing is mandatory; however reporting of results should be handled per local regulations. • The SoA footnote "n" and Section 7.3.7 are being updated to clarify that subjects with a positive documented IGRA TB test (eg, QuantiFERON®-TB GOLD (QFT-G) performed within 12 weeks prior to Screening are excluded. The specific IGRA method, or test, used should comply with local country-specific guidelines. The type (name) and results of the IGRA TB test must be known and located in source documentation. A subject who is currently being treated for either latent or active TB infection is to be excluded. • The SoA and footnote "w" are being updated to allow for more efficient management of investigational product. • CCI [redacted]

Document	Version Date	Summary of Changes

		CCI [redacted]
		• Protocol summary is being updated to make the following administrative changes:
		  • Primary endpoints: delete repeated "Simplified Disease Activity Index."
		  • Secondary clinical efficacy endpoints: update ARC 50 and ARC 70 to ACR 50 and 70.
		  • Statistical methods: delete "*[per body]*".
		  • Add missing punctuation marks.
		  • Correct discrepancy in the program number PF-6650833 in Tables 7 and 8 and correct EQ-5D-3L throughout the protocol.
		• Study design in protocol summary, Sections 3, 5.1 and 9.1 are being updated to clarify that approximately 20-30 subjects are to be randomized into the tofacitinib arm.
		• Inclusion criteria #7 is being updated to correct an administrative error: hsCRP must be >7 mg/L at screening.
		• Inclusion criteria #9 is being updated to correct an administrative error: Rand was changed to Randomization.
		• Inclusion criteria #11 is being updated to clarify that "anti-TNFs" (not TNFs) should have been discontinued for a minimum washout period described in inclusion #11.

Document	Version Date	Summary of Changes
		• Exclusion criteria #3 and Section 4.4.1 are being updated to exclude male subjects with partners currently pregnant and male subjects able to father children for the duration of the study and for at least 90 days (instead of 28 days) after the last dose of investigational product. • Exclusion criteria #20 is being updated to clarify that subjects with an oral, tympanic, temporal or axillary temperature of 38°C or higher at baseline will be excluded. • CCI [redacted] • Section 5.4.2 is being updated to correct that visit dates are calculated such that visit windows are not cumulative and are anchored on Day 1. • Section 5.7.1 is being updated to correct a discrepancy in allowed methotrexate doses and replace “15-25 mg, inclusive” with “10-25 mg, inclusive”. • Section 6.2.1 is being updated to correct an administrative error and replace “administration of the study products” with “administration of PF-06650833, placebo or tofacitinib”. • CCI [redacted] • Section 7.3.1, Table 9 is being updated to add “Color, clarity and Specific Gravity” as part of urinalysis tests.

Document	Version Date	Summary of Changes
		• Section 7.3.6 and footnote "f" are being updated to clarify that ECGs are to be transferred from the sites to a central vendor for assessment. • Section 7.6.3 is being updated to clarify that subjects who develop evidence of acute kidney injury will be discontinued from the study and, unless clinically contraindicated encouraged to drink water to produce dilute urine CCI [redacted] Supportive and other treatments for acute kidney injury may be instituted as deemed clinically appropriate by the PI. • Section 7.7 is being updated to clarify that criteria listed in this section will apply to all subjects by deleting "Tofacitinib" in the section heading. • Sample size determination table in Section 9.1, is being updated to clarify that tofacitinib 5 mg is being administered BID. • Appendix 14 (EQ-5D-3L) is being updated to include the additional scale page. • Appendix 15 (Oral Corticosteroid Equivalents) is being updated to correct a discrepancy in tapering or discontinuation of the corticosteroid treatment and replace "Week 52" with "Week 12".
Original protocol	19 July 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

Rationale:

Rheumatoid arthritis (RA) is a chronic, autoimmune disease characterized by joint inflammation and destruction, progressive disability and adverse psychological effects. There is currently no cure for RA. The purpose of treatment is to control disease activity, alleviate signs and symptoms, maintain physical function, optimize quality of life, reduce the rate of joint damage, and, if possible, induce complete remission.

Disease-modifying antirheumatic drugs (DMARDs) partially fulfill these goals, but often fall short of adequate minimization or prevention of progressive joint damage and optimization of quality of life, and are not infrequently associated with clinical tolerability and/or safety issues. Biologic DMARDs, such as tumor necrosis factor (TNF) inhibitors (TNFi), are more efficacious than conventional synthetic DMARDs and successfully halt or slow joint damage. Additional approved therapeutics include tocilizumab (interleukin (IL)-6 receptor neutralizing antibody) and, in the US and more than 40 countries worldwide, tofacitinib (a small molecule Janus kinase (JAK) inhibitor). Despite the considerable list of approved treatments for RA, there are significant numbers of patients who do not achieve remission or indeed adequate reduction in disease activity.

This study will evaluate the efficacy and safety of PF-06650833, a selective, reversible inhibitor of IL-1 receptor associated kinase 4 (IRAK4), as a treatment of RA.

Background information on PF-06650833 can be obtained from the current version of the PF-06650833 Investigator's Brochure, which is the single reference safety document (SRSD) for information relating to PF-06650833.

Primary Objectives:

- To evaluate the efficacy of PF-06650833 at 12 weeks, in subjects with moderate-severe active RA who have had an inadequate response to methotrexate (MTX).

Secondary Objectives:

- To assess the safety of PF-06650833 for 12 weeks in subjects with RA.
- To explore the dose – response relationship for efficacy in RA.
- To assess other signs of clinical efficacy over 12 weeks.
- To assess the effect of PF-06650833 on patient reported outcome measurements.

CCI [redacted]

CCI

Primary Endpoints

- Change from baseline in the Simplified Disease Activity Index (SDAI) at Week 12.

Secondary Endpoints

Secondary Clinical Efficacy Endpoints

- Change from baseline in SDAI at Weeks 4 and 8.
- SDAI low disease activity score (LDAS) and remission rates at 4, 8 and 12 weeks.
- Disease activitiy score (DAS) 28 LDAS and remission rates at 4, 8 and 12 weeks.

The following will also be calculated at Week 4, 8 and 12:

- Change from baseline, DAS28-3, DAS28-3 CRP, DAS28-4 (Erythrocyte Sedimentation Rate (ESR)) and DAS28-4 (CRP).
- American College of Rheumatology (ACR) 20, ACR 50 and ACR 70 responder rates.
- Change from baseline in the Tender/Painful and Swollen Joint Counts.
- Change from baseline in high sensitivity C-reactive protein (hsCRP).
- Change from baseline in the Physician's Global Assessment of Arthritis (PhGA).

Safety Endpoints

- Safety and tolerability of PF-06650833: vital signs (blood pressure (BP), pulse and temperature), laboratory tests, Adverse Events (AEs) and Serious Adverse Events (SAEs), 12-lead electrocardiogram (ECG).

- Urinalysis including urine microscopy.

Secondary Patient Reported Outcome Endpoints

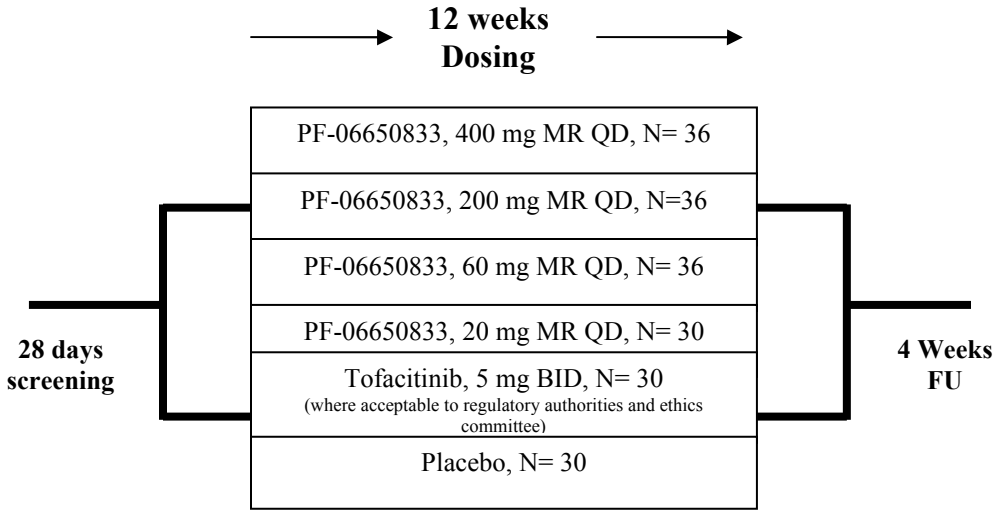
- Change from baseline in the Patient's Assessment of Arthritis Pain (PAAP) VAS and Patient Global Assessment of Arthritis (PtGA, VAS) at Week 4, 8, and 12.
- Change from baseline in the Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 4, 8, and 12.
- Change from baseline in the SF-36v.2 (acute) 8 Domain scores and Physical Component Score (PCS) and Mental component score (MCS) at Week 12.
- Change from baseline in the European Quality of Life – 5 Dimensions-3 Level (EQ-5D-3L) score at Week 12.
- Change from baseline in the Functional Assessment of Chronic Illness Therapy (FACIT-F) total score at Week 12.

CCI [redacted]

Study Design and Trial Treatments:

This is a Phase 2, multicenter, randomized, double-blind, double dummy, placebo- and active-controlled, parallel group study to assess the efficacy and safety of PF-06650833 at Week 12 in subjects with moderate-severe, active, ACPA-positive RA who have had an inadequate response to MTX (up to approximately 50% of subjects may have also received one (and only one) approved TNF-inhibiting biologic agent administered in accordance with its labeling recommendations. The TNF-inhibiting biologic could have been discontinued due to its being deemed inadequately effective and/or not tolerated as defined, for the purpose of this study, by the Investigator's and subject's opinions that the subject did not experience adequate benefit from the anti-TNF plus the presence of sufficient residual disease activity to meet the entry criteria. The anti-TNF biologic could also have been discontinued due to lack of continued access. Eligible subjects will be randomized into one of the 6 treatment arms described in the schematic below where use of tofacitinib as an active control in this study is acceptable to regulatory authorities and ethics committees. PF-06650833 or matching placebo MR tablets will be administered orally QD under fasting conditions, and tofacitinib or matching tofacitinib placebo tablets will be administered orally BID for 12 weeks in a blinded fashion. Up to approximately 230 subjects may be randomized globally into the study to ensure at least approximately 198 subjects complete 12 weeks of active dosing (assuming a dropout rate of approximately 15%). Since the use of tofacitinib in this study may be not be acceptable by regulatory authorities/ethics committess in all countries, achieving full randomization into the tofacitinib arm may prove logistically challenging. Since the tofacitinib arm is serving as an active control for the study, enrollment of approximately 20-30 subjects into that arm will be acceptable. Subjects will participate in this study for approximately 20 weeks. This includes an up to 28 dayscreening period, a 12 week treatment period, and a 4 week follow-up period.

Study Design Schematic



In order to maintain the blind and minimize bias, all subjects will receive the same number and types of tablets each day as described in the Tables below. Subjects assigned to PF-06650833 will all take 4 MR tablets, consisting of a mixture of active PF-06650833 and/or matching placebo tablets dispensed in a blister pack, once per day. In countries in which regulatory authorities and ethics committes accept the use of tofacitinib as an active control in this trial, subjects also will take 1 matching tofacitinib placebo tablet (dispensed in bottles) BID. Subjects assigned to receive tofacitinib will take 1 tablet (dispensed in bottles) of tofacitinib citrate (5 mg) BID. These subjects will also take 4 MR tablets of placebo matching PF-06650833 MR tablets (dispensed in a blister pack) once daily. In regions where tofacitinib's inclusion in this study as an active control is not accepted by local regulatory authorities and ethics committees, subjects will only be randomized to PF-06650833 or matching placebo (dispensed in blister packs) and will not receive bottles of tofacitinib or matching placebo (Table below).

Dosing and administration of investigational products in regions where the use of tofacitinib in this study is acceptable to regulatory authorities and ethics committees.

Treatment group (n)	Treatment PF-06650833 or matching placebo (packaging)	Tofacitinib or matching Placebo (Packaging)	Total number tablets per day
PF-06650833 400 mg, QD n=36	4 x100 mg PF-06650833 tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6
PF-06650833 200 mg, QD n=36	2 x 100 mg PF-06650833 + 2 x PF-06650833 placebo tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6
PF-06650833 60 mg, QD n=36	3 x 20 mg PF-06650833 + 1 PF-06650833 placebo tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6
PF-06650833 20 mg, QD n=30	1 x 20 mg PF-06650833 + 3 PF-06650833 placebo tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6
Tofacitinib 5 mg, BID n=30	4 x PF-06650833 placebo tablets, QD, (Blister Pack)	1 x 5 mg tofacitinib, BID, (Bottle)	6
Placebo n=30	4 x PF-06650833 placebo tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6

Dosing and administration of investigational products in regions where the use of tofacitinib as an active control in this study is not acceptable to regulatory authorities and ethics committees.

Treatment group (n)	Treatment PF-06650833 or matching placebo (packaging)	Total number tablets per day
PF-06650833 400 mg, QD n=36	4 x100 mg PF-06650833 tablets, QD, (Blister Pack)	4
PF-06650833 200 mg, QD n=36	2 x 100 mg PF-06650833 + 2 x PF-06650833 placebo tablets, QD, (Blister Pack)	4
PF-06650833 60 mg, QD n=36	3 x 20 mg PF-06650833 + 1 PF-06650833 placebo tablets, QD, (Blister Pack)	4
PF-06650833 20 mg, QD n=30	1 x 20 mg PF-06650833 + 3 PF-06650833 placebo tablets, QD, (Blister Pack)	4
Placebo n=30	4 x PF-06650833 placebo tablets, QD, (Blister Pack)	4

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 and/or acetaminophen/paracetamol for pain control; and/or low dose oral corticosteroids (≤10 mg prednisone or equivalent per day). Methotrexate must have been dosed orally or, at equivalent doses parenterally (intramuscular (IM) or subcutaneous (SC), only; intravenous (IV) administration is not permitted) for at least 3 months prior to baseline (randomization) to establish inadequate response, 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, acetaminophen 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 5.7).

Statistical Methods:

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP) that will be maintained by the sponsor. The primary endpoint of the study is the change from baseline in the simplified disease activity index (SDAI) at 12 weeks. The primary analyses will include: Analysis of Covariance (ANCOVA) models adjusting for SDAI baseline value and Bayesian analyses of posterior distributions of the SDAI scores and placebo adjusted change from baseline. Missing values due to a subject dropping from the study for lack of efficacy or adverse event, will be handled by setting the SDAI score to nonresponsive (baseline observation carried

forward, BOCF). Missing values that occur while the subject is still enrolled (eg, due to a protocol deviation where the data were not collected), will be handled by the method of last observation carried forward (LOCF). The most recent data on each SDAI domain will be used for calculating the missing SDAI score. The statistical analysis will not include comparison between the PF-06650833 and tofacitinib arms.

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

At least one interim analysis (IA) for futility may be performed. The final number and timing of the IA(s) will be defined by the sponsor, but preliminarily one may be conducted at approximately 6 months after the randomization of the first subject and/or after at least 50% of the planned subjects, ie, approximately 100 subjects, have completed the twelve week active treatment phase.

