A 24-WEEK RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, ACTIVE COMPARATOR, MULTICENTER STUDY TO ASSESS THE EFFICACY AND SAFETY OF PF-06650833, PF-06651600 (RITLECITINIB) AND TOFACITINIB ALONE AND IN COMBINATION IN PARTICIPANTS WITH MODERATELY-SEVERELY ACTIVE RHEUMATOID ARTHRITIS WITH AN INADEQUATE RESPONSE TO METHOTREXATE

Investigational Product Number:	PF-06650833; PF-06651600; CP-690550 MR
Investigational Product Name:	N/A; ritlecitinib; tofacitinib (Xeljanz®)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2019-002676-14
Protocol Number:	B7921023
Phase:	Phase 2

Short Title: A Study to Assess the Efficacy and Safety of PF-06650833, PF-06651600 (ritlecitinib), and Tofacitinib Alone and in Combination in Active Rheumatoid Arthritis

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amendment 3	10 February 2022	The protocol is amended to include revisions to the estimands and statistics sections of the protocol (as well as administrative changes documented in PACLs) that were needed for reporting purposes and to support updates to the data analysis and reporting plan for programming. • Synopsis and Section 3 updated. CCI [redacted] • Synopsis text updated. Rationale: per PACL text corrected to delete repetitive sentence corresponding to folate/folinic acid discontinuation. • Section 2.1 updated. Rationale: per PACL text corrected to indicate that both combination arms (not 1 combination) will be compared to tofacitinib. • Section 2.2.5.3 text corrected. Rationale: per PACL corrected the Investigator Brochure's "b" to large cap. • Synopsis and Section 3: clarified that the table of objectives, endpoints and estimands includes key estimands and additional supportive estimands will be described in the SAP. Rationale: allows inclusion supportive estimands into SAP. Modified the evaluation of estimands E1,E2,E3 so that these use the intent to treat (treatment policy) approach. The approach compares

		treatment efficacy across the treatment groups irrespective of the study participant's compliance with study treatment and use of concomitant medications. The effects of these post-randomization (intercurrent) events on the evaluation of treatment efficacy will be explored in the sensitivity analyses. The sensitivity analyses will be described in SAP. Rationale: make the analyses identical to the analyses planned in the forthcoming Phase 3 study. Replaced the estimation of the expected ratio of proportions in the analysis of secondary binary outcomes by the estimation of the expected difference of proportions. The comparison of the ratios of proportions of responders is retained for the key secondary outcome (DAS28-CRP remission at Week 24). Rationale: This comparison is preferable for the outcomes (eg, ACR 90) where the observed proportions of responders may be low. CCI [redacted] • Sections 2, 2.2 and 2.2.2 text corrected. Rationale: per PACL corrected the error "JAK3/TEC" to "JAK3" since tofacitinib does not inhibit TEC kinases. • Section 2.2.5.2 corrected text: ….(5) change in neutrophil counts; (6) decreased platelet count; (7) alterations in the lipid profile; ~~and~~ (8) dermatologic effects (rash/acne);….. .

		Rationale: per PACLcorrected error in text. • Section 4.1 deleted “study intervention”. Rationale: per PACL text corrected. • Section 6.5.2.1 corrected “desosumab” to “denosumab”. Rationale: per PACL text correction. CCI [redacted] • Section 9.1: Updated the description of key estimands (E1,E2,E3) replacing earlier version of the description. Rationale: make the analyses identical to the ones planned for the forthcoming Phase 3 study. • Section 9.2: Updated the text for the key secondary outcome so that it matches the updated definition of the key secondary estimand E2. Rationale: support consistency with Sections 9.1, 9.4.1. • Section 9.3: Removed populations for the censored mITT and composite analysis. Rationale: these populations and corresponding data sets are no longer needed for the analyses described in the protocol. • Section 9.4.1: Updated the description of the efficacy analyses to match the updates in the estimands. Rationale: support consistency with Sections 9.1, 9.4.1.

		Updated the statistical inference method used in the analysis of key secondary outcome. The exact method will replace the method based on normal approximation. Rationale: updated approach will be more precise if the numbers of responders at Week 24 are small. • Section 9.4.2 removed 3 tier safety analysis CCI [redacted] • For consistency 'Subject' changed to 'study participant' throughout the protocol.
Amendment 2	07 July 2021	• Synopsis, Study Design, Section 4.1 and 5.1 (inclusion #7): methotrexate (MTX) discontinuation and prohibition clarification. Rationale: text clarification. • Synopsis and Section 4.1: folinic acid intake clarification. Rationale: text clarification. • Synopsis and Section 3: clarified objectives, estimands and endponits text. Rationale: text clarification. • Section 1.3 Schedule of Activity, footnote "i": updated to include Rheumatoid Factor (RF) in the list of labs that may be repeated once during the screening period. Rationale: to correct omission of RF from the list of labs.

		• Section 1.3 Schedule of Activity, footnote "k": revised to include a urine culture when urine microsopy is suggestive of infection. Rationale: to clarify procedure for collecting urinalysis samples. CCI [redacted] • Section 2.2.5.2: PF-06651600 updated the clinical overview summary. Rationale: to align with the PF-06651600 Dec 2020 Investigator's Brochure. • Section 2.2.5.3: Tofacitinib (CP-690550, Xeljanz®) updated the clinical overview summary. Rationale: to align with the Tofacitinib Apr 2020 Investigator's Brochure. • Section 2.3: added new risk text for tofacitinib. Rationale: reflects emerging safety information from A3921133 provided as a Provision of Critical Safety Information to RAs, investigators, ECs. • Section 4.1: updated to clarify the study design. Rationale: text clarification. • Section 4.2.3 title revised. Rationale: to reflect changes to the study design. • Section 5.1, inclusion #4: clarified to allow participants to enroll into the study provided

		that re-testing Erythrocyte Sedimentation Rate (ESR) result is >28 mm/h. Rationale: text clarification. • Section 5.2, exclusion #3 (b, c, d, e) are added to clarify exclusion of participants with COVID-19. Rationale: this update is to clarified that participants with an active infection due to SARS-CoV-2 are excluded from randomization consistent with the exclusion for other active infections. • Section 5.2, exclusion #3 (f) updated. Rationale: to clarify and add the criterion of 60 days within "randomization" for exclusion of participants with infection requiring hospitalization, parenteral antimicrobial therapy. • Section 5.2, exclusion #3 (h): clarified the herpes zoster exclusion language. Rationale: text clarification. • Section 5.2: added exclusion criterion #21 to exclude participants with history of any medical condition associated with an increased risk of venothromboembolism (eg, paroxysmal atrial fibrillation) unless properly anti-coagulated. Rationale: to minimize potential risk of participants developing a major adverse cardiac event. • Section 5.2, exclusion #24: clarified that participants with any known "history" of coagulopathy or hypercoagulation syndrome are excluded.

		Rationale: to clarify exclusion criteria clarification. • Section 5.2, exclusion #27: deleted the word "recent" in reference to prohibited DMARDs. Rationale: corrected text. • Section 5.2, exclusion #33: clarified that participants with an electrocardiogram (ECG) performed prior to randomization that demonstrates atrial fibrillation are excluded unless subject is on a stable, therapeutic dose of non-excluded anti-coagulant. Rationale: to minimize potential risk of participants developing a major adverse cardiac event. • Section 6: text clarified. Rationale: text clarification. • Section 6.1.1, Table 1 updated to clarify that ritlecitinib tablets are immediate release. Rationale: text clarification. • Section 6.4: added the word "treatment" that is missing from the study intervention compliance paragraph. Rationale: corrected omission of text. • Section 6.5.2.1: created new subsection related to concomitant medications used to increase bone mineral density. Rationale: clarification of text related to dosing of permitted medications. • Section 6.5.2.3: corrected a discrepancy in the wording of "background arthritis therapy". Rationale: text corrected.

		• Sections 6.5.3.3 and 6.5.3.4: updated to specify that the use of substrates of CYP3A4 and BCRP be avoided within 4 weeks or 5 half-lives (whichever is longer) prior to the Randomization Visit (Visit 2) and during the trial. Rationale: potential to increase exposure when co-administered with PF-06651600. • Section 7.1: clarified that when IP is permanently discontinued, the participant will enter the required 4-week FU period. Rationale: text clarification. • Section 7.2: clarified that interruption in dosing of study treatment for more than 7 consecutive days may be due either to lack of compliance or in response to an AE. Rationale: clarified guidance about the definition of study treatment interruption. • Section 8.1.1.1: clarified the definition of blinded joint assessor. Rationale: text clarification. CCI [redacted] • Sections 8.1.2.1 and Appendix 10.10: clarified that the Disease Activity Scores DAS28-CRP

		CCI [redacted] Rationale: provided detail about DAS28-CRP CCI [redacted] CCI [redacted] • Section 8.2.5.3: clarified that the investigators will complete the "rash assessment CRF" not a questionnaire. Rationale: text clarification. • Section 8.2.5.3: corrected and replaced the word "will" with "may" as the study team may consult an independent dermatologist to review all relevant data and summarize the data at the end of the study. Rationale: text corrected. • Section 8.3.6: added new adjudication committees that will be used in the study. Rationale: to enhance assessment of targeted AEs. • Sections 8.3.7 and 8.4: corrected and replaced the word "immediately" with "within 24 hours".

		Rationale: to align with Pfizer May 2020 protocol template updates. • Section 8.4: corrected and replaced "until investigational products can no longer be detected systemically (at least 2 days)" with "for at least 5 half-lives or 28 calendar days after the overdose of investigational products (whichever is longer)". Rationale: to align with Pfizer May 2020 protocol template updates. • Section 8.11: corrected and replaced the word "jaundiced participant" with "jaundiced person". Rationale: text corrected. • Section 9.1: corrected the definition of the noncompliant participant. Rationale: text corrected. • Section 9.2: described the sample size estimation in the updated design. Rationale: to describe the sample size estimation in the updated design and clarify that additional participants may be enrolled into the study if the dropout rate of enrolled participants exceed 18% due to the COVID-19 pandemic. • Section 9.3: corrected a discrepancy in the definition of non-responders. Rationale: text corrected. • Section 10.2 Appendix 2: added "urine culture" test that is missing from Table 3 and updated footnote 'e'. Rationale: corrected Table 3.

		• Section 10.2 Appendix 2: deleted 'Microscopy' test from Table 3. Rationale: listed twice. • Section 10.3.2:"Definition of the SAE, section e updated". Rationale: to align with Pfizer May 2020 protocol template updates. • Section 10.3.3: Recording/Reporting and Follow up of AEs and/or SAEs updated. Rationale: text was accidently deleted. • Section 10.3.4: Reporting of SAEs. Rationale: section reordered. • Section 10.4.4: deleted "injectable" from contraception highly effective methods that are user dependent. Rationale: to align with Pfizer May 2020 protocol template updates. CCI Rationale: text clarification. • Section 10.11, Appendix 11 updated. Rationale: included a list of CYP3A4 substrates with NTI prohibited concomitant medications. • Section 10.12: adjusted the list of corticosteroid equivalents to a 7.5 mg dose of prednisone. Rationale: corrected the list of corticosteroid equivalents.

		• Section 10.13: Appendix 13 is added to the protocol. Rationale: to provide guidance on the alternative study measures to be followed during public emergencies, including the COVID-19 pandemic. • Section 10.14: Appendix 14, abbreviation table updated. • JAK3 changed to JAK3/TEC throughout. Rationale: text corrected.
Amendment 1	08 April 2020	To comply with Health Canada Information Request, the contraception requirement in Appendix 10.4.2 is updated to the use of two forms of contraception regardless of the user dependency of the method(s) for participants enrolled at Canadian sites. This includes at least one form of highly effective and one effective method of contraception.
Original protocol	22 October 2019	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title:

A STUDY TO ASSESS THE EFFICACY AND SAFETY OF PF-06650833, PF-06651600, AND TOFACITINIB ALONE AND IN COMBINATION IN ACTIVE RHEUMATOID ARTHRITIS

Rationale

Rheumatoid arthritis (RA) is characterized by joint inflammation and destruction, progressive disability, and adverse psychological effects. Disease-modifying antirheumatic drugs (DMARDs) are the standard treatments for RA. However, despite the considerable list of approved treatments for RA, disease remission (or even low disease activity, [LDA]) is achieved in only a minority of patients and none completely cures the disease. Clearly, there is a need for therapeutics with enhanced efficacy that drive a higher proportion of patients to LDA and remission. It is also becoming evident, given the results with biologic and newer advanced therapeutic DMARDs administered alone or in combination with methotrexate (MTX), that such levels of activity may be difficult to achieve with drugs targeting a single pathway or cytokine. Combinations of drugs with complementary mechanisms of action offer the potential to achieve the goal of improved efficacy without incurring additional safety liabilities.

The aim of the current study is to evaluate two different drug combinations to see if either can achieve the dual objectives of increased efficacy compared to currently available standard of care RA drugs while maintaining an acceptable safety profile (and therefore an overall positive benefit : risk relationship). All of the individual components of the combinations being explored in the current study have demonstrated efficacy in RA--either showing clinical benefit in Phase 2 studies (PF-06650833 and PF-06651600) or having completed registration and approval (tofacitinib). The components of the combinations to be evaluated, PF-06650833 + tofacitinib and PF-06650833 + PF-06651600, have non-overlapping mechanisms of action. Moreover, PF-06650833 and PF-06651600 have appeared generally well-tolerated in their Phase 2 studies so have the potential for not having increased safety liabilities in combination with each other, or, for PF-06650833 with tofacitinib.

Objectives, Estimands, and Endpoints

Objectives	Endpoints	Estimands***
Primary	**Primary**	**Primary**
• To compare the efficacy of each of 2 combinations (PF-06650833 + PF-06651600, PF-06650833 + tofacitinib) individually to tofacitinib alone at Week 12 in participants with moderately - severely active RA who have had an inadequate response to MTX.	• Change from baseline in Disease Activity Score (DAS)28-C Reactive protein (CRP) at Week 12.	• E1: Evaluates the difference across the treatment arms in the mean values of change from baseline of continuous outcome of interest. The treatment effect is evaluated in the population of study participants who are randomized and treated irrespective of their compliance to the planned course of treatment or use of concomitant medications.
Key Secondary	**Key Secondary**	**Key Secondary**
• To compare the remission rates of each of 2 combinations (PF-06650833 + PF-06651600, PF-06650833 + tofacitinib) individually to tofacitinib alone at Week 24 in participants with moderately - severely active RA who have had an inadequate response to MTX.	• DAS28-CRP remission (<2.6) at Week 24.	• E2: Evaluates the ratio of the probability of response in the treatment arm of interest to the probability of response in the tofacitinib treatment arm. The treatment effect is evaluated in the population of study participants who are randomized and treated irrespective of their compliance to the planned course of treatment or use of concomitant medications.

Secondary	Secondary	Secondary
• To assess the safety of PF-06650833, PF-06651600, and tofacitinib alone and of the combinations of PF-06650833 with PF-06651600 and tofacitinib in participants with moderately - severely active RA who have had an inadequate response to MTX.	• Incidence and severity of adverse events, serious adverse events, and withdrawals due to adverse events. • Change from baseline in clinical laboratory values (chemistry, hematology parameters). • Change from baseline in vital signs (blood pressure, pulse rate and temperature measurements). • Incidences of severe and opportunistic infection AEs; herpes virus infection AEs; clinically significant categorical increases in hepatic enzymes Aspartate aminotransferase (AST), and Alanine aminotransferase (ALT) and total bilirubin, and potential cases meeting Hy's Law criteria for increased risk of drug-induced liver injury [DILI]; major adverse cardiovascular events (MACE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), Cerebrovascular accident (CVA); Adverse events (AEs) for decreased renal function, acute kidney injury, clinically significant increases in	• There is no defined estimand for these endpoints. They will be analyzed using Pfizer data standards as applicable.

	serum creatinine (Scr) and decreases in estimated glomerular filtration rate (eGFR).	
• To evaluate other signs of clinical efficacy of all treatment arms in participants with moderately - severely active RA who have had an inadequate response to MTX.	• Change from baseline in DAS28-CRP at Week 24. • American College of Rheumatology (ACR)20, ACR 50, ACR 70, and ACR 90 responder rates at Week 12 and Week 24. • Change from baseline in the Tender/Painful and Swollen Joint Count at Week 12 and Week 24. • Change from baseline in the Physician's Global Assessment (PhGA) of Arthritis at Week 12 and Week 24.	• E1 estimand for continuous and E3 estimand for binary efficacy outcomes. • E3: Evaluates the differences in probability of response of the treatment arm of interest in comparison to the tofacitinib treatment arm. The treatment effect is evaluated in the population of study participants who are randomized and treated irrespective of their compliance to the planned course of treatment or use of concomitant medications.

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• To collect blood for the potential exploratory analyses of pharmacodynamic activity of PF-06650833, PF-06651600, and tofacitinib alone and in combination with PF-06650833 in participants with moderately - severely active RA.	• Change from baseline: anti-citrullinated protein antibodies (ACPA), rheumatoid factor (RF) and Ig levels. • Change from baseline of Interferon Gamma-Induced Protein 10 (IP-10), if performed. • Endpoints may also include circulating proteins and protein fragments.	• All continuous endpoints will be analyzed descriptively. Other analyses may be done and will be described in the statistical analysis plan (SAP). • All other categorical endpoints will be analyzed descriptively. Other analyses may be done and will be described in the SAP.

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• To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision.	• Not applicable.
• To evaluate the effects of PF-06650833, PF-06651600, and tofacitinib alone and in combination on joint inflammation assessed by magnetic resonance imaging (MRI), in a	• Change from baseline in Rheumatoid Arthritis MRI Score (RAMRIS) and exploratory measures of joint inflammation (eg, RAMRIQ, DCE), if performed, in hand MRI at Weeks 12 and 24.	• All continuous endpoints will be analyzed descriptively. Other analyses may be done and will be described in the statistical analysis plan (SAP). • All other categorical endpoints will be analyzed

subset of participants, if performed.		descriptively. Other analyses may be done and will be described in the SAP.

* Efficacy evaluations that are otherwise classified in the table as primary, key secondary o[redacted]

[redacted]

*** The additional supportive estimands will be described in the SAP.

Overall Design

This is a Phase 2, 24-week, multicenter, randomized, double-blind, 5-arm, parallel group, active comparator study to evaluate the efficacy and safety profiles of 2 combinations of investigational products (IPs): PF-06650833 coadministered with PF-06651600 (PF-06650833 + PF-06651600) and PF-06650833 coadministered with tofacitinib (PF-06650833 + tofacitinib), as well as the efficacy and safety of each IP individually in the absence of background MTX in participants with moderately - severely active RA who have had an inadequate response to MTX (MTX-IR).

Both PF-06650833 and tofacitinib will be administered as modified release (MR) tablets to allow for once daily administration. The study is powered to show statistical superiority of the combination to tofacitinib monotherapy at Week 12.

