CLINICAL PROTOCOL

A RANDOMIZED COMPARATIVE STUDY ASSESSING THE SWITCHING BETWEEN PF-06410293 AND HUMIRA® IN COMBINATION WITH METHOTREXATE IN PARTICIPANTS WITH MODERATELY TO SEVERELY ACTIVE RHEUMATOID ARTHRITIS

Investigational Product Number:	PF-06410293
Investigational Product Name:	Adalimumab-Pfizer
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	2019-000284-24
Protocol Number:	B5381012
Phase:	3

Short Title:

A Comparative Study Between PF-06410293 And Humira in Combination with Methotrexate in Participants with Active Rheumatoid Arthritis

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	28 June 2019	Not applicable (N/A)
Amendment 1	19 May 2020	Protocol Administrative Clarification Letters (PACLs) were incorporated: • Women of Childbearing Potential (WOCBP) Contraceptive use after last study dose is updated from "a minimum of 28 days" to "at least 5 months" to follow the study's single reference safety document (SRSD), which is the Humira label in Appendix 4. • Typographic error corrected for white blood cell count, lymphocyte count and platelets lab tests listed in Exclusion Criteria 19. • Updated instruction on empty drug containers in Sections 6.1.1 and 6.2. They need to be returned, not destroyed for investigational product accountability purpose. • Text update in the protocol title: "interchangeability of" is replaced by "switching between". • Week 22 injection site updated to abdomen instead of abdomen or either upper front thigh to support primary data analysis in Schedule of Activities (SoA), Table 1, Sections 6.1.1 and 6.1.2. • Alternative solutions that are only acceptable during the COVID-19 pandemic language have been added in SoA, Sections 6.2.1, 6.4, 7.1, 7.2 and Appendix 11.

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		Updated status of *expecting* PF-06410293 approval as a biosimilar to Humira from Food and Drug Administration (FDA) and regulatory agencies to approval for PF-06410293 as a biosimilar to Humira *was received* from the FDA in Sections 1.1, 2, 2.2 and 2.3. • Mention of marketing applications under review with other agency(s) is removed from Section 2.2.
		Corrected participant's age range from age of 18 and older to between age of 18 to 70 years in Section 1.1.
		Corrected definition for end of Treatment Period (TP) 4 to include Week 32 dose administration, and Safety Follow Up Period to begin after the last investigational dose at Week 32 in Sections 1.1 and 4.1.
		Added clarification in Table 1, Sections 1.1, 4.1 and 8.5 that the 2-week pharmacokinetic (PK) sampling period starts with Week 30 predose PK collection and ends with predose PK collection at Week 32.
		Added clarification in Section 1.1 that immune-related safety will be described for the safety population including injection site reactions, hypersensitivity, anaphylaxis and angioedema.
		CCI [redacted]
		Added utilization of home healthcare service as an option during the 2 week PK

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		sampling period in SoA, Table 1 and Section 8.5.
		Clarified that only applicable adalimumab injection details will be recorded in the electronic Participant Dosing Log in SoA, Sections 6.1.1 and 6.4.
		Clarifications made to the following inclusion/exclusion criteria to stay consistent with Humira label: • Removal of Inclusion Criterion 7 as it is a duplication of Exclusion Criterion 14. Additionally, clarification is made to Exclusion Criterion 14. • Clarification provided to Section 5.2, Exclusion Criteria 4c and Section 8.2.8 that confirmed positive HIV, Hepatitis B and Hepatitis C are excluded. More specifically, Hepatitis B DNA test has been added. • Clarification provided on prohibited biologic therapy in Exclusion Criterion 13, Section 6.5 and Appendix 9 (Prohibited Concomitant Medication and Procedures). • Added new Exclusion Criterion 18 that unstable dose of oral and intramuscular (IM) corticosteroid is prohibited. Updated Sections 6.5.2 and removed Appendix 9 (Oral Corticosteriod in FAP).
		Add clarification to Exclusion Criterion (#3) that active significant infection,

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		eg, SARS-CoV2 (COVID-19) infection and any active infection considered to be clinically significant by the investigator should be excluded. Updates are also made in Sections 7.1.1 and 7.1.2.
		Language in Section 7.2 has been updated to follow Pfizer's latest protocol template.
		Updated population for analysis in Section 9.3 and AE analysis in Section 9.4.2.1.
		Updated contraceptive requirements to follow Humira label for male participants Section 10.4.1. Additionally, removed text "highly" from highly effective contraceptive methods in Exclusion Criterion 24, Sections 5.3.1 and 10.4.4 to keep consistent with Humira label.
		Additional typographic errors were corrected and editorial changes provided, as deemed necessary, throughout the protocol.
		Blood sample volume was updated in Section 8.5
		Section 8.9 Immunogenicity Assessments have been added to follow Pfizer's protocol template, as a result Section 8.5.1 in protocol (28 June 2019) has been reformatted to Section 8.9.1 in Amendment 1.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Comparative Study Between PF-06410293 And Humira in Combination with Methotrexate in Participants with Active Rheumatoid Arthritis

Rationale

Regulatory approval for PF-06410293 as a biosimilar to Humira was received from United States (US) FDA. The purpose of conducting this trial is to support the application for the interchangeability designation with the FDA, not to re-establish "PK equivalence" between licensed Humira and PF-06410293. The objectives and design of this study are consistent with recommendations for establishing interchangeability (IC) found in the corresponding guidance.[7]

A designation of IC for an approved biosimilar drug is granted by the US FDA based on information demonstrating that 'the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch' (FDA Guidance, 2019).[7] In reference to a biological product, interchangeability means that "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product".[7] This study has been designed with input from FDA to deliver sufficient information to support the interchangeability of PF-06410293 with the reference product, Humira.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To evaluate interchangeability of PF-06510293 and Humira by examining adalimumab steady-state pharmacokinetics in a switching arm (following 3 switches between Humira and PF-06410293) as compared to a non-switching arm (receiving only Humira).	• Evaluate the equivalence of primary endpoints (maximum observed concentration (C_{max}) and area under the concentration-time curve over the dosing interval (AUC_{τ}) obtained during the intensive PK sampling interval) between the switching arm and non-switching arm in participants who meet the PK population criteria,that include criteria for the number and timing of missing doses, availability of PK data, adherence to background therapy, and major protocol	• C_{max} and AUC_{τ} obtained during the intensive PK sampling interval.

	deviations related to PK assessment.	
Objectives	**Estimands**	**Endpoints**
Secondary:	**Secondary:**	**Secondary:**
• To evaluate other serum adalimumab PK parameters in the switching arm and the non-switching arm. • To evaluate the overall safety and tolerability of the switching arm and the non-switching arm. • To evaluate immunogenicity of the switching arm and the non-switching arm.	• Summarize other serum adalimumab PK parameters, including time at which C_{max} occurs (T_{max}), average concentration over the dosing interval (C_{av}), and apparent clearance (CL/F) obtained during the intensive PK sampling interval in participants who meet the PK population criteria, and predose concentration during multiple dosing (C_{trough}) obtained at scheduled PK sample timepoints in participants who meet the safety population criteria, for the switching arm and non-switching arm. • Summarize safety endpoints for the switching arm and non-switching arm in participants who meet the safety population criteria. • Summarize percent of participants with antidrug antibodies (ADA), and neutralizing antibodies (NAb) and ADA/NAb titers over time for the switching arm and non-switching arm in participants who meet the Safety population criteria.	• Other serum adalimumab PK parameters, including T_{max}, C_{av}, and CL/F obtained during the intensive PK sampling interval and C_{trough} obtained at scheduled PK sample timepoints. • Safety measures characterized by type, incidence, severity, timing, seriousness and relatedness of treatment-emergent AEs and laboratory test abnormalities. • Percent of participants with ADA/NAb and ADA/NAb titers over time.

Overall Design

This is an open-label, 2-arm, randomized, parallel-group study conducted to assess the impact of multiple switches between Humira and PF-06410293 on steady state adalimumab PK compared to the steady state PK of adalimumab following continuous dosing with Humira. This study is also designed to evaluate safety and immunogenicity after investigational product (IP) switching between the switching arm (Humira and PF-06410293), as compared with non-switching arm (Humira). For purposes of this

protocol, the treatment arm that includes switches between PF-06410293 and Humira will be referred to as the "switching" arm, while the treatment arm that comprises continuous Humira treatment will be referred to as the "non-switching" arm.

The study will include adult participants between the age of 18 and 70 years with moderate to severe rheumatoid arthritis (RA) who are on background methotrexate (MTX). This study has two arms and comprises 3 switches in the switching arm, which has a total of four treatment periods (TP).

- TP1 (Lead In Period) will begin with the first dose of investigational product Humira on Week 0 (Day 1) and conclude with the completion of Week 10 pre-dose assessments.
- TP2 will begin with the 1:1 randomization of the participants to either the switching arm or the non-switching arm at Week 10. Investigational product dosing for Week 10 will begin after the randomization process in the respective treatment arms and will conclude with the completion of Week 16 pre-dose assessments.
- TP3 will begin with investigational product dosing on Week 16, and conclude with the completion of Week 22 pre-dose assessments.
- TP4 will begin with investigational product dosing on Week 22 and continue through Week 30, where onsite investigational product dosing is scheduled at Weeks 22, 24, 26, 28, and 30, followed by a 2-week PK sampling period from Week 30 to Week 32. TP4 will conclude with end of treatment (EoT) assessments and final dose administration at Week 32.
- The 2-week PK sampling period starts with Week 30 predose PK collection and ends with predose PK collection on Week 32.
- Safety Follow-Up Period begins after the last investigational product dosing on Week 32, and concludes at completion of the Week 36 assessments. All participants (including early discontinuations) will be followed for at least 28 calendar days from the date of their last dosed investigational product. Week 36 safety follow up may be conducted via phone.

Number of Participants

A maximum of approximately 420 participants will be enrolled into the study such that approximately 314 evaluable participants complete the study.

Intervention Groups and Duration

The total duration of study participation is 36 weeks. Participants will receive investigational product for the first 30 weeks over 4 treatment periods, followed by a 2-week intense PK sample collection period, last investigational product dosing at the end of the PK sampling period and a 4 week safety follow up. The duration and details of each treatment period are described in the previous section.

Every participant will receive adalimumab 40 mg to be administered subcutaneously (SC) every 2 weeks; on-site injections will occur at the clinic during scheduled visits. The first injection is to be administered at the site under the supervision of the investigator or designee, where the participant and/or care giver will be assessed for their ability to administer adalimumab. Any issues may be reviewed at that time. The first injection should be an abdominal injection. Subsequently, the injection location may be the abdomen or upper front of either thigh, unless otherwise specified in the Schedule of Activities (SoA). Following the first injection at the site, the participant should select a day of the week to administer their investigational product injections at home every other week, on the same day, except on the weeks where an onsite visit is scheduled. Injections will occur during the scheduled visits under the supervision of the site's investigator or designee. Every effort should be made for participants to return for the scheduled visits and investigational product administration within the visit windows outlined in the SoA to support the PK endpoints of this study.

Please refer to Section 6 for additional investigational product information.

Data Monitoring Committee:

This study will not use a data monitoring committee (DMC).

Statistical Methods

Pharmacokinetics

The serum concentrations between Week 30 and Week 32 will be analyzed for the PK population using standard non-compartmental analysis to estimate the PK parameters for each individual participant. The PK parameters: maximum observed concentration (C_{max}), area under the concentration - time curve over the dosing interval (AUC_{τ}), time at which C_{max} occurs (T_{max}), average concentration (C_{av}), predose concentration during multiple dosing (C_{trough}), and apparent clearance (CL/F), and the serum concentrations will be summarized descriptively.

Interchangeability will be assessed by constructing the point estimate and the 90% confidence intervals (CIs) for the geometric mean ratio (GMR) for the primary endpoints C_{max} and AUC_{τ}. Interchangeability will be established statistically if the 90% CI for the GMR is within (80.00%, 125.00%) for both endpoints. The GMR and CI will be obtained using analysis of variance (ANOVA) applied to log-transformed data, with terms for treatment and randomization stratification factors (weight categories).