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, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Protocol Activity	**Screening**	**Treatment Period**							**FU**	**FU/EOS**	**EW**[b]
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Study Day/Week[a]	**Days -28 to 0**	**Week 0**	**Week 1**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	
		Day 1/ Baseline	**Day 8**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	
Visit Window	**Days -28 to 0**	**±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[c]	X										
Medical history and prior non RA medication history	X										
History of Alcohol and Drug Abuse	X										
Height & Weight	X										
Vital Signs (Pulse, blood pressure), temperature[d]	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination[e]	X									X	
Targeted Physical Examination		X	X	X	X	X	X	X	X		X
ECG (12 lead)[f]	X	X	X					X		X	X
Chest X-ray[g]	X										
Laboratory Evaluations											
Blood Chemistry, Hematology[h]	X	X	X	X	X	X	X	X	X	X	X
Rheumatoid Factor (RF)	X	X						X			
C-Reactive Protein (hsCRP)	X	X	X	X		X		X		X	X
Erythrocyte Sedimentation Rate (ESR)[i]	X	X	X	X		X		X		X	X
Anti CCP Antibodies (ACPA)	X	X						X		X	X
Serum Ig (IgA, IgM, IgG, IgE)		X						X			X

Protocol Activity	Screening	Treatment Period							FU	FU/EOS	EW[b]
Visit Identifier	1	2	3	4	5	6	7	8	9	10	
Study Day/Week[a]	Days -28 to 0	Week 0	Week 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	
		Day 1/ Baseline	Day 8	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	
Visit Window	Days -28 to 0	±2 Days based on Week 0/Day 1 visit									
Urinalysis (including, protein creatinine, pH color, clarity, specific gravity) with microscopy (to be processed at central lab)[j]	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy test[k]	X	X	X	X	X	X	X	X	X	X	X
Contraception check	X	X	X	X	X	X	X	X	X	X	X
Serum FSH (WONCBP only)	X										
HBsAg, HbcAb, HBsAB and HCVAb [l]	X										
HIV testing[m]	X										
Tuberculosis test[n]	X										
CCI											

Protocol Activity	Screening	Treatment Period							FU	FU/EOS	EW[b]
Visit Identifier	1	2	3	4	5	6	7	8	9	10	
Study Day/Week[a]	Days -28 to 0	Week 0	Week 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	
		Day 1/ Baseline	Day 8	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	
Visit Window	Days -28 to 0	±2 Days based on Week 0/Day 1 visit									
CCI											
Efficacy assessments											
Tender/Painful Joint Count (68)	X	X		X		X		X		X	X
Swollen Joint Count (66)	X	X		X		X		X		X	X
Patient Assessment of Arthritis Pain (PAAP) VAS		X		X		X		X		X	X
Patient Global Assessment (PtGA) of Arthritis VAS		X		X		X		X		X	X
Physician Global Assessment (PhGA) of Arthritis[r]		X		X		X		X		X	X
Health Assessment Questionnaire – Disability Index (HAQ-DI)		X		X		X		X		X	X
SF-36 Version 2 (Acute)		X						X		X	X
FACIT-Fatigue		X						X		X	X
EQ-5D-3L		X						X		X	X
Log into IRT system	X	X	X	X		X				X	X
Investigational Product Dispensing		X	X[w]	X		X					
Randomization (after all screening procedures are complete and reviewed)[s]		X									

Protocol Activity	Screening	Treatment Period							FU	FU/EOS	EW[b]
Visit Identifier	1	2	3	4	5	6	7	8	9	10	
Study Day/Week[a]	Days -28 to 0	Week 0	Week 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	
		Day 1/ Baseline	Day 8	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	
Visit Window	Days -28 to 0	±2 Days based on Week 0/Day 1 visit									
Administration of PF-06650833, Placebo or Tofacitinib[t]		X	X	X	X	X	X	X			
Review of subject diary (review of subject dosing record), IP accountability and compliance check throughout the study[u]		X	X	X	X	X	X	X			X
Dispensing of subject diary		X	X	X	X	X	X				
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	X	X
Prior/Concomitant Medication & Treatments		X	→	→	→	→	→	→	→	X	X
Discharge from the study										X	X

Abbreviations: → = ongoing/continuous event; ACR = American College of Rheumatology; ACPA = Anti CCP Antibodies; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; EW = early withdrawal; ESR = Erythrocyte Sedimentation Rate; EQ-5D-3L = European Quality of Life – 5 Dimensions 3 Level; CCI [redacted] FACIT-Fatigue Scale = Functional Assessment of Chronic Illness Therapy fatigue scale; FSH = follicle stimulating hormone; FU = Follow-up; HAQ-DI = Health Assessment Questionnaire – Disability Index; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBsAb = hepatitis B surface antibody; HBcAb = hepatitis B core antibody; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; IgA, G, M, E = Immunoglobulin of the A, G, M, E isotypes; IGRA = interferon-gamma release assay; IP = investigational product; IRB = institutional review board; CCI [redacted] PAAP = Patient Assessment of Arthritis Pain;
PtGA = patient global assessment; PhGA = Physician Global Assessment; WONCBP = women of non-childbearing potential

a. Visits should occur when scheduled, within the time window indicated in the column headings. On study drug dosing days, assessments (including joint counts and questionnaires), and pre-dose blood collections are to be performed prior to dosing unless otherwise stated. Patient reported assessments, including PtGA and PAAP VAS measures and HAQ-DI questionnaires, should be performed prior to any other assessments. Additional unscheduled assessments should be performed as clinically indicated.

b. Any subject who prematurely withdraws from the treatment period should undergo the procedures for an early withdrawal visit and return for follow up visits as medically indicated in the opinion of the PI.

c. RA medications taken before and after informed consent are signed.

d. Vital Signs include: sitting blood pressure, pulse, and temperature (oral, temporal, tympanic or axillary same throughout the study), measured after approximately 5 minutes of rest.

e. Complete physical exam (PE) of major body systems Additional brief PE may be performed during the study at the investigator's discretion.

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).

g. Chest radiograph (posterior-anterior and lateral views are recommended, however local guidelines should be followed) is required at Screening. A chest X-ray or other appropriate diagnostic imaging modality (ie, CT or MRI) performed within 12 weeks prior to screening and read by a qualified radiologist with no evidence of current, active TB or previous inactive TB, general infections, heart failure or malignancy may substitute for the chest X-ray taken at Screening. Documentation of the official reading must be located and available in the source documentation.

h. Laboratory tests may be repeated once during the screening period; the last value will be used to determine eligibility. Single repeats of laboratory tests are inclusive of Blood Chemistry, Hematology, C-Reactive Protein (hsCRP), Erythrocyte Sedimentation Rate (ESR), Anti CCP Antibodies (ACPA) and Urinalysis. Fasting lipid profile will be asssessed at Baseline, Week 4 and Week 12 (samples must be collected after a minimum 6-hour fasting), and includes: fasting total cholesterol, LDL, HDL, triglycerides and apolipoproteins A-1 and B (and other lipoprotein tests potentially including particle size measurements). Laboratory tests at Weeks 6, 10, and 14 will only include standard blood chemistry panels (not hematology).

i. ESR will be analyzed locally using the Westergren method. ESR kits will be provided by the central laboratory. ESR results will be reported to the 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.

j. Collect pre-dose urine sample for central laboratory urinalysis and urine microscopy.

k. Required for women of childbearing potential that are not surgically sterilized or do not meet the definition of menopause as per the inclusion/exclusion criteria. Pregnancy test must be performed.as described in Section 7.3.4 and be negative prior to randomization on Day 1. A delay in randomization for WOCBP in order to collect the second pregnancy test within 5 days after the first day of the menstrual period will not be considered a protocol deviation (PD).

l. 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 negative, the subject will be excluded from the study.

m. Human immunodeficiency virus (HIV) testing is mandatory (unless local regulations prohibit mandatory testing); however reporting of results should be handled per local regulations.

n. Subjects with a positive documented IGRA TB test (eg, QuantiFERON®-TB GOLD (QFT-G) performed within 12 weeks prior to Screening are excluded. The specific IGRA method, or test, used should comply with local country-specific guidelines. The type (name) and results of the IGRA TB test must be known and located in source documentation. A subject who is currently being treated for either latent or active TB infection is to be excluded.

o. [redacted] CCI

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p. CCI [redacted]

q. CCI [redacted]

r. Physician assessment should be performed without knowledge of patient reported VAS assessments.

s. If the ANC is ≤2500/mm^3 at Screening, and the subject is eligible to enter the study, the ANC counts will need to be repeated prior to the randomization visit, and the ANC must be ≥1500/mm^3 for the subject to be eligible for randomization. A delay in randomization (ie, date of Visit 2) up to 14 days beyond the 28 day Screening window (total interval between Screening and Visit 2 must be ≤ 42 days) solely due to IP unavailability will not be considered a protocol deviation (PD).

t. 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.

u. Subject diary dispensed and/or collected. Subject diary, study compliance and investigational product administration are reviewed Visit 2-8.

v. CCI [redacted]

w. Only PF-06650833 will be dispensed at Week 1.

[redacted]

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 of developed regions with a 4-fold higher frequency in women than in men.[1] 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 patients tend to have more rapidly progressive disease and are less likely to respond to current therapy.[2] Of note, ACPA-mediated stimulation of inflammation has been shown to require both IgG receptor and Toll Like Receptor (TLR) receptor mediated signaling.[3]

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)[4] aims toward achieving the lowest possible level of arthritis disease activity (ideally, remission), minimizing joint damage, and enhancing physical function and quality of life. Disease-modifying antirheumatic drugs (DMARDs) are the standard treatments for RA. Conventional synthetic DMARDs (csDMARDs), such as MTX, 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 tumor necrosis factor - α (TNFα) inhibitors, is indicated when symptoms are not adequately controlled with csDMARDs. Additional approved therapeutics include tocilizumab (interleukin (IL)-6 receptor neutralizing antibody) and, in the US and more than 40 countries worldwide, tofacitinib (a small molecule pan-Janus kinase (JAK) inhibitor). Despite the considerable list of approved treatments for RA, there are significant numbers of patients who do not achieve remission or indeed adequate reduction in disease activity.

IL -1 receptor associated kinase 4 (IRAK4) is a serine, threonine kinase that serves as a key node in intracellular signaling downstream of the mydossome associated toll-like receptors (TLRs: TLR 1, 2, 4, 5, 6, 7, 8, 9 and 10) and the IL-1 family receptors (IL-1R, IL-18R and IL-33R). TLRs are cell surface receptors involved in activation of the innate immune system. The lipopolysaccharide (LPS) receptor, TLR4, unlike the other receptors listed, can signal via both IRAK4-dependent pathways and the IRAK4-independent, Toll/interleukin-1 receptor (TIR) domain-containing adapter inducing interferon-β (IFNβ) (TRIF) pathway.[5] Inhibition of IRAK4 blocks the production of cytokines such as type I interferons (IFN), the inflammatory cytokines IL-6, TNFα, and IL-1β and IL-12 that are key drivers of autoimmune and inflammatory diseases, including RA and Systemic Lupus Erythematosus (SLE).

Therefore, a key signaling molecule like IRAK4, which is downstream of IL-1R and TLRs would be an attractive therapeutic target for various diseases associated with dysregulated inflammation, such as RA.

1.1. Mechanism of Action/Indication

PF-06650833 is a selective, small molecule, reversible inhibitor of IRAK4 that is currently under development for the treatment of RA and Systemic Lupus Erthematosus (SLE).

1.2. Background and Rationale

1.2.1. Drug Development Rationale

PF-06650833 is a highly selective, small molecule inhibitor of IRAK4. IRAK4 is a key node in the signal transduction of many TLR-induced pro-inflammatory pathways. TLR signaling has also been implicated pre-clinically and clinically in RA, variously mediating inflammatory responses to damage associated molecular patterns (DAMPs) such as HMGB1, nucleic acids, extracellular matrix components and citrulline-modified self-antigens by cells of the immune system as well as synoviocytes. The results of this signaling process include release of the pro-inflammatory cytokines (IL-1β, IL-6, and TNFα) and matrix degrading proteases, all of which have been implicated in the ongoing inflammatory process of RA, release of chemokines to promote the recruitment of additional leukocytes into the joint space, and promotion of T and B cell maturation to maintain the autoimmune process.

Therefore, it is hypothesized that inhibition of IRAK4 may be beneficial as a treatment for RA.

1.2.2. Overview of Biopharmaceutics

PF-06650833 is a small molecule with high solubility and high permeability in nonclinical assays.

In the current study, the drug will be administered orally as manufactured modified release (MR) tablets. The tablets are manufactured with nominal dose strengths of 20 mg and 100 mg using small-size active pharmaceutical ingredient (API), and may be administered in multiple units to meet the needs of the study design.

1.3. Non-Clinical Experience with PF-06650833

1.3.1. Primary Pharmacology

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PF-06650833 is efficacious in in vitro and nonclinical in vivo assays of inflammation in RA. The compound potently inhibits the ability of immune complexes isolated from ACPA+ serum from RA patients to induce TNFα release from human macrophages, and the ability of TLR ligands and IL1β to induce the secretion of inflammatory cytokines and matrix metalloproteases in synovial fibroblasts from RA patients and healthy volunteers. It was also efficacious in the collagen-induced arthritis model.

1.3.2. Secondary Pharmacology and Safety Pharmacology

PF-06650833 was profiled in vitro against a broad panel of receptors, enzymes, ion channels and transporters in a broad ligand profile screen. These data indicate that PF-06650833 is highly selective for IRAK4, with little or no potential for off-target pharmacology.

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1.3.3. Non-Clinical Pharmacokinetics and Metabolism

Single dose PK studies with PF-06650833 were conducted after Intravenous (IV) and oral (PO) administration to male rats and dogs. CCI

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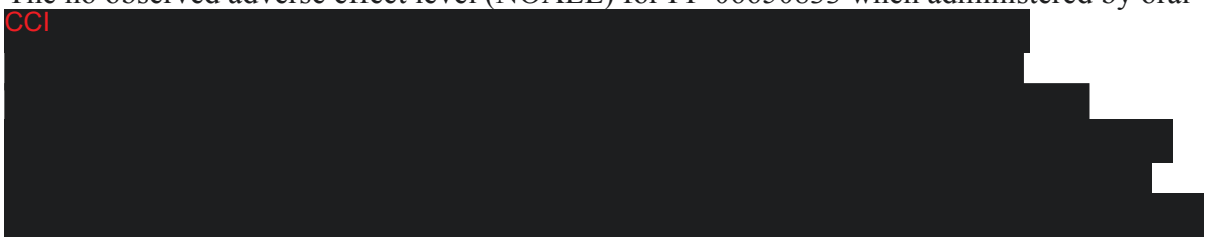
1.3.4. Non-Clinical Toxicology Studies with PF-06650833

PF-06650833 was negative for mutagenicity in bacterial reverse mutation assays. PF-06650833 did not induce micronuclei, in vivo, in polychromatic erythrocytes in peripheral blood of rats, at any dose tested. PF-06650833 absorbs in the Ultra Violet A (UVA) range but was not phototoxic in an in vivo assay.

The no observed adverse effect level (NOAEL) for PF-06650833 when administered by oral



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In conclusion, the results from the nonclinical pharmacology, pharmacokinetics and toxicology studies support the clinical testing of PF-06650833 in clinical trials in males and females (including women of childbearing potential with appropriate contraception) up to 3 months in duration.

Further information on the nonclinical properties of PF-06650833 may be found in the current PF-06650833 Investigator's Brochure.

1.4. Clinical Experience with PF-06650833

The safety and tolerability of PF-06650833 has been assessed in a development program that to date has included single and multiple dose studies in healthy volunteers. As of 01 April 2016 (the date of the last data cut-off), a Phase 1 single ascending dose study (Study B7921001) in healthy subjects is completed, and 2 Phase 1 studies in healthy volunteers are ongoing—Study B7921002, a multiple ascending dose study in healthy subjects, and Study B7921004, an open label single dose study to evaluate the pharmacokinetics (PK) of the MR tablets of PF-06650833 under fasted and fed conditions in healthy subjecs. Final data are available for Study B7921001 and are reflected in the discussion below. Clinical activities in Study B7921004 have completed, the database has been released, but the clinical study report is not yet available. Final clinical safety and preliminary PK data are therefore available for Study B7921004 and are reflected in the discussion below. Study B7921002 is still ongoing, with only preliminary, blinded safety, tolerability, and PK summary data available. Data for Study B7921002 are subject to modification with final database release. The results presented below (except as indicated) reflect data in the clinical databases as of 01 April 2016 (the date of the most recent database data cut-off).

As of 01 April 2016, a total of 127 healthy adult subjects have received 1 or more doses of PF-06650833 or blinded therapy in the 3 Phase 1 clinical studies conducted to date. Study B7921001 explored doses of an extemporaneously prepared immediate release (IR) formulation of PF-06650833 up to 6000 mg under fed (high fat meal) conditions. Single doses of an extemporaneously prepared MR formulation of PF-06650833 up to 300 mg under fasted conditions were also tested in this study. As of the date of the data cut-off, Study

B7921002 has explored repeat doses of an extemporaneously prepared IR formulation of PF-06650833 up to 1000 mg QID under fed (standard meal) conditions, and was in the midst of a cohort exploring repeat doses of 300 mg MR tablets QD, also under fed (standard meal) conditions. This latter cohort has since completed, but the additional data are not included in the discussions below. Study B7921004 has tested single doses of 20 mg, 100 mg, and 400 mg of MR tablets of PF-06650833 under fasted and fed (high fat meal) conditions.