After an up to 28-day screening period, eligible participants will enter a 24-week active treatment period after being randomly assigned to one of the 5 treatment groups shown in Section 1.2 Schema.

All doses will be administered orally once daily in a fasted state (about 4 hours after the last and 1.5 hours before the next meal). In order to maintain the blind and minimize bias, all participants will receive the same number and types of tablets each day as a mix of active and placebo tablets. MTX is to be discontinued (last MTX dose is to occur) during the week before randomization on Day 1 and be washed out during the active treatment phase. The MTX washout is intended to reduce the potential for excessive immune suppression and additive safety liability. Participants whose regularly scheduled MTX dose would have been on the day of randomization (Day 1) should not take that dose of MTX. No further MTX dosing is permitted during the active dosing phase of the study. Participants may restart MTX dosing beginning 14 days after the last dose of study intervention. Folate/folinic acid taken with MTX may also be discontinued in a manner consistent with local standard of care practice.

No changes in the background concomitant steroid dose is allowed during the study. During the active dosing period, no "rescue" treatment is pre-specified. However, limited – duration increases in permitted analgesic medication (acetaminophen/paracetamol, nonsteroidal anti-inflammatory drugs [NSAIDs], opiates) will be permitted for acute worsening of arthritis pain (see Permitted Concomitant Medications, Section 6.5.1 and Section 6.5.2). Participants,

who after at least a 12-week trial on the assigned investigational product have not achieved at least a minimal clinical response (as defined by the American College of Rheumatology [ACR] 20% response criteria [ACR20]) are to be discontinued from the study treatment and begin treatment for their RA according to local standard of care (SoC) practice. The Principal Investigator (PI) may also discontinue participants at any time during the study if in the PI's opinion, worsening RA signs and symptoms unresponsive to limited-duration increases in analgesic medications requires more urgent advancement of RA treatment. Additional treatment for participants meeting either of these criteria for discontinuation from the study will be provided by the investigator, and upon withdrawal from the study treatment, participants will enter a 4-week follow-up period and after which they will have End of Study (EOS)/follow-up (FU) visit. Investigational product will not be provided after the participant completes the study.

Number of Participants

A maximum of up to approximately 450 participants will be randomized into the study to ensure at least up to approximately 370 participants complete the study through Week 12.

Intervention Groups and Duration

Participants will be randomly assigned to 1 of the following 5 treatment groups in a 4:4:3:3:4 ratio (see also study schematic design in Section 1.2):

- PF-06650833 400 mg MR + tofacitinib 11 mg MR.
- PF-06650833 400 mg MR + PF-06651600 100 mg.
- PF-06650833 400 mg MR.
- PF-06651600 100 mg.
- Tofacitinib 11 mg MR.

All participants will receive up to 24 weeks of study treatment.

Data Monitoring Committee:

An Independent Oversight Committee (IOC) will be constituted and be responsible for review of unblinded safety and laboratory data on a regularly scheduled, periodic basis (eg, after 25%, 50% and 75% of participants have been randomized, and at specified times thereafter), as well as on an ad hoc basis at the request of the study team. The IOC may also have access to unblinded efficacy data from any interim analyses (if performed) for ongoing assessment of overall benefit: risk.

For this study, the IOC will be an Internal Review Committee (IRC) comprised of Sponsor personnel (at least one of whom is medically qualified and one of whom is a clinical statistician) not directly involved in study conduct or in interactions with site personnel or participants. The IRC will be responsible for ongoing monitoring of safety of participants in the study according to the Charter. Any recommendations made by the IRC to alter the conduct of the study will be forwarded to the Executive Committee for final decisions. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

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 is the mean change from baseline DAS28-CRP at Week 12. The primary analysis will use a mixed model repeated measures (MMRM) model applied to all post-baseline data up through Week 12 to estimate the effect of the initially randomized treatment at Week 12. The MMRM analysis will contain fixed effect terms for treatment, scheduled study visit, baseline DAS28-CRP, treatment by visit interaction, baseline by visit interaction. The model will use an unstructured covariance matrix. The analysis will use the mITT analysis set up to Week 12 Missing data will not be imputed for this analysis. The primary analysis comparing the combination arm to the tofacitinib monotherapy arm will be done using estimated least squares means at Week 12. The comparison will be made at the one-sided significance level of 0.05 and no adjustment for multiplicity of comparisons will be attempted.

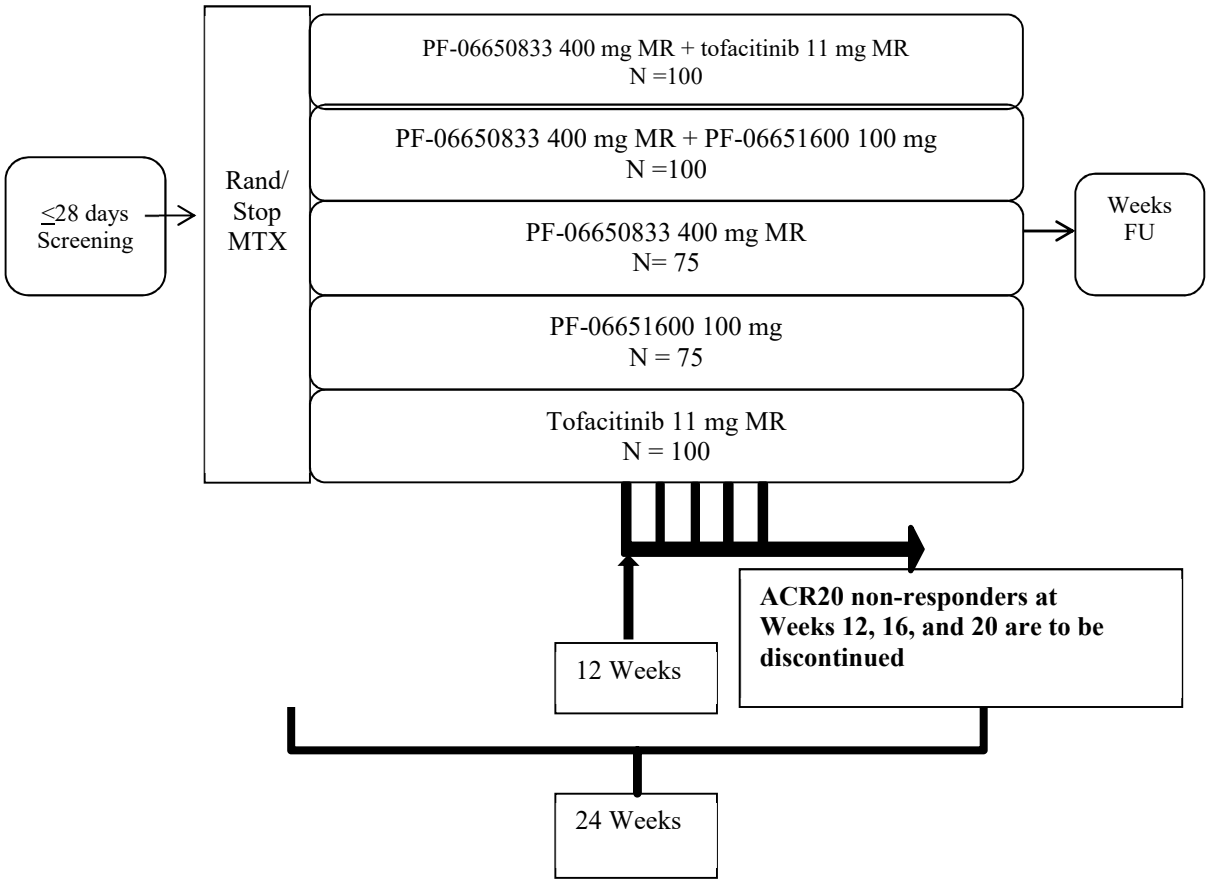
The key secondary endpoint is DAS28-CRP remission (DAS28-CRP <2.6) at Week 24. The key secondary analysis will estimate the relative risk of DAS28-CRP remission comparing each combination arm to the tofacitinib monotherapy arm.

This analysis will use the mITT analysis set and the non-responder imputation method (NRI). The NRI treats missing value of the binary outcome as non-response with the exception of the two special cases of the reason for missing data. These special reasons include missingness related to the COVID infection (either patient illness or COVID-related problem of attending the visit) and missingness when subject attended the visit but some of the components for the calculation of the outcome (eg, ACR20) are missing. The observations that are missing for these special reasons will be excluded from the calculation of the probabilities of response at a given visit. Exact statistical inference will be used.

The comparison will be made at the one-sided significance level of 0.05. No adjustment for multiplicity of comparisons will be attempted.

One or more interim analyses (IA) may be performed for internal business decision-making or sample size reestimation (there is no intention a priori to terminate the study or a treatment arm based on the results of the IA). The final number and timing of any IA, if performed, will be defined by the sponsor.

1.2. Schema



All doses are orally administered once daily under fasted conditions
Non-responders (defined as not meeting ACR20 response criteria) by Week 12 (or later) are to be discontinued from study.
MR=modified release; MTX=methotrexate; Rand=randomization; FU=follow-up; ACR=American College of Rheumatology.

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section 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 in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Protocol Activity	**Screening**	**Treatment Period**								**FU[b]/EOS**	**EW[b]**
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Study Day/Week[a]	**Screening**	**Day 1/ Baseline**	**Day 15 ±2**	**Day 29 ±2**	**Day 57 ±3**	**Day 85 ±3**	**Day 113 ±3**	**Day 141 ±3**	**Day 169 End of Treatment ±3**	**Follow-up[b] ±3**	
	Days -28 to 0	**Week 0**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	
Informed consent	X										
Inclusion/Exclusion Criteria	X	X									
Demographics	X										
RA history, Prior RA medications[c]	X										
Medical history and prior non RA medication history[d]	X										
Height	X										
Weight	X					X			X		
Vital Signs (Pulse, blood pressure), temperature[e]	X	X	X	X	X	X[e]	X	X	X	X	X
Complete Physical Examination[f]	X								X		X
Targeted Physical Examination[f]		X	X	X	X	X	X	X		X	
ECG (12 lead)[g]	X	X	X	X	X	X			X		X
Chest radiograph[h]	X										
Audiogram[w]	X								X		X
Magnetic resonance imaging (MRI) of hand[x]	X					X			X		
Laboratory Evaluations											
Blood chemistry (fasting), Hematology[i]	X	X	X	X	X	X	X	X	X	X	X
[redacted]											

Protocol Activity	Screening	Treatment Period								FU[b]/EOS	EW[b]
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Study Day/Week[a]	**Screening**	**Day 1/ Baseline**	**Day 15 ±2**	**Day 29 ±2**	**Day 57 ±3**	**Day 85 ±3**	**Day 113 ±3**	**Day 141 ±3**	**Day 169 End of Treatment ±3**	**Follow-up[b] ±3**	
	Days -28 to 0	**Week 0**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	
CCI [redacted]											
Blood sample for viral surveillance		X		X		X			X		
Urinalysis (including, protein creatinine, pH color, clarity, specific gravity) with microscopy (to be processed at central lab)[i,k]	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[l]	X	X	X	X	X	X	X	X	X	X	X
Contraception check[m]	X	X	X	X	X	X	X	X	X	X	X
Serum FSH (WONCBP only)	X										
HBsAg, HbcAb, HBsAB and HCVAb[n]	X										
HIV testing[o]	X										
Tuberculosis test[p]	X										
Banked biospecimen (whole blood, prep R1) for potential exploratory RNA Analysis		X	X			X			X		
Banked biospecimen (serum, Prep B2) for exploratory protein biomarker analysis		X	X			X			X		
Genomic banked biospecimens Prep D1 for potential DNA analysis[q]		X									
CCI [redacted]											

Protocol Activity	Screening	Treatment Period								FU[b]/EOS	EW[b]
Visit Identifier	1	2	3	4	5	6	7	8	9	10	
Study Day/Week[a]	Screening	Day 1/ Baseline	Day 15 ±2	Day 29 ±2	Day 57 ±3	Day 85 ±3	Day 113 ±3	Day 141 ±3	Day 169 End of Treatment ±3	Follow-up[b] ±3	
	Days -28 to 0	Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	
Efficacy assessments											
Tender/Painful Joint Count (68)	X	X	C	[redacted]	[redacted]	X	C	[redacted]	X	C	[redacted]
Swollen Joint Count (66)	X	X	C	[redacted]	[redacted]	X	C	[redacted]	X	C	[redacted]
Physician Global Assessment (PhGA) of Arthritis[r] VAS	X	X	C	[redacted]	[redacted]	X	C	[redacted]	X	C	[redacted]
Patient reported outcomes											
CCI [redacted]											
Dispensing of Investigational Product											
Investigational Product Dispensing		X		X	X	X	X	X			
Randomization (after all screening procedures are complete and reviewed)[s]		X									
Administration of IP[t]		X	X	X	X	X	X	X			
Review of participant diary (distribution and instructions on use of the diary on Week 0, review of participant dosing record at all other visits), IP accountability throughout the study		X	X	X	X	X	X	X	X		X
Prior/Concomitant treatment(s)		X	→	→	→	→	→	→	→	X	
Serious and nonserious adverse event monitoring	X	→	→	→	→	→	→	→	→	X	X
Discharge from the study										X	X

Abbreviations: →= ongoing/continuous event; CCI ; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; EW = early withdrawal; CCI FSH = follicle stimulating hormone; FU = Follow-up; CCI ; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBsAb = hepatitis B surface antibody; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; CCI IGRA = interferon-gamma release assay; CCI ; IP = investigational product; CCI ; MRI = Magnetic resonance imaging; CCI ; PhGA = Physician Global Assessment; RA = rheumatoid arthritis; CCI RNA = ribonucleic acid; WONCBP = women of non-childbearing potential; CCI VAS = Visual Analog Scale; w = week.

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 predose blood collections are to be performed prior to dosing unless otherwise stated. Additional unscheduled assessments should be performed as clinically indicated.

b. Any participant who prematurely withdraws from the treatment period should undergo the procedures for an early withdrawal visit and return for follow up visits approximately 4 weeks after the last dose of study drug as medically indicated in the opinion of the PI.

c. RA medications taken since diagnosis and before informed consent is signed (document non-drug treatment for RA in non-drug treatment CRF page).

d. Medical history includes history of: alcohol and drug abuse; tobacco and related product use; herpes virus infection; vaccination (particularly for HZV); major cardiovascular events including DVT, PE, and ischemic cerebral vascular accidents (CVA); skin rash; skin infection and any abnormalities that may predispose the subject to infection.

e. Vital Signs include sitting/semi-supine blood pressure, pulse rate, and temperature (oral, temporal and tympanic, using the same methods throughout the study), measured after approximately 10 minutes of rest. At W12 pulse will also be collected at approximately 2 to 4 hrs post dose.

f. Complete physical exam (PE) of major body systems. Additional targeted (limited) PE may be performed during the study at the investigator's discretion. Full and targeted physical examinations must include full body skin and neurologic examinations. Skin examinations should include visual inspection of the breasts and external genitalia. Neurologic examination would include assessment of cerebellar function (see Section 8.2.5).

g. 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). On Week 0, Week 2, Week 4, Week 8, Week 12 and Week 24 an ECG will be done before dosing.

h. Chest radiograph (posterior-anterior and lateral views are recommended; however local guidelines should be followed) is required at Screening. A chest radiograph or other appropriate diagnostic imaging modality (ie, computerized tomography 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.

i. 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, Rheumatoid Factor, CCI and Urinalysis. A delay in randomization up to 7 days for repeating labs will not be considered a protocol deviation. Fasting lipid profile will be assessed at Baseline, Week 12 and Week 24 (samples must be collected after a minimum 4-hour fasting), and includes: fasting total cholesterol, LDL, HDL and triglycerides.

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k. Collect urine samples for central laboratory urinalysis and urine microscopy, and urine culture. Urine microscopy is to be performed on all urine samples. Urine culture is indicated if the urinalysis is positive for blood, nitrite, leukocyte esterase and/or protein, the microscopic examination reveals numbers of neutrophils suggestive of infection, there is clinical suspicion of urinary tract infection, there is a decrease in renal function; or if otherwise clinically indicated.

l. 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.

m. Record all non-drug treatments, including non-drug contraception methods (eg, IUD placement), and contraception medications in medical history CRF page.

n. Participants will be screened for hepatitis B virus infection and will be excluded if positive for hepatitis B surface antigen (HBsAg). Participants with HBsAg negative testing but who test positive for hepatitis B core antibody (HBcAb) will be reflex tested for hepatitis B virus deoxyribonucleic acid (HBV DNA) and, if HBV DNA is negative, will be allowed to enroll in the study. Participants will be screened for hepatitis C virus (HCV Ab) and will be reflex tested for HCV ribonucleic acid (HCV RNA) if positive for HCV Ab. Only participants with negative HCV Ab or HCV RNA, will be allowed to enroll in the study.

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

p. Participants with a positive IGRA TB test performed within 12 Weeks prior to Screening are excluded except as noted below. 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 participant who is currently being treated for either latent or active TB infection is to be excluded. Participants with a positive IGRA test who do not have a reliable history of adequate treatment with an effective regimen of anti-tuberculous combination therapy to which the TB strain is sensitive are excluded. Participants with a positive test and history of adequately treated active or latent TB should be referred to an appropriate specialist (eg, pulmonologist or infectious disease physician) for assessment for evidence of active TB. Participants with a positive IGRA who have been documented by this review not to have active TB may be enrolled in the study. The following are acceptable assays prior to screening: QuantiFERON® - TB Gold test (QFT-G), QuantiFERON® - TB Gold Plus test (QFT-G), QuantiFERON® - TB Gold In-Tube test (QFT-GIT) and T-SPOT® - TB test.

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r. Physician assessment should be performed without knowledge of PRO assessments.

s. If the absolute neutrophil count (ANC) is ≤1500/mm^3 at Screening, and the participant is eligible to enter the study, the ANC counts will need to be repeated (once) prior to the randomization visit, and the ANC must be ≥1500/mm^3 for the participant to be eligible for randomization. A delay (<2 Weeks) in randomization for repeating labs will not be considered a protocol deviation.

t. Investigational product tablets will be administered to the participant in the clinic on the morning of clinic visits and all other dosing will be performed by the participant outside of the clinic.

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w. Audiograms may be performed within a ±2-week window relative to the study visit.

x. MRIs, if performed, will be conducted in a subgroup of participants. Participants in the MRI subgroup will be recruited globally in the order of enrollment in the IVRS up to a maximum number as defined by the sponsor. Participants who refuse to undergo MRI may still be eligible for enrollment into the study. Baseline MRIs should be acquired after all other eligibility criteria have been met and at least 1 week prior to randomization. After randomization, MRIs will be performed at Visit 6/Week 12 (±1 week), and Visit 9/Week 24 (-2 to +1 week). A delay in acquisition of the Baseline MRI up to 1 week (7 days) after Randomization at Visit 2 (Week 0, Day 1) solely due to scheduling availability will not be considered a protocol deviation (PD).

y. Additional sample will be collected upon on presentation of infection.