Safety

Adverse Events will be summarized descriptively using Safety-TP1 population for Humira group in TP1 and using Safety-Randomized populations for switching arm and non-switching arm during TP2 through TP4.

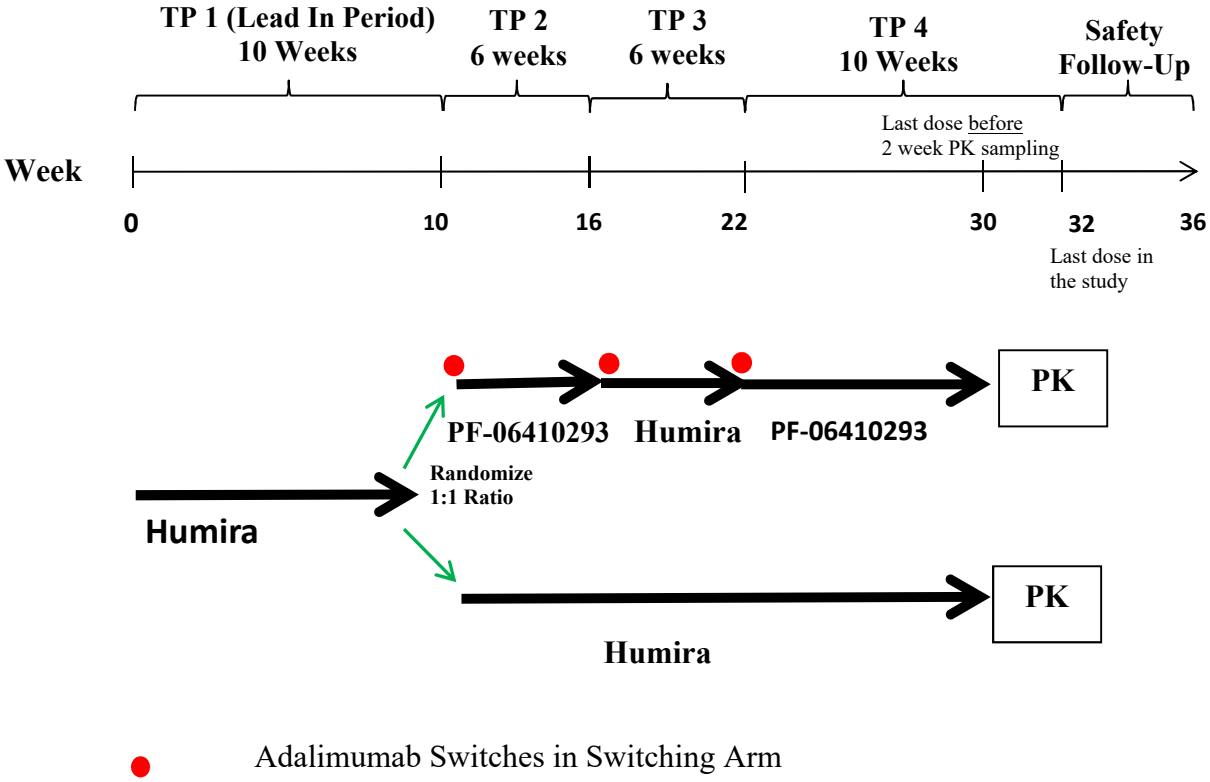
Immunogenicity

For the ADA (antidrug antibodies) and NAb (neutralizing antibodies) data, the percentage of participants with positive ADA and NAb will be summarized for the safety-randomized population by each visit in each Treatment Period. For participants with positive ADA and NAb, the magnitude (titer), time of onset, and duration of ADA and NAb response will also be described. In addition, immune-related safety will be described for the safety population including injection site reactions (ISR), hypersensitivity, anaphylaxis, and angioedema.

Efficacy

This study will not evaluate efficacy.

1.2. Schema



TP = Treatment Period.

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.

Study related visits and procedures may be disrupted during the Coronavirus Disease 2019 (COVID-19) pandemic, please see Appendix 11 for alternative solutions, if applicable.

Study Period	**Screen**	**Treatment Period 1 (Lead In)**			**Treatment Period 2**	**Treatment Period 3**	**Treatment Period 4**						**Safety Follow up**
Visit Identifier	**1**	**2 (BL)**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**PK Profile Phlebotomy[14]**	**11 (EOT /ET)[16]**	**12[18]**
Study Week[1]	**-6 to -1**	**0**	**4**	**10**	**16**	**22**	**24**	**26**	**28**	**30**	**30, 31**	**32**	**36**
Study Day	**-42 to -1**	**1**	**29**	**71**	**113**	**155**	**169**	**183**	**197**	**211**	**211 - 224**	**225**	**253**
Visit Window in Days			**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**[±1]**	**±1**	**+14**
Informed Consent	X												
Inclusion/Exclusion Criteria	X	X											
Contraception check	X												
Medical History	X												
Demography	X												
Prior Treatments for RA	X												
HIV, Hepatitis B & C[2]	X												
FSH[3]	X												
Tuberculosis Test[4]	X												
Chest Radiography[5]	X												
Single ECG (12-Lead)	X												
Participant ID number (IWRS)[6]	X												
Randomization (IWRS)[7]				X									
Complete Physical Examination[8]	X											X[16]	
Vital Signs[9]	X	X		X								X	
Body Weight[10]	X	X		X[10]								X	

Study Period		**Screen**	**Treatment Period 1 (Lead In)**			**Treatment Period 2**	**Treatment Period 3**	**Treatment Period 4**						**Safety Follow up**
Visit Identifier		**1**	**2 (BL)**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**PK Profile Phlebotomy[14]**	**11 (EOT /ET)[16]**	**12[18]**
Study Week[1]		**-6 to -1**	**0**	**4**	**10**	**16**	**22**	**24**	**26**	**28**	**30**	**30, 31**	**32**	**36**
Study Day		**-42 to -1**	**1**	**29**	**71**	**113**	**155**	**169**	**183**	**197**	**211**	**211 - 224**	**225**	**253**
Visit Window in Days				**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**[±1]**	**±1**	**+14**
Pregnancy Test[11]		X	X										X	
Contraception Verification			X											
Safety Laboratory	Hematology	X	X		X								X	
	Chemistry	X	X		X								X	
	Urinalysis	X	X		X								X	
Urine Drug screen		X												
ADA/NAb Samples[12]			X		X	X	X	X	X	X	X		X	
CCI [redacted]			[redacted]		[redacted]			[redacted]	[redacted]	[redacted]				
Drug Concentration Samples[14]			X		X	X	X	X	X	X	X	X[14] (7 samples)	X	
Adalimumab SC Injection[15]			X	X	X	X	X	X	X	X	X		X	
Background Methotrexate and folic/folinic acid		X	X	X	X	X	X----------X							
Assessment of AEs[17]		X	X	X	X	X	X----------X							
Assessment of Concomitant Medications[18]		X	X	X	X	X	X----------X							

Abbreviations: ADA = Anti-drug Antibody; AE = Adverse Event; BL = Baseline; ECG = Electrocardiogram; EOT = End of Treatment Period; ET = Early Termination; FSH = follicle stimulating hormone; HCG = human chorionic gonadotropin; HIV = Human Immunodeficiency Virus; ID = Identification; IWRS = InteractiveWeb-based response system; NAb = Neutralizing antibody; PK = Pharmacokinetics; CCI [redacted]; SC = Subcutaneous.

Footnotes:

1. Visits should occur when scheduled, within the time window indicated in the column headings. When a visit does not happen on the scheduled day within or outside the window, the next visit should still be on the initially scheduled calendar date to restore the original calendar. On investigational product dosing days, assessments and lab tests are to be performed prior to dosing unless otherwise stated. This will require special attention to ensure participants do not administer the corresponding visit's adalimumab injection prior to the clinic visit. Additional unscheduled assessments should be performed as clinically indicated.
2. Viral disease screening, including hepatitis screening (HBsAg, HBcAb, HBsAb, HCVAb and HCV RNA) and HIV screening (HIV-1 Ab and HIV-2 Ab). HIV screening (HIV-1 Ab and HIV-2 Ab) may be performed by the central lab or a local lab (if required by local regulations) at screening or within 6 weeks prior to the first dose of investigational product on Day 1.
3. Screening test for female participants who are amenorrheic for at least 12 consecutive months at the time of study screening with no alternative pathological or physiological cause. A serum FSH level within the central laboratory's reference range will confirm the participant's non-childbearing status.
4. Tuberculosis test will use QuantiFERON® (QFT) – TB Gold In-Tube Test and must be performed within 6 weeks prior to the first dose of investigational product on Day 1. Participants with positive or indeterminate screening QFT result must be re-tested with QFT – TB Gold In-Tube Test and referred to a specialist (eg, pulmonologist, TB specialist or infectious disease specialist) for further evaluation of latent or active TB or false positive QFT test result, unless they have past history of having been adequately treated with appropriate chemoprophylaxis for latent TB or have completed treatment for active TB previously, in which case re-testing is not required. Participants who test positive and are considered to have current latent TB can enroll in the study if they are on chemophrophylaxis for at least 4 weeks.
5. Chest radiography (lateral and posterior-anterior views) must be performed within a 12-week window prior to Screening. If a chest computed tomography (CT) exam (or an alternative chest imaging) is performed within 12 weeks prior to Screening, a chest x-ray is not required.
6. Individuals who do not meet the criteria for participation in this study (screen failure) within the 6 week screening period may be rescreened.
7. Participants completing Treatment Period 1 will be randomized into switching or non-switching treatment arms in a 1:1 ratio prior to dosing on Week 10, stratified based on 3 weight groups (Week 10 weight). Participants randomized to the non-switching arm will continue on Humira for the remainder of the study, and participants randomized to the switching arm will continue switching in each TP (TP2: PF-06410293; TP3: Humira; TP4: PF-06410293).
8. Complete physical exam (PE) of major body systems. Additional targeted PE may be performed during the study at the investigator's discretion, as indicated by signs and symptoms of ongoing AEs.
9. Vital signs include blood pressure, respiratory and pulse rate, body temperature, body weight, with height measured at Screening only. Blood pressure and pulse rate should be taken from the participant in the supine position after the participant has been resting quietly for at least 5 minutes.
10. Body weight (BW) for Randomization should use the one collected at Week 10. Every effort should be made to obtain BW at Week 10 prior to randomization, however, if the Week 10 BW is not available, Screening or Baseline BW (whichever is closest to Week 10 visit) may be used to randomize.
11. Pregnancy testing at Screening in female participants of childbearing potential by central lab serum HCG test. Pregnancy testing (HCG) after Screening will be performed locally using urine samples. Pregnancy testing may be repeated more frequently if required by IRB/ECs or local regulations, or if potential pregnancy is suspected.
12. Blood samples should be collected for ADA and NAb testing at the time when PK samples are also collected and prior to the next investigational product administration.

CCI [redacted]

14. Please refer to Table 1 (PK Sampling Table). **ALL PK samples will be collected prior to study dose (pre-dose)** at visits where onsite injection is scheduled**.** Blood samples for determination of adalimumab trough drug concentrations will be collected within 6 hours prior to the investigational product administration on Weeks 22, 24, 26, 28, and on Day 1 (time 0), Weeks 10 and 16 at a maximum of 48 hours prior to, but as close as possible prior to the next investigational product administration (ie, pre-dose). The 2-week PK sampling period starts with Week 30 predose PK collection and ends with Week 32 predose PK collection. Blood samples for determination of adalimumab drug concentrations for the 2-week PK profile will be collected starting with the Week 30 injection of investigational product (PK Profile Day 1): blood will be collected within 6 hours prior to investigational product administration. For the subsequent PK Profile Days, post-Week 30 dosing times for serum collections are 48 (±4) hrs on PK Profile Day 3, 72 (±6) hrs on PK Profile Day 4, 96 (±8) hrs on PK Profile Day 5, 144 (±8) hrs on PK Profile Day 7, 240 (±24) hrs on PK Profile Day 11, and 336 (±24) hrs on PK Profile Day 15. **Every effort should be made to draw samples within the scheduled time points.** The 2-week PK Profile collections may be completed using home health care service.