PF-06650833 was generally safe and well tolerated in clinical studies to date in healthy subjects. There were no deaths, serious adverse events, or discontinuations due to serious adverse events in any study conducted to date. Adverse events were generally few and mild – moderate in severity. The most common adverse effects were headache and an assortment of gastrointestinal effects (principally, abdominal pain, nausea, and vomiting) that have been self-limited. Transient increases in liver enzymes, most commonly of ALT, were observed, without clear association with dose, and no cases have satisfied Hy's law criteria (that would be suggestive of drug-induced liver injury). There was no clear association of adverse event incidence or severity, or laboratory (liver function) abnormalities with increasing dose, and no dose-limiting adverse effects have been identified in the escalating single and multiple dose Phase 1 studies. None of these effects preclude the safe exploration of the safety, tolerability, PK, pharmacodynamics (PD), and efficacy in patient populations.

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There have been no clinical or laboratory signs of adverse effects on renal function in any

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More detailed information on the clinical experience with PF-06650833 can be found in the current version of the PF-06650833 Investigator's Brochure.

1.4.1. Pharmacokinetic Data with PF-06650833

1.4.1.1. Pharmacokinetics in B7921001 (Single Ascending Dose Study)

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1.4.1.2. Preliminary Pharmacokinetics Data in B7921002 (Multiple Ascending Dose Study)

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and placebo have been proposed for this study in order to explore the dose – response relationship of PF-06650833 in RA subjects and to underwrite dose selection for future clinical trials. The doses are selected to encompass a broad range of targeted IRAK4 inhibition to support hypothesis -testing of the clinical efficacy of PF-06650833 in RA, and to detect a dose response and estimate the dose-response curve.

The MR tablets being used in the current study are the same as in the Phase 1 multiple ascending dose study and the MR PK study (Studies B7921002 and B7921004, respectively). The doses of PF-06650833 in this study will be administered once daily in the morning. To minimize PK and PD variability due to the impact of food intake, PF-06650833 should be administered under fasted conditions (minimally 2 hour fasting prior to and after dosing) in this study.

Steady-state exposures of PF-06650833 were projected based on a population PK model constructed using the data for 20 mg, 100mg, and 400 mg MR tablets administered under a fasted state from the Study B7921004, and assuming time-linear PK as observed in the multiple ascending dose study (Study B7921002). A PK model incorporating transit compartments for absorption to describe the prolonged absorption and assuming dose-dependent saturable absorption adequately described the single dose MR PK data. The projected steady-state exposures are presented in Table 4, below.

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The additional two doses of 60 and 200 mg have been selected to help define the dose-response curve to support optimal dose selection in next stage confirmatory trials.

Overall, the currently proposed doses of PF-06650833 of 20 mg, 60 mg, 200 mg and 400 mg MR tablets QD dosed under fasted conditions will provide adequate exposures and IRAK4 inhibition over a wide dose range for testing the clinical efficacy, safety and tolerability of PF-06650833 to support future clinical development. CCI

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dose, and no dose-limiting adverse effects have been identified in the escalating dose Phase 1 studies. Transient increases in liver enzymes, most commonly of alanine aminotransferase (ALT), have been observed, without clear association with dose. None of these effects preclude the continued exploration of the safety, tolerability, PK, PD, and efficacy of PF-06650833 in patient populations.

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During this study, urine will be monitored by urinalysis and microscopic examination. Clinically significant effects on renal function will be monitored by adverse event reporting, physical examination, and standard clinical laboratory analyses including urinalysis and urine microscopy (as have been routinely performed in clinical trials with PF-06650833 to date).

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As noted in the Dose Rationale section, the doses proposed in this study (up to 400 mg PF-06650833 MR tablets QD) has a reasonable expectation to be safe and well-tolerated based upon accumulated clinical data to date, and to provide an adequate test of the PD activity of PF-06650833. Thus, the overall benefit-risk for PF-06650833 for subjects participating in this clinical trial remains favorable.

1.7. Background on Tofacitinib Immediate Release Formulation (Used as Active Control)

Tofacitinib was approved on 06 November 2012 in the United States at a dose of 5 mg twice daily (BID) for the treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to MTX. As of 05 November 2015, tofacitinib 5 mg BID is approved as 2nd line therapy for the treatment of adults with moderate to severe RA in 45 countries and marketed in 29 countries worldwide including the United States, Canada, Switzerland, Australia and Japan. Tofacitinib 10 mg BID is also approved for the treatment of RA in 3 countries (Switzerland, Russia, and Botswana). It may be used in combination with MTX or other non-biologic disease modifying antirheumatic drugs (DMARDs).

Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome.[7] In kinase assays, tofacitinib, inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TyK2). In cellular settings where JAK kinases signal in pairs, tofacitinib (also known as CP–690,550) preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2.[8] Inhibition of

JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including IL -2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, development, homeostasis, proliferation, and function; therefore, inhibition of their signaling may result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and IFNγ.[9 10] At higher exposures, inhibition of erythropoietin, prolactin, and other hormones can occur via inhibition of JAK2 signaling.

Phase 2 and 3 studies in the RA development program demonstrated that tofacitinib IR 5 mg twice daily (BID) consistently reduces signs and symptoms of RA, improves physical function and other subject-reported outcomes such as fatigue, pain and health-related aspects of quality of life in subjects with moderate to severe RA. Combined with its inhibition of the progression of structural damage, the development program has demonstrated tofacitinib as an effective targeted synthetic DMARD in treating RA.[11, 12] Ongoing long-term extension and Phase 3b/4 post authorization safety studies are aimed to demonstrate sustained efficacy and a consistent safety profile as seen in the Phase 2 and 3 controlled clinical trials.

Data from completed and ongoing clinical studies demonstrate tofacitinib's manageable safety profile. As of April 2014, over 10,000 subjects have received at least 1 study dose of oral tofacitinib in either a randomized clinical study or a long-term extension (LTE) study in multiple indications. Approximately 6100 adult RA subjects have been exposed to tofacitinib with greater than 16,800 subject years of exposure in Phase 2, 3, 3B/4 post-authorization and LTE studies. Important safety risks that have been observed with the oral use of tofacitinib in the Phase 2 and Phase 3 studies include serious and other important infections, including tuberculosis (TB) and herpes zoster; the potential for malignancies including lymphoma; and the potential for gastrointestinal (GI) perforations. Subjects receiving tofacitinib are at increased risk of nonmelanoma skin cancers (NMSC). Cardiovascular disease and interstitial lung disease (ILD) are findings seen in RA subjects receiving tofacitinib, and are recognized comorbidities for RA. Changes in laboratory values have also been observed including a dose-dependent increase in low density lipoprotein (LDL) cholesterol and dose-dependent decreases in neutrophils and hemoglobin. Other laboratory changes observed with tofacitinib treatment include decreases in lymphocytes and increases in transaminases, serum creatinine, and creatine kinase (CK). Laboratory changes observed with tofacitinib treatment are manageable; recovery of laboratory changes upon discontinuation of tofacitinib treatment is characteristically observed. Based on nonclinical data, there is the potential for tofacitinib to have effects on pregnancy and the fetus. Since there are no controlled studies in pregnant women, tofacitinib should not be used in women of childbearing potential (WOCBP) without the use of appropriate contraception as defined by individual protocols, women who are pregnant or intend to become pregnant, or women who intend to breastfeed postpartum. Use of tofacitinib in any of these patients should be limited to situations in which the potential benefit justifies the potential risk to the mother, fetus or neonate. Based on lack of effect on male fertility, sperm, or the testes, no special precautions are necessary for male patients administered tofacitinib. More details of identified risks with tofacitinib in RA are presented in the current version of the Tofacitinib Investigator's Brochure.

Based on the most recent data from clinical trials and post-marketing experience, the overall benefit-risk profile of the tofacitinib IR formulation remains favorable (refer to current Tofacitinib Invesitigator's Brochure for further details).

1.8. Study Rationale

Study B7921005 is the first study of PF-06650833 in subjects with RA. It is designed to evaluate the efficacy and safety of PF-06650833 in patients with moderate – severe, active, ACPA+ RA who have had an inadequate response to MTX (and, potentially, other DMARDs). Up to approximately 50% of subjects may have also received one (and only one) approved TNF-inhibiting biologic agent administered in accordance with its labeling recommendations. The TNF-inhibiting biologic could have been discontinued due to its being deemed inadequately effective and/or not tolerated as defined, for the purpose of this study, by the Investigator's and subject's opinions that the subject did not experience adequate benefit from the anti-TNF plus the presence of sufficient residual disease activity to meet the entry criteria. The anti-TNF biologic could also have been discontinued due to lack of continued access. Clinical evaluations of RA in this study will include assessments of the American College of Rheumatology (ACR) Core Data Set (Tender / Painful Joint Count (TJC); Swollen Joint Count (SJC); patient's assessment of disease activity; health professional's assessment of disease activity; patient's assessment of physical function; patient's assessment of pain; and acute phase reactants (erythrocyte sedimentation rate (ESR)/high sensitivity C-reactive protein (hsCRP))), from which various composite indices of disease activity may be derived (such as the simplified disease activity index (SDAI) and the Disease Activity Score (DAS)). The effect of PF-06650833 on general health status will be evaluated with the Medical Outcome Survey Short Form – 36, Acute (SF-36, Acute).

The study also will explore the efficacious dose range for PF-06650833 in RA to support dose selection for future clinical trials. Doses will cover a 20-fold range from 20 mg modified release (MR) tablets once daily (QD) to 400 mg MR tablets QD. CCI [redacted]

The study will include tofacitinib (5 mg twice daily) as an active control where acceptable to local regulatory authorities and ethics committees. Tofacitinib is a newer csDMARD marketed in many countries worldwide for the treatment of RA. It was selected as an active control since it is effective in the same populations that are being targeted with PF-06650833 and, as a small molecule; it is believed to be more comparable in terms of dosing regimen and response characteristics. Moreover, the Sponsor has an extensive database of subject level information from tofacitinib clinical trials in similar populations. These provided the basis for sample and effect size estimates for this study. Inclusion of tofacitinib in the current study will therefore increase the confidence in the conduct of and data from this study. There are also operational advantages for using an orally administered control agent compared to a parenterally administered biologic DMARD.

1.9. Single Reference Safety Documents

Additional information for this compound, PF-06650833, may be found in the single reference safety document (SRSD), which for this study is the current version of the PF-06650833 Investigator's Brochure. The SRSD for the active control agent in this study is the current version of the Tofacitinib Investigator's Brochure.

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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

2.1. Primary Objectives

- To evaluate the efficacy of PF-06650833 at 12 weeks, in subjects with moderate -severe active RA who have had an inadequate response to methotrexate.

2.2. Secondary Objectives

- To assess the safety of PF-06650833 for 12 weeks in subjects with RA.
- To explore the dose – response relationship for efficacy in RA.
- To assess other signs of clinical efficacy over 12 weeks.
- To assess the effect of PF-06650833 on patient reported outcome measurements.

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- CCI [redacted]

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2.4. Primary Endpoints

- Change from baseline in the SDAI at Week 12.

2.5. Secondary Endpoints

Secondary Clinical Efficacy Endpoints

- Change from baseline in SDAI at Weeks 4 and 8.
- SDAI low disease activity score (LDAS) and remission rates at 4, 8, and 12 weeks.
- DAS28 LDAS and remission rates at 4, 8, and 12 weeks.

The following will also be calculated at Weeks 4, 8, and 12:

- Change from baseline DAS28-3, DAS28-3 (CRP), DAS28 -4 (ESR), and DAS28-4 (CRP).
- ACR 20, ACR 50, and ACR 70 responder rates.
- Change from baseline in the Tender/Painful and Swollen Joint Counts.
- Change from baseline in hsCRP.
- Change from baseline in the Physician's Global Assessment of Arthritis (PhGA).

Safety Endpoints

- Safety and tolerability of PF-06650833: vital signs (blood pressure, pulse, and temperature), laboratory tests, Adverse Events (AEs) and Serious Adverse Events (SAEs), 12-lead ECG.
- Urinalysis including urine microscopy.

Secondary Patient Reported Outcome Endpoints

- Change from baseline in the Patient's Assessment of Arthritis Pain (PAAP) VAS and Patient Global Assessment of Arthritis (PtGA) VAS at Week 4, 8, 12.

- Change from baseline in the HAQ-DI at Week 4, 8, and 12.
- Change from baseline in the SF-36v.2 (acute) 8 Domain scores and Physical Component Score (PCS) and Mental component score (MCS) at Week 12.
- Change from baseline in the EQ-5D-3L score at Week 12.
- Change from baseline in the FACIT-F total score at Week 12.

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3. STUDY DESIGN

This is a Phase 2, multicenter, randomized, double-blind, double dummy, placebo- and active-controlled, parallel group study to assess the efficacy and safety of PF-06650833 at Week 12 in subjects with moderate-severe active, ACPA positive RA who have had an inadequate response (IR) to methotrexate (up to approximately 50% of subjects may have also received one (and only one) approved TNF-inhibiting biologic agent administered in accordance with its labeling recommendations. The TNF-inhibiting biologic could have been discontinued due to its being deemed inadequately effective and/or not tolerated as defined, for the purpose of this study, by the Investigator's and subject's opinions that the subject did not experience adequate benefit from the anti-TNF plus the presence of sufficient residual disease activity to meet the entry criteria. The anti-TNF biologic could also have been discontinued due to lack of continued access.

After an up to 28 day screening period, eligible subjects in regions where tofacitinib's inclusion as an active control is accepted by local regulatory authorities and ethics committees will be randomized in to receive 1 of 4 dose regimens of PF-06650833 (400 mg, 200 mg, 60 mg, 20 mg MR tablets QD), tofacitinib 5 mg BID, or placebo (matching MR tablets for PF-06650833 QD and matching tofacitinib tablets BID) in a 6 : 6 : 6 : 5 : 5 : 5 ratio in a blinded fashion (Figure 2). In order to maintain the blind and minimize bias, all subjects will receive the same number and types of tablets each day. Subjects assigned to PF-06650833 will all take 4 MR tablets, consisting of a mixture of active PF-06650833 and/or matching placebo tablets dispensed in a blister pack, once per day. In countries in which regulatory authorities and ethics committes accept the use of tofacitinib as an active control in this trial, subjects also will take 1 matching tofacitinib placebo tablet (dispensed in bottles) BID. Subjects assigned to receive tofacitinib will take 1 tablet (dispensed in bottles) of tofacitinib citrate (5 mg) BID. These subjects will also take 4 MR tablets of placebo matching PF-06650833 MR tablets (dispensed in a blister pack) once daily (Table 5). In regions where tofacitinib's inclusion in this study as an active control is not accepted by local regulatory authorities and ethics committees, subjects will only be randomized to PF-06650833 or matching placebo (dispensed in blister packs) and will not receive bottles of tofacitinib or matching placebo (Table 6).