2. INTRODUCTION

PF-06650833 is a potent, selective, small molecule, reversible inhibitor of interleukin-1 receptor-associated kinase 4 (IRAK4) that is currently under development for the treatment of RA and hidradenitis suppurativa (HS).

PF-06651600 is a potent, selective, covalent inhibitor of Janus kinase (JAK) 3/tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinases that is currently being investigated in patients with RA, Alopecia Areata (AA), Vitiligo, Ulcerative Colitis (UC), and Crohn's Disease (CD).

Tofacitinib (CP-690,550), is a potent, selective inhibitor of the JAK family of kinases. In kinase assays, tofacitinib, inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TyK2). Tofacitinib (as of 05 May 2018) has been approved (as an Immediate Release tablet) for the treatment of RA in 90 countries (including the US, Japan, and the EU) and is marketed in 54 countries (including the US, Japan, and the EU) for the treatment of RA; tofacitinib has also been approved in 5 countries as a Modified Release (MR) (also referred to as Extended Release [XR]) formulation.

2.1. Study Rationale

The aim of the current study is to evaluate 2 different drug combinations to see if either can achieve the dual objectives of increased efficacy compared to currently available standard of care RA drugs while maintaining an acceptable safety profile (and therefore an overall positive benefit : risk relationship). All of the individual components of the combinations being explored in the current study have demonstrated efficacy in Phase 2 studies in RA--either showing clinical benefit in Phase 2 studies (PF-06650833 and PF-06651600) or having completed registration and approval (tofacitinib). The components of the combinations to be evaluated, PF-06650833 coadministered with tofacitinib (PF-06650833 + tofacitinib) and PF-06650833 coadministered with PF-06651600 (PF-06650833 + PF-06651600), have non-overlapping mechanisms of action. Moreover, PF-06650833 and PF-06651600 have appeared generally well-tolerated in their Phase 2 studies so they have the potential for not having increased safety liabilities in combination with each other, or, for PF-06650833 with tofacitinib.

The study employs an active treatment period of 24 weeks to allow for a more robust assessment of remission rates, which generally require at least 6 months of drug treatment to manifest maximal drug activity. The longer treatment period will also provide greater insight into the overall safety profiles of the assigned study treatments. The study will be powered to show statistical superiority on DAS28-CRP of the combination to tofacitinib monotherapy at Week 12 and will include approximately 100 participants/arm for the combination and tofacitinib monotherapy arms, and approximately 75 participants/arm for the PF-06650833 and PF-06651600 monotherapy arms.

2.2. Background

Rheumatoid arthritis (RA) is a chronic, autoimmune disease characterized by joint inflammation and destruction, progressive disability, and adverse psychological effects. There are multiple therapeutic options for managing the pain and slowing the progression of RA rheumatoid arthritis, but none completely cures the disease. 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 they uncommonly induce clinical remission. Use of biologic DMARDs (bDMARDs), most commonly tumor necrosis factor alpha (TNFα) inhibitors, is indicated when symptoms are not adequately controlled with csDMARDs. More recently, small molecule inhibitors of Janus kinases (JAK) have been introduced into the RA therapeutic armamentarium. Tofacitinib was the first JAK inhibitor approved as a DMARD for the treatment of RA. A number of other JAK inhibitors are now either approved or in the late stages of clinical development. Despite the considerable list of approved treatments for RA, the treatment goal of disease remission (or even low disease activity [LDA]) is achieved in only a minority of patients and none completely cures the disease. Clearly, there is a need for therapeutics with enhanced efficacy that drive a higher proportion of patients to LDA and remission. It is also becoming evident given the results with biologic and newer advanced therapy DMARDs administered alone or in combination with MTX, that such levels of activity may be difficult to achieve with drugs targeting a single pathway or cytokine. Combinations of drugs with complementary mechanisms of action offer the potential to achieve the goal of improved efficacy without incurring additional safety liabilities.

IRAK4 is a serine, threonine kinase that serves as a key node in intracellular signaling downstream of the mydossome associated Toll Like Receptors (TLR 1, 2, 4, 5, 6, 7, 8, 9 and 10) and the Interleukin (IL)-1 family receptors (IL-1R, IL-18R and IL-33R). TLR signaling has been implicated pre-clinically and clinically in RA, variously mediating inflammatory responses to damage associated molecular patterns (DAMPs), such as nucleic acids, extracellular matrix components, and citrulline-modified self-antigens, by cells of the immune system as well as synoviocytes. Inhibition of IRAK4 blocks the production of cytokines such as type I interferons (IFN), and the inflammatory cytokines IL-6, TNFα, IL-1β, and IL-12, that are key drivers of autoimmune and inflammatory diseases such RA. Significantly, as noted below, the role of innate immune signaling in RA through these pathways has recently been validated in a proof-of-concept study of the IRAK4 inhibitor PF-06650833 (on a background of MTX) in patients with moderately to severely active RA.

The JAK family of kinases mediate pro-inflammatory signals induced by activation of type I and type II cytokine receptors. Many of the cytokines involved in synovial inflammation in RA utilize JAK-dependent signal transduction pathways, particularly those involving JAK1 and/or JAK3. This provides the rationale for targeting these cytokine signaling pathways in RA. The therapeutic benefit of inhibiting JAK signaling in RA has been validated clinically with the development initially of tofacitinib, and, more recently, by the Phase 3 clinical data with other JAK inhibitors.

2.2.1. PF-06650833

PF-06650833 is a highly selective, small molecule inhibitor of IRAK4 that is the first to have entered clinical development and successfully completed a Phase 2 clinical study in RA.

In preclinical experiments, PF-06650833 has been shown to inhibit inflammatory cytokine release induced by anti-citrullinated protein antibody – positive ($ACPA^+$) RA serum in primary human macrophages and to inhibit IL-1 and TLR ligand-induced inflammatory mediators in synovial fibroblasts from RA patients. As described in greater detail below, in a 12-week proof-of-concept study in patients with active RA, PF-06650833 (on a background of MTX) showed activity in reducing the signs and symptoms of RA with a safety profile compatible with a positive benefit: risk relationship.

As an inhibitor of TLR signaling, PF-06650833 targets a different part of the immune system from the JAK inhibitors. Given the partial redundancy of innate immune signaling through IRAK4-independent TLR pathways and the lack of direct suppression of T- and B-cell signaling, PF-06650833 is unlikely to lead to over immunosuppression. Thus, a combination of PF-06650833 with either tofacitinib or PF-06651600 has the potential for complementary anti-inflammatory activity that could lead to additive or synergistic efficacy in patients with RA while having the potential to avoid increasing adverse effects due to excessive immunosuppression.

The current study is designed to evaluate if either (or both) combination can achieve the dual objectives of superior efficacy while maintaining an acceptable safety profile.

Further details about PF-06650833 may be found in the current version of the single reference safety document (SRSD), which for PF-06650833, is the current version Investigator's Brochure (IB).

2.2.2. Tofacitinib

Tofacitinib (CP-690,550) 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 (Karaman et al, 2008).[3] 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 preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2 (Meyer et al, 2010).[4] At the clinical dose of 5 mg twice daily (BID) of the IR formulation, tofacitinib provides high level suppression of IL-21, IL-15, IL-6, Interferon-alpha (IFN-α), and Interferon-gamma (IFN-γ), as well as other cytokines. It also modestly inhibits JAK2 which may explain some of its less desirable effects on hematopoiesis. Further details about tofacitinib may be found in the current version of the SRSD), which for this study is the current version of the tofacitinib IB.

2.2.3. PF-06651600

PF-06651600 is an orally bioavailable small molecule that irreversibly inhibits JAK3/TEC with selectivity over the other 3 JAK isoforms; JAK1, JAK2 and TyK2. PF-06651600 also inhibits irreversibly the TEC kinase family (Bruton's tyrosine kinase, [BTK], bone marrow tyrosine kinase on chromosome X [BMX], interleukin-2-inducible T-cell kinase [ITK], TEC, and tyrosine kinase expressed in T cells [TXK]), with high selectivity over the broader kinome. JAK3/TEC inhibition will lead to modulation of γ-common chain cytokine pathways, such as IL-7, IL-9, IL-15, and IL-21, some of which have been implicated in the pathophysiology of RA. PF-06651600 is expected to spare inhibition of key immuno-regulatory cytokines, such as IL-10, IL-27, and IL-35, which play a protective role. Inhibition of JAK2 cytokine signaling, implicated to be associated with adverse effects such as neutropenia, thrombocytopenia, and anemia (O'Shea et al, 2013),[5] will also be spared. Additionally, PF-06651600 inhibits the cytotoxic function of $CD8^+$ T cells and natural killer (NK) cells. Thus, PF-06651600 and tofacitinib have overlapping but distinct anti-inflammatory activities that have the potential for differential efficacy and safety profiles in RA. Further details may be found in the current version of the SRSD, which for this study is the current version of the PF-06651600 IB.

2.2.4. Nonclinical Overview

The nonclinical studies supporting the current clinical study include 3-month combination studies of PF-06650833 + PF-06651600 (Study 18GR138, a 3-Month Oral Gavage Combination Toxicity Study of PF-06650833 and PF-06651600 in Wistar Han Rat) and PF-06650833 + CP-690550 (tofacitinib) (Study 18GR099, 3-Month Oral Gavage Study of PF-06650833 and CP-690550 in Sprague-Dawley Rats) along with the nonclinical studies conducted with individual test articles (PF-06650833, PF-06651600, and tofacitinib [CP-690550]). These latter studies include safety pharmacology chronic toxicity studies sufficient to support chronic dosing of each of the individual investigational products, including with women of childbearing potential (WOCBP) using appropriate contraception. No new adverse effects were observed in the combination toxicity studies. Detailed nonclinical information may be found in the current versions of the Investigator's Brochures (IBs) for PF-06650833, PF-06651600, and tofacitinib.

Conclusions for Nonclinical Safety

The nonclinical data package consisting of results from the combination toxicity studies conducted in rats administered PF-06650833 + CP-690550 (tofacitinib), or PF-06650833 + PF-06651600, and the results from toxicity studies for the individual test articles, support the clinical evaluation of these combinations. Details on the combination toxicity studies with PF-06650833 may be found in Section 5 of the current PF-06650833 IB. Further details for the individual IPs may be found in Section 5 of the current IB for each individual IP.

2.2.5. Clinical Overview

2.2.5.1. PF-06650833

As of the date of this protocol, the safety, tolerability, and pharmacokinetic (PK) profiles of PF-06650833 have been evaluated in 5 Phase 1 studies in healthy participants. These have included single and repeat ascending dose studies, relative bioavailability studies, and a drug-drug interaction study (with PF-06651600). PF-06650833 was generally well-tolerated in these studies with no dose-limiting adverse effect defined for escalating single doses of an immediate release (IR) formulation, up to 6000 mg with food, and for repeat dosing up to 1000 mg IR four times a day (QID) and 300 mg of modified release (MR) tablets once daily, with a standard meal for 14 days. The most frequently reported Treatment Emergent Adverse Events (TEAEs) (>3 participants) in the repeat dose study were headache (9 participants), acne, abdominal pain, and nausea (3 participants each). There were no deaths, severe Adverse Events (AEs), or Serious Adverse Events (SAEs) reported. There were no clinically significant Electrocardiogram (ECG) abnormalities, and no clinically significant changes in vital signs (blood pressure or pulse) or in laboratory test results, at any dose. Sporadic, asymptomatic, self-limited increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were observed without a clear relationship to dose or duration of treatment. Asymptomatic manifestations of atypical, needle-like crystals in the urine were reported intermittently in participants receiving immediate release doses >250 mg BID, and in the 300 mg MR once daily (QD) dose, as well as in 3 participants receiving placebo. No AEs related to the urine crystals were reported and the findings were not associated with any clinical or laboratory evidence of adverse effects on kidney function.

The efficacy and safety of PF-06650833 were evaluated in a Phase 2, dose-ranging, multicenter, randomized, double-blind, double dummy, placebo- and active-controlled, parallel group, 12-week study in participants with moderately to severely active, anti-anticitrullinated protein antibody positive ($ACPA^+$) RA who have had an inadequate response to MTX. PF-06650833 doses of 20 mg, 60 mg, 200 mg, and 400 mg MR tablets administered once daily under fasted conditions compared to placebo were explored. Tofacitinib 5 mg twice daily (BID) was included as an active control in this study (but no formal statistical comparisons with PF-06650833 were performed).

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The PK profile of PF-06650833 is discussed in Section 4.2.1.

Further details about the safety, tolerability, PK, and efficacy of PF-06650833 may be found in the current version of the PF-06650833 IB.

2.2.5.2. PF-06651600

As of 31 August 2020, PF-06651600 has been explored in 3 Phase 1 trials in healthy participants, and in 2 completed Phase 2 trials, in participants with RA and AA. There are ongoing Phase 2 studies in ulcerative colitis, Crohn's Disease, alopecia areata, and vitiligo; a Phase 2b/3 study in alopecia areata, and a Phase 3 study in alopecia areata.

Based on the current clinical and nonclinical experience with PF-06651600 and other information from other JAK inhibitors (eg, Xeljanz® [tofacitinib], Jakafi® [ruxolitinib], baricitinib, GLPG0634, and VX-509), the potential risks for PF-06651600 include: (1) viral reactivation; (2) serious infections and opportunistic infections; (3) malignancy and lymphoproliferative disorders; (4) decreased lymphocyte counts; (5) change in neutrophil counts; (6) decreased platelet count; (7) alterations in the lipid profile; (8) dermatologic effects (rash/acne); and (9) thromboembolism. Increased incidences of deep vein thrombosis

(DVT) and pulmonary embolism (PE) have recently been identified as potential risks for these other JAK inhibitors. To date, no adverse drug reactions for ritlecitinib have been identified.

Additional information on the safety, tolerability, and efficacy of PF-06651600, including information about ongoing Phase 2/3 studies in other indications may be found in the current version of the PF-06651600 IB.

2.2.5.3. Tofacitinib (CP-690550, Xeljanz®)

Tofacitinib is approved for treatment of RA, PsA, and UC, and is currently being investigated as a treatment for juvenile idiopathic arthritis (JIA) and ankylosing spondylitis (AS). Tofacitinib was investigated for the treatment of psoriasis (approved in Russia only), prevention of acute renal allograft rejection, and CD; however, there are no ongoing or planned clinical trials for these indications at this time.

As stated in the current version (April 2020) of the tofacitinib Investigator's Brochure, as of 05 May 2019, it is estimated that 23,338 unique study participants have participated in tofacitinib clinical trials worldwide, with 19,597 study participants exposed to tofacitinib. Phase 1 studies are described in Section 6.1 and Phase 2, Phase 3 and Phase 4 studies are described in Section 6.2 of the current tofacitinib Investigator's brochure. From 06 November 2012 through 05 May 2019, there have been approximately 209,081 patient-years of exposure to tofacitinib from marketing experience. Approximately 460 humans have applied at least 1 dose of topical tofacitinib in the completed Phase 2 studies; there have not been any Phase 1 or Phase 3 studies for the dermal formulations. The topical administration for dry eye disease as well as plaque psoriasis and atopic dermatitis is discussed separately in the Topical Formulation Section (Sections 2-6.2) of the current version of the tofacitinib Investigator's brochure. Currently, there are no ongoing or planned studies of topical formulations of tofacitinib.

Tofacitinib is an immunomodulator with important safety risks that include serious and other infections including tuberculosis and herpes zoster infections, and potential for malignancies including lymphoma, and potential for GI perforations. Patients receiving tofacitinib may be at increased risk of Non-Melanoma Skin Cancer (NMSC). Cardiovascular disease and Interstitial Lung disease (ILD) are findings seen in RA patients receiving tofacitinib, and are recognized comorbidities for RA as well as being associated with other RA therapies.

Changes in laboratory values have also been observed with oral tofacitinib including a dose-dependent increase in LDL cholesterol and dose-dependent decreases in neutrophils and hemoglobin. Other laboratory changes observed with oral tofacitinib treatment include decreases in lymphocytes and increases in transaminases, serum creatinine, and CK.

Laboratory changes observed with oral tofacitinib treatment are monitorable and manageable and recovery of laboratory changes upon discontinuation of oral tofacitinib treatment is characteristically observed.

These topics are described in greater detail in Section 6.2.3 of the current version of the tofacitinib IB, including relevant differences in the clinical experience in the various indications in which tofacitinib has been studied.

Interpretation of these results and the possible risks associated with the administration of tofacitinib are summarized in Section 7 of the current version of the Tofacitinib IB.

Study A3921133 was an event-driven, postmarketing requirement study evaluating the safety of tofacitinib at 2 doses (5 mg BID and 10 mg BID) versus TNFi in participants with moderate to severe RA. Participants who enrolled in this study were required to be 50 years of age or older with at least 1 cardiovascular risk factor and be on a stable background dose of MTX treatment. On 05 February 2019, the Rheumatology Data Safety Monitoring Board (DSMB) for Study A3921133 communicated to Pfizer their observation of a statistically and clinically important difference in the occurrence of PE with the tofacitinib 10 mg BID treatment arm compared to the active tumor necrosis factor inhibitor (TNFi) control. VTE was subsequently considered to be an important identified risk for tofacitinib. In February 2021, based on initial review of the primary endpoint data deriving from Study A3921133 pertaining to the co-primary endpoint results for MACE (Major Adverse Cardiovascular Events) and malignancies excluding NMSC (Non-Melanoma Skin Cancer) for tofacitinib, relative to a TNFi, MACE has been identified as a new important potential risk and malignancies (excluding NMSC) remains as an important potential risk.

2.3. Benefit: Risk Assessment

Tofacitinib, as noted above and in the tofacitinib IB, has a number of important and potentially important safety risks that include serious and other infections, malignancies (excluding NMSC), a potential for GI perforations, blood and lymphatic system disorders, drug hypersensitivity, and MACE (including VTE). Tofacitinib also has a number of monitorable effects on laboratory values, including both hematology and clinical chemistry parameters. Given the totality of efficacy and safety data, the overall benefit: risk relationship for approved doses of tofacitinib (including, 5 mg IR BID and 11 mg MR QD) continues to remain favorable.