15. Investigational product will be administered by the participant, care giver or site personnel every other week using pre-filled syringes provided by the sponsor; on-site injections will occur during every scheduled visits after PK and ADA/NAb sample collection. The first SC injection should be administered by the participant while at the clinic under the supervision of the site's investigator or designee. Any issues may be reviewed at that time. The first injection must be an abdominal injection. Subsequently, the injection location may be the abdomen or upper front of either thigh. The first TP4 injection at Week 22 and injections at Weeks 24, 26, 28 and 30 (before starting the PK profile) must also be administered in the abdomen under the supervision of the site's investigator or designee. Applicable injection details (eg, date) will be recorded in the electronic Participant Dosing Log. Investigational product will be dispensed to the participant at each visit.

16. After 30 weeks of investigational product plus 2 weeks of PK profile participants are required to return for an end of treatment (EOT) visit at Week 32 where the last investigational product dose is scheduled, then will be followed up for final safety evaluation at Week 36, which may be a phone visit. Early terminated (ET) participants are required to return to the clinic as soon as possible after the last investigational product dose for an ET visit and safety phone follow up is also required at least 28 calendar days after the last investigational product. Additional targeted PE may be performed at the ET and/or post-treatment follow up visits at the investigator's discretion, as indicated by signs and symptoms of ongoing AEs.

17. The time investigational product period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, through and including a minimum of 28 calendar days after the last administration of the investigational product. Week 36 safety follow up may be conducted via phone.

18. Concomitant medications will be routinely collected from the time the consent form is signed through the final study visit/contact. If a participant discontinues early, concomitant medications must be followed for 28 calendar days after last dose of investigational product. Week 36 safety follow up may be conducted via phone.

Table 1. PK Sampling Table

Study Period	Treatment Period 1		Treatment Period 2	Treatment Period 3	Treatment Period 4									
Visit ID	**Day 1 Abd Inj**	**Wk 10 Abd Inj**	**Wk 16 Abd Inj**	**Wk 22 Abd Inj**	**Wk 24 Abd Inj**	**Wk 26 Abd Inj**	**Wk 28 Abd Inj**	**Wk 30 Abd Inj**	**PK Day 3**	**PK Day 4**	**PK Day 5**	**PK Day 7**	**PK Day 11**	**Wk 32**
PK Profile Day								*1*	*3*	*4*	*5*	*7*	*11*	*15*
Time (h) Post-Dose	0[a,b]	0[a,b]	0[a,b]	0[a,b]	0[a,b]	0[a,b]	0[a,b]	0[a,b]	48	72	96	144	240	336[a]
PK Tolerance Window (h)[d]	-48	-48	-48	-6	-6	-6	-6	-6[c]	±4[c]	±6[c]	±8[c]	±8[c]	±24[c]	±24[c]

a. Predose PK sample.
b. Injection on-site.
c. PK sample must fall within the PK sampling time window for the participant to be Per Protocol (for the primary endpoint).
d. Blood samples for determination of adalimumab trough drug concentrations will be collected within 6 hours prior to the investigational product administration on Weeks 22, 24, 26, 28, and on Day 1 (time 0), Weeks 10 and 16 at a maximum of 48 hours prior to, but as close as possible prior to the next investigational product administration (ie, pre-dose). The 2-week PK sampling period starts with Week 30 predose PK collection and end with Week 32 predose PK collection. Blood samples for determination of adalimumab drug concentrations for the 2-week PK profile will be collected starting with the Week 30 injection of investigational product (PK Profile Day 1): blood will be collected within 6 hours prior to investigational product administration. For the subsequent PK Profile Days, post-Week 30 dosing times for serum collections are 48 (±4) hrs on PK Profile Day 3, 72 (±6) hrs on PK Profile Day 4, 96 (±8) hrs on PK Profile Day 5, 144 (±8) hrs on PK Profile Day 7, 240 (±24) hrs on PK Profile Day 11, and 336 (±24) hrs on PK Profile Day 15. **Every effort should be made to draw samples within the specified time windows.** The 2-week PK Profile collections may be completed using home health care service

Abbreviations: Abd = abdominal; h = hour; Inj = injection; PK = pharmacokinetic; Wk = week.

2. INTRODUCTION

Adalimumab (marketed under the brand name HUMIRA®) is a recombinant fully human Immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that specifically binds to TNFα and blocks its interaction with the p55 and p75 cell surface TNF receptors, thereby neutralizing the effect of TNF in inflammatory conditions. HUMIRA is approved for use in both the United States (US) and European Union (EU) for the treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PSA), polyarticular juvenile idiopathic arthritis, Crohn's disease (CD), pediatric CD, ulcerative colitis (UC), plaque psoriasis (PS), adult and adolescent hidradenitis suppurativa (HS), and pediatric and adult uveitis (UV); it is also approved in the EU for axial spondyloarthropathy (radiographic-negative), pediatric plaque psoriasis, and juvenile enthesitis-related arthritis.

PF-06410293 is a fully human IgG1 monoclonal antibody (mAb) and has been approved by the FDA as a biosimilar of adalimumab, also referred by the brand name HUMIRA in this protocol. The general term “adalimumab” is sometimes used for convenience when discussing the treatments in the 2 arms: switching and non-switching.

2.1. Study Rationale

The purpose of the trial is to support obtaining the FDA's interchangeability designation, not to re-establish "PK equivalence" between licensed Humira and PF-06410293. The objectives and design of this study are generally consistent with recommendations found in the corresponding FDA Interchangeability guidance.[7] In reference to a biological product, interchangeability means that "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product".[7] This study has been designed with input from FDA to deliver sufficient information to support the interchangeability of PF-06410293 with the reference product, Humira.

2.2. Background

Pfizer is developing PF-06410293 as a biosimilar and interchangeable product to Humira. Biosimilarity has been established through quality, nonclinical, and clinical assessments. Regulatory approval for PF-06410293 as a biosimilar to Humira was received from United States (US) Food and Drug Administration (FDA). Pfizer seeks to demonstrate that PF-06410293 is interchangeable under Section 351(k)(4) of the PHS Act (FDA Guidance 2015).[8] A designation of interchangeability means that 'the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch' (FDA Guidance, 2019).[7]

This IC study has been designed to support the FDA interchangeability designation.

Humira is approved for use in both the United States (US) (first licensed on 31 December 2002) and European Union (EU) (first authorized on 8 September 2003).

2.2.1. Clinical Overview

The clinical development program for PF-06410293 consisted of 4 completed clinical studies: 3 single-dose PK studies (B5381001, B5381007, and B5381005) in healthy subjects using a pre-filled syringe (PFS) and a pre-filled pen (PFP) and 1 multidose safety and efficacy study (B5381002) in patients with moderately to severely active RA using a PFS, which included a device substudy using PFP. This program demonstrated the clinical similarity between PF-06410293 and Humira that supported the extrapolation to the Humira indications.

The safety profile of PF-06410293 is consistent with that reported in the US Prescribing Information (USPI) and Summary of Product characteristics (SmPC) of Humira.[1,2] Data from the PF-06410293 clinical development program did not reveal any new safety risks for PF-06410293. A summary of the clinical safety in the USPI is shown below:

Serious Infections[1]

- Increased risk for developing serious infections.
- Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.
- Treatment should not be initiated in patients with an active infection, including localized infections.
- Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants, may be at greater risk of infection.

Tuberculosis[1]

- Reactivation of tuberculosis and new onset tuberculosis infections have been reported.
- Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy.
- Consider anti-tuberculosis therapy prior to initiation of treatment.

Invasive Fungal Infections[1]

- Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy.
- Consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Hepatitis B Virus Reactivation[1]

- Use of TNF blockers may increase the risk of reactivation of hepatitis B virus.

Malignancies[1]

- Non-Melanoma Skin Cancer (NMSC): The rate (95% confidence interval) was 0.8 (0.52, 1.09) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients.
- Lymphoma and Leukemia: The observed rate of lymphomas was approximately 3-fold higher than expected in the general U.S. population according to the Surveillance, Epidemiology, and End Results (SEER) database (adjusted for age, gender, and race). Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

- *Malignancies in Pediatric Patients and Young Adults:* Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤18 years of age). These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Hypersensitivity Reactions[1]

- Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration.

- Allergic reactions (eg, allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

Neurologic Reactions[1]

- Rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system, and peripheral demyelinating disease.

Hematological Reactions[1]

- Rare reports of pancytopenia including aplastic anemia, medically significant cytopenia.

Heart Failure[1]

- Worsening congestive heart failure (CHF) and new onset CHF.

Autoimmunity[1]

- HUMIRA treatment may result in the formation of autoantibodies.

- Development of a lupus-like syndrome.

2.3. Benefit/Risk Assessment

PF-06410293 has been approved by the US FDA as a biosimilar to Humira. The clinical benefit of adalimumab (Humira®) is well established and applies to both drugs used in this trial: PF-06410293 and Humira.

The safety profile of adalimumab is well established. The most common adverse reaction to adalimumab are injection site reactions, while the important identified risks include serious infections, malignancies, hypersensitivity reactions, hematologic disorders, gastrointestinal disorders, heart failure and demyelinating disorders.

PF-06410293 is approved by US FDA with the same safety profile as described in the adalimumab (Humira®) USPI and SmPC. Appropriate risk evaluation and mitigation strategies have been incorporated into this protocol.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of adalimumab may be found in the Humira label, which is the SRSD for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To evaluate interchangeability of PF-06510293 and Humira by examining adalimumab steady-state pharmacokinetics in a switching arm (following 3 switches between Humira and PF-06410293) as compared to a non-switching arm (receiving only Humira).	• Evaluate the equivalence of primary endpoints (maximum observed concentration (C_{max}) and area under the concentration-time curve over the dosing interval (AUC_{τ}) obtained during the intensive PK sampling interval) between the switching arm and non-switching arm in participants who meet the PK population criteria,that include criteria for the number and timing of missing doses, availability of PK data, adherence to background therapy, and major protocol deviations related to PK assessment.	• C_{max} and AUC_{τ} obtained during the intensive PK sampling interval.
Objectives	**Estimands**	**Endpoints**
Secondary:	**Secondary:**	**Secondary:**
• To evaluate other serum adalimumab PK parameters in the switching arm and the non-switching arm. • To evaluate the overall safety and tolerability of the switching arm and the non-switching arm. • To evaluate immunogenicity of the switching arm and the non-switching arm.	• Summarize other serum adalimumab PK parameters, including time at which C_{max} occurs (T_{max}), average concentration over the dosing interval (C_{av}), and apparent clearance (CL/F) obtained during the intensive PK sampling interval in participants who meet the PK population criteria, and predose concentration during multiple dosing (C_{trough}) obtained at scheduled PK sample timepoints in participants who meet the safety population criteria, for the switching arm and non-switching arm.	• Other serum adalimumab PK parameters, including T_{max}, C_{av}, and CL/F obtained during the intensive PK sampling interval and C_{trough} obtained at scheduled PK sample timepoints. • Safety measures characterized by type, incidence, severity, timing, seriousness and relatedness of treatment-emergent adverse events (AEs) and laboratory test abnormalities. • Percent of participants with ADA/NAb and ADA/NAb titers over time.

	• Summarize safety endpoints for the switching arm and non-switching arm in participants who meet the safety population criteria. • Summarize percent of participants with antidrug antibodies (ADA), and neutralizing antibodies (NAb) and ADA/NAb titers over time for the switching arm and non-switching arm in participants who meet the Safety population criteria.	

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, multi-national, 2-arm, randomized, parallel-group study designed to evaluate the interchangeability of the switching arm (PF-06410293 and Humira), compared to non-switching arm (Humira), in participants with moderately to severely active RA on background methotrexate (MTX). For purposes of this protocol, the treatment arm that includes switches between PF-06410293 and Humira will be referred to as the "switching" arm, while the treatment arm that comprises continuous Humira treatment will be referred to as the "non-switching" arm.

This study will enroll a maximum of approximately 420 participants such that approximately 314 evaluable participants complete the study.

Study treatment will be provided through 4 treatment periods. For the first 10 weeks, all participants will receive Humira [Treatment Period (TP) 1]. Upon completion of TP1, participants will be randomized (1:1 ratio) into either the switching or the non-switching arm prior to dosing on Week 10. Randomization will be stratified by 3 body weight groups (Week 10 weight) (≥40 kg to <70 kg; ≥70 kg to <100 kg; ≥100 kg to ≤130 kg). Participants randomized to the non-switching arm will continue on Humira for the remainder of the study, and participants randomized to the switching arm will continue switching in each TP (TP2: PF-06410293; TP3: Humira; TP4: PF-06410293).