Figure 2. Study Design Schematic

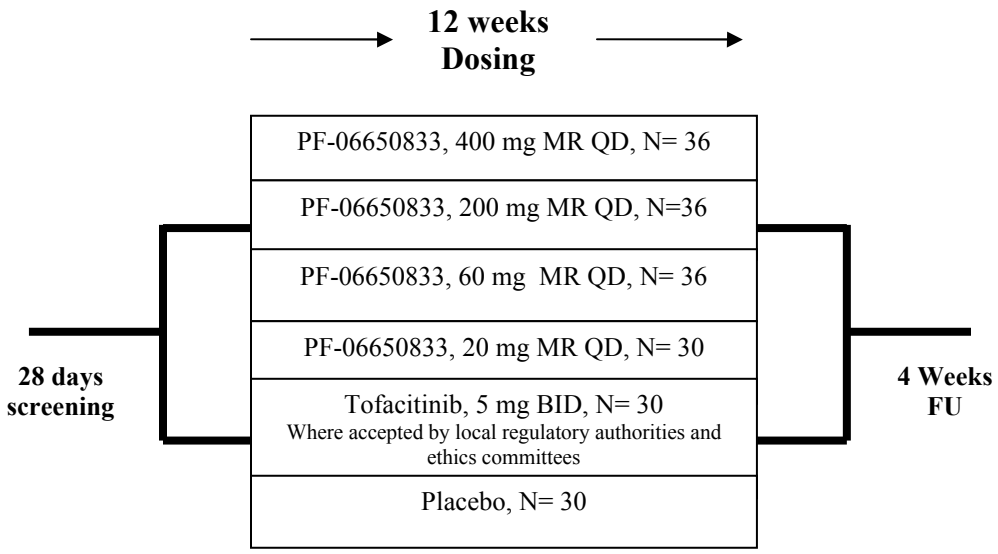

Table 5. Dosing and Administration of Investigational Products in Regions Where the Use of Tofacitinib in This Study is Acceptable to Regulatory Authorities and Ethics Committees

Treatment group (n)	Treatment PF-06650833 or matching placebo (packaging)	Tofacitinib or matching Placebo (Packaging)	Total number tablets per day
PF-06650833 400 mg, QD n=36	4 x100 mg PF-06650833 tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6
PF-06650833 200 mg, QD n=36	2 x 100 mg PF-06650833 + 2 x PF-06650833 placebo tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6
PF-06650833 60 mg, QD n=36	3 x 20 mg PF-06650833 + 1 PF-06650833 placebo tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6
PF-06650833 20 mg, QD n=30	1 x 20 mg PF-06650833 + 3 PF-06650833 placebo tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6
Tofacitinib 5 mg, BID n=30	4 x PF-06650833 placebo tablets, QD, (Blister Pack)	1 x 5 mg tofacitinib, BID, (Bottle)	6
Placebo n=30	4 x PF-06650833 placebo tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6

Table 6. Dosing and Administration of Investigational Products in Regions Where the use of Tofacitinib as an Active Control in This Study is not Acceptable to Regulatory Authorities and Ethics Committees

Treatment group (n)	Treatment PF-06650833 or matching placebo (packaging)	Total number tablets per day
PF-06650833 400 mg, QD n=36	4 x100 mg PF-06650833 tablets, QD, (Blister Pack)	4
PF-06650833 200 mg, QD n=36	2 x 100 mg PF-06650833 + 2 x PF-06650833 placebo tablets, QD, (Blister Pack)	4
PF-06650833 60 mg, QD n=36	3 x 20 mg PF-06650833 + 1 PF-06650833 placebo tablets, QD, (Blister Pack)	4
PF-06650833 20 mg, QD n=30	1 x 20 mg PF-06650833 + 3 PF-06650833 placebo tablets, QD, (Blister Pack)	4
Placebo n=30	4 x PF-06650833 placebo tablets, QD, (Blister Pack)	4

Up to approximately 230 subjects may be randomized globally into the study to ensure at least approximately 198 subjects complete 12 weeks of active dosing (assuming a dropout rate of approximately 15%). Since the use of tofacitinib in this study may be not be acceptable by regulatory authorities/ethics committess in all countries, achieving full randomization into the tofacitinib arm may prove logistically challenging. Since the tofacitinib arm is serving as an active control for the study, enrollment of approximately 20-30 subjects into that arm will be acceptable. Subjects will participate in this study for approximately 20 weeks. This includes an up to 28 day screening period, a 12 week treatment period, and a 4 week follow-up period.

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 NSAIDs, COX-2 inhibitors, allowed opioids and/or acetaminophen/paracetamol for pain control; and/or low dose oral corticosteroids (≤10 mg prednisone or equivalent per day). Methotrexate must have been dosed orally or, at equivalent doses, parenterally (IM or SC, only; IV administration is not permitted) for at least 3 months (prior to baseline randomization) to establish inadequate response, 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, acetaminophen 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 5.7).

4. SUBJECT ELIGIBILITY CRITERIA

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

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

4.1. Inclusion Criteria

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

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

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

3. Male and female (including WOCBP) subjects 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 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 (MTX-IR) (see below).

7. 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 fulfills 1 of the following 2 criteria at Screening:

    - 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 once within 14 days and, if the repeat hsCRP concentration is >7 mg/L will be eligible to enroll into the study provided all other inclusion/exclusion criteria are met.

    - Erythrocyte sedimentation rate (ESR) (Westergren method) >28 mm/hr;

8. Meets Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA (see Appendix 3).

9. Subjects must be seropositive at the time of randomization (ACPA positive). If subjects are RF+ but ACPA- at screening, the subject may be carried to randomization at risk. The ACPA must be repeated and be positive before the targeted Randomization Visit.

10. Subjects must have been taking oral or equivalent parenteral (IM or SC, only; IV administration is not permitted) MTX for at least 3 months (prior to baseline randomization) 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 between 15 and 25 mg weekly (inclusive). Doses between 10 and 15 mg weekly are allowed only in the presence of documented intolerance to or toxicity from higher doses (See Section 5.7.1 for guidance on required MTX doses and permitted concomitant medications).

    - 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 study medication or oral folinic acid (≥5 mg once per week) supplementation for at least 21 days 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. 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 (and only one) approved TNF-inhibiting biologic agent administered in accordance with its labeling recommendations. The TNF-inhibiting biologic could have been discontinued due to its being deemed inadequately effective and/or not tolerated as defined, for the purpose of this study, by the Investigator's and subject's opinions that the subject did not experience adequate benefit from the anti-TNF plus the presence of sufficient residual disease activity to meet the entry criteria. The anti-TNF biologic could also have been discontinued due to lack of continued access. The anti-TNF s should have been discontinued for a minimum of the washout period defined as follows (biosimilars of the below agents should be considered the same as the originators):

    - entanercept (Enbrel®), adalimumab (Humira®): 6 weeks.
    - infliximab (Remicade®), golimumab (Simponi®): 10 weeks.
    - certolizumab pegol (Cimzia®): 12 weeks.

12. Subjects receiving non-prohibited concomitant medications 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.

4.2. Exclusion Criteria

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

1. Investigational 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 4 weeks or 5 half-lives (whichever is longer) prior to study entry.

3. Female subjects who are pregnant or wish to become pregnant, breastfeeding female subjects; male subjects with partners currently pregnant; male subjects able to father children and female subjects of childbearing potential who are unwilling or unable to use at least 1 highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days (90 days for male subjects) after the last dose of investigational product.

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

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

6. Subjects with any of the following infections or infections history:

    a. Any infection requiring treatment within 2 weeks prior to screening (Visit 1).

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

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

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

    e. Subjects will be screened for HIV (unless local regulations prohibit mandatory testing). Subjects who test positive for HIV will be excluded from the study.

f. 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 negative, the subject will be excluded from the study.

g. Subjects with clinically significant active hepatic disease or hepatic impairment by laboratory assessment.

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.

7. Evidence of active or latent, untreated or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined by the following:

   - A positive QuantiFERON®-TB Gold (QFT-G) test performed at or within the 3 months prior to Screening;

   or

   - A chest radiograph (taken at or within the 3 months prior to Screening) with changes suggestive of active TB infection;

   Subject who is currently being treated for either latent or active TB infection is to be excluded.

   Subjects with prior active tuberculosis (except for multi drug resistant TB) that has no current evidence of active disease and has completed an adequate course of therapy for active tuberculosis (a multi-drug regimen recognized by the World Health Organization to which the organism has demonstrated appropriate sensitivity) has a chest radiograph that is negative for active disease, and has a negative QFT-G are eligible; the chest radiograph must be obtained at screening or, if previously performed and documented, within 3 months prior to screening. Subjects that have an indeterminate QFT-G may have QFT-G test repeated and, will be eligible if the repeat (QFT-G) test is negative at time of randomization.

8. Subjects may not receive any live/attenuated vaccine from 30 days prior to screening, during the course of the study, or for 30 days after the last dose of study medication. Subjects who have current routine household contact with children who have received varicella or oral polio vaccine within 2 months of first study dose are also excluded,

9. History of any lymphoproliferative disorder (such as 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.

10. Subjects treated with prohibited medications will be excluded (see Section 5.7.2).

11. Have a history of a major organ transplant (eg, heart, lung, kidney and liver) or hematopoietic stem cell/marrow transplant.

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

13. Known history of diverticulitis or symptomatic diverticulosis, perineal abscess or fistulae.

14. Subjects with malignancy or history of malignancy (including 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.

15. Pre-existing chronic autoimmune disease (eg, inflammatory bowel disease, SLE, moderate-severe atopic dermatitis, dermatomyositis) other than RA. Secondary Sjogren's Syndrome (due to RA) may be included.

16. Subjects with fibromyalgia will be excluded.

17. Major surgery within 4 weeks of screening or scheduled to occur during the study, excluding diagnostic surgery.

18. Previous treatment with total lymphoid irradiation.

19. Subjects with any condition possibly affecting oral drug absorption (eg, bariatric/obesity surgery (such as gastric bypass or gastric banding), gastrectomy, or clinically significant diabetic gastroenteropathy).

20. Screening 12-lead ECG that demonstrates clinically relevant abnormalities (eg, QTc >450 msec or a QRS interval >120 msec) which may affect subject 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.

21. Subjects with an oral, tympanic, temporal, or axillary temperature of 38°C or higher at baseline.

22. Renal disease manifested by eGFR <80 mL/min per 1.73 m^2 (based on MDRD calculation), creatinine >1.5 X ULN, proteinuria 500 mg/day (or spot urine albumin to creatinine ratio ≥3mg/mmol or ≥30 mg/g)). (Sites may use either MDRD or Cockroft/Gault methods for estimating GFR for local, real-time monitoring of subject safety, provided the same method is used for a subject throughout the study. However, the eGFR derived by the Central Laboratory using the MDRD method will be the definitive value entered into the clinical database and used for adverse event reporting).

23. Presence of any of the following laboratory abnormalities at screening or within the 3 months prior to first study dose:

    - Alanine aminotransferase (ALT) or asparatate aminotransferease (AST) levels ≥1.5 x the upper limit of normal (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.

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

    - Absolute lymphocyte count of <0.5 x 10^9/L (<500/mm^3).

    - Absolute white blood cell (WBC) count of < 3.0 x 10^9/L (<3000/mm^3).

    - Hemoglobin <9.0 g/dL (90 g/L).

    - Thrombocytopenia, as defined by a platelet count <100 x 10^9/L (< 100,000/mm^3) at screening visit or within the 3 months prior to first study dose.

    - CCI [redacted]

Screening laboratory tests with abnormal results may be repeated once to confirm abnormal results. If results return to normal protocol acceptable limits within the 4-week screening period, the subject may enter the study.

24. Grade 3 or greater laboratory abnormality based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 toxicity scale except for the following that are allowed:

    - Grade 3 prothrombin time (PT) secondary to warfarin treatment.

    - Grade 3 partial thromboplastin time (PTT) due to lupus anticoagulant and not related to liver disease or anti-coagulant therapy.

4.3. Randomization Criteria

Subjects must meet all inclusion/exclusion criteria as well as all criteria for concomitant medications (including stability criteria) at time of randomization.

4.4. Lifestyle Requirements

4.4.1. Contraception

In this study, fertile male subjects and female subjects who are of childbearing potential as applicable to the study will receive PF-06650833 or tofacitinib, both of which have been associated with a potential for teratogenicity in rat embryofetal development studies. Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use at least 1 method of highly effective contraception throughout the study and for at least 28 days (90 days for male subjects) after the last dose of PF-06650833. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected at least 1 appropriate method 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 1 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 the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner. Use of contraception methods must be consistent with local medical, Ethics Committee, and Regulatory Authority guidelines.

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

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

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

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

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

In addition to the 1 highly effective method of contraception selected from the list above, 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 90 days after the last dose of PF-06650833.

4.5. Sponsor's Qualified Medical Personnel

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

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

5. STUDY TREATMENTS

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

For this study, the investigational product(s) are PF-06650833 and tofacitinib citrate. 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 and the date of birth of the subject. The site personnel will then be provided with a treatment assignment and dispensable unit (DU) or container number when drug is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number and DU or container number assigned. The confirmation report must be stored in the site's files.

There is a 24-hour-a-day, 365-days-a-year IRT helpdesk available for any questions or issues. The study specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

Note: The IRT is the source of the subject number. The IRT system will provide the subject number at the end of the first IRT subject transaction.

A subject will be randomized to one of 6 treatment sequences: 20 mg PF-06650833 MR tablet QD: 60 mg PF-06650833 MR tablet QD; 200 mg PF-06650833 MR tablet QD; 400 mg PF-06650833 MR tablet QD; tofacitinib 5 mg BID; placebo (for both PF-06650833 and tofacitinib). In those regions in which tofacitnib may not be used as an active control, the tofacitinib cohort (and corresponding placebo allocations) will be eliminated. Randomization will be balanced across the treatment groups with respect to prior exposure to a TNFα inhibitor. Since the use of tofacitinib in this study may be not be acceptable by regulatory authorities/ethics committess in all countries, achieving full randomization into the tofacitinib arm may prove logistically challenging. Since the tofacitinib arm is serving as an active control for the study, enrollment of approximately 20-30 subjects into that arm will be acceptable.

5.2. Breaking the Blind

This is a double blind, double dummy study. At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be either a manual or an electronic process. Blinding codes should be broken only in emergency situations for reasons of subject safety. Whenever possible, the investigator or subinvestigator consults with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

5.3. Subject Compliance

Subject compliance will be verified by the accounting of study medication at each visit. When study medication is administered at the research facility, it will be administered under the supervision of study personnel. Compliance of the study medication will be monitored by the accounting of unused medication returned by the subject. Subjects will be directed to bring any used and unused bottles and diaries to each visit after randomization. The number of tablets issued minus the number of tablets returned will be used to calculate the number of tablets taken and compliance. Compliance will be documented on the source record. If compliance is <80%, the investigator or designee is to counsel the subject and ensure steps are taken to improve compliance. Subjects, who are less than 80% compliant with the dosage regimen for any two consecutive visit periods during the study, will be withdrawn from the study.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

Blinded PF-06650833 and its matched placebo will be provided as MR tablets for oral administration. The 20 mg, 100 mg MR tablets and their matching placebos will be supplied in blisters and labeled according to local regulatory requirements. Tablets are described in

the table below. The abbreviations CR (controlled release) and MR (modified release) tablets are synonymous for this protocol. Tofacitinib citrate tablets described in the table below are immediate release formulations.

CCI [redacted]

Total Daily Dose Dose	Number of Tablets	Packaging
PF-06650833 400 mg, QD	4 x100 mg PF-06650833 tablets	Blister
PF-06650833 200 mg, QD	2 x 100 mg PF-06650833 + 2 x PF-06650833 placebo tablets	Blister
PF-06650833 60 mg, QD	3 x 20 mg PF-06650833 + 1 PF-06650833 placebo tablets	Blister
PF-06650833 20 mg, QD	1 x 20 mg PF-06650833 + 3 PF-06650833 placebo tablets	Blister
PF-06650833 PBO, QD	4 x PF-06650833 placebo tablets	Blister
Tofacitinib 5 mg, BID	2 x 5 mg tofacitinib tablet	Bottle
Placebo for Tofacitinib 5 mg, BID	2 x tofacitinib placebo tablets	Bottle

When received by the pharmacy, PF-06650833 20 mg, 100 mg and matching placebo tablets and tofacitinib 5 mg or matching placebo tablets will be in containers that will sufficiently blind all site staff to contents.

In regions where tofacitinib's inclusion as an active control in this study is not accepted by local regulatory authorities and ethics committees, subjects will only be randomized to PF-06650833 or matching placebo.

5.4.2. Preparation and Dispensing

The study medication should be dispensed using a drug management system at each dispensing visit indicated in the Schedule of Activities. Each dispensing visit will provide sufficient study medication 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 1.

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. It will be witnessed by a second qualified dispensing agent. Dispensing will be via a unique container numbers on packaged goods. 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.

5.4.3. Administration

In order to maintain the blind and minimize bias, all subjects will receive the same number and types of tablets each day as described in the Tables 7 and 8. Subjects assigned to PF-06650833 will all take 4 MR tablets, consisting of a mixture of active PF-06650833 and/or matching placebo tablets dispensed in a blister pack, once per day. In countries in which regulatory authorities and ethics committes accept the use of tofacitinib as an active control in this trial, subjects also will take 1 matching tofacitinib placebo tablet (dispensed in bottles) BID. Subjects assigned to receive tofacitinib will take 1 tablet (dispensed in bottles) of tofacitinib citrate (5 mg) BID. These subjects will also take 4 MR tablets of placebo matching PF-06650833 MR tablets (dispensed in a blister pack) once daily. In regions where tofacitinib's inclusion in this study as an active control is not accepted by local regulatory authorities and ethics committees, subjects will only be randomized to PF-06650833 or matching placebo (dispensed in blister packs) and will not receive bottles of tofacitinib or matching placebo (Table 8).