PF-06651600 is a selective inhibitor of a member of the JAK family and, therefore, may (or may not) have a safety profile distinct from other, less selective JAK inhibitors. However, until more clinical trial data are available for it and other selective JAK inhibitors, a risk profile similar to other JAK inhibitors for which more data are available cannot formally be excluded. Therefore, as noted above and in the PF-06651600 IB, based on the current clinical and nonclinical experience with PF-06651600 and other JAK inhibitors, the potential risks for PF-06651600 include: viral reactivation; serious infections and opportunistic infections; malignancy and lymphoproliferative disorders; decreased lymphocyte counts; change in neutrophil counts; decreased platelet count; alterations in the lipid profile; and dermatologic effects (rash/acne); and thromboembolism. Given the efficacy seen in the Phase 2 RA study and in Phase 2/3 studies in alopecia areata and vitiligo, the potential benefit: risk of PF-06651600 in RA at proposed doses appears favorable.

To date, no safety risks or potentially important safety risks have been identified for PF-06650833. However, based on nonclinical and clinical data, and theoretical considerations derived from its mechanism of action as a modulator of innate immune signaling, effects of PF-06650833 on rates of infection, including serious and other infections, renal function, and liver transaminases are possible. The accumulated safety data and the efficacy demonstrated in the Phase 2 study in RA are consistent with a potentially favorable benefit: risk relationship for PF-06650833 in RA.

In light of accumulated nonclinical toxicity, and clinical safety and efficacy data for the individual components, the lack of new adverse effects being identified in the combination toxicity studies of PF-06650833 + PF-06651600 and of PF-06650833 + tofacitinib suggest that positive benefit: risk relationships will be maintained for these combinations in participants with moderately - severely active RA.

More detailed information about the known and expected benefits and risks, and reasonably expected adverse events (AEs) of PF-06650833, PF-06651600, and tofacitinib (Xeljanz®) may be found in the current versions of the respective IB which are the SRSDs for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Endpoints	Estimands***
Primary	**Primary**	**Primary**
• To compare the efficacy of each of 2 combinations (PF-06650833 + PF-06651600, PF-06650833 + tofacitinib) individually to tofacitinib alone at Week 12 in participants with moderately - severely active RA who have had an inadequate response to MTX.	• Change from baseline in Disease Activity Score (DAS)28-C Reactive protein (CRP) at Week 12.	• E1: Evaluates the difference across the treatment arms in the mean values of change from baseline of continuous outcome of interest. The treatment effect is evaluated in the population of study participants who are randomized and treated irrespective of their compliance to the planned course of treatment or use of concomitant medications.

Objectives	Endpoints	Estimands***
Key Secondary	**Key Secondary**	**Key Secondary**
• To compare the remission rates of each of 2 combinations (PF-06650833 + PF-06651600, PF-06650833 + tofacitinib) individually to tofacitinib alone at Week 24 in participants with moderately - severely active RA who have had an inadequate response to MTX.	• DAS28-CRP remission (<2.6) at Week 24.	• E2: Evaluates the ratio of the probability of response in the treatment arm of interest to the probability of response in the tofacitininib treatment arm. The treatment effect is evaluated in the population of study participants who are randomized and treated irrespective of their compliance to the planned course of treatment or use of concomitant medications.
Secondary	**Secondary**	**Secondary**
• To assess the safety of PF-06650833, PF-06651600, and tofacitinib alone and of the combinations of PF-06650833 with PF-06651600 and tofacitinib in participants with moderately - severely active RA who have had an inadequate response to MTX.	• Incidence and severity of adverse events, serious adverse events, and withdrawals due to adverse events. • Change from baseline in clinical laboratory values (chemistry, hematology parameters). • Change from baseline in vital signs (blood pressure, pulse rate and temperature measurements). • Incidences of severe and opportunistic infection AEs; herpes virus	• There is no defined estimand for these endpoints. They will be analyzed using Pfizer data standards as applicable.

Objectives	Endpoints	Estimands***
	infection AEs; clinically significant categorical increases in hepatic enzymes Aspartate aminotransferase (AST), and Alanine aminotransferase (ALT) and total bilirubin, and potential cases meeting Hy's Law criteria for increased risk of drug-induced liver injury [DILI]; major adverse cardiovascular events (MACE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), Cerebrovascular accident (CVA); Adverse events (AEs) for decreased renal function, acute kidney injury, clinically significant increases in serum creatinine (Scr) and decreases in estimated glomerular filtration rate (eGFR).	
• To evaluate other signs of clinical efficacy of all treatment arms in participants with moderately - severely active RA who have had an inadequate response to MTX.	• Change from baseline in DAS28-CRP at Week 24. • American College of Rheumatology (ACR)20, ACR 50, ACR 70, and ACR 90 responder rates at Week 12 and Week 24. • Change from baseline in the Tender/Painful and	• E1 estimand for continuous and E3 estimand for binary efficacy outcomes. Evaluates the differences in probability of response of the treatment arm of interest in comparison to the tofacitinib treatment arm The treatment effect is evaluated in the population of study

Objectives	Endpoints	Estimands***
	Swollen Joint Count at Week 12 and Week 24. • Change from baseline in the Physician's Global Assessment (PhGA) of Arthritis at Week 12 and Week 24.	participants who are randomized and treated irrespective of their compliance to the planned course of treatment or use of concomitant medications.

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• To collect blood for the potential exploratory analyses of pharmacodynamic activity of PF-06650833, PF-06651600, and tofacitinib alone and in combination with PF-06650833 in participants with	• Change from baseline: anti-citrullinated protein antibodies (ACPA), rheumatoid factor (RF) and Ig levels. • Change from baseline of Interferon Gamma-Induced Protein 10 (IP-10), if performed.	• All continuous endpoints will be analyzed descriptively. Other analyses may be done and will be described in the statistical analysis plan (SAP). • All other categorical endpoints will be analyzed descriptively.

Objectives	Endpoints	Estimands***
moderately - severely active RA.	• Endpoints may also include circulating proteins and protein fragments.	Other analyses may be done and will be described in the SAP.
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• To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision.	• Not applicable.
• To evaluate the effects of PF-06650833, PF-06651600, and tofacitinib alone and in combination on joint inflammation assessed by magnetic resonance imaging (MRI), in a subset of participants, if performed.	• Change from baseline in Rheumatoid Arthritis MRI Score (RAMRIS) and exploratory measures of joint inflammation (eg, RAMRIQ, DCE), if performed, in hand MRI at Weeks 12 and 24.	• All continuous endpoints will be analyzed descriptively. Other analyses may be done and will be described in the statistical analysis plan (SAP). • All other categorical endpoints will be analyzed descriptively. Other analyses may be done and will be described in the SAP.

* Efficacy evaluations that are otherwise classified in the table as primary, key secondary or secondary are not viewed as exploratory.

** The remission threshold definition for DAS28-ESR will be defined in the SAP.

*** The additional supportive estimands will be described in the SAP.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, 24-week, multicenter, randomized, double-blind, 5-arm, parallel group, active comparator study to evaluate the efficacy and safety profiles of 2 combinations of investigational products (IPs): PF-06650833 coadministered with PF-06651600 (PF-06650833 + PF-06651600) and PF-06650833 coadministered with tofacitinib (PF-06650833 + tofacitinib), as well as the efficacy and safety of each IP individually in the absence of background MTX in participants with moderately - severely active RA who have had an inadequate response to MTX (MTX-IR).

The primary objective is to demonstrate superiority of at least 1 combination arm to tofacitinib monotherapy with the primary endpoint being change from baseline (CFB) in DAS28-CRP at Week 12. A key secondary endpoint is remission rates of the combination and individual IPs at Week 24, as defined by DAS28-CRP <2.6. The study is powered to show statistical superiority of the combination to tofacitinib monotherapy at Week 12.

Up to approximately 450 participants are planned to be randomized globally into the study to ensure at least up to approximately 370 participants complete at least 12 weeks of active dosing (assuming a dropout rate of approximately 18%). Participants will be randomly assigned to 1 of the following 5 treatment groups in a 4:4 3:3:4 ratio: PF-06650833 + tofacitinib, PF-06650833 + PF-06651600, PF-06650833, PF-06651600, and tofacitinib (see also study schematic design in Section 1.2).

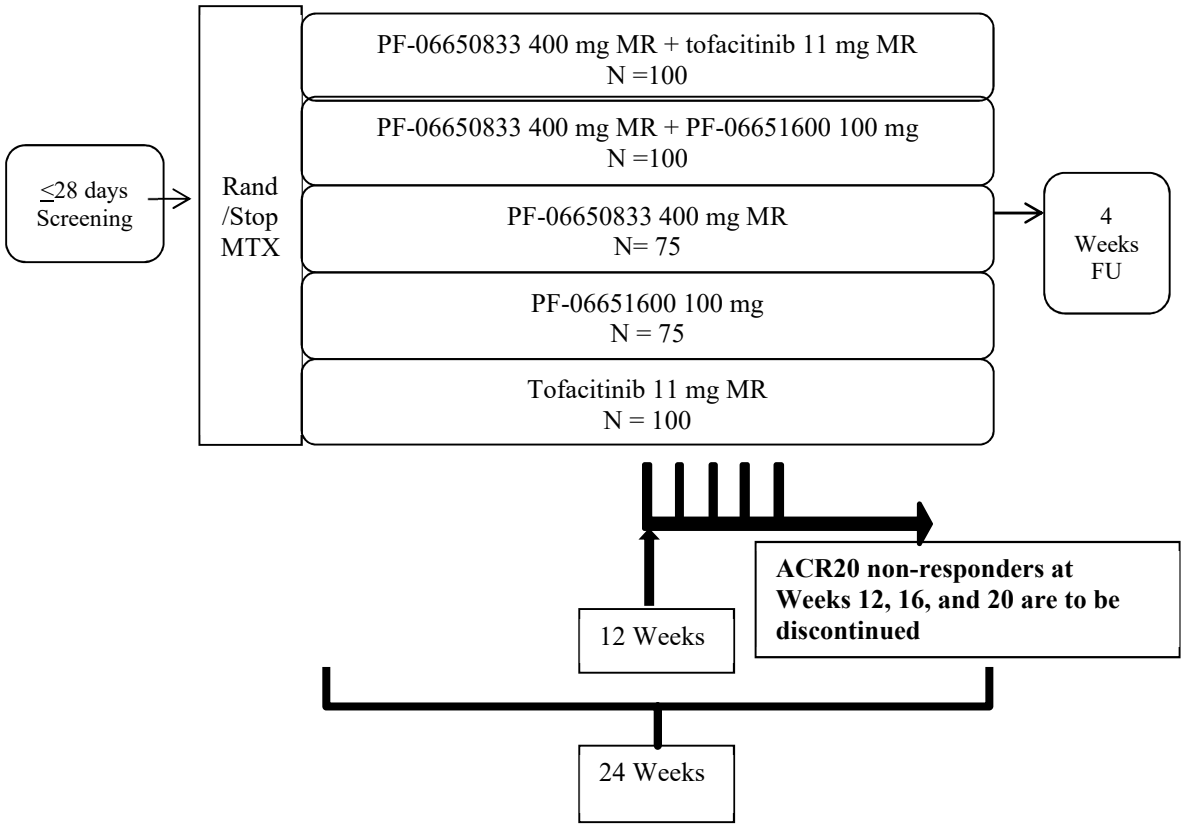
After an up to 28-day screening period, eligible participants will enter a 24-week active treatment period after being randomly assigned to one of the 5 treatment groups shown in Section 1.2. Participants will be in this study for a total of approximately 32 weeks which includes the screening period, the 24-week active treatment period, and a 4-week drug-free follow-up period.

All doses will be administered orally once daily in a fasted state (about 4 hours after the last and 1.5 hours before the next meal). Both PF-06650833 and tofacitinib will be administered as modified release (MR) tablets to allow for once daily administration, whereas PF-06651600 will be administered as immediate release tablets. In order to maintain the blind and minimize bias, all participants will receive the same number and types of tablets each day as a mix of active and placebo tablets (see Table 1). MTX (and folate/folinic acid taken with MTX) will be discontinued at the time of randomization and washed out during the active treatment phase. The MTX washout is intended to reduce the potential for excessive immune suppression and additive safety liability.

Folate/folinic acid taken with MTX may also be discontinued in a manner consistent with local standard of care practice. MTX is to be discontinued (last MTX dose is to occur) during the week before randomization on Day 1 and be washed out during the active treatment phase. No changes in the background concomitant steroid dose is allowed during the study. During the active dosing period**,** no “rescue” treatment is pre-specified. However, limited – duration increases in permitted analgesic medication (acetaminophen/paracetamol,

nonsteroidal anti-inflammatory drugs [NSAIDs], opiates) will be permitted for acute worsening of arthritis pain (see Permitted Concomitant Medications, Sections 6.5.1 and 6.5.2). Participants, who, after at least a 12-week trial on the assigned investigational product have not achieved at least a minimal clinical response (as defined by the American College of Rheumatology [ACR] 20% response criteria [ACR20]) are to be discontinued from the study treatment and begin treatment for their RA according to local standard of care (SoC) practice. The Principal Investigator (PI) may also discontinue participants at any time during the study if, in the PI's opinion, worsening RA signs and symptoms unresponsive to limited-duration increases in analgesic medications requires more urgent advancement of RA treatment. Additional treatment for participants meeting either of these criteria for discontinuation from the study will be provided by the investigator, and upon withdrawal from the study treatment, participants will enter a 4-week follow-up period and after which they will have End of Study (EOS)/follow-up (FU) visit. IP will not be provided after the participant completes the study.

Figure 1. Schema



All doses are orally administered once daily under fasted conditions
Non-responders (defined as not meeting ACR20 response criteria) by Week 12 (or later) are to be discontinued from study.
MR=modified release; MTX=methotrexate; Rand=randomization; FU=follow-up; ACR=American College of Rheumatology.

4.1.1. Study Rationale

There are multiple therapeutic options for managing the pain and slowing the progression of RA, but none completely cures the disease. Despite the considerable list of approved treatments for RA, the treatment goal of clinical remission (or LDA) is achieved in only a minority of patients. Clearly, there is a need for therapeutics with enhanced efficacy that drive a higher proportion of patients to LDA and clinical remission.

The clinical hypothesis is that combinations of drugs with complementary mechanisms of action would offer the potential to achieve the goal of improved efficacy while still maintaining a positive benefit: risk profile. As discussed above, it is becoming evident, given the results with biologics and even with newer, advanced synthetic DMARDs administered alone or in combination with MTX, that "treat-to-target" levels of efficacy on

remission and LDA rates may be difficult to achieve with drugs targeting a single pathway or cytokine.

The aim of the current study is to evaluate whether or not a combination of drugs with complementary mechanisms of action can achieve the dual objectives of increased efficacy compared to currently available standard of care RA drugs while maintaining an acceptable safety profile (and therefore an overall positive benefit: risk relationship). Both components (PF-06650833 and PF-06651600) of the combination being explored in the current study have demonstrated efficacy in Phase 2 studies in RA. Moreover, PF-06650833 and PF-06651600-appeared to be generally well-tolerated in their Phase 2 studies so they have the potential for not having increased safety liabilities in combination.

Depending on technical and logistical feasibility, the current study may include an exploratory imaging component consisting of hand magnetic resonance imaging (MRI) procedures conducted in a subset of participants (up to approximately 60 participants per arm), as permitted by local regulatory and ethical guidelines. MRI offers the potential for an earlier, more sensitive, and more quantitative assessment of joint inflammation than afforded by traditional X-ray analyses. In the context of the current study, the MRI analyses may afford a heightened ability to detect and discriminate among the anti-inflammatory and disease-modifying effects of the study interventions and greater discriminatory power. The data will also help support development of this methodology for future studies and clinical development programs. Further details on the imaging methods will be provided separately (in the form of an imaging manual, or similar document).

Banked biospecimens will be collected for exploratory pharmacogenomic/ genomic/biomarker analyses and retained in the Biospecimen Banking System (BBS), which makes it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

4.2. Justification for Dose

Since this is the initial exploration of safety and efficacy for the proposed combination, maximal doses of the individual study drugs that could, based on prior clinical and preclinical experience, be expected to be safely administered during the 6-month active dosing period were selected, in order to increase the probability of achieving desired improvements in overall remission rates.

- PF-06650833 400 mg MR QD + tofacitinib 11 mg MR QD.
- PF-06650833 400 mg MR QD + PF-06651600 100 mg IR QD.
- PF-06650833 400 mg MR QD.
- PF-06651600 100 mg IR QD.

- tofacitinib 11 mg MR QD.

4.2.1. Dose Rationale for PF-06650833 400 mg MR QD

PF-06650833 is considered to have an acceptable safety profile based on clinical studies to date in healthy participants and patients with moderately to severely active RA (see Section 2.2.1 and the PF-06650833 IB). It was tested as an orally administered extemporaneously prepared immediate release formulation in doses up to 1000 mg four times-a-day (QID) for up to 14 days in healthy participants without a dose-limiting adverse effect being demonstrated.

The efficacy, safety, and pharmacokinetics (PK) of PF-06650833 were evaluated in a 12-week study (Study B7921005) in participants with moderately – severely active RA at doses up to 400 mg MR administered QD in a fasted state. The dose of 400 mg MR tablets was efficacious in reducing the signs and symptoms of RA in this study as defined by change from baseline (CFB) in the Simplified Disease Activity Index (SDAI) at Week 12, the primary efficacy endpoint, that was statistically superior to placebo. CCI

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As noted above, all doses of PF-06650833 in Study B7921005 were generally well-tolerated for 12 weeks in patients with RA with an overall safety profile consistent with a favorable benefit: risk relationship.

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Therefore, based on the accumulated, available clinical and comprehensive nonclinical toxicity data package for PF-06650833, a 400 mg MR QD dose is expected to be well-tolerated and have an acceptable safety profile while providing the best opportunity to maximize efficacy.

4.2.2. Dose Rationale for PF-06651600 100 mg QD

PF-06651600 is considered to have an acceptable safety profile based on clinical studies to date in healthy participants, and in patients with moderately to severely active RA which is supplemented by emerging data in alopecia areata patients. It was tested as an orally administered extemporaneously prepared IR formulation in doses up to 400 mg QD or 200 mg BID for 14 days in healthy participants without a dose-limiting adverse effect being demonstrated.

PF-06651600 was evaluated in participants with moderately to severely active RA at 200 mg QD for 8 weeks in Study B7981006. Analysis of the primary efficacy endpoint demonstrated a statistically significant change from baseline (CFB) in the simplified disease activity index (SDAI) at 8 weeks, that was superior to placebo. This dose was generally well-tolerated with an acceptable safety profile. In addition, PF-06651600 was demonstrated to be efficacious with an acceptable safety profile in participants with moderate to severe AA treated with an induction dose of 200 mg for 4 weeks followed by 50 mg QD for additional 20 weeks.

At the proposed dose of 100 mg QD of PF-06651600, the maximal dose supported by the nonclinical toxicity data, the γ-common chain cytokine pathways are expected to be selectively inhibited to approximately 64% and 49% based on in vitro IC_{50} values of 198 nM and 362 nM determined by inhibition of signal transducer and activator of transcription (STAT5 and STAT3 phosphorylation in lymphocytes, respectively. Therefore, PF-06651600 is predicted to be pharmacologically active at a 100 mg QD dose and is expected to be effective in reducing the signs and symptoms of RA.