- TP1 (Lead In Period) will begin with the first dose of investigational product on Week 0 (Day 1) and conclude with the completion of Week 10 pre-dose assessments.

- TP2 will begin with the 1:1 randomization of the participants to either the switching arm or the non-switching arm at Week 10. Investigational product dosing for Week 10 will begin after the randomization process in the respective treatment arms and will conclude with the completion of Week 16 pre-dose assessments.

- TP3 will begin with investigational product dosing on Week 16, and conclude with the completion of Week 22 pre-dose assessments.

- TP4 will begin with investigational product dosing on Week 22 and continue through Week 30, where onsite investigational product dosing is scheduled at Weeks 22, 24, 26, 28, and 30, followed by a 2-week PK sampling period from Week 30 to Week 32. TP4 will conclude with end of treatment (EoT) assessments and final dose administration at Week 32.

    - The 2-week PK sampling period starts with Week 30 predose PK collection and ends with predose PK collection on Week 32.

- Safety Follow-Up Period begins after the last investigational product dosing on Week 32, and concludes at completion of the Week 36 assessments. All participants (including early discontinuations) will be followed for at least 28 calendar days from the date of their last dosed investigational product. Week 36 safety follow up may be conducted via phone.

4.2. Scientific Rationale for Study Design

This study design is consistent with recommendations outlined in the FDA Interchangeability guidance[7] and FDA Clinical Pharmacology guidance 2016.[9] These recommendations include lead-in period, switching and non-switching treatment arms, for which the switching arm should have at least 3 switches between the biosimilar and reference products. Furthermore, the duration of each treatment period should be sufficient to establish PK steady state, with PK samples collected at the end of the last treatment period in both treatment arms for determination of steady state PK parameters. PK parameters should be analyzed using a standard bioequivalence (BE) approach with acceptance margins of 80.00% to 125.00%.

Specific details regarding statistical approaches to data analysis for this study are discussed further in Section 9.

This study is also designed to evaluate safety and immunogenicity after several investigational product switches between the switching and non-switching arms.

4.3. Justification for Dose

The 40 mg dose is the recommended dose for RA participants in the HUMIRA and PF-06410293 labels for moderately to severely active RA patients. Dose modification is not allowed in this trial to avoid potential confounding factors that could impact ADA formation and PK, as well as safety (see Section 6.6).

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all treatment periods of the study, including the EoT visit (Week 32). The final safety follow-up is at Week 36, which may be done by phone. Early discontinuation from investigational product requires participants to return as soon as possible after the last dose of investigational product

for an EoT visit. A safety follow-up (may be done by phone) at least 28 calendar days after the last investigational product is also required.

The end of the study is defined when the last participant in the trial completes the date of last scheduled visit or contact as shown in the SoA.

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 (or the minimum country-specific age of consent if >18) and 70 years, inclusive, at Visit 1 (Screen 1).

    - 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, laboratory tests, lifestyle considerations, and other study procedures.

3. Diagnosis of rheumatoid arthritis (RA) based on 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA for at least a 4 month duration.

4. Moderately to severely active RA disease based on local standard of care.

5. Must have received oral, subcutaneous (SC), or IM methotrexate for at least 12 weeks and been on a stable dose for at least 4 weeks prior to first dose of investigational product on Day 1 of TP1. The stable dose must be 10 to 25 mg per week, with the exception of 6 to 25 mg per week where 6 mg per week is a recommended initial dose by local guidance or standard of care.

6. Stable dose of oral folic acid (at least 1 mg/day on ≥5 days per week) or oral folinic acid (≥5 mg once per week) supplementation for at least 21 days prior to the first dose of investigational product on Day 1 of TP1. In countries which do not have approved folic acid 1 mg or folinic acid 5 mg presentations, a regimen of folic acid of ≥5 mg weekly is acceptable.

Weight:

7. Body mass index (BMI) of 18 to 45 kg/m^2 and a total body weight of ≥40 kg (88 pounds) to ≤130 kg (287 pounds).

Informed Consent:

8. Capable of giving signed informed consent as described in Appendix 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. Evidence or history of nervous system demyelinating diseases (including multiple sclerosis, optic neuritis, Guillain-Barré syndrome).

2. History of seizure disorder requiring treatment in the previous 5 years prior to Screening.

3. History of or active significant infection defined by:

    a. History of recurrent (more than one episode) limited herpes simplex which requires current chronic antiviral therapy, or disseminated (a single episode) herpes simplex.

    b. History of disseminated or recurrent infection with Epstein Barr virus (EBV), human papilloma virus (HPV), or varicella zoster. A single, limited episode in the past is not exclusionary.

    c. Any infection requiring hospitalization or parenteral antimicrobial therapy judged clinically significant by the investigator within 6 months prior to first dose of investigational product.

    d. History of an infected joint prosthesis at any time, with the prosthesis still in situ.

    e. SARS-CoV2 infection (COVID-19) should be considered clinically significant, local guidelines on COVID-19 and medical judgement should be followed.

f. Any other active infection considered to be clinically significant as assessed by the investigator.

4. Known or screen test confirmed positive for human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C (HCV) virus (please see Section 8.2.8 for details on testing).

   a. Positive for HIV.

   b. Positive hepatitis B surface antigen (HBsAg).

   c. Positive hepatitis B core antibody (HBcAb) without positive hepatitis B surface antibody (HBsAb) (unless it is documented that hepatitis B DNA test is negative).

   d. Positive hepatitis C antibody (HCV Ab) results and positive confirmatory HCV riboneucleic acid (HCV RNA) results.

5. Evidence of current or recent history of uncontrolled, clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, hepatic, infectious, psychiatric, neurologic, allergic, or cardiovascular disease including evidence or history of moderate or severe heart failure (NYHA Class III/IV) or Screening 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities which may affect participant safety, and participants who are contraindicated for treatment with adalimumab in accordance with the approved local label.

6. History of any lymphoproliferative disorder (eg, EBV related lymphoproliferative disorder, lymphoma, or leukemia). Evidence or history of a malignancy within the past 5 years (with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ with no evidence of recurrence).

7. History of recurrent inflammatory joint disease other than RA (eg, post infectious arthritis, gout, etc.) or history of any other autoimmune rheumatic diseases (eg, vasculopathies, spondyloarthropathies, etc.) other than Sjogren's syndrome.

8. Significant trauma or surgical procedure within 4 weeks prior to first dose of investigational product.

9. History of severe allergic or hypersensitivity or anaphylactic reaction to a biologic drug or to active or inactive components of the investigational product.

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

Prior/Concomitant Therapy:

11. Prior/Current treatment with adalimumab.

12. More than 3 disease modifying anti-rheumatic drugs (DMARDs) in combination therapy; concomitant DMARD therapy including small molecules, biologics, and biosimilars, with the exception of methotrexate (as specified in Section 6.5.1.1) and stable dose (at least 4 weeks) of leflunomide, anti-malarials and sulfasalazine (please reference Section 6.5 and Appendix 9).

13. Prior lymphocyte depleting therapies (eg, rituximab, Campath) with remaining lymphocyte depletion.

14. Known requirement for treatment with prohibited concomitant medications during the study.

15. Exposure to any live vaccines within 4 weeks prior to administration of the first dose of investigational product, or lack of willingness to avoid exposure to any live vaccines during the trial and for at least 2 months after the last dose of investigational product.

16. Intra- articular (IA) corticosteroids administered within 4 weeks prior to Screening.

17. Unstable dose (less than 4 weeks) of oral and IM corticosteroid prior to first study dose.

Prior/Concurrent Clinical Study Experience:

18. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or within 5 half-lives preceding the first dose of investigational product used in this study (whichever is longer) is not permitted.

Diagnostic Assessments:

19. Clinically significant laboratory abnormalities at Screening, including but not limited to inadequate bone marrow, liver, renal and immune system function as defined by the following lab criteria:

    a. Hemoglobin (Hgb) <9 g/dL.

    b. Absolute neutrophil count (ANC) ≤1500 cells/mm^3.

    c. White blood cell (WBC) count <3.0 x 10^9/L.

    d. Lymphocyte count of <0.5 x 10^9/L

    e. Platelets <100 x 10^9/L.

f. Aspartate aminotransferase/alanine aminotransferase (AST/ALT) ≥2 times the upper limit of normal.

g. Total bilirubin ≥1.5 times the upper limit of normal.

h. Serum creatinine ≥1.5 mg/dL.

i. Serum albumin <3.0 g/dL.

20. Evidence of untreated or inadequately treated latent or active tuberculosis (TB) infection as defined below (See Sections 6.5 and Section 8.2.6):

    a. If screening QuantiFERON-TB test is positive or indeterminate in a participant without history of active or latent TB, a retest of QuantiFERON-TB is required and the participant should be referred to a specialist according to local practice (eg, pulmonologist, TB specialist or infectious disease specialist) for further evaluation of latent or active TB or false positive QuantiFERON-TB test result. Participants who are determined to have a false positive QuantiFERON-TB test result by the specialist are eligible to enroll.

    b. Participants diagnosed with latent TB at Screening are required to receive at least 4 weeks of chemprophylaxis according to local clinical guidelines and repeat aminotransferases (ALT/AST) within at least 4 weeks prior to receiving study dose on Day 1 to confirm participants still fulfill entry criteria. Participants need to commit to completion of the chemoprophylaxis course.

    c. Participants previously treated for active TB must have completed a successful course of treatment in accordance with local guidelines.

    d. Participants previously treated for latent TB infection, must have completed a successful course of chemoprophylaxis in accordance with local guidelines; or if chemoprophylaxis is still ongoing, participants must have received at least 4 weeks before receiving study dose on Day 1. Participants need to commit to completion of the chemoprophylaxis course.

21. Chest radiography (or alternative chest imaging, ie, chest computed tomography (CT) scan) with evidence of active TB, fungal infections, or other clinically significant abnormalities taken within 12 weeks prior to Screening. If the TB has been adequately treated as specified in Exclusion Criteria 20, a chest imaging result consistent with prior TB (active or latent) will not exclude the participant. (See Section 8.2.3)

22. Positive urine drug test at Screening for substances of abuse that is not due to prescribed medication, or past or current history of addiction to or dependence on non-prescribed substances within 12 months prior to Screening.

Other Exclusions:

23. 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.

24. Pregnant females and breastfeeding females, male participants with partners currently pregnant who are unwilling to use a condom, or male and female participants of childbearing potential who are unwilling or unable to use an effective method of contraception as outlined in this protocol for the duration of the study and for at least 5 months after the last dose of investigational product.

5.3. Lifestyle Considerations

No lifestyle restrictions are required.

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 and 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 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.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled to receive 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 SAE.

Participants who do not meet all eligibility criteria may be retested (under the same screening number) within the 6 week screening period, and if the retest result(s) meet the eligibility criteria, the participant will not be considered as a screen fail and may enroll into the study.

Individuals who do not meet the criteria for participation in this study within the 6 week screening period will be considered as screen failure, they may be rescreened.

6. INVESTIGATIONAL PRODUCT

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 investigational product.

6.1. Investigational Product(s) Administered

The following table outlines the two investigational products used in this protocol. For more detailed information please refer to the Investigational Product (IP) Manual.

Intervention Name	PF-06410293	Humira
Type	Biologic	Biologic
Dose Formulation	solution for injections/solution for injection	solution for injections/solution for injection
Unit Dose Strength(s)	40 mg /**0.8 mL**	40 mg/**0.4 mL**
Dosage Level(s)	40 mg every 2 weeks	40 mg every 2 weeks
Route of Administration	Subcutaneous (SC)	Subcutaneous (SC)
Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Investigational product will be provided in an Open Labeled Carton. Each carton will contain one syringe and will be labeled as required per country requirement.	Investigational product will be provided in an Open Labeled Carton. Each carton will contain one syringe and will be labeled as required per country requirement.