Table 7. Treatment Groups in Regions Where Tofacitinib use in This Study is Acceptable to Regulatory Authorities and/or Ethics Committees

Treatment group (n)	Treatment PF-06650833 or matching placebo (packaging)	Tofacitinib or matching Placebo (Packaging)	Total number tablets per day
PF-06650833 400 mg, QD n=36	4 x100 mg PF-06650833 tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6
PF-06650833 200 mg, QD n=36	2 x 100 mg PF-06650833 + 2 x PF-06650833 placebo tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6
PF-06650833 60 mg, QD n=36	3 x 20 mg PF-06650833 + 1 PF-06650833 placebo tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6
PF-06650833 20 mg, QD n=30	1 x 20 mg PF-06650833 + 3 PF-06650833 placebo tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6
Tofacitinib 5 mg, BID n=30	4 x PF-06650833 placebo tablets, QD, (Blister Pack)	1 x 5 mg tofacitinib, BID, (Bottle)	6
Placebo n=30	4 x PF-06650833 placebo tablets, QD, (Blister Pack)	1 tofacitinib matching placebo, BID, (Bottle)	6

Table 8. Treatment Groups in Regions Where Tofacitinib use in This Study is not Acceptable to Regulatory Authorities and/or Ethics Committees

Treatment group (n)	Treatment PF-06650833 or matching placebo (packaging)	Total number tablets per day
PF-06650833 400 mg, QD n=36	4 x100 mg PF-06650833 tablets, QD, (Blister Pack)	4
PF-06650833 200 mg, QD n=36	2 x 100 mg PF-06650833 + 2 x PF-06650833 placebo tablets, QD, (Blister Pack)	4
PF-06650833 60 mg, QD n=36	3 x 20 mg PF-06650833 + 1 PF-06650833 placebo tablets, QD, (Blister Pack)	4
PF-06650833 20 mg, QD n=30	1 x 20 mg PF-06650833 + 3 PF-06650833 placebo tablets, QD, (Blister Pack)	4
Placebo n=30	4 x PF-06650833 placebo tablets, QD, (Blister Pack)	4

5.4.3.1. PF-06650833 MR Tablets and Matching Placebo

All tablets are for oral administration.

PF-06650833 MR tablets should be taken under fasted conditions (minimally 2 hours after the last food consumption and 2 hours prior to the next meal consumption), but preferably should be taken consistently in the same manner and at the same time each day. The exception will be on study visit days when subjects will be instructed to refrain from dosing at home, and will take the study medication at the clinic. Subjects should swallow the tablets with water at ambient temperature to a total volume of approximately 240 mL (8 ounces). It is important that subjects swallow the investigational product whole, and that they not manipulate or chew the investigational product prior to swallowing. Subjects should be encouraged to maintain adequate hydration during the study period.

Sites will instruct subjects on the proper way to remove tablets from blister packs and how subjects will administer the investigational product at home. Subjects will be instructed to self-administer their study medication according to Administration instructions provided to the subject. Subjects will be instructed not to remove tablets from the blister packaging until the time of dosing. Subjects will be given a subject diary and provided with instructions on the completion of the diary.

5.4.3.2. Tofacitinib and Matching Placebo (Where Accepted for use in This Study)

All tablets are for oral administration.

Tofacitinib should be taken at home as a single tablet 2 times a day with or without food. Subjects should swallow the tablets with ambient water to a total volume of approximately 240 mL (8 ounces). If taken at the time of PF-06650833 tablet dosing, a total of 240 mL water is sufficient for administration. Subjects will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing.

Sites will instruct subjects on the proper way to remove tablets from bottles and how subjects will administer the investigational product at home. Subjects will be instructed to self-administer their study medication according to Administration instructions provided to the subject. Subjects will be given a subject diary and provided with instructions on the completion of the diary.

5.5. 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.

Storage conditions stated in the SRSD eg, Investigator's Brochure [IB], will be superseded by the storage conditions stated on the product label.

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

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

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the

temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

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

5.6. Investigational Product Accountability

The investigative 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. Subjects must return to the investigator all unused investigational product taken home. The site will perform accountability on drug returned by subjects.

5.6.1. Destruction of Investigational Product Supplies

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

Returned test article can be destroyed only after the sponsor monitor has verified the accuracy of the dispensing and inventory record. The monitor must verify that site staff follows instructions regarding the return of investigational product to the Supply Chain Organization or vendor for destruction.

5.7. Concomitant Treatment(s)

It is recommended that subjects avoid changing other prescription or non-prescription drugs, vitamins, and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication and throughout the study. Herbal medications with pharmaceutical properties must be discontinued at least 4 weeks before the first dose of study medication.

All concomitant medication taken during the study must be recorded with indication, daily dose, and start and stop dates of administration.

Medications taken after informed consent is obtained but before the first dose of study medication, will be documented as prior medications. Medications taken after the first dose of study drug has been administered will be documented as concomitant medications.

Subjects receiving non-prohibited concomitant medications 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.

5.7.1. Permitted Background Arthritis Therapy

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 and have been stable or the stipulated interval before Randomization and dosing with the investigational product.

- 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 or equivalent parenteral (IM or SC, only; IV administration is not permitted) methotrexate for at least 3 months (prior to baseline randomization) 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. The MTX 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.

- 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.
- 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 (Appendix 15).
- Treatment with bisphosphonates (oral or parenteral) should ideally be administered after the baseline/randomization (Visit 2) and Week 12 (Visit 8) visits, and under any circumstances, must not to be administered within 1 week preceding these visits.

5.7.2. Prohibited Concomitant Medications

5.7.2.1. Strong and Moderate Inhibitors and Inducers of CYP3A4

Systemic therapy with medications that are strong or moderate CYP3A4 inhibitors, strong CYP3A inducers (some common examples are provided in Appendix 5) are prohibited within 4 weeks or 5 half-lives (whichever is longer) prior to the Baseline Visit (Visit 2) and during the trial.

5.7.2.2. Strong Inhibitors/Inducers of BCRP

Systemic therapies with medications that are strong inhibitors of BRCP (some common examples are provided in Appendix 5) are prohibited within 4 weeks or 5 half-lives (whichever is longer) prior to the Baseline Visit (Visit 2) and during the trial.

5.7.2.3. Strong Inhibitors of CYP2C19

Tofacitinib exposure is increased when co-administered with medications that result in potent inhibition of CYP2C19 (eg, fluconazole). To ensure sufficient washout of these effects on safety and efficacy endpoints, drugs that are potent CYP2C19 inhibitors must be discontinued for at least 4 weeks or 5 half-lives (whichever is longer) prior to the Baseline Visit (Visit 2) and during the trial (some common examples are provided in Appendix 5).

5.7.2.4. Other Prohibited Concomitant Medications

Any other experimental, small molecule, non-RA therapy must be discontinued for 4 weeks or 5 half-lives (whichever is longer) prior to the first dose of study medication. Subjects with prior exposure to small molecule or biologic investigational RA therapies other than anti-TNFs are excluded. Concomitant use of tofacitinib (other than as prescribed by the randomization scheme) or other JAK inhibitor is prohibited.

Intra-articular, intravenous or intramuscular corticosteroids, DMARDs other than methotrexate (including tacrolimus or other calcineurin inhibitors), and biologic response modifiers (including natalizumab or other anti-integrin biologics) are not allowed during this study.

Special restrictions regarding prior RA drugs are outlined below.

5.7.2.5. Prohibited Background Arthritis Therapies

5.7.2.5.1. Disease Modifying Antirheumatic Drugs (DMARDs)

Patients 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 study medication.

- Biologics TNF inhibitors:
    - Up to 50 % of subjects may have received one (and only one) approved TNF-inhibiting biologic agent administered in accordance with its labeling recommendations. The TNF-inhibiting biologic could have been discontinued due to its being deemed inadequately effective and/or not tolerated as defined, for the purpose of this study, by the Investigator's and subject's opinions that the subject did not experience adequate benefit from the anti-TNF plus the presence of sufficient residual disease activity to meet the entry criteria. The anti-TNF biologic could also have been discontinued due to lack of continued access. The anti-TNF should have been discontinued for a minimum of the washout period defined as follows (biosimilars of the below agents should be considered the same as the originators):
        - Entanercept (Enbrel®), adalimumab (Humira®): 6 weeks.
        - infliximab (Remicade®), golimumab (Simponi®): 10 weeks.
        - certolizumab pegol (Cimzia®): 12 weeks.
- Other Biologic 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], natalizumab (Tysabri®), alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation) are excluded from participation in the current study.

Other RA Drugs

The following concomitant background arthritis therapies are prohibited during the study:

- Intravenous, intra-articular, and intramuscular corticosteroids.
- csDMARDs other than methotrexate (including tacrolimus or other calcineurin inhibitors) and biologic response modifiers (including natalizumab or other anti-integrin biologics) are not allowed during this study.
- Subjects with prior use of tofacitinib or other JAK inhibitor are excluded. Concomitant use of tofacitinib (other than as prescribed by the randomization scheme) or other JAK inhibitor is prohibited.

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 study medication.
- 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 study medication.
- Leflunomide (Arava®) must be discontinued 8 weeks prior to the first dose of study medication if no elimination procedure is followed. Alternately, it should be discontinued with the following elimination procedure at least 4 weeks prior to the first dose of study medication:
    - Cholestyramine at a dosage of 8 grams three times daily for at least 24 hours, or activated charcoal at a dosage of 50 grams 4 times a day for at least 24 hours (US PI, Elimination Procedure to significantly lower leflunomide drug levels) Appendix 4.
- 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 study medication.

5.8. Rescue Treatment of RA

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 g/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 gm/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 gm/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 12). (Note: baseline stable doses of acetaminophen/ paracetamol or opioids should NOT be discontinued in advance of study visits (See Appendix 15).

6. STUDY PROCEDURES

6.1. Screening

Patients will be screened within 28 days prior to administration of study medication to confirm that they meet the entrance criteria for the study. The study investigator or a sub-investigator will discuss, with each patient, the nature of the study, its requirements, and its restrictions. Written informed consent must be obtained prior to performance of any protocol-specific procedures.

Subjects must complete all screening procedures and assessments and have test results available prior to the baseline visit (Visit 2). If a subject is not enrolled within 28 days after the screening visit, all screening procedures and assessments must be repeated unless otherwise noted (below). Sponsor approval must be obtained prior to re-screening a subject.

Subjects who do not have all tests completed within screening period or who temporarily do not meet study entry criteria (eg, treatment with antibiotics during the screening period or for administrative reasons) may be re-screened one time; the subject's prior ID number and reason for re-screening must be documented.

- Informed Consent;
- Review of inclusion/exclusion criteria;
- Log into IRT system;
- The subject's demographics, RA history and prior RA medication history (this includes start dates and stop dates with reason for discontinuation, if available), dosage and frequency of administration, and indication treated (make sure all indications are listed in the medical history) for all current medications, any medications taken within the 4 weeks prior to screening procedures, and a complete history of all DMARDs ever taken including the dates of administration and the reasons for discontinuation;
- Medical History: include previous vaccination, specifically influenza, pneumococcus, and herpes zoster and other non RA medications;
- History of alcohol and drug abuse;
- Height and weight;
- Vital signs: sitting blood pressure, pulse and temperature (tympanic, oral, axillary, or temporal);

- Complete Physical Examination, minimally including: vital signs, general appearance, skin (presence of rash, skin lesions with malignant features), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (peripheral edema), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes. (Additional brief PE may be performed during the study at the investigator's discretion);

- 12-lead electrocardiogram [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)];

- Chest radiograph (posterior-anterior and lateral views are recommended, however local guidelines should be followed) is required at Screening. A chest X-ray or other appropriate diagnostic chest imaging modality [ie, Computerised Tomography (CT) or Magnetic Resonance Imaging (MRI)] performed within 12 weeks prior to screeningand read by a qualified radiologist with no evidence of current, active TB or previous inactive TB, general infections, heart failure or malignancy may substitute for the Chest X-ray taken at Screening. Documentation of the official reading must be located and available in the source documentation;

- Collect blood samples for clinical chemistry (including hsCRP) and hematology;

- Collect blood sample for local ESR testing;

- Collect blood sample for RF, ACPA;

- Collect blood samples for HIV Serology, HBsAg, HBcAb, HBsAb, HCV Ab or HCV RNA; Human immunodeficiency virus (HIV) testing is mandatory; however reporting of results should be handled per local regulations;

- Collect blood sample for FSH (Women of Non Child Bearing Potential (WONCBP), only);

- Collect blood for tuberculosis (QuantiFERON Gold®™ In-Tube) test: Unless tested and documented within 3 months of screening visit;

- CCI [redacted]

- Collect urine sample for urinalysis (proteinuria, pH color, clarity) and urine microscopy;

- Urine pregnancy testing must be completed for all women of childbearing potential; A delay in randomization for WOCBP in order to collect the second pregnancy test within 5 days after the first day of the menstrual period will not be considered a protocol deviation (PD);

- Confirm proper contraception is being used;
- CCI [redacted]
- CCI [redacted]
- Perform assessment of tender/swollen joints RA Activity;
- SAE and AE monitoring.

6.2. Study Period

Study visits are calculated from Visit 2 Baseline/Day 1/Week 0. Visit dates and windows are anchored on the first day of dosing. All visits should be conducted as close to the scheduled visit day as possible. Exceptions may be made to accommodate holidays and unexpected events, such as weather-related site closures or illnesses requiring hospitalization. In these cases, the visit should be scheduled or re-scheduled as close to the original visit schedule as possible.

6.2.1. Visit 2, Baseline Day 1/Week 0

Patients are required to fast for at least 6 hours prior to the visit. The patient reported outcome (PRO) assessments (Patient Assessment of Arthritis Pain, Patient Global Assessment of Arthritis, Physician Global Assessment of Arthritis, Health Assessment Questionnaire - Disability Index (HAQ-DI), SF-36 Version 2 (Acute), FACIT Fatigue Scale, EuroQol EQ-5D-3L) should be done before other study-related procedures and before significant contact with the principal investigator (PI) and site personnel. Vital signs, physical examination and ECG, should be conducted next.

The Investigator will review all inclusion/exclusion criteria. If the subject is eligible to continue, the following should be conducted:

Procedures that will be performed predose:

- ACR/DAS Assessments: Tender/Painful Joint Counts (68), Swollen Joint Count (66), Patient Assessment of Arthritis Pain, Patient Global Assessment of Arthritis, Physician Global Assessment of Arthritis, Health Assessment Questionnaire – Disability Index (HAQ-DI);
- Collect additional PROs: SF-36 Version 2 (Acute), FACIT-fatigue scale, EQ-5D-3L;
- Prior Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;
- Measure vital signs: sitting blood pressure, pulse, and temperature (tympanic, oral, axillary, or temporal);

- Perform targeted physical examination;
- Perform 12-lead electrocardiogram;
- Collect blood samples for chemistry (including hsCRP) and hematology laboratory assessments;
- Collect blood sample for local ESR assessment;
- Collect blood samples for RF, ACPA;
- Collect blood sample for immunoglobulin Ig (IgA, IgM, IgG, IgE) analyses;
- Collect urine sample for central laboratory urinalysis and urine microscopy;
- Confirm proper contraception is being used;
- Collect urine for local urine pregnancy testing (women of childbearing potential, only);
- CCI [redacted]
- Randomization (after all screening procedures are complete and reviewed);
- Administration of investigation of PF-06650833, placebo or tofacitinib;
- CCI [redacted]
- Log into IRT system, dispense investigational products as identified by the drug dispensing system. Dispense dosing diary to subject and instruct subject on proper use of the diary;

- Dispense subject diary, where they can record daily study medications (including new, stopped and changes in medications in addition to the study medication) they are taking during the study.

- Serious and non serious adverse events monitoring.

6.2.2. Visit 3, Day 8/Week 1

Procedures that will be performed on Visit 3, Day 8 include:

- Review concomitant Medication and Treatments (RA and non RA) : Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;

- Measure vital signs: sitting blood pressure, pulse, and temperature (tympanic, oral, axillary, or temporal);

- Perform targeted physical examination;

- 12-lead electrocardiogram;

- Collect blood samples for chemistry (including hsCRP) and hematology laboratory assessments;

- Collect blood sample for local ESR assessment;

- Collect urine sample for central laboratory urinalysis and urine microscopy;

- Confirm proper contraception is being used;

- Collect urine for local urine pregnancy testing (women of childbearing potential, only);

- CCI [redacted]

- CCI [redacted]

- CCI [redacted]

- CCI [redacted]

- CCI [redacted]

- Administration of PF-06650833, placebo or tofacitinib;

- Review of the diary for compliance with daily diary completion (and provide subject retraining as required), IP accountability and compliance check through the study; reinforce dosing instructions and compliance, as needed;

- Log into IRT system; dispense investigational products (only PF-06650833) as identified by the drug dispensing system. Dispense dosing diary to subject and instruct subject on proper use of the diary;

- Dispense subject diary, where they can record daily study medications (including new, stopped and changes in medications in addition to the study medication) they are taking during the study;

- Serious and non serious adverse events monitoring.