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Given the overall safety profile of PF-06651600 in clinical studies and the comprehensive nonclinical toxicity package, a chronic dose of PF-06651600 of 100 mg QD should provide an acceptable safety and tolerability profile with a favorable benefit: risk relationship.

4.2.3. Dose Rationale for Tofacitinib 11 mg MR QD

As noted in Section 2.2.5.3 and as discussed extensively in the tofacitinib IB, the efficacy and safety of tofacitinib administered as an IR tablet have been extensively evaluated in multiple Phase 2, Phase 3, and post-marketing studies in patients with active RA. It has a well-characterized safety and tolerability profile and has been shown to be efficacious as a DMARD in patients with moderately–severely active RA both alone and in combination with MTX. The 5-mg BID dose (IR formulation) has received market authorization in numerous countries globally and continues to maintain a favorable benefit: risk profile. Tofacitinib 11 mg MR has been evaluated in 7 Phase 1 studies, 1 Phase 3 study in Japanese RA patients (A3921215) and 1 Phase 4-3b/4 global study (A3921192). The 7 healthy volunteer studies include 4 studies (A3921113, A3921131, A3921132, and A3921163) which evaluated PK of the pilot or initial commercial-scale formulations; a food effect (A3921180) and a single- and multiple-dose PK study with the proposed commercial formulation (A3921212); and an in vitro dissolution with in-vivo plasma drug concentrations (IVIVC) study (A3921195) which investigated the relationship between in vitro dissolution and in vivo PK performance of the MR formulations.

Given its QD administration, tofacitinib 11 mg MR was selected as an appropriate active comparator in the current study.

4.2.4. Dose Rationale for PF-06650833 400 mg MR QD in Combination with PF-06651600 100 mg IR QD or Tofacitinib 11 mg MR QD

The doses of PF-06651600 and tofacitinib used in combination with PF-06650833 will be the same as the doses used in their monotherapy arms. As noted previously (Section 2.1), combinations of PF-06650833 + PF-06651600 or PF-06650833 + tofacitinib have the potential for increased efficacy compared to tofacitinib monotherapy without increased safety liabilities due to increased pharmacology.

Based on metabolic profiling, the exposure of PF-06651600 is not expected to change meaningfully when dosed in combination with PF-06650833. Based on in vitro metabolic profiling of PF-06650833 and tofacitinib, their exposures when dosed in combination are not expected to change meaningfully. CCI

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Given observed and expected exposures of PF-06650833, PF-06651600, and tofacitinib, adequate safety margins, lack of new adverse effects or target organs in the nonclinical combination toxicity studies, and accumulated clinical safety data, the proposed coadministration of PF-06650833 400 mg MR QD + tofacitinib 11 mg MR QD and of PF-06650833 400 mg MR QD + PF-06651600 100 mg IR QD are expected to have acceptable safety and tolerability. Moreover, the selected doses of the components of the combination have the highest potential to demonstrate superior efficacy.

4.3. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants 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 participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 70 years, inclusive, at time of randomization (Visit 2).

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan (including washout of MTX at randomization), laboratory tests, lifestyle considerations, and other study procedures.

3. Diagnosis of RA and meeting the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria (see Appendix 8) 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 MTX inadequate response (MTX-IR) (see Inclusion 7).

4. The participant has active disease at both Screening and Randomization, as defined by both:

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

   and fulfills 1 of the following 2 criteria at or before randomization:

   - High sensitivity C reactive protein (hsCRP) >7 mg/L at Screening (Visit 1) as performed by the central laboratory.

     OR

   - Erythrocyte sedimentation rate (ESR) (Westergren method) >28 mm/h.

   Participants who do not meet this entry criterion but satisfy all other study entry criteria may have ESR or serum hsCRP concentration re-tested once within 14 days and, if the repeat hsCRP concentration is >7 mg/L or ESR >28 mm/h, will be eligible to enroll into the study provided all other inclusion/exclusion criteria are met.

5. Meets Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA (see Appendix 9).

6. Participants must be seropositive at the time of randomization (ACPA or RF positive).

7. Participants must have been taking oral MTX (or equivalent parenteral MTX) at an adequate dose (generally between 15 and 25 mg weekly [inclusive] unless documented to be intolerant to these doses) and for a sufficient duration (generally at least 3 months but may be as short as at least 8 weeks if consistent with local standard of care treatment guidelines) prior to Screening (Visit 1). To determine that the participant had an inadequate response to MTX, defined, for the purpose of this study, by the investigator's and participant's opinions that the participant did not experience adequate benefit from MTX plus the presence of sufficient residual disease activity to meet the entry criteria. Current treatment with methotrexate is not required for participant eligibility, provided documentation of prior inadequate response to or intolerance of MTX is available and provided in source documentation.

8. Participants 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.

Weight:

9. Body weight must be >40 kg.

Informed Consent:

10. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

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

2. Participants with a known immunodeficiency disorder or a first degree relative with a hereditary immunodeficiency.

3. Participants with any of the following infections or infections history:

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

   b. Active COVID-19 as defined by a positive test for SARS-CoV-2 or an exposure history with compatible symptoms (as defined by WHO).

c. Asymptomatic participants with an exposure history while under quarantine or pending results of a SARS-CoV-2 test (which if negative would allow the patient to be eligible).

d. Participants with a history of COVID-19 in the last 3 months unless asymptomatic for at least the last 30 days with a negative SARS-CoV-2 test in the last 7 days. Asymptomatic patients with a more remote (>3 months) history of COVID-19 do not need a confirmatory SARS-CoV-2 test to be eligible.

e. Participants with COVID-19 who are symptomatic irrespective of the interval since infection.

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

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

h. Recurrent (1 or more lifetime episodes after the initial episode) herpes zoster; or severe or disseminated (a single lifetime episode of either) herpes simplex. Note that for the purposes of this study the initial infection (eg, chicken pox) is considered the initial episode of herpes zoster. A recurrent episode of herpes zoster is any subsequent manifestation of active herpes zoster (eg, shingles).

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

4. Participants with positive hepatitis B surface antigen (HBsAg) will be excluded. Participants who are HBsAg negative but HBcAb positive will be reflex tested for hepatitis B virus deoxyribonucleic acid (HBV DNA) and, if HBV DNA is negative, will be allowed to enroll in the study, provided other inclusion/exclusion criteria are met if HBV DNA is positive, they will be screen failed.

5. Participants will be screened for hepatitis C virus (HCV Ab). Participants with positive HCV Ab tests will be reflex tested for HCV ribonucleic acid (HCV RNA). Only participants with negative HCV Ab or HCV RNA, and normal liver function (as assessed by liver transaminases and bilirubin within protocol-permitted limits, and no other evidence of compromised liver synthetic ability (eg, albumin and coagulation tests within protocol-permitted limits]) will be allowed to enroll in the study, provided other inclusion exclusion criteria are met.

6. Any history of either untreated or inadequately treated latent or active tuberculosis (TB) infection, current treatment for active or latent TB infection or evidence of currently active TB by chest x-ray, CT or MRI, residing with or frequent close contact with individual(s) with active TB. Participants who have a positive Interferon

Gamma Release Assay during screening or within 12 weeks prior to randomization, except as noted below.

- Participants with prior active or latent tuberculosis (except for multidrug-resistant TB) who have 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), negative chest radiograph for active disease, and negative Interferon Gamma Release Assay (IGRA) are eligible.

- Participants who have an indeterminate IGRA results may have the test repeated and, will be eligible if the repeat IGRA test is negative at time of randomization. A positive test on repeat is exclusionary unless the participant meets the criteria below.

- Participants who test positive for IGRA test (including borderline T-SPOT result) who do not have a reliable history of having received an adequate course of therapy for active or latent tuberculosis with a recognized effective combination drug regimen to which the TB organism was sensitive.

- Participants who test positive for IGRA test (including borderline T-SPOT result), have a reliable history of having received an adequate course of therapy for active or latent tuberculosis with a recognized effective combination drug regimen to which the TB organism was sensitive, and in the opinion of the PI are at low risk of currently have active or latent TB infection may be referred to pulmonary or infectious disease specialist for consultation and may have the IGRA test repeated once. Participants will be eligible if the repeat test is negative before the randomization. Alternatively, a participant with a positive IGRA may be eligible if the participant lives in a country/region without a high prevalence of multi-drug resistant TB (and has not recently traveled to a region with a high prevalence of MDR TB) and if the pulmonary or infectious disease specialist, after review of all relevant clinical and medical imaging data attests that the participant does not have active or latent TB infection.

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

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

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

10. Participants with malignancy or history of malignancy (including lymphoma, leukemia, or lymphoproliferative disease), with the exception of participants with adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.

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

12. Participants with fibromyalgia will be excluded.

13. Major surgery within 4 weeks of screening or planned surgery scheduled to occur during the study.

14. Previous treatment with total lymphoid irradiation.

15. Participants 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).

16. Participants with an oral, tympanic, or temporal temperature of 38°C (100.4°F) or higher at baseline.

17. Participants may not receive any live/attenuated vaccine from 30 days prior to randomization during the course of the study, or for 30 days after the last dose of study medication. Participants 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.

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

19. Have hearing loss with progression over the previous 5 years, sudden hearing loss, or middle or inner ear disease such as otitis media, cholesteatoma, Meniere's disease, labyrinthitis, or other auditory condition that is considered current, fluctuating or progressive.

20. History of any prior deep vein thrombosis (DVT) or pulmonary embolism [PE].

21. History of any medical condition associated with an increased risk of venothromboembolism (eg, paroxysmal atrial fibrillation) unless properly anti-coagulated.

22. Recent (within 6 months of screening) myocardial infarction, coronary revascularization, or percutaneous angioplasty with or without placement of a coronary artery stent; acute coronary syndrome; chronic uncompensated heart failure or New York Heart Association Functional Class III or IV; left ventricular assist devices; implanted defibrillators.

23. Current severe chronic renal insufficiency or renal failure as defined by persistent (on repeated measurements) eGFR <60 mL/min per 1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculation.

24. Any known history of coagulopathy or hypercoagulation syndrome.

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

    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥1.5 x the upper limit of normal (ULN).
        - Participants 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). Participants with cyclic (benign ethnic) neutropenia will be excluded.
    - 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).
    - Platelet count ≤100 x 10^9/L (100,000 cells/mm^3) or ≥1000 x 10^9/L (1,000,000 cells/mm^3).
    - 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.

    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 participant may enter the study.

26. Grade 3 or greater laboratory abnormality based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 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.

Prior/Concomitant Therapy:

27. Participants previously treated with a biologic DMARD (except for up to 25% of participants who may have been treated with 1, and only 1 prior TNF inhibitor) or any other targeted synthetic (ie, small molecule) approved DMARD treatment (eg, a JAK inhibitor), or participants currently treated with any other prohibited medications as specified in Section 6.5.3 will be excluded.

28. Prior use of tofacitinib or other JAK inhibitor in the context of a clinical trial is excluded. Concomitant use of tofacitinib (other than as prescribed by the randomization scheme) or other JAK inhibitor is prohibited.

29. Prior use of PF-06650833 or PF-06651600 in the context of a clinical trial is excluded.

30. Participants who have previously been treated with other, non-TNFα inhibiting biologic DMARDs [including, abatacept (Orencia®), tocilizumab (Actemra®), Sarilumab (Kevzara®), anakinra (Kineret®), rituximab (Rituxan®) or other selective B lymphocyte depleting agents, or other lymphocyte depleting agents/therapies (such as alemtuzab [CamPath®], natalizumab (Tysabri®), alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation) are excluded from participation in the current study.

Prior/Concurrent Clinical Study Experience:

31. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of IP used in this study (whichever is longer).

32. As noted above and in Section 6.5.3, up to 25% of participants may have previously taken a TNF inhibitor (originator or biosimilar), which includes prior use in the context of a clinical trial, provided the clinical trial was the participant's only exposure to a TNF inhibitor. If the participant was previously in a clinical trial for a TNF inhibitor and is known not to have been assigned to the TNF inhibitor (or other prohibited concomitant medication), then the participant may be eligible.

Diagnostic Assessments:

33. Any 12-lead electrocardiogram (ECG) performed prior to randomization that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline corrected QT [QTc] interval >450 msec, complete left bundle branch block [LBBB], signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia,

second- or third-degree atrioventricular [AV] block, or serious bradyarrhythmias or tachyarrhythmias, any cardiac rhythm associated with increased risk of thrombosis or thromboembolism, eg atrial fibrillation, unless on a stable, therapeutic dose of non-excluded anti-coagulant). If the baseline uncorrected QT interval is >450 msec, this interval should be rate-corrected using the Fridericia method and the resulting corrected QT (Fridericia method) (QTcF) should be used for decision making and reporting. If QTc exceeds 450 msec, or ventricular depolarization (QRS) duration exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS duration values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants.

Other Exclusions:

34. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

5.3. Randomization Criteria

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

5.4. Lifestyle Considerations

5.4.1. Contraception

The investigator (or his or her designee), in consultation with the participant, will confirm that the participant has selected an appropriate method of highly effective contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4), and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly, and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to investigational product. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Participants who do not have all tests completed within the screening period or who temporarily do not meet study entry criteria for participation in this study (eg, screen failure due to treatment with antibiotics during the screening period, or for administrative reasons) may be re-screened 1 time under a new participant number; the participant's prior ID number and reason for re-screening must be documented.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

For this study, the investigational product(s) are PF-06650833, PF-06651600, and tofacitinib administered as individual products, and the combination of PF-06650833 administered together with PF-06651600 and of PF-06650833 coadministered with tofacitinib. Investigational product will be administered only to participants who have provided informed consent. Once a participant's participation in the study has ended, investigational product will no longer be supplied to the participant by the investigative site and/or sponsor.

6.1. Study Intervention(s) Administered

Intervention Name	PF-06650833/ Tofacitinib/ Placebo for PF-06651600	PF-06650833/ PF-06651600/ Placebo for tofacitinib	PF-06650833/ Placebo for PF-06651600/ Placebo for tofacitinib	Placebo for PF-06650833/ PF-06651600/ Placebo for tofacitinib	Placebo for PF-06650833/ Placebo for PF-06651600/ tofacitinib
ARM	*1	2	3	4	5
Type	Drug				
Dose Formulation	Tablets				
Unit Dose Strength	200 mg/ 11 mg/ 0 mg	200 mg/ 50 mg/ 0 mg	200 mg/ 0 mg/ 0 mg	0 mg/ 50 mg/ 0 mg	0 mg/ 0 mg/ 11 mg
Dosage Level	400 mg QD/ 11 mg QD/ 0 mg QD	400 mg QD/ 100 mg QD/ 0 mg QD	400 mg QD/ 0 mg QD/ 0 mg QD	0 mg QD/ 100 mg QD/ 0 mg QD	0 mg QD/ 0 mg QD/ 11 mg QD
Route of Administration	Oral				
Investigational Medicinal Product (IMP)	IMP				

Sourcing	Provided centrally by the Sponsor
Packaging and Labeling	Study intervention will be provided in blister packs in cartons containing one month of supplies. Each blister pack and carton will be labeled as required per country requirement.
Current Name	tofacitinib is also called Xeljanz®

6.1.1. Administration

Participants will swallow the investigational products whole and will not manipulate or chew the investigational products prior to swallowing. IP will be provided in cartons containing 4 blister cards of IP in individual blisters. A single dose (administration) of IP will consist of 5 tablets provided as a row in a blister card Table 1. The row will contain different tablet types corresponding to the different study drugs and matching placebos. Participants are to take all tablets in 1 row of the blister card each day orally in a fasted state (at least approximately 4 h after the last and approximately 1.5 h before the next meal), but preferably should be taken consistently in the same manner, ideally in the AM before breakfast. Those participants who cannot take the dose in the morning due to work or other regularly occurring issue may take the dose later in the day provided the fasting requirements are met and the doses are taken at approximately the same time each day. Participants will record dosing in a dosing log (diary).

Table 1. Dosing and Administration of Investigational Products

Treatment Arm	Treatment group (QD)	Treatment Assignment (Blister Pack)	Matching Placebo (Blister Pack)	Total Tablets per Day
1	PF-06650833 (400 mg) + tofacitinib (11 mg)	2 x 200 mg PF-06650833 MR tablets AND 1 x 11 mg tofacitinib MR tablet	2 PF-06651600 IR matching placebo tablets	5
2	PF-06650833 (400 mg) + PF-06651600 (100 mg)	2 x 200 mg PF-06650833 MR tablets AND 2 x 50 mg PF-06651600 IR tablets	1 tofacitinib MR matching placebo tablet	5
3	PF-06650833 400 mg	2 x 200 mg PF-06650833 MR tablets	2 PF-06651600 IR and 1 tofacitinib MR matching placebo tablets	5
4	PF-06651600 100 mg	2 x 50 mg PF-06651600 IR tablets	2 PF-06650833 MR and 1 tofacitinib MR matching placebo tablets	5
5	Tofacitinib 11 mg	1 x 11 mg tofacitinib MR tablet	2 PF-06650833 MR and 2 PF-06651600 IR matching placebo tablets	5

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an IP accountability form/record.

4. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

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

6. Study interventions should be stored in their original containers and in accordance with their labels.

7. See the IP manual, package insert, or equivalent for storage conditions of the study intervention.

8. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

9. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP Manual.

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

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP Manual.

6.2.1. Preparation and Dispensing

The IP will be provided as 4 weekly blister cards packaged and dispensed in cartons with tamper-evident seals. It will be dispensed using an Interactive Response Technology (IRT) system at each dispensing visit specified in the SoA. A qualified staff member will dispense the IP via the unique container number identified by the IRT system in the cartons provided, in quantities appropriate for the study visit schedule. The participant/caregiver should be instructed to maintain the product in the carton and blister cards provided throughout the course of dosing and return the carton and blister cards to the site at the next study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

Allocation of participants to treatment groups will proceed through the use of an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to their Login Identification (ID) and password, the protocol number, and the Single Subject Identification Number (SSID or Subject ID) assigned by the IRT system. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number when IP is being supplied via the IRT system. The IRT system will provide a confirmation report containing the SSID or Subject ID, randomization number and DU or container number assigned. The confirmation report must be stored in the sites' files.

Investigational product will be dispensed at the study visits summarized in the SoA.

Returned IP must not be redispensed to the participants. The study-specific IRT Quick Reference Guide (QRG) and investigator Site Overview will provide contact information and further details on the use of the IRT system.

6.3.2. Breaking the Blind

The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management

of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF)/data collection tool (DCT).

6.4. Study Intervention Compliance

Participant compliance with completion of Diary and study intervention will be assessed at each visit. Participants interrupting study medication for more than 7 consecutive days, or participants who are less than 80% compliant with the dosage regimen for any 2 consecutive visit periods should be withdrawn from the study treatment. Upon discontinuation of the study treatment, participants will enter a FU period of 4 weeks, after which they will complete the FU/EOS visit and will be withdrawn from the study.