6.1.1. Administration

Investigational product will be administered by the participant, care giver or site personnel every other week using pre-filled syringes provided by the sponsor. All participants will receive instruction on administration of investigational product by SC injection and may only inject following the Instructions for Use (IFU) (see Section 6.1.2). Participants who are not capable of, or choose not to administer investigational product, may have their injections administered by a care-giver following the IFU. Onsite injections will occur at every scheduled visit, **after** the PK and ADA/NAb sample is collected (See SoA and Table 1. PK Sampling Table).

The first SC injection should be administered at the site under the supervision of the site's investigator or designee, and the participant will be assessed for their ability to inject adalimumab. Any issues may be reviewed at that time. The first injection must be an abdominal injection. The first TP4 injection at Week 22 and injections at Weeks 24, 26, 28 and 30 (before starting the PK profile) must also be administered in the abdomen under the supervision of the site's investigator or designee. All other injections may be administered in

the abdomen or upper front of either thigh. Applicable injection details (eg, date) will be recorded in the electronic Participant Dosing Log. Investigational product will be dispensed to the participant at each visit.

Following the first injection at the site, the participant should select a day of the week for their every other week injections at home. For example, if the first injection occurred on a Monday (study Day 1) the participant should continue every other week injections on a Monday (study Day 15). Participants should select a day of the week which will most likely ensure compliance (eg, no late or forgotten doses). On-site injections will occur under the supervision of the site's investigator or designee during the scheduled visits (See SoA). Any participant found to be non-compliant for any reason other than safety should be instructed to administer the non-compliant dose as soon as he/she remembers, as long as the time elapsed following the intended dosing time is ≤7 days. He/she should inject the next dose as scheduled. Once 7 days passes from a regularly scheduled dose, the delayed dose in the previous 2 week dosing period will be considered missing (not delayed), and shall not be administered. It is critical for participants be compliant with the dosing schedule. In particular, participant dosing compliance during TP4 is critical in order to achieve the primary objective of this study. In order to support PK collection starting at Week 30, participants **must** have received (at a minimum) 3 doses, specifically those at Week 26, Week 28 and Week 30. These injections must be administered in the abdomen while at the clinic under the supervision of the site's investigator or designee.

Applicable adalimumab injection details (eg, dates) will be recorded in the electronic Participant Dosing Log by the participant. Once the pre-filled syringe is used the empty investigational product container should be returned. The drug will be injected into a quadrant of the abdominal wall, remaining 2" inches/5 cm away from the navel, or upper front of either thigh. Participants should carefully inspect the adalimumab solution in the syringe for particulate matter and discoloration prior to SC administration. If particulates or discolorations are noted, the product should not be used. Participants should use the next available pre-filled syringe for the scheduled dose and contact the investigator. Participants should rotate injection sites and not administer injections into areas where the skin is tender, bruised, red or hard. If any unused portion of the drug remains in the syringe after the drug administration, the remaining drug should be discarded with no attempt to re-inject. Participants should call the study site to discuss any problems, issues, and concerns related to the drug administration. Participants should return any dropped (while uncapped) or frozen unused syringes. If a potential defect is noted in the prefilled syringe (or its labeling or packaging), or the syringe fails to perform, the syringe should be returned to the site and the site should file a Medical Device Complaint (Refer to the IP Manual for specific instructions related to the form). Site staff should also follow the above described process to inspect the pre-filled syringe for onsite injections and report issues as noted.

Participants will be instructed to dispose of their used needles and syringes in a FDA-cleared biohazard disposal container immediately after use. Participants must not dispose their used biohazard disposal container in their household trash but may return them to the site, or they may dispose of them locally according to local guidelines.

Reference the IP manual for further details.

6.1.2. Training for Adalimumab Subcutaneous Injections

All participants will be provided the Instruction For Use (IFU) and will be supervised for the administration of their first dose of investigational product on study Day 1. As noted above, the first SC injection must be an abdominal injection. The first TP4 injection at Week 22 and injections at Weeks 24, 26, 28 and 30 (before starting the PK profile) must also be administered in the abdomen under the supervision of the site's investigator or designee (please also refer to Section 6.1). All other injections may be administered in the abdomen or upper front of either thigh. IFU of the investigational product will be provided to the participant on Day 1 by the investigator or designee, and explanations will be provided as necessary. Study staff, caregivers, and participants should refer to the participant dosing instructions on the handling and administration of the investigational product.

6.1.3. Medical Devices

1. The Pfizer manufactured medical device (or device manufactured for Pfizer by a third party) provided for use in this study is the PF-06410293 solution for injection prefilled syringe.

2. Other medical device (not manufactured by or for Pfizer) provided for use in this study is the Humira solution for injection syringe.

3. Instructions for medical device use are provided in the Instruction For Use.

4. Medical device incidents must be detected, documented, and reported by the investigator throughout the study (see Section 8.3.7). For device incidents resulting from malfunctions of the device please also refer to the Investigational Product Manual for the device complaint process instructions.

6.2. Preparation/Handling/Storage/Accountability

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

2. Only participants enrolled in the study may receive investigational product and only authorized site staff may supply or administer investigational product. All investigational products 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 investigational product accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All investigational products will be accounted for using an investigational product accountability form/record. Once the pre-filled syringe is used, the empty investigational product container should be returned.

4. Further guidance and information for the final disposition of unused investigational products 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. Investigational products should be stored in their original containers and in accordance with the labels.

7. Site staff will instruct participants on the proper storage requirements for take-home investigational product.

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

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

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

6.2.1. Preparation and Dispensing

No preparation is required for either investigational product prior to use.

Single use PF-06410293 and Humira will be provided to the participants in pre-filled syringe (PFS) which are individually packaged in containers with tamper evident seals. The cartons should not be opened until the drug is to be administered. The investigational product will be dispensed using an interactive response technology (IRT) drug management system at each visit from Week 0 to Week 32; investigational product will be given to the participants for the exact number of doses needed between visits from Week 0 to Week 22. A qualified staff member will dispense the investigational product via unique container numbers in the cartons provided, and in quantities appropriate so that participants will receive enough PFSs to cover the exact number of doses until the next scheduled clinic visit. Participants will receive a carry case and cool pack for transport of investigational product, which must remain cool but not frozen.

When handling investigational product at the site, it is important that the study personnel handle only one participant's investigational product container(s) at a time, to avoid a mix up with another participant's investigational product container(s).

If applicable, please reference Appendix 11 for alternative options on investigational product dispensing during the COVID-19 pandemic.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study.

Upon successful completion of TP1, participants will be randomized (1:1 ratio) into either the switching arm (ie, to PF-06410293) or the non-switching arm (ie, continue to receive Humira). Randomization will be stratified by 3 body weight groups (≥40 kg to <70 kg; ≥70 kg to <100 kg; ≥100 kg to ≤130 kg). Participants randomized to the Humira arm will continue on Humira for the remainder of the study, and participants randomized to switch to PF-06410293 will continue switching in each TP (TP2: PF-06410293; TP3: Humira; TP4: PF-06410293).

6.3.1. Allocation to Investigational Product

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

This is an open-label study; however, the specific investigational product dispensed to the participant will be assigned using an IRT. The site will contact the IRT upon the completion of Screening assessments on Study Day 1, if the participant is found to be eligible for the study. On Study Day 1 and throughout Treatment Period 1 all participants will receive Humira. Upon successful completion of TP1, the site will contact the IRT prior to the start

of Week 10 investigational product administration for each participant to randomize the participant into the study (see Section 6.3). The site will record the investigational product assignment on the applicable case report form. Potential bias will be reduced by central randomization.

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

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

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

6.3.2. Breaking the Blind (Not Applicable)

This is an open-label trial.

6.4. Investigational Product Compliance

Participant compliance will be verified by the review of the electronic Participant Dosing Log (or relevant source document), the returned unused investigational product, and accounting for any unused investigational product by the participant. When investigational product is administered at the study center (eg, Day 1 dosing), it will be administered under the supervision of study personnel (see Section 6.1). Compliance will be evaluated at all study visits beginning at Week 4. Participants will be directed to record the applicable injection details (eg, date) in the electronic Participant Dosing Log, and site personnel will enter this information onto electronic case report form (eCRF). Any participant found to be non-compliant for a reason other than safety should be instructed to self-administer the missed dose as soon as possible, as long as the time elapsed following the intended dosing time is ≤7 days. He/she should inject the next dose as scheduled. Once 7 days passes from a regularly scheduled dose, the delayed dose in the previous 2 week dosing period will be considered missing (not delayed), and shall not be administered. The participant should be reeducated on the every other week dosing regimen, and to revert to the original calendar day scheduled after any single dose outside the original calendar schedule. The investigator or designee should assess potential factors leading to less than complete compliance and take steps to improve compliance (see Section 7.1.1). Compliance and non-compliance of study participants will be monitored by study personnel at the site by using the source documents including the electronic Participant Dosing Log as noted above. See Section 7.1 for discontinuation of participants with noncompliance.

If applicable, please reference Appendix 11 for alternative options on investigational product compliance during the COVID-19 pandemic.

6.5. Concomitant Therapy

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

Medications that are taken after informed consent is obtained, but before the first dose of investigational product is received, will be documented as prior medications. The dosage and duration of all background RA medications will also be recorded on the eCRF for documentation of study eligibility. Medications taken after the first dose of investigational product has been administered will be documented as concomitant medications. Use of any allowed concomitant medications must follow local standard of care practices and regulations for the treated indication.

For participants who are on DMARD therapy (with the exception of methotrexate as specified in Section 6.5.1.1) and stable dose (at least 4 weeks) of leflunomide, anti-malarials and sulfasalazine the doses can be reduced or discontinued as per medical judgement. In the case of suspected COVID-19 infection, continuation of concomitant DMARD therapy should be carefully evaluated following local guidance and medical judgement, until full clinical assessment is completed. Initiation of additional DMARDs or an increase in the dose of current DMARD therapy during the study is prohibited. A combination of no more than 3 DMARDs is permitted during the study.

Participants are encouraged to bring their vaccinations up to date prior to initiating adalimumab; any live attenuated vaccine must have been administered at least 4 weeks prior to Day 1.

Participants previously treated for active TB infection, must have completed and documented a successful course of treatment in accordance with local guidelines. Participants detected with latent TB at Screening are eligible providing they have received at least 4 weeks of chemoprophylaxis and commit to completion of the full course of treatment, in accordance with local standard of care, before starting the study treatment. Participants whose chest radiography (or alternative chest imaging) and QuantiFERON®-TB Gold In-Tube Test results indicate no evidence of TB infection, but who are considered by the investigator to be at high risk to develop tuberculosis (eg, residing in high-risk areas or travel to high-risk areas), may be started on a course of TB prophylaxis or treatment in accordance with local guidelines at the discretion of the investigator. If TB prophylaxis treatment is started after the Screening visit, aminotransferases (ALT/AST) levels should be checked within at least 4 weeks prior to first investigational product in TP1 to confirm results fulfill entry criteria.

It is recommended that participants avoid changing prescription or non-prescription drugs, vitamins, and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of investigational product and prior to study visits unless otherwise noted below, throughout the study.

Concomitant medications will be collected at each visit/contact from the time the consent form is signed to the final study visit/contact. All concomitant medication taken during the study (prescription, non-prescription drugs, and non-drug therapy as appropriate) must be recorded on the eCRF with daily dose, and start and stop dates of administration. If a participant discontinues early, concomitant medications must be followed at the EoT visit, the safety follow-up visit at least 28 calendar days after the last dose of investigational product, and any additional post-treatment phone contact and/or extended safety follow-up.

Concomitant medications prohibited in the study are summarized in Appendix 10.

6.5.1. Stable Background Therapies

6.5.1.1. Methotrexate

Adalimumab must be administered concomitantly with a stable dose of MTX throughout the course of study treatment.

The administration of MTX, including dosage, laboratory testing, follow-up care (including contraception requirements), and contraindications should be performed according to local standards of care throughout the study.

At study entry, participants must have received oral or IM MTX for at least 12 weeks and have been on a stable dose of 10 to 25 mg per week for at least 4 weeks prior to first dose of investigational product. In geographic regions where 6 mg per week is a recommended initial dose by local guidance or standard of care, a stable dose of as low as 6 mg per week for at least 4 weeks prior to first dose of investigational product will be permitted.