6.2.3. Visit 4, Day 29/Week 4

Patients are required to fast for at least 6 hours prior to the visit. Procedures that will be performed on Visit 4, Day 29/Week 4 include:

- ACR/DAS Assessments: Tender/Painful Joint Counts (68), Swollen Joint Count (66), Patient Assessment of Arthritis Pain, Patient Global Assessment of Arthritis, Physician Global Assessment of Arthritis, Health Assessment Questionnaire – Disability Index (HAQ-DI);

- Review concomitant Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;

- Measure vital signs: sitting blood pressure, pulse, and temperature (tympanic, oral, axillary, or temporal preferred);

- Perform targeted physical examination;

- Collect blood samples for chemistry (including hsCRP) and hematology laboratory assessments;

- Collect blood sample for local ESR assessment;

- CCI [redacted]

- CCI [redacted]

- CCI [redacted]

- Confirm proper contraception is being used;

- Collect urine sample for central laboratory urinalysis and urine microscopy;

[redacted]

- Collect urine for local urine pregnancy testing (women of childbearing potential, only);
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Administration of PF-06650833, placebo or tofacitinib;
- Log into IRT system, dispense investigational products as identified by the drug dispensing system. Review of the diary for compliance with daily diary completion (and provide subject retraining as required), IP accountability and compliance check through the study;
- Dispense subject diary, where they can record daily study medications (including new, stopped and changes in medications in addition to the study medication) they are taking during the study treatment;
- Serious and non serious adverse events monitoring.

6.2.4. Visit 5, Day 43/Week 6

Procedures that will be performed on Visit 5, Day 43/Week 6 include:

- Review concomitant Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;
- Measure vital signs: sitting blood pressure, pulse, and temperature (tympanic, oral, axillary, or temporal);
- Perform targeted physical examination;
- Collect blood samples for chemistry laboratory assessments (will only include standard blood chemistry panels – not hematology);
- Confirm proper contraception is being used;
- Collect urine sample for central laboratory urinalysis and urine microscopy;
- Collect urine for local urine pregnancy testing (women of childbearing potential, only);

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Administration of PF-06650833, placebo or tofacitinib;
- Review of the diary for compliance with daily diary completion (and provide subject retraining as required), IP accountability and compliance check through the study;
- Dispense subject diary, where they can record daily study medications (including new, stopped and changes in medications in addition to the study medication) they are taking during the study treatment period;
- Serious and nonserious adverse events monitoring.

6.2.5. Visit 6, Day 57/Week 8

Procedures that will be performed on Visit 6, Day 57/Week 8 include:

- ACR/DAS Assessments: Tender/Painful Joint Counts (68), Swollen Joint Count (66), Patient Assessment of Arthritis Pain, Patient Global Assessment of Arthritis, Physician Global Assessment of Arthritis, Health Assessment Questionnaire – Disability Index (HAQ-DI);
- Review concomitant Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;
- Vital signs: sitting blood pressure, pulse, and temperature (tympanic, oral, axillary, or temporal);
- Perform targeted physical examination;
- Collect blood samples for chemistry (including hsCRP) and hematology laboratory assessments;
- Collect blood sample for local ESR assessment;
- Confirm proper contraception is being used;
- Collect urine sample for central laboratory urinalysis and urine microscopy;

- Collect urine for local urine pregnancy testing (women of childbearing potential, only);
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Administration of PF-06650833, placebo or tofacitinib;
- Log into IRT system, dispense investigational products as identified by the drug dispensing system. Review of the diary for compliance with daily diary completion (and provide subject retraining as required), IP accountability and compliance check through the study;
- Dispense subject diary, where they can record daily study medications (including new, stopped and changes in medications in addition to the study medication) they are taking during the study;
- Serious and non serious adverse events monitoring.

6.2.6. Visit 7, Day 71/Week 10

Procedures that will be performed on Visit 7, Day 71/Week 10 include:

- Review concomitant Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;
- Measure vital signs: sitting blood pressure, pulse, and temperature (tympanic, oral, axillary, or temporal);
- Perform targeted physical examination;
- Collect blood samples for chemistry laboratory assessments (will only include standard blood chemistry panels – not hematology);
- Confirm proper contraception is being used;
- Collect urine sample for central laboratory urinalysis and urine microscopy;
- Collect urine for local urine pregnancy testing (women of childbearing potential, only);

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Administration of PF-06650833, placebo or tofacitinib;
- Review of the diary for compliance with daily diary completion (and provide subject retraining as required), IP accountability, and compliance check through the study;
- Dispense subject diary, where they can record daily study medications (including new, stopped and changes in medications in addition to the study medication) they are taking during the study;
- Serious and non serious adverse events monitoring.

6.2.7. Visit 8, Day 85/Week 12

Patients are required to fast for at least 6 hours prior to the visit. Procedures that will be performed on Visit 8, Day 85/Week 12 include:

- ACR/DAS Assessments: Tender/Painful Joint Counts (68), Swollen Joint Count (66), Patient Assessment of Arthritis Pain, Patient Global Assessment of Arthritis, Physician Global Assessment of Arthritis, Health Assessment Questionnaire – Disability Index (HAQ-DI);
- Collect additional PROs: SF-36 Version 2 (Acute), FACIT-fatigue scale, EQ-5D-3L;
- Review concomitant Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;
- Vital signs: sitting blood pressure, pulse, and temperature (tympanic, oral, axillary, or temporal;
- Perform targeted physical Examination;
- 12-lead electrocardiogram;
- Collect blood samples for chemistry (including hsCRP) and hematology laboratory assessments;
- Collect blood sample for local ESR assessment;
- Collect blood samples for RF, ACPA;

- Collect blood sample for immunoglobulin Ig (IgA, IgM, IgG, IgE) analyses;
- CCI [redacted]
- Confirm proper contraception is being used;
- Collect urine sample for central laboratory urinalysis and urine microscopy;
- Collect urine for local urine pregnancy testing (women of childbearing potential, only);
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Administration of PF-06650833, placebo or tofacitinib;
- CCI [redacted]
- CCI [redacted]
- Review of the diary for compliance with daily diary completion (and provide subject retraining as required), IP accountability and compliance check through the study;
- Serious and non serious adverse events monitoring.

6.2.8. Follow-Up/Visit 9, Day 99/Week 14

Procedures that will be performed on Visit 9, Day 99/Week 14 include:

- Review concomitant Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;

- Measure vital signs: sitting blood pressure, pulse, and temperature (tympanic, oral, axillary or temporal preferred);
- Perform targeted physical examination;
- Collect blood samples for chemistry laboratory assessments (will only include standard blood chemistry panels – not hematology);
- Confirm proper contraception is being used;
- Collect urine sample for central laboratory urinalysis and urine microscopy;
- Collect urine for local urine pregnancy testing (women of childbearing potential, only);
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Serious and non serious adverse events monitoring.

6.2.9. Follow-Up/Visit 10, Day 113/ Week 16

Procedures that will be performed on Visit 10, Day 113/Week 16 include:

- ACR/DAS Assessments: Tender/Painful Joint Counts (68), Swollen Joint Count (66), Patient Assessment of Arthritis Pain, Patient Global Assessment of Arthritis, Physician Global Assessment of Arthritis, Health Assessment Questionnaire – Disability Index (HAQ-DI);
- Collect additional PROs: SF-36 Version 2 (Acute), FACIT-fatigue scale, EQ-5D-3L;
- Review concomitant Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;
- Vital signs: sitting blood pressure, pulse, and temperature (tympanic, oral, axillary or temporal preferred);
- Perform complete physical Examination;
- 12-lead electrocardiogram;

- Collect blood samples for chemistry (including hsCRP) and hematology laboratory assessments;
- Collect blood sample for local ESR assessment;
- Collect blood sample for ACPA;
- CCI [redacted]
- Collect urine sample for central laboratory urinalysis and urine microscopy;
- Confirm proper contraception is being used;
- Collect urine for local urine pregnancy testing (women of childbearing potential, only);
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Serious and non serious adverse events monitoring;
- Log into IRT system and register the subject's status as completed and discharge the subject from the study.

6.3. Subject Withdrawal/ Discontinuation Criteria

A subject 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 Pfizer for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

The sponsor's Clinical team should be consulted as soon as possible and subjects should be discontinued if any of the following occur during the study:

- Subjects who have a flare of RA requiring treatment with prohibited concomitant medication should be discontinued.

- Subjects who require rescue doses of acetaminophen/paracetamol or opioid for more than 10 consecutive days for treatment of increased RA symptoms should be discontinued.

- Subjects interrupting study medication for more than 7 consecutive days, or patients who are less than 80% compliant with the dosage regimen for any two consecutive visit periods should be withdrawn from the study.

- Subjects manifesting a serious infection, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials.

- Any laboratory (defined by changes in serum creatinine or eGFR) or clinical manifestation of acute renal injury (Section 7.6.2 CCI [redacted]

6.4. Subject Withdrawal/Early Termination Visit

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

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. 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 patient outcome, if possible. The investigator should inquire about the reason for withdrawal; request that the patient return all unused investigational product(s); request that the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events.

If the patient 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.

Procedures that will be performed on early withdrawal visit include with subject consent:

- ACR/DAS Assessments: Tender/Painful Joint Counts (68), Swollen Joint Count (66), Patient Assessment of Arthritis Pain, Patient Global Assessment of Arthritis, Physician Global Assessment of Arthritis, Health Assessment Questionnaire – Disability Index (HAQ-DI);

- Collect additional PROs: SF-36 Version 2 (Acute), FACIT-fatigue scale, EQ-5D-3L;
- Review concomitant Medication and Treatments (RA and non RA): Current and prior medications (noting exclusions and required DMARD restrictions) taken with reasons and should include dose/duration;
- Vital signs: sitting blood pressure, pulse, and temperature (tympanic, oral, axillary or temporal);
- Perform targeted physical Examination;
- 12-lead electrocardiogram;
- Collect blood samples for chemistry (including hsCRP) and hematology laboratory assessments;
- Collect blood sample for local ESR assessment;
- Collect blood sample for ACPA;
- Collect blood sample for immunoglobulin Ig (IgA, IgM, IgG, IgE) analyses;
- CCI [redacted]
- Confirm proper contraception is being used;
- Collect urine sample for central laboratory urinalysis and urine microscopy;
- Collect urine for local urine pregnancy testing (women of childbearing potential, only);
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Review of the diary for compliance with daily diary completion (and provide subject retraining as required), IP accountability and compliance check through the study;
- Serious and nonserious adverse events monitoring;

- Log into IRT system and register the subject's status as discontinued and discharge the subject from the study.

6.4.1. Withdrawal of Consent

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

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 and Section 6.

7.1.2. Tender/Painful Joint Count (68)

Sixty-eight (68) joints will be assessed by a blinded 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 blinded 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.

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. This count will be calculated by Pfizer from the 68 tender/painful joint count assessed by the blinded joint assessor as described in Section 7.1.2.

This 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 blinded joint assessor as described in Section 7.1.3.

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

Patients 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 9). This assessment must be performed early in the clinic visit and before the subject has hextensive contact with site personnel and/or investigator.

7.1.4.1. Patient's Global Assessment (PtGA) of Arthritis

Patients will answer the following question, "Considering all the ways your arthritis affects you, how are you feeling today?" The patient's response will be recorded using a 100 mm visual analog scale (VAS) (See Appendix 10). This assessment must be performed early in the clinic visit and before the subject has has extensive contact with site personnel and / or investigator.

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

The investigator will assess how the patient's overall arthritis appears at the time of the visit. This is an evaluation based on the patient'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 11).

7.1.4.3. C-Reactive Protein (CRP)

Samples for analysis of high sensitivity CRP (hsCRP) will be collected at the visits specified in the Schedule of Activities and Section 6. 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 and Section 6. Details of the collection and processing of ESR samples will be specified in the Laboratory Manual. ESR will be analyzed by a local laboratory (results will be reported to the central laboratory) using the Westergren method. ESR kits will be provided by the central laboratory. The local laboratory will report results to the 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.

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

The HAQ-DI assesses the degree of difficulty a patient 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.[13] Each activity category consists of 2-3 items. For each question in the questionnaire, the level of difficulty is scored from 0 to 3 with 0 representing "no difficulty," 1 as "some difficulty," 2 as "much difficulty," and 3 as "unable to do." Any activity that requires assistance from another individual or requires the use of an assistive device adjusts to a minimum score of 2 to represent a more limited

functional status. This questionnaire must be performed early in the clinic visit and before the subject has 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 8. This must be performed early in the clinic visit and before the subject has has extensive contact with site personnel and / or investigator.

7.1.5. Composite Efficacy Assessments Derived from the ACR Core Dataset

7.1.5.1. Simplified 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).

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 and physician global assessments, pain, disability, and an acute-phase reactant which for this study will be CRP. 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 7. Components of DAS-3, 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:

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

7.2. Patient Reported Outcomes (PROs)

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

The SF-36 v.2 (Acute) is a 36-item generic health status measure. It measures 8 general health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. These domains can also be summarized as physical and mental component scores. This must be performed early in the clinic visit and before the subject has has extensive contact with site personnel and / or investigator. The form should be checked for completeness by the site staff. A copy of the questionnaire can be found in Appendix 12. The SF-36 will be collected as indicated in the Schedule of Activities and Section 6.

7.2.2. Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)

The FACIT – F is a patient completed questionnaire consisting of 13 items that assess fatigue. Instrument scoring yields a range from 0 to 52, with higher scores representing better patient status (less fatigue). This questionnaire must be performed early in the clinic visit and before the subject has has extensive contact with site personnel and/or investigator.The form should then be checked by site staff for completeness. A copy of the questionnaire can be found in Appendix 13. The FACIT-F will be collected as indicated in the Schedule of Activities and Section 6.

7.2.3. European Quality of Life – 5 Dimensions-3 Level (EQ-5D-3L)

The EQ-5D-3L Health State Profile is a patient completed questionnaire designed to assess impact on health-related quality of life in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Additionally, scores from the five domains may be used to calculate a single index value, also known as a utility score. The validity and reliability of the EuroQol EQ-5D-3L has been established in a number of disease states, including rheumatoid arthritis. This questionnaire must be performed early in the clinic visit and before the subject has has extensive contact with site personnel and / or investigator. The form should then be checked by site staff for completeness. A copy of the questionnaire can be found in Appendix 14. The EQ-5D-3L will be collected as indicated in the Schedule of Activities and Section 6.

7.3. Safety 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 study medication. Investigators and Pfizer Clinicians will review individual subject data throughout the conduct of the trial to ensure subjects' well-being.

7.3.1. Clinical Safety Laboratory Tests

The following safety laboratory tests will be performed at times defined in the Schedule of Activities. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

Table 9. Safety Laboratory Tests

Hematology	Chemistry Panel	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCH MCHC RBC morphology and MCV Platelet count WBC count Total neutrophils (Abs and %) Eosinophils (Abs and %) Basophils (Abs and %) Lymphocytes (Abs and %) Monocytes (Abs and %) Reticulocyte count WBEDT Reticulocyte count %	BUN/Urea & Creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (Bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein Serum myoglobin[d] Lipid profiles [c] Cardiac troponin-I (cTn-I), CK and CK-MB[d]	pH Glucose Creatinine Protein Blood Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Color and clarity Specific gravity Microscopy	FSH[a] Pregnancy Tests [b] HIV, HepBsAg, HepBc Ab and HCVAb or HCV RNA QuantiFERON® TB Gold test[d]

a. In females who are amenorrheic for at least 12 consecutive months.

b. Urine pregnancy tests for women of childbearing potential.

c. Lipid Profile includes fasting total cholesterol, LDL, HDL, triglycerides and may include fasting apolipoprotein A-1 and B and other lipoprotein tests potentially including particle size measurements.

d. At screening only, additional tests may be performed during the study at the investigator's discretion, as indicated by signs and symptoms of ongoing AEs.