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

6.5. Concomitant Therapy

It is recommended that participants 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.

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.

Participants 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.

6.5.1. Rescue Treatment of RA

During the active dosing period**,** no "rescue" treatment is pre-specified. Rescue therapy for RA per se is not permitted during the study. Transient (up to 5 consecutive days) addition or increased doses of acetaminophen/paracetamol (dosed no more than 2.6 g/day if not on background acetaminophen/paracetamol), NSAIDs (up to maximal doses prescribed in the product label of package insert), or an opioid (not exceeding the potency equivalent of 20 mg of orally-administered morphine) is permitted for limited duration control of pain. If a participant is already taking stable background doses of acetaminophen/paracetamol, she/he may increase the dose up to 4 gm/day for up to 5 consecutive days. Participants who require increased pain control medication for more than 5 consecutive days should be discontinued from the trial and treated for worsening RA as per local standard of care practice. Acetaminophen/paracetamol or NSAID 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)

of acetaminophen/paracetamol does not exceed 2.6 gm/day (or 4 g/d if on background acetaminophen/paracetamol) and the NSAID dose is limited to lowest recommended anti-pyretic dose. Rescue pain medications will not be provided by the sponsor.

Participants (to the extent possible) should not be dosed with increased doses of pain control medication during the 24 hours prior to interval study visits and 7 days prior to Week 0, Week 12, and Week 24 visits. (Note: stable background doses of acetaminophen/paracetamol or opioids should NOT be discontinued in advance of study visits).

Although the use of additional/increased doses of pain control medications as described above is allowable, their use should be delayed, if possible, during the screening period and for at least the first 12 weeks following randomization. The date and time of the additional/increased doses of pain control medication administration as well as the name and dosage regimen of these medications must be recorded in the CRF.

Participants, who after at least a 12-week trial on the assigned investigational product who have not achieved at least a minimal clinical response (as defined by the American College of Rheumatology [ACR] 20% response criteria [ACR20]) are to be discontinued from the study and treated for their RA according to local standard of care (SoC) practice. The SoC treatment will not be provided by the sponsor. The Principal Investigator (PI) may also discontinue participants at any time during the study if in the PI's opinion, worsening RA signs and symptoms unresponsive to limited-duration increases in analgesic medications requires more urgent advancement of RA treatment. Additional treatment for participants meeting either of these criteria for discontinuation from the study will be provided by the investigator, and upon withdrawal from the study, participants will enter the follow-up phase of the study.

6.5.2. Permitted Concomitant Medications

It is recommended that study participants 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.

Study participants 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.

6.5.2.1. Osteoporosis Drugs

To the extent possible, dosing of concomitant medications indicated to increase bone mineral density (eg, bisphosphonates, denosumab) should not occur immediately before study visits, and in particular, Day 1 (randomization), Week 12, and Week 24 visits. A minimal interval of approximately 4 weeks prior to a clinic visit is preferred (ie, dosing would occur just after a study visit). Ideally, drugs dosed every 3 months would be administered just after the

Week 0 (Day 1), Week 12, and Week 24 visits; drugs dosed every 6 months should not be dosed during the active treatment period with doses administered before screening (and approximately 4 weeks prior to randomization) and after Week 24. If a dose of drugs administered every 6 months must be given during the active dosing period, the dose should optimally be given after the Week 12 visit.

6.5.2.2. Hormonal Contraception

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are women of childbearing potential (WOCBP) (see Appendix 4).

6.5.2.3. 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 for the stipulated interval before Randomization.

- Anti-malarials (eg, chloroquine, hydroxychloroquine) at doses consistent with their labeling.

- 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 the first dose of study drug or “randomization”. Transient increased doses of NSAIDs are permitted for limited duration control of pain (see Section 6.5.1 for rescue treatment). Topical NSAIDs are allowed at any time during the study.

- Acetaminophen/paracetamol at doses ≤2.6 grams per day. Non-prohibited opioids at doses ≤ the potency equivalent of 20 mg of orally-administered morphine at a stable dose beginning at least 4 weeks prior to the first dose of study drug or “randomization”. Since PF-06651600 may increase the exposure of drugs metabolized predominantly by CYP3A, participants using opiate analgesics should be cautioned about increased opiate side effects (eg, somnolence) and should be cautious about driving or using heavy machinery until the effects of IP administration is known. Doses of opioids may be reduced if needed to address the increase in opiate side effects.

- Low dose oral corticosteroids (≤7.5 mg prednisone or equivalent [see Appendix 12 for potency equivalency] per day) at a stable dose beginning at least 4 weeks prior to the first dose of study drug or “randomization”. Reductions in oral corticosteroid dose are only allowed as needed to protect a participant’s safety.

6.5.3. Prohibited Concomitant Medications

6.5.3.1. 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 11) are prohibited within 4 weeks or 5 half-lives (whichever is longer) prior to the Randomization Visit (Visit 2) and during the trial.

6.5.3.2. Strong Inhibitors/Inducers of BCRP

Systemic therapies with medications that are strong inhibitors of Breast Cancer Resistance Protein (BCRP) (some common examples are provided in Appendix 11) are prohibited within 4 weeks or 5 half-lives (whichever is longer) prior to the Randomization Visit (Visit 2) and during the trial.

6.5.3.3. Substrates of CYP3A4

The exposure of CYP3A4 substrates may increase when co-administered with PF-06651600. The use of drugs primarily metabolized and cleared by CYP3A4 should be either avoided within 4 weeks or 5 half-lives (whichever is longer) prior to the Randomization Visit (Visit 2) and during the trial or used with caution using clinical judgement. Please follow the respective approved prescribing guidelines (some common examples are provided in Appendix 11).

6.5.3.4. Substrates of BCRP

The exposure of substrates of BCRP substrates may increase when co-administered with PF-06650833. The use of BCRP substrates listed in Appendix 11 is prohibited within 4 weeks or 5 half-lives (whichever is longer) prior to the Randomization Visit (Visit 2) and during the trial. Other BCRP substrates should be used with caution using clinical judgement. Please follow the respective approved prescribing guidelines (some common examples are provided in Appendix 11).

6.5.3.5. Other Prohibited Concomitant Medications

Herbal medications with pharmaceutical properties must be discontinued at least 4 weeks before the first dose of study medication.

Special restrictions regarding prior and concomitant RA drugs are outlined in the Section below.

6.5.4. Prohibited Background Rheumatoid Arthritis Therapies

6.5.4.1. Disease Modifying Antirheumatic Drugs (DMARDs)

Conventional synthetic, biologic, or other advanced therapy DMARD concomitant medications are prohibited during the study. Specific washout requirements for non-prohibited prior DMARDs are as follows:

- Biologic TNF inhibitors:
  - As noted in Section 5.1, up to 25% of participants may have previously received 1 (and only 1) approved TNF-inhibiting biologic DMARD administered in accordance with its labeling recommendations. The prior TNF-inhibiting biologic DMARD 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 participant's opinions that the participant 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 or biologic DMARD biologic could also have been discontinued due to lack of continued access. The anti-TNF or biologic DMARD 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.
- MTX
  - MTX is to be discontinued (last MTX dose is to occur) during the week before randomization on Day 1. Participants whose regularly scheduled MTX dose would occur on or up to Day -1 should take that dose. Participants whose regularly scheduled MTX dose would have been on the day of randomization (Day 1) should not take that dose of MTX. No further MTX dosing is permitted during the active dosing phase of the study. Participants may restart MTX dosing beginning 14 days after the last dose of IP (Week 26).

6.5.4.2. Other Rheumatoid Arthritis Drugs

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

- Intravenous, and intra-articular corticosteroids.
- Other csDMARDs, immunosuppressants/immunomodulators (including tacrolimus or other calcineurin inhibitors) and biologic response modifiers (including natalizumab or other anti-integrin biologics).
- Participants with prior use of tofacitinib or other JAK inhibitor are excluded. Concomitant use of tofacitinib or other JAK inhibitor (other than as prescribed by the randomization scheme) 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 Product Insert (USPI), Elimination Procedure to significantly lower leflunomide drug levels).

6.6. Dose Modification

This protocol does not allow alteration from the currently outlined dosing schedule.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to discontinue IP permanently. If IP is permanently discontinued, the participant will enter the required 4-week FU period, after which the participant will not remain in the study unless the participant is being treated/followed for an adverse event and agrees to the non-drug follow-up.

Note that discontinuation of IP does not represent withdrawal from the study.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early withdrawal (EW) visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) 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.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

The Sponsor's clinical team should be consulted as soon as possible if a participant is being considered for or has been discontinued from study treatment for an adverse event or other safety issue.

Participants interrupting study medication for more than 7 consecutive days (either due to lack of compliance or in response to an AE), or patients who are less than 80% compliant with the dosage regimen for any 2 consecutive visit periods should be withdrawn from the study. Upon discontinuation of the study treatment, participants will enter a FU period of 4 weeks, after which they will complete the FU/EOS visit and will be withdrawn from the study.

Any participant who meets discontinuation criteria as specified in Section 8.10 should be discontinued from the study.

ECG Changes

A participant who meets either of the bulleted criteria based on the average of triplicate ECG readings will be withdrawn from the study.

- QTcF >500 msec.

- Change from baseline: QTc >60 msec.

If a clinically significant finding is identified (including, but not limited to, changes from baseline/randomization in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Withdrawal of Consent:

Participants 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 participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants 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 participant 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.

Participants who discontinue receipt of treatment due to lack of response will be discontinued from this study and will be treated for their RA according to local standard of care (SoC) practice. Upon discontinuation of the study treatment, participants will enter a FU period of 4 weeks, after which they will complete the FU/EOS visit and will be withdrawn from the study.

Participants who discontinue receipt of treatment due to AE will be discontinued from this study and followed until the event is considered resolved or the participant is considered clinically stable.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

Blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

8.1.1. 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).

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4. Patient's Global Assessment (PtGA) of Arthritis.
5. Physician's Global Assessment (PhGA) of Arthritis.
6. C-Reactive Protein (CRP), measured by high sensitivity methodology (hsCRP).

CCI [redacted]

[redacted]

Components of the ACR Core Dataset will be collected at the visits indicated in the SoA. Details regarding the physician-conducted and laboratory assessments are provided below. Details on the participant-provided assessments are described in Section 8.1.3. CCI [redacted] The responder according to this definition has the TJC68 ≤1 SJC66 ≤1, CRP ≤1 mg/dL and PtGA ≤10 (on 1-100 scale).

8.1.1.1. Tender/Painful Joint Count (68)

Sixty-eight (68) joints will be assessed by a blinded joint assessor (ie, someone not otherwise involved in the conduct of the study, and not having interactions with study participants or site personnel directly involved in the study) 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 1 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).

8.1.1.2. 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.

8.1.1.3. Tender and Swollen Joint Counts (28)

The twenty-eight tender/painful and swollen joint counts are a subset of the 68/66 tender and swollen joint counts and includes the following joints: shoulders, elbows, wrists, metacarpophalangeal joints (MCP), proximal interphalangeal joints (PIP), and knees. The 28 tender/painful join count will be calculated by Pfizer from the 68 tender/painful joint count assessed by the blinded joint assessor as described in Section 8.1.1.

The 28 swollen joint count uses the same joints as the 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 8.1.2.

8.1.1.4. 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).

8.1.1.5. C-Reactive Protein (CRP)

Samples for analysis of high sensitivity CRP (hsCRP) will be collected at the visits specified in the SoA. 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.

8.1.2. Composite Efficacy Assessments Derived from the ACR Core Dataset

The ACR core data set are used in various combinations to produce composite scores or indices which are used as more wholistic assessments of disease activity and study efficacy endpoints. The details of these composite efficacy endpoints are provided in the sections below.

8.1.2.1. Disease Activity Score (DAS) Assessments

The Disease Activity Score (DAS) assessment is a continuous composite measure of TJC, SJC, PhGA, and an acute phase reactant that is either CRP CCI . The DAS is derived using differential weighting given to each component. DAS28 is a measure based on assessment of 28 joints for tenderness and swelling (tender and swollen joint counts). DAS28 will be calculated with 4 components (TJC, SJC, PtGA, and either CRP CCI [DAS28-CRP CCI]). The formulae for calculation of DAS28-CRP, CCI are presented in the Appendix 10.

Remission and low disease activity were defined as scores <2.6 and ≤3.2, respectively for DAS28-CRP.

8.1.2.2. 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 or ESR. Similarly, ACR50, ACR70, and ACR 90 are calculated with the respective percent improvement.

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[redacted]

CCI

[redacted]

8.1.4. Rater Qualifications

Clinical evaluations of RA (eg, tender/painful joint assessments) will be performed by an experienced and qualified rheumatologist (board certified or equivalent). An experienced and qualified non-rheumatologist physician or experienced medical professional with experience in the conduct of RA clinical trials may be permitted to perform the clinical evaluations of RA when designated by primary site investigator. The evaluator must be able to document competency in performing the efficacy assessment scales (eg, through prior training with certification, or at least 3 years' experience performing the assessments in Industry-sponsored clinical trials) prior to performing these evaluations. **To assure consistency and reduce variability, the same evaluator must assess all rheumatology clinical evaluations for any individual participant throughout the study whenever possible**; a back-up experienced and qualified, protocol-trained evaluator will only be allowed and documented in case of emergency or special situations when the designated evaluator is unable to perform the evaluation. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study. Sixty-eight (68) joints will be assessed by a blinded joint assessor (not otherwise involved in the conduct of the study, and not have other interactions with study participants or site personnel directly involved in the study) to determine the number of joints that are considered tender or painful.

8.1.5. Imaging Assessments/MRI of Hand/Wrist

Depending on logistical and feasibility considerations, MRIs of the hand may be performed in a subset of participants (up to approximately 60 participants per arm) who agree to be included in this aspect of the study as allocated according to the study randomization scheme. Participants who refuse to undergo MRI may still be eligible for enrollment into the study. Participants in the MRI subgroup will be recruited globally in the order of enrollment in the Integrated Voice Response System (IVRS) up to a maximum number as defined by the sponsor.

If the substudy is conducted, a baseline MRI of a single hand and wrist will be performed during screening period after all other eligibility criteria have been met and at least 1 week prior to randomization (Visit 2). Follow-up MRIs will be performed at Visit 6/Week 12 (±1 week), and Visit 9/Week 24 (-2 to +1 week), as specified in the imaging guidelines (which for these procedures will supersede the SoA). A delay in acquisition of the Baseline MRI up to 1 week (7 days) after Randomization at Visit 2 (Week 0, Day 1) solely due to scheduling availability will not be considered a protocol deviation. At all visits, MRI will be performed on the same hand and wrist, both before, during and after intravenous administration of a gadolinium contrast agent. All images will be evaluated by centralized reviewers blinded to the treatment designation. MRI assessments will include evaluation of synovitis, bone marrow edema, and bone erosions using the RAMRIS and RAMRIQ scoring methods. RAMRIS is a semi-quantitative scoring system to evaluate longitudinal changes in RA patients. RAMRIQ is a quantitative version of the RAMRIS scoring system. When image quality permits, dynamic contrast enhanced-MRI (DCE-MRI) analysis will also be evaluated**.** Procedures for obtaining MRI images and evaluating images will be described in separate imaging guidelines and an image review charter. The imaging guidelines will be provided to investigators and radiology personnel prior to initiation of the study. Details of the statistical analyses of the results will be provided in the statistical analysis plan (SAP).

Management of Incidental Findings

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

MRI images will be reviewed by a central review facility. The purpose of this review is to evaluate images for synovitis, bone marrow edema, and bone erosions. Central image review is not a complete medical review of the participant. If, during the central review process, an unexpected observation is identified and this finding could, in the opinion of the central reviewer, have a significant health or reproductive consequence, this finding may be shared with the study sponsor for disclosure to the principal investigator (PI). All follow-up testing and final diagnosis will be left to the discretion of the medical professionals at the site or those with an existing physician-participant relationship. The PI will be responsible for reporting any AEs identified from incidental findings as described in the AE reporting section. Identification of such incidental findings during the central review process should

not be expected, and the site maintains responsibility for performing a general safety review of all images as per site protocols.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Safety will be assessed by the spontaneous reporting of AEs, physical examinations, vital signs, ECGs, and clinical laboratory results in all participants who received at least 1 dose of study medication. Investigators and Pfizer Clinicians will review individual participant data throughout the conduct of the trial to ensure participant's well-being.

8.2.1. Creatinine and estimated Glomerular Filtration Rate

Estimated GFR will be calculated via the 2012 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine, for reporting purposes. Investigators may also use other methods for following renal function if eGFR from the central laboratory is not readily available.

Serum creatinine will be measured and creatinine based eGFR will be calculated at times specified in the SoA in order to facilitate calculation of eGFR and assess renal function.at these time points.

8.2.2. Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 2 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline (prior the participant's receiving the investigational product) or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.3. Viral Surveillance

A blood sample for potential viral load surveillance will be collected as indicated in the SoA. Assessment may include EBV and cytomegalovirus (CMV).

8.2.4. Medical History

Medical history, including history of alcohol, tobacco and drug abuse; RA history, including disease duration and extent of disease; major cardiovascular events including DVT, PE, and ischemic cerebral vascular accidents (CVA); history of herpes virus infection, vaccination (particularly for HZV); skin rash; skin infection and any abnormalities that may predispose the subject to infection and smoking history will be collected at Screening. Height and weight will be measured without the participant wearing shoes. Height (inches or centimeters) and weight (lbs or kg) will be measured up to 1 decimal place and recorded in the source document per the SoA.

8.2.5. Physical Examinations

8.2.5.1. Complete Physical Examination

A standard/complete physical examination will be performed by a qualified physician (Doctor of Medicine [MD], or equivalent) or other experienced medical professional (eg, Doctor of Osteopathic (DO)), Nurse Practitioner, Physician's Assistant) at the visits identified in SoA. The following parameters and body systems will minimally be examined and any abnormalities described: General appearance, skin (eg, presence of rash), Head, Eye, Ear, Nose and Throat (HEENT), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs, peripheral edema), abdominal (palpation and auscultation), neurologic (including cranial nerves, reflexes, motor and sensory function and assessment of cerebellar function such as gait, coordination, ataxia) and, lymph nodes.

8.2.5.2. Targeted Physical 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. Both full and targeted physical examinations must include a full body skin and neurologic examinations (neurologic examination would include assessment of cerebellar function). Skin examinations should include a visual inspection of the breasts and external genitalia.

8.2.5.3. Dermatology/Skin

Skin lesions will be evaluated as defined in the National Cancer Institute Common Toxicity Criteria for Adverse Events v5.0 and managed as shown below in Table 2.