Participants are required to continue their stable dose of MTX background therapy throughout the study. Dose reduction of MTX therapy during the study treatment is not recommended, with the exception of significant intolerance, and the dose reduction must be documented with the investigator's medical justification. Participants will not be discontinued from study treatment following a justified dose reduction of MTX, unless the MTX is adjusted below the minimal required dosage level of 7.5 mg/week (or a dose as low as 6 mg/week in geographic regions where permitted by local guidance or standard of care).

6.5.1.2. Folic/Folinic Acid Supplements

Participants are required to receive a stable background dose of oral folic/folinic acid supplementation throughout the study. Participants must have received an adequate stable dose of oral folate (at least 1 mg/day on ≥5 days per week) or oral folinic acid (≥5 mg once per week) for at least 21 days prior to first dose of investigational product and will continue on the regimen throughout the study treatment. In countries which do not have approved folic acid 1 mg or folinic acid 5 mg presentations, a regimen of folic acid of at least ≥5 mg weekly is acceptable.

6.5.1.3. Additional Background Therapies

Participants may also continue additional concomitant therapies, including corticosteroids, a NSAID or Cyclooxygenase-2 (COX-2) inhibitor, and non-opioid and allowed opioid/narcotic analgesics (see Section 6.5.2, Section 6.5.3 and Appendix 9).

6.5.2. Pain or Other Arthritis Therapy

Participants may receive the following concomitant medications during the study under restricted conditions as specified below:

1. Participants may be taking one NSAID, including a COX-2 inhibitor. At the discretion of the investigator, the dosage may be adjusted to protect a participant's safety during the study.

2. Participants may additionally be receiving low dose aspirin for cardiovascular use (≤325 mg per day).

3. Intra articular (IA) corticosteroids, oral and IM corticosteroids are allowed as rescue therapy, as described in Section 6.5.3. Participants who enter the study with oral or IM corticosteroids must be on stable dosing regimen for at least 4 weeks prior to the first study treatment dose. At the discretion of the investigator, the corticosteroid dosage may be adjusted during the trial as per investigator's medical judgment. Tapering or discontinuation of the corticosteroid treatment should be performed as per local standard of care.

4. Participants receiving regular daily doses of only one of the allowed immediate-release opioids/narcotics (including tramadol) as listed in Table 2, and/or a regular a daily dose of up to 2 grams/day (or maximal local label daily dosage) of acetaminophen or 3 grams/day of paracetamol (eg, not using analgesic medication 'as needed') according to local guidance, must be on stable doses for at least 2 weeks prior to Day 1. Less frequent dosing or cessation of analgesic therapy should be performed as per investigator's medical judgment.

5. New or increased doses of following medications will be allowed as rescue therapy, as described in Section 6.5.3.

Table 2. Permitted Opioid/Narcotic Drugs

Drug	Example Trade Names	Maximum Allowed Total Daily Dose
Tramadol	Ultram, Zydol, Zamadol, Ultracet, Tramal	300 mg
Codeine	Tylenol #2 and #3, Paveral	200 mg
Hydrocodone	Vicodin, Lortab	30 mg
Oxycodone	Roxicodone, Percocet, Tylox (not: OxyContin®)	15 mg
Propoxyphene HCl or **Propoxyphene napsylate**	Darvon, Darvocet, Doloxene, Darvon-N, Darvocet-N 100	300 mg propoxyphene HCl 400 mg propoxyphene napsylate

6.5.3. Rescue Medicine

1. Analgesics: New or increased acetaminophen/paracetamol, current tramadol or other single opioid/narcotic drug (see Table 2), or another allowed opioid (see Table 3) are allowed as rescue medications according to the local label.

Table 3. Additional Opioid Drugs for Rescue Therapy

Drug	Example Trade Names	Maximum Allowed Total Daily Dose
Morphine	Short acting formulations (not: MS Contin®)	30 mg
Hydromorphone	Dilaudid	7.5 mg
Meperidine	Demerol, Pethidine	300 mg

For participants who are receiving regular daily doses of one of the allowed opioids/narcotics:

- If the opioid/narcotic is tramadol, hydrocodone, or oxycodone, the dosage may be increased up to the maximum total daily dosage limits for rescue purposes. However, participants can NOT add a second opioid/ narcotic agent for rescue; therefore, any original opioid should be discontinued if a new opioid/narcotic is started for rescue.

For participants who are not on a regular daily opioid/narcotic therapy:

- Sustained release morphine formulations (eg, MS Contin®), sustained release oxycodone formulations (eg, OxyContin®), and propoxyphene HCL/napsylate are not allowed for rescue medication.

2. IA corticosteroids may not be administered within 4 weeks prior to Screening visit. However, IA injections of corticosteroids are allowed as rescue therapy in this study in accordance with the local label.

The following restrictions will apply when the rescue injections are performed:

- Rescue injections should be performed following the joint assessment after Screening visit.

- Investigators should follow local standard of care where participants should receive no more than one injection per month and no more than three injections per year.

- Arthrocentesis without injection of any IA medication is allowed. The joint having arthrocentesis will be considered as having its pre-injection status for the joint counts.

3. Non-pharmacologic treatment, including application of heat and cold, massage, physical therapy, splinting, or ultrasound is allowed.

6.6. Dose Modification

No dose adjustment (dosage or dosing frequency) will be allowed in the study.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Investigational product

In rare instances, it may be necessary for a participant to permanently discontinue investigational product prior to completing the study. If investigational product is permanently discontinued, the participant will remain in the study to be evaluated for at least 28 calendar days after last dose of investigational product for monitoring of AEs/SAEs and concomitant medications.

Reasons for discontinuation from study treatment may include, but will not be limited to:

- AE potentially attributable to investigational product that in the opinion of the investigator endangers participant health or safety, including but not limited to severe hypersensitivity reactions, serious infections (see Section 2.3 Benefit/Risk Assessment), active/latent tuberculosis, serious cardiac arrhythmias, or new or worsening congestive heart failure.
- Inadequate response to study treatment, in the judgment of the investigator (per local standard of care and/or guidelines).
- Participant noncompliance.
- Participant choice to withdraw from treatment (follow-up permitted by participant).
- Participant choice to withdraw from study participation (cessation of follow-up).
- Participant lost to follow-up.
- Participant pregnancy.

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

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.

7.1.1. Temporary Discontinuation

Temporary treatment discontinuation may be allowed in the case of an infectious AE or other potentially related AE occurring during the first 3 study Treatment Periods and the first 2 doses of TP4. Temporary treatment discontinuation should also be considered in the case of a known SARS-CoV2 exposure or suspected COVID-19 infection until full clinical assessment is completed.

Participants who experience a serious infectious AE (eg, life-threatening, requiring hospitalization, documented COVID-19 infection, etc.) or sepsis should be permanently discontinued from study treatment.

Delayed treatment due to other non-medical reasons (eg, participant is out of town and forgets to take their investigational product container) should be prevented as much as possible by discussing the participant's plans and educating him/her about the regular every other week dosing schedule. In TPs 1 – 3 and the first 2 doses in TP4, a participant who misses a dose should be instructed to take the missed dose as soon as he/she remembers, as long as the time elapsed following the intended dosing time is <7 days. He/she should take the next dose as scheduled. To be included in the PK analysis, it is critical for participants to not miss (see Section 9.3):

- The last 3 doses in TP4;
- The first dose of the study in TP1;
- No more than 1 missed dose per TP;
- No more than 2 missed doses allowed in TP1 through TP4;
- Participants can only miss or have an incomplete dose for either the first or second dose in TP4 (but not both).

A delayed treatment dose should be administered once the AE is resolved if the dose can be administered no later than 7 days before the next regularly scheduled dose of investigational product. Once 7 days passes from a regularly scheduled dose, the delayed dose in the previous 2 week dosing period will be considered missing (not delayed), and shall not be administered. For example, if the participant does not administer the investigational product on Monday (July 1), but is able to resume treatment on Sunday (July 8), the delayed July 1 dose may be administered on July 8. If the participant cannot resume treatment on July 8, the July 1 dose will not be administered (recorded as a missed dose), and the participant will receive the next regularly scheduled dose on Monday (July 15).

7.1.2. Permanent Discontinuation

Participants who experience a serious infectious AE (eg life-threatening, requiring hospitalization, documented COVID-19, etc.) or sepsis should be permanently discontinued from study treatment.

Permanent discontinuation would be considered for safety reasons or when either the participant or the investigator deemed necessary to discontinue investigational product.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request.

At the time of discontinuing from the study, if possible, an early discontinuation 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 enrolled in the study or those 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 investigational product and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

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.

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.

Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment will be discontinued from the study. 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 post treatment 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.

Please reference Appendix 11 for details on participants discontinuing during the COVID-19 pandemic.

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 investigational product.

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.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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.

The total blood sampling volume for individual participants in this study is approximately 350 mL. The actual collection times of blood sampling may change. Additional 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

Efficacy measures are not included as endpoints in this study design. (see SoA).

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.

8.2.1. Physical Examinations

A complete physical examination will include assessments of general appearance, skin (including presence of rash), head, eyes, ears, nose and throat (HEENT), lymph nodes, cardiovascular, respiratory, gastrointestinal, musculoskeletal and neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed as detailed in the SoA table. Height and body weight will also be measured and recorded.

Pulse rate and supine blood pressure (in the participant's arm and recorded to the nearest mmHg) measurements will be assessed with an automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

When timing of these measurements coincides with blood collection, the blood pressure and pulse rate should be obtained first. For visits with investigational product dosing, vital signs should be taken prior to adalimumab injection.

8.2.3. Chest Radiograph

A chest radiograph (lateral and posterior-anterior view chest X-rays) will be obtained at the Screening Visit in all participants, unless it has been taken and documented within 12 weeks prior to Screening. The chest radiograph should be performed according to local health authority guidance. To be considered eligible for the study, the screening radiograph must be negative for active tuberculosis infection, fungal infection, or any other clinically significant abnormalities unless the TB infection (evident by scar or granuloma) has been successfully treated (see Section 5.2 Exclusion Criteria). If a chest CT exam (or an alternative chest imaging) is performed within 12 weeks prior to the Screening, a chest x-ray is not required at Screening.

8.2.4. Electrocardiograms

12-Lead ECG is only required at Screening to determine participant's eligibility, see SoA section of this protocol. ECG should be performed after the participant has rested quietly for about 10 minutes in a supine position as deemed appropriate by the personnel acquiring ECG tracings. ECGs will be read locally. Participants with a screening 12-lead electrocardiogram that demonstrates clinically significant abnormalities requiring urgent treatment (eg, acute myocardial infarction, serious tachy- or bradyarrhythmias) or that is indicative of serious underlying heart disease (eg, cardiomyopathy, major congenital heart disease, low voltage in all leads) should not be enrolled in the study. These participants should be referred to a specialist for further assessment.

ECG values of potential clinical concern are listed in Appendix 6.

8.2.5. Clinical Safety Laboratory Assessments

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 28 calendar days after the last dose of investigational product should be repeated until the values return to normal or baseline 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 Appendix 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.

8.2.6. QuantiFERON®-TB Gold In-Tube Test

QuantiFERON® - TB Gold In-Tube test (QFT) is an in vitro indirect diagnostic test for *M. tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography (and or alternative imaging) and other medical and diagnostic evaluations. Screening QuantiFERON®-TB Gold In-Tube test must be performed in every participant within 6 weeks prior to the first investigational product at Day 1 with the exception of participants with documented history of latent or active TB who completed TB chemoprophylaxis and treatment in accordance with local guidelines.

In the case of a positive or indeterminate screening QuantiFERON-TB Gold In-Tube test result, the participant must receive a re-test with QFT-TB Gold In-Tube Test and referred to a specialist according to local practice (eg, pulmonologist or infectious disease specialist) for further evaluation of latent TB, active TB or false positive QFT test result, unless they have a past history of having been adequately treated with appropriate chemoprohylaxis for latent TB or have completed treatment for active TB previously, in which case re-testing is not required. Participants who test positive and are considered to have current latent TB can enroll in the study if they are on chemophrophylaxis for at least 4 weeks. (see Section 5.2 and Section 6.5).