7.3.2. Physical Examination

Complete Physical Examination:

A standard physical examination will be performed at the visits identified in SoA. The following parameters and body systems will minimally be examined and any abnormalities described: General appearance, skin (presence of rash), HEENT, lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs, peripheral edema), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and, lymph nodes.

Weight will be recorded as listed in Schedule of Activity.

Targeted Examination:

At all other visits, as defined in the SoA, an abbreviated physical examination will be performed that will minimally include the following: Skin, lungs, heart, abdomen and lymph nodes. Additional organ systems may be examined at the investigator decision. Any clinically significant changes from the baseline examination should be recorded as AEs. Body temperature also will be collected at these visits.

7.3.3. Medical History

Medical history in addition to RA history including disease duration and extent of disease, cardiac history and smoking history will be collected at Screening. Height and weight will be measured without the subject wearing shoes. Height (inches or centimeters) and weight (lbs or kg) will be measured up to one decimal place and recorded in the source document at the screening visit.

7.3.4. Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. For female subjects of childbearing potential, 2 negative pregnancy tests are required before receiving PF-06650833 (1 negative pregnancy test at screening and 1 at the baseline visit immediately before PF-06650833 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 PF-06650833. 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 all visits and at the end of the study to confirm that the subject has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period and when potential pregnancy is otherwise suspected, and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

7.3.5. Blood Pressure and Heart Rate

Blood pressure will be measured in the subject's dominant arm and recorded to the nearest mmHg. The same arm will be used throughout the study. All blood pressure in this study will be measured with the subject in the sitting position after resting for at least 5 minutes. The same blood pressure cuff, which has been properly calibrated, should be used to measure blood pressure each time. When the timing of these measurements coincides with a blood collection, blood pressure and heart rate should be obtained first.

7.3.6. 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. ECGs are to be transferred from the sites to a central vendor for assessment. The ECG results provided by the central vendor will be stored in the study database and used for the planned analysis.

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.

7.3.7. QuantiFERON Test

A QuantiFERON Gold®™ test will be used to test for active / latent tuberculosis (TB). A description of the QuantiFERON Gold test follows:

"This Enzyme-linked Immunosorbent Assay (ELISA) test detects the release of Interferon-gamma (IFN-γ) in fresh heparinized whole blood from sensitized persons when it is incubated with mixtures of synthetic peptides simulating two proteins present in *M. tuberculosis*: Early Secretory Antigenic Target--6 (ESAT-6) and Culture Filtrate Protein-10 (CFP-10). ESAT-6 and CFP-10 are secreted by all *M. tuberculosis* and pathogenic *M. bovis* strains. Because these proteins are absent from all Bacille Calmette-Guérin (BCG) vaccine strains and from commonly encountered NonTuberculous Mycobacteria (NTM) except *M. kansasii*, *M. szulgai,* and *M. marinum*, QFT-G is expected to be more specific for *M. tuberculosis* than tests that use tuberculin Purified Protein Derivative (PPD) as the antigen."

Subjects with a documented positive IGRA TB test (eg, QuantiFERON®-TB GOLD (QFT-G) performed within 12 weeks prior to Screening are excluded. The specific IGRA method, or test, used should comply with local country-specific guidelines. A subject who is currently being treated for either latent or active TB infection is to be excluded. The type (name) and results of the IGRA TB test must be known and located in source documentation.

7.3.8. Chest X-Ray

Chest radiograph (posterior-anterior and lateral views are recommended, however local guidelines should be followed) is required at Screening. A chest X-ray or other appropriate diagnostic chest imaging modality [ie, Computerised Tomography (CT) or Magnetic Resonance Imaging (MRI)] performed within 12 weeks prior to screening and read by a qualified radiologist with no evidence of current, active TB or previous inactive TB, general infections, heart failure or malignancy may substitute for the Chest X-ray taken at Screening. Documentation of the official reading must be located and available in the source documentation.

CCI [redacted]

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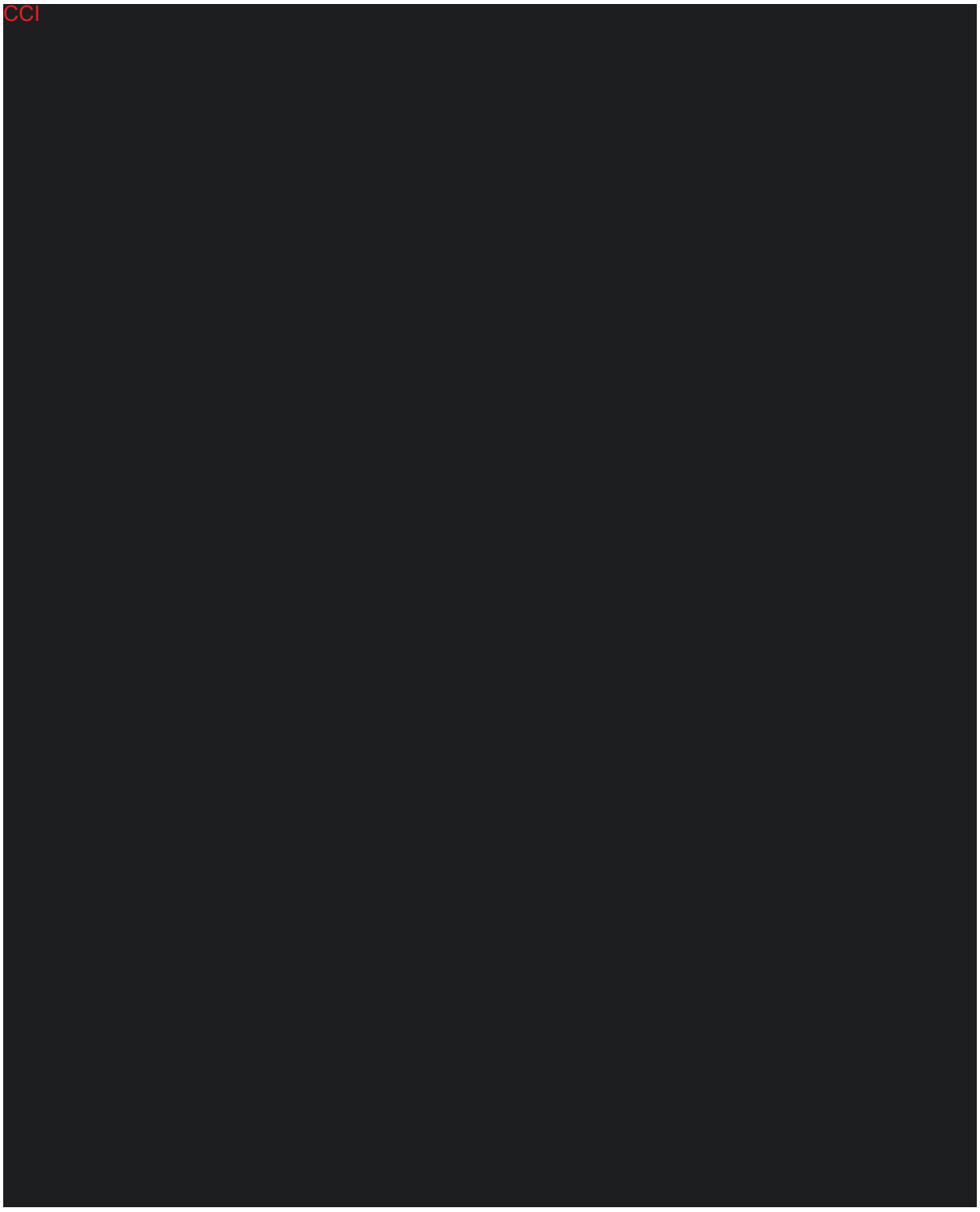

7.6. PF-06650833 Triggered Requirements

7.6.1. Hypotension, and Tachycardia

Symptomatic hypotension should be treated with supportive measures (eg, supine or Trendelenburg positioning) and fluid resuscitation as deemed appropriate by the Investigator. Tachycardia associated with hypotension would likely respond to the measures to treat the hypotension, so no specific targeted treatment may be needed. Isolated tachycardia should be treated expectantly and with supportive measures as for hypotension. Specific pharmacologic interventions to treat hypotension or tachycardia should be avoided if possible.

7.6.2. Potential Cases of Acute Kidney Injury

Abnormal values in serum creatinine (SCr) concurrent with absence of increase in BUN (blood urea nitrogen) that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events. An increase of ≥0.3 mg/dL (or ≥26.5 μmol/L) in serum creatinine relative to subjects' own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48-hours from awareness.

If the second assessment (after the 1st observations of ≥0.3 mg/dL (or ≥26.5 μmol/L) in serum creatinine relative to subjects' own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 μmol/L), the subject should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Subjects should return to the investigational site and be evaluated as soon as possible, preferably within 48-hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include: serum blood-urea-nitrogen, serum creatine kinase, serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute-kidney-injury, with no other cause(s) of laboratory abnormalities identified should be considered as potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. Evaluation by a trained nephrologist may be appropriate if kidney injury is suspected.

If ≥2 subjects in a given period are noted to have 2 *consecutive* SCr results of ≥0.3 mg/dL (or ≥26.5 μmol/L), an assessment of whether the finding may be considered adverse drug reaction should be undertaken.

CCI

[redacted]

7.7. Triggered Requirements

Condition	Action
Neutrophil counts <1000 cells/mm^3	The subject should return to the study site for prompt retesting, ideally within 3-5 days.
Platelet counts <100,000 platelets/mm^3	The subject should return to the study site for prompt retesting, ideally within 3-5 days.
Lymphocyte counts <500 lymphocytes/mm^3	The subject should return to the study site for prompt retesting, ideally within 3-5 days.
Any single AST and/or ALT elevation >3 times the upper limit of normal (ULN)*	The subject should return to the study site for prompt retesting, ideally within 3-5 days*.
Any single hemoglobin value <8.0 g/dL or one that drops ≥2 g/dL below baseline.	The subject should return to the study site for prompt retesting, ideally within 3-5 days.
Any serum creatinine increase >50% over the average of screening (most recent value prior to baseline) and baseline values OR an absolute increase in serum creatinine >0.3 mg/dL (>26.5 µmol/L) over the average of screening (most recent value prior to baseline) and baseline values	The subject should return to the study site for prompt retesting, ideally within 3-5 days. If the second assessment (after the 1st observations of ≥0.3 mg/dL (or ≥26.5 µmol/L) in serum creatinine relative to subjects' own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 µmol/L), the subject should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

* The subject must return to the study site for prompt retesting and include the following tests: albumin, creatine kinase (CK), total bilirubin, direct and indirect bilirubin, GGT, PT/INR, and alkaline phosphatase. Additional investigations include a detailed history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, work exposure, history of ethanol, recreational drug and dietary supplement consumption. Testing for acute hepatitis A, B or C infection and biliary tract imaging may be considered. A subject with a total bilirubin value
≥2 × ULN concurrently may need to return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results (refer to 8.4.2).

Condition	Action
2 sequential AST or ALT elevations ≥3 x ULN with a total bilirubin value ≥2 x ULN	Treatment with all study drugs will be discontinued and the subject withdrawn from this study.
2 sequential AST or ALT elevations ≥3 x ULN with an elevated INR	Treatment with all study drugs will be discontinued and the subject withdrawn from this study.
2 sequential AST or ALT elevations ≥3 x ULN accompanied by symptoms consistent with hepatic injury	Treatment with all study drugs will be discontinued and the subject withdrawn from this study.
2 sequential AST or ALT elevations ≥5 x ULN, regardless of Total Bilirubin or accompanying symptoms	Treatment with all study drugs will be discontinued and the subject withdrawn from this study.
Two sequential hemoglobin values <8.0 g/dL or a decrease of more than 30% from baseline value;	Treatment with all study drugs will be discontinued and the subject withdrawn from this study. Follow up to resolution
Two sequential platelet counts <75,000 platelets/mm^3;	Treatment with all study drugs will be discontinued and the subject withdrawn from this study. Follow up to resolution
2 sequential neutrophil counts <1000 cells/mm^3	Treatment with all study drugs will be discontinued and the subject withdrawn from this study. Follow up to resolution
Confirmed lymphocyte counts <500 lymphocytes/mm3 by repeat testing	Treatment with all study drugs will be discontinued and the subject withdrawn from this study. Follow up to resolution
Confirmed increases in serum creatinine >50% over the average of screening and baseline values and the absolute value of serum creatinine is above upper limit of normal range.	Treatment with all study drugs will be discontinued and the subject withdrawn from this study. Retesting should occur until the serum creatinine is within 10% of the pretreatment value.
Serious infections defined as any infection (viral, bacterial, or fungal) requiring parenteral antimicrobial therapy or hospitalization for treatment, or meeting other criteria that require the infection to be classified as a serious adverse event.	Treatment with all study drugs will be discontinued and the subject withdrawn from this study
Opportunistic infection judged significant by investigator	Treatment with all study drugs will be discontinued and the subject withdrawn from this study
Malignancies excluding adequately treated non melanoma skin cancer (NMSC) and cervical carcinoma in situ	Treatment with all study drugs will be discontinued and the subject withdrawn from this study
Increase lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)	Monitor and treat according to local guidance (eg, diet and behavior modification, statin therapy)

Condition	Action
Pregnancy or refusal to use appropriate contraception	Permanently withdraw the subject from the study and follow any pregnancy to resolution.
Use of prohibited concomitant medications	See 5.7.2 Concomitant Medications of the protocol for specific actions.
Anaphylactic or other serious allergic reaction	Immediately discontinue study drug and institute appropriate therapy.
Symptoms suggestive of a lupus-like syndrome	Discontinue study drug and institute appropriate therapy
ALT = alanine aminotransferase; AST = aspartate aminotransferase; g/dL = grams per deciliter; GGT = gamma-glutamyl transpeptidase, PT/INR = Prothrombin Time International Normalized Ratio; mm = millimeter; x ULN = times the upper limit of normal	

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7.9. Investigator Site RA Rater Qualifications

Tender and swollen joint counts will be evaluated by an independent blinded assessor designated at the clinic for the joint count assessment. The independent blinded assessor will only perform the joint counts and will not participate in any other aspect of subject care or data gathering.

For consistency, the same assessor should perform all 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 12 to ensure integrity of the eligibility criteria and the ACR clinical response up to the Week 12 primary endpoint. If the assigned independent blinded assessor cannot be present, the joint counts should be performed by a different blinded assessor. The identity of the independent blinded assessor should be recorded in the source document for each visit.

The independent blinded assessor must have a background in performing RA or other rheumatology clinical trials (eg, systemic lupus erythematosus) 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. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see Also the Subject Withdrawal Section)

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

8.1.5. Causality Assessment

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

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

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

8.2.2. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms; and/or

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

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

8.2.3. Serious Adverse Events

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

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

Or that is considered to be:

- An important medical event.

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

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

8.2.4. Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the 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 will be documented in a statistical analysis plan (SAP) that will be maintained by the sponsor. The SAP may modify the plans outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions and/or their analyses will also be reflected in a protocol amendment.

The statistical analysis will not include comparison between the PF-06650833 and tofacitinib arms.

9.1. Sample Size Determination

The primary endpoint of the study will be the change from baseline in the simplified disease activity index (SDAI) at 12 weeks. The study will enroll approximately 198 completers allocated as follows:

PF-06650833 400 mg	PF-06650833 200 mg	PF-06650833 60 mg	PF-06650833 20 mg	Tofacitinib 5 mg BID	Placebo
36	36	36	30	30	30

Assuming a 15% dropout rate the study will enroll approximately 230 subjects. Since the use of tofacitinib in this study may be not be acceptable by regulatory authorities/ethics committess in all countries, achieving full randomization into the tofacitinib arm may prove logistically challenging. Since the tofacitinib arm is serving as an active control for the study, enrollment of approximately 20-30 subjects into that arm will be acceptable.

9.2. Efficacy Analysis

Analysis of the Primary Endpoint Primary efficacy analysis will be conducted on SDAI change from baseline at 12 weeks.

Analysis will include data on all PF-06650833 arms and placebo. Data on the 5 mg tofacitinib arm will not be included in the analysis.

The primary analysis will be conducted on intention-to-treat population, defined as all randomized patients who received at least one dose of investigational drug or a placebo. The sensitivity data sets will be outlined in the SAP and will include per-protocol data set.