Table 2. Management of Dermatological Events

Dermatologic Event (CTCAE v 5.0)	Course of Management
Acne/Acneiform Rash/Maculopapular Rash	
Grade 1/2	1. Investigator's discretion for withdrawing IP. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 3	1. Discontinue IP. 2. Monitor to resolution (defined as a Return to Baseline status). 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Pruritus	
Grade 1 Mild or localized	1. Investigator's discretion for withdrawing IP. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 2 Intense or widespread	1. Discontinuation of the IP may not be required unless condition is sustained >4 days or at the investigator's discretion. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 3 Intense or widespread and interfering with activities of daily living	1. Permanently discontinue IP. 2. Monitor to resolution (Return to Baseline). 3. Consider treatment with topical agents such as clindamycin or corticosteroids.

In any event of an **unexplained rash**, a blood sample for viral surveillance will be collected for the analysis of viral load including but not limited to CMV, EBV, Herpes Simplex Virus type 1 (HSV1), HSV2, and varicella-Zoster Virus (VZV). For a suspected infectious rash, a swab (for microbiological assessment) of the affected area will also be taken for culture and sensitivity to assess for any bacterial or fungal pathogens. For any occurrence of a suspected herpetiform rash (eg, herpes zoster and herpes simplex) an additional swab of the affected area will be collected for confirmation. Details for these collections will be provided in the laboratory manual.

Investigators will complete the rash assessment CRF and take appropriate photographs of the rash in order to provide information necessary for a dermatologist's assessment of the event.

All participants reporting an unexplained skin rash should be referred to a local dermatologist according to local guidelines for formal comprehensive dermatologic evaluation. A 4 mm punch biopsy should be taken and sent to the local laboratory for histological investigation of the rash in order to gain insight into potential etiology of the rash. If the rash is present on the face or other cosmetically exposed area, biopsy can be at the discretion of the dermatologist. All events of rash should be treated according to international and local guidelines for the treatment of rash, eg, where appropriate, topical corticosteroids and/or agents such as antibiotics or antivirals could be prescribed.

All treatment-related reports of rash will be followed up until resolution or clinically stable or agreement with Pfizer. Upon resolution of a Grade 1 or 2 rash/pruritus, including confirmed herpes zoster, participants **may** be re-challenged with IP at the discretion of the investigator. Re-challenge is not permitted with Grade 3 rash/pruritus.

All de-identified dermatologic consultation reports, biopsy results, culture results, photographs, and any additional relevant test results will be forwarded to Pfizer/designee for review within 30 days of receipt by the PI.

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

8.2.6. Vital Signs

Oral, tympanic, or temporal artery temperature (using the same methods throughout the study); pulse rate; and blood pressure will be assessed.

Vital signs will be measured with the participant in a sitting/semi-supine position after at least 10 minutes of rest and will include temperature, systolic and diastolic blood pressure, and pulse. Three readings of blood pressure and pulse rate will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF. At W12 pulse will also be collected at approximately 2 to 4 hrs post dose.

8.2.7. Audiogram

All participants will have an audiogram at times specified in the SoA. Audiograms may be performed within a ±2 week window relative to the study visit. When possible, the participant should have the audiogram performed at the same evaluation center during the study. Audiogram should be performed at the Early Termination (ET) visit unless the previous audiogram was less than 16 weeks prior to this.

If there is a clinically meaningful, treatment related decline in hearing from baseline screening the subject will be followed off treatment with appropriate testing at regular intervals, until hearing returns to baseline (prior to the participant's receiving the investigational product) or is determined to be clinically stable.

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

Any de-identified audiogram results/reports and any additional relevant test results (if applicable) may be requested to be forwarded to Pfizer (and/or designee) at any time during the study. Further details will be provided to investigators prior to the start of the study.

8.2.8. Electrocardiograms

Single 12-lead ECGs will be obtained on all participants at times specified in the SoA. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position. ECG results (heart rate, PR interval, RR interval, QRS duration, QT interval, rhythm, waveform abnormalities, or other clinically significant findings) will be recorded in the CRF. Any clinically significant changes from the baseline/Day 1 (Visit 2) ECG may potentially be AEs (Appendix 7) and should be evaluated further, as clinically warranted. ECG values of potential clinical concern are listed in Appendix 7.

If QTc interval exceeds 450 msec, or QRS duration exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the participant's eligibility.

If a postdose QTc interval remains ≥30 msec from the baseline **and** is >450 msec; or an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), QRS duration exceeds 120 msec, or QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

8.2.9. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced, and a second negative pregnancy test result will be required at the baseline visit (Visit 2) prior the participant's receiving the investigational product. Pregnancy tests will also be done at every study visit, and whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or that caused the participant to discontinue the study (see Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant'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, except as indicated below, after the last administration of the investigational product.

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

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.

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.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

SAEs occurring in a participant 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.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information 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 participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until 4 weeks after the last dose of study medication (Week 28).

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

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

8.3.5.3. Occupational Exposure

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

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a participant 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.

8.3.6. Adjudication of Targeted Adverse Events

Certain targeted adverse events, as enumerated below, will be subject to adjudication by an adjudication/review committee. These events will be forwarded for adjudication either by the study team or by its designee. Documents or additional information related to the event may be requested from sites and may vary with the event requiring adjudication and may include (but not be limited to): hospital discharge summaries, operative reports, clinic notes, diagnostic tests, pathology reports, autopsy reports and death certificate information, as applicable. Details on the adjudication process, will be provided in an adjudication committee charter.

8.3.6.1. Major Adverse Cardiovascular Events (MACE)

All major adverse cardiovascular events requiring hospitalization and deaths will be recorded as SAEs and additional data solicited in the CRF. Venous thromboembolic events (VTE) such as deep vein thrombosis (DVT) and pulmonary embolism (PE) will be adjudicated and will have additional information requested on separate CRF pages.

8.3.6.2. Opportunistic and Serious Infections

AEs of opportunistic or serious infections will be adjudicated and will have additional information requested on separate CRF pages.

8.3.6.3. Elevated Liver Enzymes and Liver Injury

AEs for elevated liver enzymes (AST, ALT, total bilirubin) and liver injury will be adjudicated and will have additional information requested on separate CRF pages.

8.3.6.4. Malignancies

All AEs of malignancies will be adjudicated and will have additional information requested.

8.3.6.5. Neurosensory Adverse Events

Neurosensory adverse events will be adjudicated and will have additional information requested.

8.3.6.6. Interstitial Lung Disease (ILD)

AEs of ILD will be adjudicated and will have additional information requested.

8.3.7. Medication Errors

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

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

Medication errors include:

- Medication errors involving participant 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 study participant.

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 within 24 hours.

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 nonserious, 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.**

8.4. Treatment of Overdose

For this study, any dose of investigational product greater than 1 row of tablets in the IP dosing card or multiple tablets within 1 or more columns of the IP blister card within a 24-hour (-2 hours) time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose. Treatment of overdose should consist of general supportive measures.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of investigational products (whichever is longer).

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4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

5. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

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8.6. Pharmacodynamics

Pharmacodynamic (PD) parameters (other than CRP and ESR, ACPA and RF, described above) are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected as local regulations and IRBs/ECs allow.

Banked biospecimens may be used for research related to drug response and RA. Genes and other analytes (eg, proteins, ribonucleic acid [RNA], nondrug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This component of the sampling banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their banked biospecimens. The optional additional research does not require the collection of any further samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided in the lab manual.

8.8. Biomarkers

8.8.1. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

8.8.2. Specified Protein Research

Details on processes for collection and shipment of these sample(s) can be found in the lab manual.

8.8.2.1. Anti-Citrullinated Protein Antibodies (ACPA)

Blood samples of approximately 3-ml will be collected as specified in the SoA. The sample(s) may be analyzed for anti-citrullinated protein antibodies.

8.8.2.2. Rheumatoid Factor (RF)

Blood samples of approximately 3-mL will be collected as specified in the SoA. The sample(s) may be analyzed for Rheumatoid Factor.

8.8.2.3. Interferon Gamma-Induced Protein 10 (IP-10)

Blood samples of approximately 3-ml will be collected as specified in the SoA. The sample(s) may be analyzed for IP-10 protein.

8.8.2.4. Immunoglobulin Subtypes

Separate blood samples for immunoglobulin subtype analyses of approximately 6-ml will be collected as specified in the SoA. Serum sample(s) will be evaluated for IgG, IgA, IgM, and IgE.

8.8.2.5. Serum for Exploratory Analysis

Blood samples of approximately 6-ml will be collected and as specified in the SoA. Serum sample(s) may be analyzed for circulating proteins and protein fragments.

Samples may be stored at a facility selected by the sponsor for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study.

8.8.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.8.4. Banked Biospecimens for Biomarkers

10-mL serum (Prep B2) samples will be collected as local regulations and IRB/ECs allow as specified in the SoA.

2.5-mL whole blood (Prep R1) samples will be collected as local regulations and IRB/ECs allow as specified in the SoA.

Banked biospecimens may be used for research related to drug response and RA. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked samples to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This component of the sampling banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their banked samples. The optional additional research does not require the collection of any further samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the lab manual.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.10. Triggered Requirements

Triggered requirements are specified in the Table in Section 8.11.

8.11. Guidelines for Monitoring and Discontinuations

Condition	Action
Renal function	
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 participant 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 study participants' 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. Participant followed until resolution or deemed medically stable by PI.
Liver Function	
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 participant withdrawn from this study. Participant followed until resolution or deemed medically stable by PI.
2 sequential AST or ALT elevations ≥3 x ULN with an elevated INR.	Treatment with all study drugs will be discontinued and the participant withdrawn from this study. Participant followed until resolution or deemed medically stable by PI.
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 participant withdrawn from this study. Participant followed until resolution or deemed medically stable by PI.
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 participant withdrawn from this study. Participant followed until resolution or deemed medically stable by PI.
Any single AST and/or ALT elevation >3 times the upper limit of normal (ULN).*	The participant should return to the study site for prompt retesting, ideally within 3-5 days.*
* The participant 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 person, 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 participant 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 Appendix 6).	

Condition	Action
Hematology	
Neutrophil counts <1000 cells/mm^3.	The participant should return to the study site for prompt retesting, ideally within 3-5 days.
Platelet counts <100,000 platelets/mm^3.	The participant should return to the study site for prompt retesting, ideally within 3-5 days.
Lymphocyte counts <500 lymphocytes/mm^3.	The participant 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 participant should return to the study site for prompt retesting, ideally within 3-5 days.
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 participant withdrawn from this study. Participant followed until resolution or deemed medically stable by PI.
Two sequential platelet counts <75,000 platelets/mm^3.	Treatment with all study drugs will be discontinued and the participant withdrawn from this study. Participant followed until resolution or deemed medically stable by PI.
2 sequential neutrophil counts <1000 cells/mm^3	Treatment with all study drugs will be discontinued and the participant withdrawn from this study. Participant followed until resolution or deemed medically stable by PI.
Confirmed lymphocyte counts <500 lymphocytes/mm^3 by repeat testing.	Treatment with all study drugs will be discontinued and the participant withdrawn from this study. Participant followed until resolution or deemed medically stable by PI.
Infections	
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 participant withdrawn from this study. Participant followed until resolution or deemed medically stable by PI.
Opportunistic infection judged significant by investigator.	Treatment with all study drugs will be discontinued and the participant withdrawn from this study. Participant followed until resolution or deemed medically stable by PI.
Other	
Participants who have a flare of RA requiring treatment with prohibited concomitant medication are to be discontinued from the study treatment.	Treatment with all study drugs will be discontinued and participants will be treated for their RA according to local standard of care (SoC) practice. Upon discontinuation of the study treatment, participants will enter a FU period of 4 weeks, after which they will complete the FU/EOS visit and will be withdrawn from the study.

Condition	Action
Participants who require additional/increased doses of pain control medication for more than 5 consecutive days for treatment of increased RA symptoms should be discontinued from the study treatment.	Treatment with all study drugs will be discontinued and participants will be treated for their RA according to local standard of care (SoC) practice. Upon discontinuation of the study treatment, participants will enter a FU period of 4 weeks, after which they will complete the FU/EOS visit and will be withdrawn from the study.
Participants who at any time from Week 12 to Week 24 do not manifest a minimal clinical response as defined by meeting ACR20 criteria.	Treatment with all study drugs will be discontinued and participants will be treated for their RA according to local standard of care (SoC) practice. Upon discontinuation of the study treatment, participants will enter a FU period of 4 weeks, after which they will complete the FU/EOS visit and will be withdrawn from the study.
Venous thromboembolic events (including DVT, PE).	Withdraw the participant from the study treatment and follow participant until the event is confirmed. Participants suspected of having VTE should be questioned for VTE risk factors and have appropriate diagnostic testing (such as d-dimers, lupus anticoagulant, PT/PTT, platelet counts and imaging as deemed appropriate by the PI or consultant) to confirm the VTE event. If the VTE event is confirmed, investigational product is to be withdrawn permanently and the participant followed until the event is considered resolved or the participant is considered clinically stable by the PI.
Other major cardiovascular events [MACE] (eg, acute coronary syndrome, ischemic stroke).	Permanently withdraw the participant from study treatment until the event is confirmed. Participants suspected of having other MACE should be questioned for risk factors and have appropriate diagnostic testing as deemed appropriate by the PI or consultant. Participants with confirmed other MACE should be permanently discontinued once the event is considered resolved or the participant is considered clinically stable by the PI.
Malignancies excluding adequately treated non melanoma skin cancer (NMSC) and cervical carcinoma in situ.	Treatment with all study drugs will be discontinued and, if possible, the participant will enter a 4-week follow-up period following which the participant should be withdrawn from this study.
Increased lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides).	Monitor and treat according to local guidance (eg, diet and behavior modification, statin therapy).
Pregnancy or refusal to use appropriate contraception.	Permanently withdraw the participant from the study and follow any pregnancy to resolution.

Condition	Action
Use of prohibited concomitant medications.	See Section 6.5.3 Concomitant Medications of the protocol for specific actions. Discontinue concomitant medications, if possible and monitor the participant. If concomitant medications are needed to treat participants then treatment with all study drugs will be temporarily or permanently discontinued. Upon permanently discontinuation of the study treatment, participants will enter a FU period of 4 weeks, after which they will complete the FU/EOS visit and will be withdrawn from the study.
Anaphylactic or other serious allergic reaction.	Immediately discontinue study drug and institute appropriate therapy. Participant followed until resolution or deemed medically stable by PI.
Symptoms suggestive of a lupus-like syndrome.	Discontinue study drug and institute appropriate therapy. Participant followed until resolution or deemed medically stable by PI.

9. STATISTICAL CONSIDERATIONS

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

9.1. Estimands and Statistical Hypotheses

The characterization of the key estimands E1,E2,E3 that are used in the analyses are described in the Table 3. The additional supportive estimands will be described in the SAP. The study objectives, endpoints and estimands are described in the Section 3.

The primary (key secondary) hypothesis is that the efficacy in the combination treatment arm based on the primary (key secondary) endpoint is not superior to the efficacy of tofacitinib treatment. The primary hypothesis needs to be rejected at the one-sided significance level of 0.05 for the declaration of the superior efficacy of the particular combination treatment arm. No adjustment for the multiplicity (n=2) comparisons of the combination treatment arms with the tofacitinib treatment arm will be applied.

Table 3. Characterization of the Estimands

Notation for the Estimand	Population Targeted by the Scientific Question	Type of Endpoint	Population-level Summary for a Given Treatment	Metric for Comparison between the Treatment Groups	Account for the Intercurrent Events
E1	All treated study participants	Continuous	Mean change from baseline	Difference of mean changes from baseline	None
E2	All treated study participants	Binary	Probability of response	Ratio of probabilities of response.	None
E3	All treated study participants	Binary	Probability of response	Difference of probabilities of response	None

Other estimands may be used for assessing the robustness of results, if performed they will be documented in the statistical analysis plan.CCI [redacted]

9.2. Sample Size Determination

9.2.1. Power for the Efficacy Evaluation Based on the Primary Outcome

A sufficient number of participants will be screened to achieve up to approximately 100 participants randomly assigned to the 2 combination arms and the tofacitinib monotherapy arms (the 3 arms used in primary and key secondary hypothesis testing), and up to approximately 75 participants to the PF-06650833 and PF-06651600 monotherapy arms. The dropout rate by Week 12, the time of the primary analysis, is expected to be no greater than approximately 18%, providing up to approximately 82 participants in the tofacitinib and combination arm used for the primary hypothesis testing with full 12-week data. If this drop-out rate is exceeded due to COVID-19, the proportion of participants discontinued due to COVID-19 may be replaced. The standard deviation of baseline-adjusted CFB DAS28-4(CRP) is approximately 1.20 based on prior RA studies run by the Sponsor. A pairwise comparison of a combination arm contrasted with the tofacitinib monotherapy arm using a one-sided alpha=0.05 testing level, with an assumed between-arm difference of 0.5 has a power of approximately 84%.

9.2.2. Power for the Efficacy Evaluation Based on the Key Secondary Outcome

A test of the key secondary hypothesis is based on the comparison of the proportions of study participants with DAS-28-CRP remission at Week 24. In the analysis of binary outcomes we will use the non-responder imputation treating missing value of the binary outcome as non-response with the exception of the two special cases of the reason for missing data. These special reasons for missing data include missingness related to the COVID infection (either patient illness or COVID-related problem of attending the visit) and missingness when subject attended the visit but some of the components for the calculation of the outcome (eg, ACR20) are missing. The observations that are missing for these special reasons will be excluded from the calculation of the probabilities of response at a given visit.