8.2.7. 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 all 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 prior the participant's receiving the adalimumab. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. 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.

8.2.8. Viral Disease Screening

HBsAg, HBcAb, HBsAb and HCVAb testing is required to determine eligibility. Hepatitis testing will be performed by the central lab. Participants who are negative for all tests are eligible. Participants with positive HCVAb will be reflex tested for HCV RNA and will be eligible to participate if HCV RNA results are negative. Participants with positive HBsAg or

HBcAb without positive HBsAb results are not eligible to participate in the study. Participants with negative HBcAb and HBsAg results but positive HBsAb are eligible to participate in the study.

HIV (HIV-1 Ab and HIV-2 Ab) testing is also required to demonstrate eligibility unless not permitted by local regulations. HIV testing will be performed by the central lab unless testing at a local lab is required per local regulations. HIV testing will be completed at Screening unless testing has been performed within 8 weeks before study dosing on Day 1 and results are available.

In the event where a false positive test result is suspected, additional testing may be done in the central or local laboratory to confirm that participants are not positive for HIV, hepatitis B or hepatitis C.

8.3. Adverse Events and Serious Adverse Events

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

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 investigational product 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 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

All nonserious AEs and SAEs occurring in a participant during the active collection period as described in Section 8.3.1.1 are recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

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 an investigational product 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 investigational product 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 and female partners of male participants will be collected after the start of investigational product and until (50 - 100 days) after the last dose that is at least 5 terminal half-lives.

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. Cardiovascular and Death Events

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical trials of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

8.3.7. Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for the purposes self-administer adalimumab injections. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a medical device incident can be found in Appendix 7.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.1 and Appendix 3 of the protocol.

8.3.7.1. Time Period for Detecting Medical Device Incidents

Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device incidents is provided in Appendix 7.

8.3.7.2. Follow-up of Medical Device Incidents

All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.3). This applies to all participants, including those who discontinue investigational product.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.7.3. Prompt Reporting of Medical Device Incidents to Sponsor

Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.

The Medical Device Incident Report Form will be sent to the sponsor by fax. If fax is unavailable, then email should be utilized.

The same individual will be the contact for the receipt of medical device reports and SAEs.

8.3.7.4. Regulatory Reporting Requirements for Medical Device Incidents

The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/EC.

8.3.8. 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. Additional examples of a medication error includes, but not limited to: outside the dosing window as per SoA, drug dispensing error, administration of two injections on the same day, incorrect route of administration, wrong medication type taken by participant.

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 immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and 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 injection of adalimumab with a dose greater than 10 mg/kg will be considered an overdose. This is based on information included in the Humira USPI[1] which indicates that multiple doses of up to 10 mg/kg IV have been administered to patients in clinical trials without evidence of dose-limiting toxicities. Based on an average absolute bioavailability estimate of 64% from three studies in which a single 40 mg SC dose was administered, this would conservatively (based on a body weight of 40 kg) equate to an approximately 15-fold higher dose than the 40 mg injection used in the protocol. The investigational products used in this study will follow Humira's USPI/SmPC. Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until adalimumab can no longer be detected systemically (at least 70 days). Appropriate treatments to relieve the symptoms should be provided to the participant.
3. Obtain a blood sample for pharmacokinetic (PK) analysis within 70 days from the date of the last dose of investigational product if requested by the medical monitor (determined on a case-by-case basis).
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.

8.5. Pharmacokinetics

Blood samples of approximately 6 mL, to provide a minimum of 1 mL of serum per aliquot (2 total), will be collected for measurement of serum concentrations of adalimumab as specified below.

- Samples for determination of adalimumab trough drug concentrations will be collected within 6 hours prior to the investigational product administration on Weeks 22, 24, 26, 28, and on Day 1 (time 0), Weeks 10 and 16 at a maximum of 48 hours prior to, but as close as possible prior to the next investigational product administration (ie, pre-dose).

- Primary endpoint data will be supported by the determination of adalimumab drug concentrations for the 2-week PK Profile.

- The 2-week PK sampling period starts with Week 30 pre-dose PK collection and ends with Week 32 pre-dose PK collection.

  - Pre-dose PK collection at Week 30/PK Profile Day 1, the blood sample will be collected within 6 hours prior to investigational product administration.

  - For the subsequent PK Profile Days, post-Week 30 dosing times for serum collections are:

    - 48 (±4) hrs on PK Profile Day 3,

    - 72 (±6) hrs on PK Profile Day 4,

    - 96 (±8) hrs on PK Profile Day 5,

    - 144 (±8) hrs on PK Profile Day 7,

    - 240 (±24) hrs on PK Profile Day 11, and

    - 336 (±24) hrs on PK Profile Day 15; before Week 32 dosing.

The 2-week PK Profile collections may be completed using home health care service. Please reference Table 1. PK Sampling Table. In order for participant's PK Profile to be included in the primary analysis **every effort should be made to draw samples within the specified time windows.**

Serum samples for PK assessment will be analyzed using a validated enzyme linked immunosorbent assay (ELISA) to quantitatively measure concentrations of Humira and PF-06410293.

For detailed PK sample collection and processing instructions, please see the study laboratory manual.

8.6. Pharmacodynamics

Pharmacodynamic (PD) parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

Genetics are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

There are no Banked Biospecimens for Genetics in this study as per all other Biosimilar programs.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.8.1. Specified Gene Expression (RNA) Research

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

8.8.2. Specified Protein Research

Specified protein research is not included in this study.

8.8.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.8.4. Banked Biospecimens for Biomarkers

There are no Banked Biospecimens for Biomarkers in this study.

8.9. Immunogenicity Assessments

8.9.1. Analysis of Anti-adalimumab Antibodies and Neutralizing Anti-adalimumab Antibodies

Blood samples will be collected at the time points specified in the SoA table to determine the presence of ADA and neutralizing antibodies (NAb), concurrently with samples for PK analysis in Treatment Periods 1 through 4. For detailed ADA and NAb sample collection and processing instructions, please see the study lab manual.

Serum samples for ADA assessment will be analyzed using a validated electrochemoluminescent (ECL) immunoassay using PF-06410293 as a capture agent. Samples positive for ADA will be further tested for neutralizing activity using a validated cell-based NAb assay that utilizes PF-06410293 as the capture agent.

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[redacted]

8.10. Health Economics

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

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

9.1.1. Estimands

The primary estimands are the geometric mean ratio (GMR) and 90% confidence interval (CI) for AUC_{τ} and C_{max} to evaluate the PK equivalence between the switching and non-switching arms, after 3 switches, in participants with RA who meet the PK population criteria, that include criteria for the number and timing of missing doses, availability of PK data, adherence to background therapy, and major protocol deviations related to PK assessment (Section 9.3).

9.2. Sample Size Determination

Assuming a GMR (switching arm vs non-switching arm) of 105% and a coefficient of variation (CV) of 55% for each of the PK parameters, AUC_{τ} and C_{max}, an anticipated non-evaluable rate of 25%, and a correlation of 0.5 between log-transformed AUCτ and log transformed C_{max}, a total sample size of approximately 420 participants (314 evaluable participants) would provide 85% power to demonstrate that the 90% CI for the GMR is within 80.00% to 125.00% for both parameters.

The %CV assumption for the power calculation was derived from data on 15 RA participants receiving MTX who participated in a PK substudy of an innovator study,[3] with %CV of 53% and 56% for AUCτ and Cmax, respectively,[4] and from 21 RA participants (6 on MTX) who participated in a PK substudy of the innovator open-label extension study, where %CV

for all participants was 48% and 49%, and for MTX only was 46% and 44%, for AUCτ and C_{max}, respectively.

9.3. Populations for Analysis

The PK Population is defined as all randomized participants who are dosed to initiate the Week 30 steady state PK profile, remain on background MTX with no major protocol deviations influencing the PK assessment, such as a missing dose (the first dose of the study in TP1 cannot be missed, no more than 1 missed dose allowed per TP except Week 32 dose, no more than 2 missed doses allowed in TP1 through TP4 except Week 32 dose, participants can only miss or have an incomplete dose for either the first or second dose in TP4 (but not both), and the study doses on Weeks 26, 28, and 30 cannot be missed or incomplete), and have at least 1 primary endpoint (AUC_{τ} or C_{max}). The last study dose in TP4 on week 32 after the PK assessments is not included in the definition of the population for analyses and can be missed or be incomplete. Subjects will be excluded from the PK population in case of missed PK sample(s) which significantly affect the calculation of PK parameters. The PK population will be used for the primary PK analysis and other secondary PK endpoint analyses (T_{max}, C_{av}, and CL/F).

The Enrolled Population is defined as all participants who are enrolled in TP1. This population will be used for participant accountability in TP1.

The Safety Population for TP1 (Safety-TP1) is defined as all participants who are enrolled in TP1 and receive at least one dose of investigational product in TP1. This population will be used for the TP1 safety analyses.

The Intent-to-Treat Population (ITT-Randomized) is defined as all participants who are randomized to a study treatment group at Study Week 10. This population will be used for participant accountability during TP2 through TP4.

The Safety Population (Safety-Randomized) is defined as all participants who are randomized and receive at least one dose of investigational product following the randomization at Study Week 10. The Safety Population will be used for the safety analyses during TP2 through TP4, ADA and NAb analyses and the secondary PK endpoint (C_{trough}).

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

Efficacy measures are not included in this study design, therefore, efficacy analyses will not be performed.

9.4.2. Safety Analyses

Safety analyses for TP1 will be performed using the Safety-TP1 population for the Humira group. Safety analyses for TP2 through TP4 will be performed using Safety-Randomized populations by treatment groups (switching arm vs non-switching arm).

9.4.2.1. Adverse Event

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system.

Adverse events (treatment-emergent adverse events; treatment-related adverse events; adverse events classified as Grade 3 or higher; and SAEs) will be summarized by body system and preferred term according to MedDRA terminology. A treatment-emergent adverse event (TEAE) is defined as any adverse event that occurs after the beginning of the study treatment.

Adverse events of special interest including opportunistic infections and immune-based adverse effects will be summarized using grouped Medical dictionary for regulatory activities (MedDRA) codes in addition to presentation of individual AE preferred terms.

Immune-based adverse effects may be both acute and delayed and include injection-site reactions (ISRs), AEs that fulfill Sampson Criteria,[4] and AEs identified as potential hypersensitivity/anaphylactic reactions using a System Medical Dictionary for Drug Regulatory Activities (MedDRA) standardized MedDRA query (SMQ) that occur in relation to the administration of the study drug. Adverse events recorded on the CRF as ISRs will be summarized both as individual event symptoms and as a group for the purpose of comparing the overall incidence of ISRs. Therefore, the following safety endpoints will be summarized for all participants, and for ADA positive and negative subgroups:

- Participants with ISRs (as per the investigators);
- Participants with AEs that fulfill Sampson's Criteria;
- Participants with AEs belonging to SMQ broad groupings of potential hypersensitivity / anaphylactic reactions.

9.4.2.2. Laboratory Test Abnormalities

Hematology and chemistry laboratory data will be summarized at week 32 Shift table from baseline to week 32 will be provided for selected laboratory.

Additionally, change from baseline to week 32 will be summarized. For the TP1 summary, the baseline value is defined as the most recent measurement prior to the first dose of investigational product in TP1. For the TP2 to TP4 summary, the baseline value is defined as the most recent measurement prior to the first dose of investigational product after randomization in TP2.

9.4.2.3. Prior and Concomitant Mediations

Prior medications and concomitant medications will be coded by WHO medical dictionary. Participants who received these medications will be listed and summarized.

9.4.3. Other Analyses

9.4.3.1. Pharmacokinetics Analysis

The serum concentrations between Week 30 and Week 32 will be analyzed for the PK population using standard non-compartmental analysis to estimate the PK parameters for each individual participant. The PK parameters (C_{max}, AUC_{τ}, T_{max}, C_{av}, and CL/F), and the serum concentrations will be summarized descriptively.

Interchangeability will be assessed by constructing the point estimate (GMR) and the 90% CIs for the GMR for the primary endpoints, C_{max} and AUC_{τ}. Interchangeability will be established statistically if the 90% CI for the GMR is within 80.00% to 125.00% for both endpoints. The GMR and CI will be obtained using analysis of variance (ANOVA) applied to log-transformed data, with terms for treatment and randomization stratification factor (body weight categories).