The primary analysis will assess the posterior distribution of the placebo adjusted SDAI Week 12 changes from baseline for each of four active arms estimated from a Bayesian ANCOVA model adjusting for baseline SDAI score. Placebo adjusted distribution of active arm is defined as distribution of the difference of two random variables: SDAI 12w change from baseline of the given active arm and the placebo (each of them assessed using Bayesian ANCOVA which is equivalent of having treatment indicator as nominal variable in the

model). The sensitivity analysis will include a model with baseline SDAI and TNF exposure as covariates. The distribution means and variances will be reported. Grid plots visualizing the distributions will be presented. The sensitivity analysis will also include models assuming beta-binomial and negative binomial distributions for SDAI score. The same covariate structure will be employed.

The secondary analyses will include pairwise comparison of the four active PF-06650833 arms and the placebo using the ANCOVA models of the same structure. No prior knowledge on placebo will be integrated. The raw and adjusted for multiplicity p-values will be reported. (Multiplicity adjustment will be performed using Hochberg's test). Means and variances of placebo adjusted treatment effects will be reported.

The secondary and sensitivity analysis will also include: ANCOVA models adjusting for SDAI baseline value, nominal treatment indicator, TNF exposure status (models including geography or country effect will also be considered). Fitting parametric monotone models for dose - response estimation after conducting Bayesian predictive checks on monotonicity (3 and 4 parameter E_{max} models, semiparametric models based on spline fitting); advanced data visualization techniques for statistical results presentations. This will include multivariate parallel coordinate plots representing each patient response across set of variables, correlation plots, density estimates for SDAI score, box-plots for SDAI and DAS score changes. Model fitting will be conducted using model discrimination approach based on AIC and BIC criteria as well as visual assessment of fit and residuals.

Missing values due to a patient dropping from the study for lack of efficacy or adverse event, will be handled by setting the SDAI score to nonresponsive (baseline observation carried forward, BOCF).

Missing values that occur while the patient is still enrolled (eg, due to a protocol deviation where the data were not collected), will be handled by the method of last observation carried forward (LOCF). The most recent data on each SDAI domain will be used for calculating the missing SDAI score.

9.2.1. Analyses of SecondaryEndpoints

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 theendpoints 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 data visualization methods.

Data obtained on tofacitinib from this study will be integrated with data 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.

9.4. Randomization

The indicator of prior exposure to anti-TNF treatment will be used as a stratification variable for randomization. The randomization will be stratified with respect to this variable to have equal balance on enrolment of TNF naïve (or TNF exposed) subjects across all arms.

9.5. Safety Analyses

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

- Adverse events will be summarized according to Pfizer standards;
- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials, will be summarized;
- Any safety events that trigger withdrawal of a subject;
- Safety laboratory tests will be summarized according to Pfizer standards.

9.6. Interim Analysis

At least one interim analysis (IA) for futility may be performed. The final number and timing of the IA(s) will be defined by the sponsor, but preliminarily one may be conducted at approximately 6 months after the randomization of the first subject and/or after at least 50% of the planned subjects, ie, approximately 100 subjects, completed the twelve week active treatment phase.

The interim analysis will not have an option to stop the trial early for efficacy.

Interim analysis details and futility boundaries will be detailed in the SAP.

No interim analysis of the kind requiring sample size re-estimation or adjustment of type-I error will be conducted.

9.7. Data Monitoring Committee

This study will have a Data Monitoring Committee (Independent Oversight Committee), which will be an Internal Review Committee (IRC) to help with safety review. The primary function of the IRC will be to perform any planned IAs, as conducted. If conducted, the IA will be used for a futility analysis and/or for the purpose of internal business decisions.

Members of the IRC will include at least two Pfizer clinicians (at least one of these shall be medically qualified) with drug development experience and at least one statistician. To ensure that the blind is maintained, individuals involved in the operational running of the study will not be members of the IRC. IRC members will not have direct involvement in the conduct of the clinical study nor will they be permitted to interact with investigators, monitors, vendors, etc. who are involved in the execution of the clinical trial activities. Strict procedures (eg, secured data transfer processes) will be implemented for maintaining data integrity and, especially, restricting access to treatment assignments or other unblinded clinical data.

During the course of the study, the study team will conduct safety monitoring using targeted and cumulative safety review of blinded data. If at any point in the conduct of the study, this safety review should identify any new emerging safety signals, the IRC will be consulted. If appropriate, the IRC will then conduct an unblinded safety data review. The chair of the IRC will provide recommendations to the Pfizer project team via the Clinical Lead based upon the unblinded safety data review. The IRC will also be responsible for any scheduled IAs.

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10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

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 is fully informed about the nature and objectives of the study and possible risks associated with participation.

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

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

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

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

12.5. Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

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 OtherParticipating Countries

End of trial in all other participating countries is defined as last patient last visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06650833 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 patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

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

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

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

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Appendix 1. Abbreviations

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

Abbreviation	Term
AE	adverse event
ACR	american college of rheumatology
ACPA	anti-citrullinated protein antibodies
AIC	Akaike Information Criterion
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the curve
BA	bioavailability
BCRP	Breast Cancer Resistance Protein
BIC	Bayesian Information Criterion
BID	twice a day
BOCF	baseline observation carried forward
BP	blood pressure
BBS	Biospecimen Banking System
BUN	blood urea nitrogen
C_{max}	peak or maximum observed concentration
CK	creatine kinase
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
cTn-I	cardiac troponin-I
CYP	Cytochrome p
DAMPs	damage associated molecular patterns
DAS	disease activity score
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMARD	Disease-modifying antirheumatic drugs
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
CCI	[redacted]
EC	ethics committee
ECG	electrocardiogram

Abbreviation	Term
eGFR	estimated glomerular filtration rate
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EFD	embryo-fetal developmental
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
EQ-5D-3L	European Quality of Life-5 dimensions-3 level
ESR	erythrocyte sedimentation rate
EU	European Union
EudraCT	European Clinical Trials Database
EULAR	European League Against Rheumatism
EW	early withdrawal
CCI	[redacted]
FACIT	Functional Assessment of Chronic Illness Therapy fatigue scale
FSH	follicle-stimulating hormone
FU	follow up
fu	fraction unbound
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
GGT	Gamma-glutamyl transferase
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HCV	hepatitis C virus
HDL	High density lipoprotein
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
hsCRP	high-sensitivity C-reactive protein
HRQL	health-related quality of life
IA	interim analysis
IB	Investigator brochure
IC50	50% inhibitive concentration
IC90	90% inhibitory 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	I interferons
IM	intramuscular

Abbreviation	Term
INR	international normalized ratio
IP	investigational product
IRAK4	Interleukin (IL) -1 receptor associated kinase 4
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
IWR	interactive web response
JAK	Janus kinase
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LDAS	low disease activity score
LDL	Low density lipoprotein
LFT	liver function test
LOCF	last observation carried forward
LPS	lipopolysaccharide
LSLV	last subject last visit
LTE	long-term extension
MATE	multidrug and toxin extrusion protein
MCP	metacarpophalangeals
MCS	mental component score
MR	Modified release
MRI	magnetic resonance imaging
MTX	Methotrexate
N/A	not applicable
NMSC	nonmelanoma skin cancers
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OATP	organic anion transporting polypeptide (OATP)
OCT	human organic cation transporter
PAAP	Patient Assessment of Arthritis Pain
PCD	primary completion date
PCS	Physical Component Score
PD	Pharmacodynamics(s)
PFS	prefilled syringe
PGx	Pharmacogenomics(s)
PhGA	Physician Global Assessment
PI	principal investigator
PK	pharmacokinetic
PT	prothrombin time
PTT	thromboplastin time
PtGA	patient global assessment
QFT-G	QuantiFERON®-TB GOLD

Abbreviation	Term
RA	Rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDAI	Simplified Disease Activity Index
SDD	spray dried dispersion (SDD)
SLE	Systemic Lupus Erthematosus
SOP	standard operating procedure
SRSD	single reference safety document
SJC	Swollen Joint Count
TB	Tuberculosis
TBili	total bilirubin
TIR	toll/interleukin-1 receptor
TJC	Tender Joint Count
TLR	toll like receptor
TRIF	Toll/interleukin-1 receptor domain-containing adapter inducing IFNβ
TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
TNFi	TNF inhibitors
ULN	upper limit of normal
US	United States
WONCBP	women of non-childbearing potential
WOCBP	women of childbearing potential
WBC	Whole blood cell

Appendix 2. 2010 ACR/ EULAR Classification Criteria for Rheumatoid Arthritis

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

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. Leflunomide Wash-out Procedures

Leflunomide: Subjects must have discontinued 4 weeks for leflunomide with an elimination procedure as follows: cholestyramine at a dosage of 8 grams 3 times daily for at least 24 hours, or activated charcoal at a dosage of 50 grams 4 times a day for at least 24 hours.

Appendix 5. Prohibited Concomitant Medications

CYP3A4, 5,7 and/or CYP2C19 Inhibitors	CYP3A Inducers	BCRP Inhibitors
	efavirenz (Sustiva)	cyclosporine
delavirdine (Rescriptor)	nevirapine (Viramune)	Elacridar (FG120918)
indinavir (Crixivan)	barbiturates	eltrombopag
nelfinavir (Viracept)	carbamazepine (Carbatrol, Tegretol)	gefitinib
ritonavir (Kaletra, Norvir)	modafinil (Provigil)	
saquinavir (Fortovase)	phenobarbital	
	phenytoin (Dilantin, Phenytek)	
amiodarone (Cordarone, Pacerone)	rifampin (Rifadin, Rifamate, Rifater)	
cimetidine (Tagamet)	St. John's wort	
ciprofloxacin (Cipro)	troglitazone (Rezulin)	
clarithromycin (Biaxin, Prevpac)	pioglitazone (Actos)	
Telithromycin (Ketek)		
chloramphenicol		
voriconazole (Vfend)		
diethyl-dithiocarbamate	rifabutin (Mycobutin)	
diltiazem (Cardizem, Tiazac)		
erythromycin		
fluconazole (Diflucan)		
fluvoxamine (Luvox)		
gestodene (Femodene, Melodene, Minulette, Mirelle, Triodene ED)		
grapefruit juice		
itraconazole (Sporanox)		
ketoconazole (Nizoral)		
mifepristone (Mifeprex, RU486)		
nefazodone (Serzone)		
norfloxacin (Shibroxin, Noroxin)		
norflouxetine		
mibefradil		
verapamil (Calan SR,Covera HS, Isoptin SR, Tarka, Verelan)		

Appendix 6. Guidelines for Monitoring and Discontinuations

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

- neutrophil counts <1000 neutrophils/mm^3,
- a decrease of hemoglobin<2.0 g/dL from baseline, regardless of baseline value,
- platelet counts <75,000 platelets/mm^3,
- an increase in serum creatinine of >30% AND >0.2 mg/dL from baseline.

Treatment with Tofacitinib will be discontinued and the subject withdrawn from this study for:

- serious infections (those requiring parenteral antimicrobial therapy or hospitalization),
- confirmed neutrophil counts <500 neutrophils / mm^3,
- confirmed hemoglobin <7.5 g/dL,
- confirmed platelet counts <50,000 platelets/ mm^3,
- confirmed AST or ALT elevations >3 X ULN which do not resolve promptly with adjustment of concomitant medications,
- confirmed increase in serum creatinine >50% over baseline value,
- other serious or severe AEs, after consultation with the Pfizer clinician.

Appendix 7. Disease Activity Score (DAS-28-4 (CRP)) Assessment

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

- Swollen Joints (0–28);
- Tender Joints (0–28);
- hsCRP (high sensitivity C-reactive protein);
- 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 (PGA [mm]) + 0.96

Appendix 8. HAQ-DI

Health Assessment Questionnaire - Disability Index (HAQ-DI)© Stanford University 1983 version:[1]

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 difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
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 9. 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 10. 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 11. 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 12. SF-36 Version 2 (Acute)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3

b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐[1]	☐[2]	☐[3]
c. Lifting or carrying groceries	☐[1]	☐[2]	☐[3]
d. Climbing several flights of stairs	☐[1]	☐[2]	☐[3]
e. Climbing one flight of stairs	☐[1]	☐[2]	☐[3]
f. Bending, kneeling, or stooping	☐[1]	☐[2]	☐[3]
g. Walking more than a mile	☐[1]	☐[2]	☐[3]
h. Walking several hundred yards	☐[1]	☐[2]	☐[3]
i. Walking one hundred yards	☐[1]	☐[2]	☐[3]
j. Bathing or dressing yourself	☐[1]	☐[2]	☐[3]

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
	▼	▼	▼	▼	▼
a. Cut down on the amount of time you spent on work or other activities	☐[1]	☐[2]	☐[3]	☐[4]	☐[5]
b. Accomplished less than you would like	☐[1]	☐[2]	☐[3]	☐[4]	☐[5]
c. Were limited in the kind of work or other activities	☐[1]	☐[2]	☐[3]	☐[4]	☐[5]

d. Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the <u>amount of time</u> you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. <u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5
c. Did work or other activities <u>less carefully than usual</u>	☐1	☐2	☐3	☐4	☐5

6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much bodily pain have you had during the past week?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b. Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f. Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g. Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h. Have you been happy?	☐1	☐2	☐3	☐4	☐5
i. Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b. I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c. I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d. My health is excellent	☐1	☐2	☐3	☐4	☐5

(SF-36v2 Acute, US Version 2.0)

THANK YOU FOR COMPLETING THESE QUESTIONS!*[1]*

Appendix 13. FACIT-Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days or last visit??.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An 12	I am too tired to eat	0	1	2	3	4
An 14	I need help doing my usual activities	0	1	2	3	4
An 15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An 16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 14. EQ-5D-3L

EQ - 5D

Health Questionnaire

English version for the US

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (eg, work, study, housework, family or leisure activities)

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

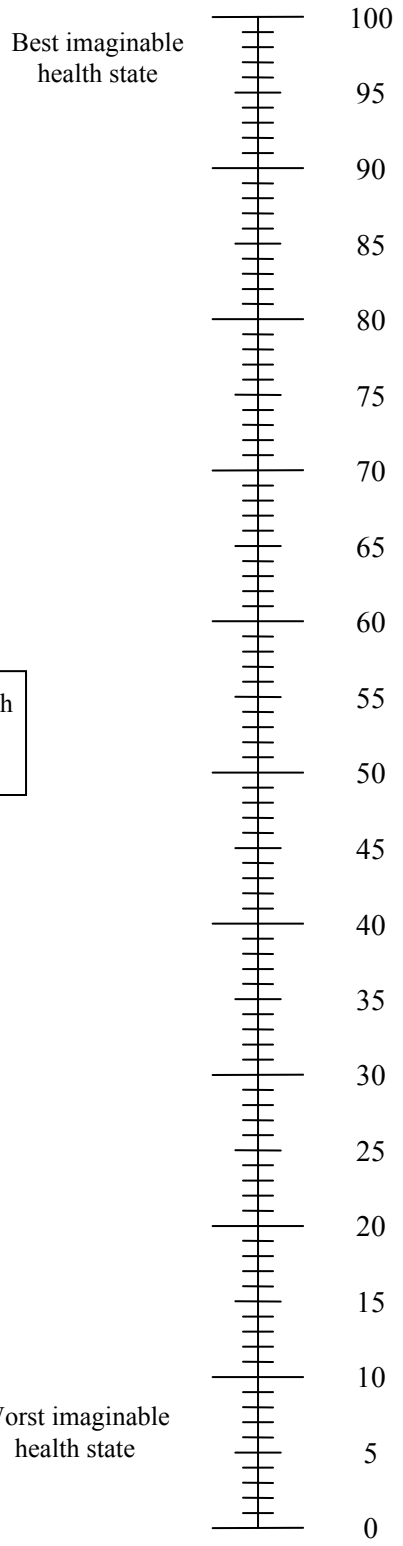
I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



Your own health state today

For Investigator's Use Only

Score ___

Appendix 15. Oral Corticosteroid Equivalents

The following is a summary of corticosteroid equivalents.

Oral corticosteroids – subjects already taking oral corticosteroids must be on a stable dose of ≤10 mg/day of prednisone or equivalent for at least 4 weeks prior to first dose of study drug. Tapering or discontinuation of the corticosteroid treatment is only allowed after Week 12, unless required for toxicity, and should be performed slowly at the discretion of the investigator.

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

Note: these dose relationships apply to oral administration.

Appendix 16. Approximate Equivalent Morphine Doses Of Opioid Analgesics

Common opioid analgesics

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

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

References:

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