This strategy will make a proportion of study participants with missing values at Week 24 very small as most of the study participants with missing observations will be assigned a non-responder status. Based on historical data the remission rate for the tofacitinib monotherapy arm is assumed to be 26%. In the absence of missing observation at Week 24 a pairwise comparison of a combination arm with the tofacitinib monotherapy arm using a one sided alpha=0.05 testing level with an assumed relative remission ratio (combinations remission percentage/tofacitinib monotherapy remission percentage) of 1.7 (equivalently a combination arm remission rate of 44.2%) has a power of approximately 84%.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Defined Population for Analysis	Description
Modified Intent to Treat (mITT)	Observations for participants randomly assigned to investigational product who take at least 1 dose of investigational product. Participants will be analyzed according to the randomized intervention
Safety analysis set	Observations for participants randomly assigned to investigational product who take at least 1 dose of investigational product. Participants will be analyzed according to the product they actually received.
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PD data set	Observations for participants randomly assigned to investigational product and who take at least 1 dose of investigational product and have at least 1 of PD parameters of interest. Participants will be analyzed according to the randomized intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary: Change from Baseline DAS28-CRP at Week 12	A Mixed Model Repeated Measures (MMRM) approach to estimate the mean change from baseline of DAS28-CRP at Week 12 using data at all visits post-baseline up to Week 12 to estimate the effect of the initially randomized treatment at Week 12. The analysis will use the mITT analysis set Missing data will not be imputed for this analysis. The MMRM analysis will contain fixed effect terms for treatment, scheduled study visit, baseline DAS 28-CRP, treatment by visit interaction, baseline by visit interaction. The model will use an unstructured covariance matrix. The primary analysis, comparing the combination arm to the tofacitinib monotherapy arm will be done using estimated least squares means for each treatment arm at Week 12. The comparison will be made at the one-sided significance level of 0.05 and no adjustment for multiplicity of comparisons will be attempted.
Key Secondary: DAS28-CRP Remission at Week 24	A landmark analysis at Week 24 will estimate the relative risk of DAS 28-CRP remission comparing each combination arm to the tofacitinib monotherapy arm. This analysis will use the mITT analysis set and the non-responder imputation method (NRI). The NRI treats missing value of the binary outcome as non-response with the exception of the two special cases of the reason for missing data. These special reasons are missingness related to the COVID infection (either patient illness or COVID-related problem of attending the visit) and missingness when subject attended the visit but some of the components for the calculation of the outcome (eg, ACR20) are missing. The observations that are missing for these special reasons will be excluded from the calculation of the probabilities of response at a given visit. Exact statistical inference will be used. The comparison will be made at the one-sided significance level of 0.05 and no adjustment for multiplicity of comparisons will be attempted.
Other Secondary CCI [redacted]	Will be described in the SAP finalized before database lock.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population derived from all participants enrolled.

Endpoint	Statistical Analysis Methods
Primary	The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive at least 1 dose of IP (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include: • Treatment-emergent AEs and SAEs; • Withdrawals from active treatment due to AEs; • Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials; • Safety laboratory tests (eg, hematology [including coagulation panel], chemistry and lipid profiles); • Vital signs; • ECG. Change from baseline on laboratory data, vital signs and ECG will be additionally summarized. Participant listings will also be produced for these safety endpoints.

9.4.2.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by treatment and time.

The number (%) of participants with maximum postdose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTc Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

9.5. Interim Analyses

One or more interim analyses (IA) may be performed for internal business decision-making or sample size reestimation (there is no intention a priori to terminate the study or a treatment arm based on the results of the IA). The final number and timing of any IA, if performed, will be defined by the sponsor.

If an IA is performed, an Interim Analysis Committee/Executive Committee will be constituted that will include members of senior Pfizer leadership. Before any interim analysis is initiated, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in an Interim Analysis Committee/Executive Committee charter. In addition, the analysis details must be documented and approved in an interim analysis SAP or final SAP. The study team will remain blinded to all interim results.

9.5.1. Data Monitoring Committee

An Independent Oversight Committee (IOC) will be constituted and be responsible for review of unblinded safety and laboratory data on a regularly scheduled, periodic basis (eg, after 25%, 50% and 75% of participants have been randomized, and periodically thereafter), as well as on an ad hoc basis at the request of the study team. The IOC may also have access to unblinded efficacy data from any interim analyses (if performed) for ongoing assessment of overall benefit: risk. For this study, the IOC will be an Internal Review Committee (IRC) comprised of Sponsor personnel (at least one of whom is medically qualified and one of whom is a clinical statistician) not directly involved in study conduct or in interactions with site personnel or participants.

The IRC will be responsible for ongoing monitoring of safety of participants in the study according to the Charter. Any recommendations made by the IRC to alter the conduct of the study will be forwarded to the Executive Committee for final decisions. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

9.6. Safety Adjudication Committees

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

The Pfizer Study Team or designee will provide a listing of specific documents needed to support event adjudication by the Adjudication/Review Committees. Obtaining and submitting the documentation will be the responsibility of the study site. Event documentation will vary with the event requiring adjudication and may include (but not be

limited to): hospital discharge summaries, operative reports, clinic notes, diagnostic tests, pathology reports, autopsy reports and death certificate information, as applicable.

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, investigator's brochure (IB), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. 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 participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICD.

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10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study 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 addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

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 product, regardless of the geographical location in which the study is conducted. US Basic Results are generally 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 participant 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 (CSR synopses in which any data that could be used to identify individual participants have 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.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of “bona-fide scientific research” that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

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

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. 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.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor 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 participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. 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 team on demand (SToD) system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant 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 participant'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 participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 4. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs and %) Eosinophils (Abs and %) Monocytes (Abs and %) Basophils (Abs and %) Lymphocytes (Abs and %) Reticulocyte count % Partial thromboplastin time (PTT) Prothrombin time (PT)	BUN/urea and 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 (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[e] Color and clarity Specific gravity Urine Culture[f]	At screening only: • FSH[a] • Pregnancy test (β-hCG)[b] • Hepatitis B surface antigen, HepBc Ab[d] • Hepatitis C antibody or HCV RNA[d] • HIV[d] • QuantiFERON® TB Gold test[d]

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CO_2 = carbon dioxide; FSH = follicle-stimulating hormone; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; qual = qualitative; RBC = red blood cell; WBC = white blood cell.

a. In females who are amenorrheic for at least 12 consecutive months, for confirmation of postmenopausal status only.
b. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or institutional review board/ethics committee (IRB/EC). Serum or urine β-hCG for female participants 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.
e. To be performed if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase;
f. If urine microscopic examination is suggestive of urinary tract infection (eg, due to the presence of neutrophils); or if deemed clinically appropriate by the PI.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Examples of such events include invasive or malignant cancers, 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.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse 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) nonserious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

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.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding. Occupational exposure is not recorded.	All (and EDP supplemental form for EDP). Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- 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. 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.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.

- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

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

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s). If the primary form of contraception is an estrogen containing hormone method, then the women or her partner must additionally use a barrier method. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. A barrier method must be used with all highly effective methods that are user dependent listed below. Participants enrolled in Canadian sites must use at least 2 forms of contraception regardless of the user dependency of the method(s),

including at least 1 form of highly effective contraception and 1 form of effective contraception.

10.4.3. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.
2. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

   - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
     - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation and a barrier method.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and a barrier method if using hormonal contraceptive agent:

    - oral;

    - intravaginal;

    - transdermal.

2. Progestogen-only hormone contraception associated with inhibition of ovulation and a barrier method:

    - oral;

    - injectable.

3. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. If during the study the subject decides to become

sexually active they must inform the study site and start using one of the effective contraception method described in this section.

Effective methods to be used with all highly effective contraceptive methods that are user dependent listed above:

4. Male or female condom with or without spermicide.

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

Collection of Pregnancy Information

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 participant or participant's partner becomes or is found to be pregnant during the participant'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 participant 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

preprocedure 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 participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-06651600 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Samples for specified genetic analysis (see Section 8.8) will be stored for up to 15 years or other period as per local requirements.

    - Samples for banking (see Section 8.7.2 and 8.8.4) will be stored indefinitely or other period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

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 participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants 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 laboratory 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 participant’s individual baseline values and underlying conditions. Participants 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:

- Participants 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 participants 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 participant 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 for suspected cases of Hy's law, additional 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, and alkaline phosphatase. 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) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 msec.
- New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset left bundle branch block (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  - In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis (RA)

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

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.

10.9. Appendix 9: 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.

10.10. Appendix 10: Disease Activity Score DAS (DAS28-CRP), CCI Assessments

The formula for calculation of DAS28-CRP uses the following 4 components:

- Swollen Joints (0–28);
- Tender Joints (0–28);
- hsCRP (high sensitivity C-reactive protein);
- Patient's Global Assessment (PtGA) of Arthritis (0 – 100 mm VAS).

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

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10.11. Appendix 11: Prohibited Concomitant Medications

Prohibited Concomitant Medications

Please note that this list addresses only CYP3A4 inhibitors and inducers, CYP3A substrates and BCRP and Pgp substrates. This is not an all-inclusive list. Study personnel should stay current and consult with their pharmacy to exclude all concomitant medications that are either moderate to potent CYP3A inhibitors or inducers or sensitive or moderate sensitive CYP3A4 substrates or BCRP or Pgp substrates with narrow therapeutic index.

Moderate to Potent CYP3A Inhibitors*		**Moderate to Potent CYP3A Inducers****
Amprenavir	Indinavir#	Avasimibe#
Amiodarone	Itraconazole#	Bosentan
Aprepitant	Ketoconazole#	Barbiturates
Atazanavir	Lopinavir#	Carbamazepine#
Boceprevir	Mibefradil#	Efavirenz
Casopitant	Mifepristone (RU486)	Etravirine
Cimetidine	Nefazodone#	Mitotane#
Ciprofloxacin	Nelfinavir#	Modafinil
Clarithromycin#	Norfloxacin	Nafcillin
Cobicistat#	Posaconazole#	Phenobarbital#
Conivaptan#	Ritonavir#	Phenytoin#
Darunavir	Saquinavir#	Rifabutin#
Diethyldithiocarbamate	Schisandra sphenanthera	Rifampin #
Diltiazem	Telaprevir	St. John's Wort#
Dronedarone	Telithromycin#	Talviraline
Elvitegravir#	Tipranavir#	
Erythromycin	Tofisopam	
Fluconazole	Troleandomycin#	
Fluvoxamine	Verapamil	
Imatinib	Voriconazole#	
Danoprevir	Crizotinib	
Grapefruit Juice***	Faldepravir	
Idelalisib	Netupitant	
Nilotinib	Isavuconazole	
CYP3A4 Substrates##	**CYP3A4 Substrates with NTI**	**Pgp Substrates**
Aprepitant	Argatroban	Digoxin
Eliglustat	Alfentanil	
Pimozide	Astemizole	**BCRP Substrates**
Conivaptan	Cisapride	Rosuvastatin
Darunavir	Cyclosporine	Glecaprevir
Dasatinib	Diergotamine	Pibrentasvir
Dronedarone	Ergotamine	
Ebastine	Fentanyl	
Indinavir	Quinidine	
Lomitapide	Terfenadine	
Nisoldipine	Valproate	
Rilpivirine		

Saquinavir		
Sirolimus		
Tacrolimus		
Tipranavir		
Tolvaptan		

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

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

Notated as potent inhibitors or inducers.

The label recommends to avoid (or contraindicate) use of these concomitant medication with moderate CYP3A4 inhibitors (eg, PF-06651600).

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

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

Concomitant Medications to be Used with Caution or Dose Reduction

CYP3A4 Substrates (Use with caution or dose reduction)[$]	
Alprozolam	Midazolam
Atorvastatin	Naloxegol
Colchicine	Quetiapine
Tadalafil	Sildenafil
Alfentanil	Simvastatin
Avanafil	Triazolam
Budesonide	Vardenafil
Buspirone	Fentanyl
Eletriptan	Tramadol
Eplerenone	Oxycodone
Everolimus	Hydrocodone
Felodipine	Codeine
Ibrutinib	Dihydrocodeine
Lovastatin	Buprenorphine
Lurasidone	Methadone
Maraviroc	Rivaroxaban[§]

[$] The label allows to use concomitant medication with moderate CYP3A4 inhibitors with caution or dose adjustment. Also, the drug will not affect PF-06651600 exposure (either no effect or weak CYP3A4 inhibitor).

[§] The label recommends to avoid use of the drug in multiple conditions (for example, avoid use in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A4 inhibitors). Clinical judgement should be used in co-administration.

10.12. Appendix 12: Oral Corticosteroid Equivalents

The following is a summary of corticosteroid equivalents.

Oral corticosteroids – participants already taking oral corticosteroids must be on a stable dose of ≤7.5 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	7.5
Prednisolone	7.5
6α-methylprednisolone	6
Triamcinolone	6
Betamethasone	1.1
Dexamethasone	1.1
Hydrocortisone	30
Cortisone	37.5
Deflazacort	10.7-11
Cloprednol	3.75
Prednylidene	7.5

Note: these dose equivalents apply to oral administration.

10.13. Appendix 13: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.13.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow-up on the safety of study participants at scheduled visits per the SoA or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing (as available). Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 and Section 10.13.2 of this appendix regarding pregnancy tests.
    - In situations where participants are unable to attend sites for protocol required pregnancy testing, the participant should if possible visit a local laboratory for pregnancy testing (where allowable by law or local guidance). If this is not possible, the study site should make every effort to develop a plan to provide a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL to be performed by the participant at home. The site should document the pregnancy test outcome in a source document and enter the result into the study database and/or CRF as required.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.13.2. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs and %) Eosinophils (Abs and %) Monocytes (Abs and %) Basophils (Abs and %) Lymphocytes (Abs and %)Reticulocyte count % **Partial thromboplastin time (PTT)** **Prothrombin time (PT)**	BUN/urea and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein Lipid profiles[b] Serum myoglobin[c] Cardiac troponin-I (cTn-I), CK and CK-MB[c]	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[d] Color and clarity Specific gravity Urine culture[e]	Pregnancy test (β-hCG)[a] C-Reactive Protein (hsCRP)

a. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or institutional review board/ethics committee (IRB/EC). Serum or urine β-hCG for female participants of childbearing potential.
b. 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.
c. 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.
d. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase
e. If urine microscopic examination is suggestive of urinary tract infection (eg, due to the presence of neutrophils); or if deemed clinically appropriate by the PI.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source

documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.13.3. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

10.13.4. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

IP may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the IP. Pfizer does not permit the shipment of IP by mail. The tracking record of shipments and the chain of custody of IP must be kept in the participant's source documents/medical records.

10.13.5. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.13.6. Independent Oversight Committees

In case of an interruption in the study conduct due to COVID-19 the frequency of the IRC meeting may be adjusted to reflect availability of personnel on the committee, rate of randomization and the accrual of new participant and new emergent safety data.

10.14. Appendix 14: Abbreviations

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

Abbreviation	Term
AA	Alopecia Areata
Abs	Absolute
ACR	American College of Rheumatology
ACPA	anti-citrullinated protein antibodies
ADA	antidrug antibodies
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{tau}	area under the concentration-time curve over dosing interval tau
AV	atrioventricular
BA	Bioavailability
BBS	Biospecimen Banking System
BCRP	Breast Cancer Resistance Protein
BE	Bioequivalence
BIC	Bayesian Information Criterion
BID	twice a day
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CD	Crohn's Disease
CCI	[redacted]
CFB	change from baseline
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CK-MB	Creatine kinase MB
C_{max}	maximum observed concentration
CMC	Chemistry, Manufacturing, and Controls
CMV	cytomegalovirus
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization

Abbreviation	Term
CRP	C reactive protein
CRU	clinical research unit
CSF	cerebrospinal fluid
CSR	clinical study report
csDMARDs	Conventional synthetic DMARDs
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
cTn-I	cardiac troponin-I
CVA	Cerebrovascular accident
CV	Cardiovascular
CYP	Cytochrome p
DAMPs	damage associated molecular patterns
DAS	Disease Activity Score
DCE-MRI	dynamic contrast enhanced-MRI
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
DO	Doctor of Osteopathic
DRE	disease-related event
DU	dispensable unit
DVT	Deep vein thrombosis
EC	ethics committee
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
eCRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
EFD	embryo-fetal developmental
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	End of the study
CCI [redacted]	[redacted]
ESR	erythrocyte sedimentation rate
EU	European Union
EudraCT	European Clinical Trials Database
EULAR	European League Against Rheumatism
CCI [redacted]	[redacted]

Abbreviation	Term
FDA	Food and drug Administration
FSH	follicle-stimulating hormone
FU	follow up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
CCI	[redacted]
HbA_{1c}	hemoglobin A_{1c}
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HDL	High density lipoprotein
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HS	hidradenitis suppurative
hsCRP	high-sensitivity C-reactive protein
IA	interim analysis
IB	investigator's brochure
IC_{50}	50% inhibitory concentration
IC_{90}	90% inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation
ID	Identification
CCI	[redacted]
IGRA	Interferon-Gamma Release Assay
IL	Interleukin
ILD	Interstitial Lung Disease
IOC	Independent Oversight Committee
IMP	Investigational Medicinal Product
IND	investigational new drug
INR	international normalized ratio
CCI	[redacted]
IP	investigational product
IP Manual or IPM	Investigational Product Manual
IR	Inadequate response
IRAK4	interleukin -1 receptor associated kinase 4

Abbreviation	Term
IRB	institutional review board
IRC	Internal Review Committee
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IVRS	Integrated Voice Response System
IWR	interactive Web-based response
JAK	Janus kinases
LBBB	left bundle branch block
LDA	Low disease activity
CCI	[redacted]
LFT	liver function test
MACE	major adverse cardiovascular events
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
CCI	[redacted]
MCV	mean corpuscular volume
mITT	modified intent to treat
mm	millimeter
MMRM	Mixed Model Repeated Measures
MnB	*Neisseria meningitidis* serogroup B
MR	modified release
MRI	magnetic resonance imaging
msec	Millisecond
MTX	methotrexate
MTX-IR	inadequate response to MTX
N/A	not applicable
NAb	neutralizing antibodies
NMSC	Non melanoma skin cancer
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
NTI	narrow therapeutic index
CCI	[redacted]
PBMC	peripheral blood mononuclear cell
PCD	primary completion date
CCI	[redacted]
PD	pharmacodynamic(s)
PE	Pulmonary embolism
PFS	prefilled syringe
PhGA	Physician Global Assessment
PI	Principal Investigator

Abbreviation	Term
PK	pharmacokinetic(s)
PRO	Patient reported outcome
PT	prothrombin time
PT/INR	Prothrombin Time International Normalized Ratio
PtGA	patient global assessment
PTT	partial thromboplastin time
PVC	premature ventricular complex
QD	Once daily
QRS	ventricular depolarization
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	Qualitative
RA	Rheumatoid arthritis
RAMRIQ	Rheumatoid Arthritis MRI Quantification
RAMRIS	Rheumatoid Arthritis MRI Score
RBC	red blood cell
RF	rheumatoid factor
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SALT	severity of alopecia tool
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
Scr	serum creatinine
SDAI	simplified disease activity index
CCI [redacted]	[redacted]
SoA	schedule of activities
SoC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
SJC	Swollen Joint Count
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
TB	Tuberculosis
TBili	total bilirubin
TEAEs	treatment-emergent adverse events
TEC	tyrosine kinase expressed in hepatocellular carcinoma
TIR	toll/interleukin-1 receptor
TJC	Tender/Painful Joint Count
TLR	Toll Like Receptor
TNF	tumor necrosis factor

Abbreviation	Term
TNFα	tumor necrosis factor alpha
TNFi	TNF inhibitors
TRIF	Toll/interleukin-1 receptor domain-containing adapter inducing IFNβ
TYK2	tyrosine kinase 2
TXK	tyrosine protein kinase that is encoded in humans by TXK gene
UC	Ulcerative Colitis
ULN	upper limit of normal
US	United States
USPI	US Product Insert
VAS	visual analog scale
VTE	venous thromboembolic events
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
XR	Extended Release

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