Additionally, adalimumab trough concentration data (C_{trough}) will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum) by treatment arm for each TP.

9.4.3.2. ADA and NAb Analysis

For the ADA and NAb data, the percentage of participants with positive ADA and NAb will be calculated and summarized for the safety-randomized population by each visit in Treatment Periods. For participants with positive ADA and NAb, the magnitude (titer), time of onset, and duration of ADA and NAb response will also be described. In addition, the impact of ADA and NAb on PK over time will be assessed for each treatment arm.

9.4.3.3. Other Endpoint Analysis

Demographic and baseline characteristics, such as participant age, sex, height, weight, race, ethnicity, MTX dose, and medical history will be tabulated and summarized using descriptive statistics. Investigational product administration will be summarized.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor will conduct ongoing reviews of the data during the course of the study for the purpose of safety.

9.5.1. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

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 or their legally authorized representative 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 or his or her legally authorized representative 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 or his or her legally authorized representative 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 or the participant's legally authorized representative.

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 form and will be password protected 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 clinical study report (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 form and are password protected 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 Binder.

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 investigational product 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. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, 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 by a central laboratory 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) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN creatinine Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Albumin Total protein	pH Glucose Protein Blood Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	At screening only: • FSH[b] • Urine drug screening • Pregnancy test (β-hCG)[c] • Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis B surface antibody • Hepatitis C antibody • HCV RNA[d] • HIV-1 antibody • HIV-2 antibody • QuantiFERON®-TB Gold In-Tube Test

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. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. For confirmation of postmenopausal status only.
c. Pregnancy testing at Screening in female participants of childbearing potential by central lab serum HCG test. Pregnancy testing (HCG) after Screening will be performed locally using urine samples. Pregnancy testing may be repeated more frequently if required by IRB/ECs or local regulations, or if potential pregnancy is suspected.
d. Required only if HCVAb test result is positive.

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 investigational product, whether or not considered related to the investigational product. • 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 investigational product.

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 investigational product 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 investigational product 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. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- 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	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- 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:

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product 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 investigational product 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 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.

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.

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

10.4.1. Male Participant Reproductive Inclusion Criteria

According to Humira label (SmPC), no specific male contraceptive measures are mandated with Humira use, although male participants with WOCBP partners should be familiar with the following Humira SmPC recommendation: "Women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and continue its use for at least 5 months after the last Humira treatment".[2]

10.4.2. Female Participant Reproductive Inclusion Criteria

According to Humira label (SmPC), women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and continue its use for at least 5 months after the last Humira treatment.

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 an acceptable contraceptive method as described below during the intervention period (for at least 5 months after the last dose of investigational product). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of investigational product.

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.

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 investigational product, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. 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.

2. 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

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner:

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

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

- oral;
- intravaginal;
- transdermal;
- injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:
   - oral;
   - injectable.
8. 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 investigational product. 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.
9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
10. Male or female condom with or without spermicide.
11. Cervical cap, diaphragm, or sponge with spermicide.
12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

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: 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.

10.6. Appendix 6: ECG Findings of Potential Clinical Concern

ECG Findings That May 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 May 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.

10.7. Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 8.3.7 and Section 6.1.3) for the list of sponsor medical devices).

Medical Device Incident Definition

- A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
- Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of healthcare personnel.

It is sufficient that:

- An **incident** associated with a device happened.

AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness;
- Permanent impairment of body function or permanent damage to body structure;
- Condition necessitating medical or surgical intervention to prevent one of the above;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

Examples of Incidents

- A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A participant's investigational product is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documentation

- Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the CRF.
- For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 3.
- The CRF will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor or designee.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

10.8. Appendix 8: Country-Specific Requirements

There is no country specific requirement of all the countries planned for this study.

10.9. Appendix 9: Prohibited Concomitant Medications and Procedures

1. Any live attenuated vaccines.

2. DMARDs including small molecules, biologics and biosimilars with the exception of:

   - methotrexate (as specified in Section 6.5.1.1).

   - leflunomide, anti-malarials and sulfasalazine (stable dose of at least 4 weeks).

   Participants who are on DMARD therapy with the exceptions noted above, the doses can be reduced or discontinued as per medical judgement. Initiation of additional DMARDs or increase dose of current DMARD therapy during the study is prohibited. A combination of no more than 3 DMARDs is permitted during the study. The following table list examples of prohibited medications but not an exhaustive list:

Small molecule DMARDs prohibited:	**Biologic/Biosimilar DMARDs prohibited:**
azathioprine	Abatacept
cyclophosphamide	Anakinra
cyclosporine	TNF inhibitors
Janus kinase (JAK) inhibitors	Tocilizumab
tacrolimus (FK506)	Rituximab
6 mercaptopurine (6-MP)	

3. Other investigational drugs or investigational biologics.

4. B-cell depleting therapy.

5. Plasma exchange therapy.

6. IV immunoglobulin (IVIG).

7. High potency, sustained release narcotics (see allowed opioids/ narcotics in Section 6.5.2).

8. Intra-articular (IA) Corticosteroid Injections (please also reference Rescue Therapy, Section 6.5.3):

   - Investigators should follow local standard of care where participants should receive no more than one injection per month and no more than three injections per year.

10.10. Appendix 10: New York Heart Associated Functional Classification Criteria

The table below describes the most commonly used classification system for heart failure, the New York Heart Association (NYHA) Functional Classification.[10] It places patients in one of four categories based on how much they are limited during physical activity.

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity.
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

10.11. Appendix 11: COVID-19 Pandemic Considerations

In response to the ongoing global pandemic COVID-19, and the increasing restrictions and concerns on public health, the following changes are being incorporated into the B5381012 protocol to clarify alternative solutions to accommodate study procedures during the unprecedented time (eg the COVID-19 pandemic).

The following alternative solutions are only acceptable during the COVID-19 pandemic:

- The PI should document the start and end date of the necessity to use alternative solutions as described herein. Local law and regulations may apply.
- For participants who have received study treatment, scheduled study visits may be done remotely.
- For study drug dispensation, study drugs may be dispensed via a courier arranged by the investigational site, the home health care service or alternative transports as agreed upon between site and study participant. Please be sure alternative drug dispensation is in accordance with applicable laws and regulations.
- A home health care service will be added as an option to scheduled study visits after the Day 1/Week 0 Visit to: provide investigational product to study participants, including administration of study treatment, collect vital signs and specimens and/or processing of laboratory tests as specified in the protocol. In these cases, the investigator or designee must contact the study participants to collect adverse event (AE)/serious adverse event (SAE) information. Investigator or designee should also confirm dosing data with the participant and record it in the site's source or eDiary.
- Randomization at Week 10 may be done off-site:
    - Body weight is required to be taken at Day 1 or at Screening, whichever is closer to the Week 10 visit, and will be used to randomize as stated in the protocol.
    - Sites will need to call IWRS to randomize the study participant into either the switching arm (PF-06410293) or non-switching arm (Humira) for treatment. Once treatment assignment is received, site may dispense the study medication and deliver it to the participant as described below.
    - The home health care service may be used to collect specimens for safety evaluation, PK, ADA/NAb, vital signs and possibly deliver study medication.
- Dosing compliance confirmation should be recorded by study site investigator(s)/staff remotely in site's source documents or in eDiary at the time of the remote visit. Dosing data must be entered timely in the eCRF.
- AEs, contraception use and concomitant medications will be collected by study site investigator(s)/staff remotely, eg by phone for each remote visit and entered timely in the eCRF.
- For participant discontinuation reporting in the CRF: select the most appropriate status for discontinuation; if the discontinuation is associated with the current COVID-19 pandemic, enter "COVID-19" in the "Specify Status" field.

10.12. Appendix 12: Abbreviations

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

Abbreviation	Term
6-MP	6 mercaptopurine
ACR	American College of Rheumatology
Abd	Abdominal
Abs	Absolute
ACR	American College of Rheumatology
ADA	antidrug antibodies
AE	adverse event
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
AS	ankylosing spondylitis
AST	aspartate aminotransferase
AUC	area under the concentration - time curve
AUC_{τ}	area under the concentration - time curve over the dosing interval
AV	Atrioventricular
BA	Bioavailability
BBS	Biospecimen Banking System
BE	Bioequivalence
β-hCG	beta-human chorionic gonadotropin
BMI	Body mass index
BP	blood pressure
Bpm	beats per minute
BUN	blood urea nitrogen
C_{av}	average concentration
CD	Crohn's disease
CFR	Code of Federal Regulations
CHF	congestive heart failure
COVID-19	Coronavirus Disease 2019
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL/F	apparent clearance
C_{max}	maximum observed concentration
CMC	Chemistry, Manufacturing, and Controls
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COX-2	Cyclooxygenase-2
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSF	cerebrospinal fluid
CSR	clinical study report

Abbreviation	Term
CT	clinical trial
CT	computed tomography
CTMS	clinical trial management system
C_{trough}	predose concentration during multiple dosing
CV	Cardiovascular
CV	Coefficient of variation
DCT	data collection tool
DILI	drug-induced liver injury
DMARD	Disease modifying anti-rheumatic drug
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRE	disease-related event
DU	dispensable unit
EBV	Epstein Barr virus
EC	ethics committee
ECL	Electrochemoluminescent
ECG	Electrocardiogram
eCRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
ELISA	enzyme linked immunosorbent assay
EMA	European Medicines Agency
EoT	End of Treatment
ET	Early Termination
EU	European Union
EudraCT	European Clinical Trials Database
EULAR	European League Against Rheumatism
FAP	Final Approved Protocol
FDA	United States (US) Food and Drug Administration
FK506	Tacrolimus
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
H	Hour
HbA_{1c}	hemoglobin A_{1c}
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCG	human chorionic gonadotropin
HCL	Hydrogen chloride
HCV	hepatitis C
HCVAb	hepatitis C antibody

Abbreviation	Term
HCV RNA	HCV riboneucleic acid
HEENT	head, eyes, ears, nose and throat
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPV	human papilloma virus
HRT	hormone replacement therapy
HS	hidradenitis suppurativa
IA	intra articular
IB	investigator's brochure
IC	Interchangeability
ICD	informed consent document
ICH	International Council for Harmonisation
ID	Identification
IFU	Instruction for Use
IgG1	Immunoglobulin G1
IM	Intramuscular
IMP	investigational medicinal product
IND	investigational new drug application
Inj	injection
INR	international normalized ratio
IP	investigational product
IP manual	investigational product manual
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ISR	injection-site reactions
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IVIG	IV immunoglobulin
IWRS	interactive Web-based response system
JAK	janus kinase inhibitor
LBBB	left bundle branch block
LDAS	low disease activity state
LFT	liver function test
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MnB	*Neisseria meningitidis* serogroup B
Msec	Millisecond

Abbreviation	Term
MTX	Methotrexate
N/A	not applicable
Nab	neutralizing antibodies
NIMP	noninvestigational medicinal product
NMSC	Non-Melanoma Skin Cancer
NOAEL	no-observed-adverse-effect level
NYHA	New York Heart Association
PACLs	Protocol Administrative Clarification Letters
CCI	[redacted]
PCD	primary completion date
PD	pharmacodynamic(s)
PFS	prefilled syringe
PFP	pre-filled pen
PI	principal investigator
PK	pharmacokinetic(s)
PS	plaque psoriasis
PSA	psoriatic arthritis
PT	prothrombin time
PVC	premature ventricular contraction/complex
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
QFT	QuantiFERON® - TB Gold In-Tube test
Qual	qualitative
RA	rheumatoid arthritis
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product characteristics
SMQ	standardized MedDRA query
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBili	total bilirubin
TEAE	treatment-emergent adverse event
T_{max}	time at which C_{max} occurs
TNF	Tumor necrosis factor
TP	treatment periods

Abbreviation	Term
TP1	treatment period 1
TP2	treatment period 2
TP3	treatment period 3
TP4	treatment period 4
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
USPI	US Prescribing Information
UV	uveitis
WBC	white blood cell
WHO	World Health Organization
Wk	week
WOCBP	woman of childbearing potential

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