Title Page

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR OPEN, PLACEBO-CONTROLLED, DOSE ESCALATING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SINGLE INTRAVENOUS AND MULTIPLE SUBCUTANEOUS AND INTRAVENOUS DOSES OF PF-07261271 IN HEALTHY PARTICIPANTS

Study Intervention Number:	PF-07261271
Study Intervention Name:	NA
US IND Number:	162,077
EudraCT Number:	NA
ClinicalTrials.gov ID:	NCT05536440
Pediatric Investigational Plan Number:	NA
Protocol Number:	C4631001
Phase:	1
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Phase 1 Study to Evaluate the Safety, Tolerability, PK, and PD of PF-07261271 in Healthy Participants

Document History

Document	Version Date
Amendment 2	18 October 2023
Amendment 1	02 March 2023
Original protocol	23 June 2022

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any global protocol administrative change letters(s).

Protocol Amendment Summary of Changes Table

Amendment 2 (18 October 2023)

Overall Rationale for the Amendment: The protocol was amended to add additional laboratory collection timepoints to characterize PK, PD, and immunogenicity better, to clarify aspects of the protocol, and to add administrative changes to align with the latest sponsor guidelines.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Added visit days 211, 241, 301, and 331 for active SAD cohorts to collect PK, ADA/NAb, PD samples, serious and non-serious AE, concomitant medication and contraception updates.	To collect additional data to characterize PK, PD, and immunogenicity better.	Section 1.3, SoA, Table 2
Added visit days 171, 231, 261, 321, and 351 for active MD cohort to collect PK, ADA/NAb, PD samples, serious and non-serious AE, concomitant medication and contraception updates.	To collect additional data to characterize PK, PD, and immunogenicity better.	Section 1.3, SoA, Table 5

Description of Change	Brief Rationale	Section # and Name
Non-substantial Modification(s)		
Removed requirement to follow SAD cohorts through Day 271.	To clarify final follow-up visit is based on emerging data and criteria noted in Section 4.1.1. Refer to PACL dated 18-Jul-2023.	Section 1.1. Synopsis and Section 4.1.1 Part A: Single Ascending Doses in Healthy Participants
Removed requirement to follow MD cohort through Day 291.	To clarify final follow-up visit is based on emerging data and criteria noted in Section 4.1.2. Refer to PACL dated 18-Jul-2023.	Section 1.1. Synopsis and Section 4.1.2 Part B: Multiple Doses in Healthy Participants
Increased total blood sampling volume to 870 mL.	To account for additional sample collection timepoints.	Section 8.1. Administrative Procedures
Replaced "standard operating procedures" with "SOPs".	To align with latest sponsor guidelines.	Section 10.1.4. Data Protection
Updated data sharing time limited from "24 months" to "18 months".	To align with latest sponsor guidelines.	Section 10.1.6. Dissemination of Clinical Study Data
Updated "source data documents" to "source records and documents".	To align with latest sponsor guidelines.	Section 10.1.7. Data Quality Assurance
Updated definition of "study start date".	To align with latest sponsor guidelines	Section 10.1.9. Study and Site Start and Closure
Corrected eGFR term.	Administrative error.	Section 10.10. Appendix 10: Abbreviations

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

PF-07261271 is a [redacted] that is being developed for the treatment of IBD, including UC and CD.

Both p40 and TL1A are clinically validated targets for IBD. The anti-p40 antibody ustekinumab (Stelara®), which blocks both IL-12 and IL-23, has demonstrated efficacy in the treatment of both UC and CD. The anti-TL1A antibody PF-06480605 was shown to be safe and efficacious in a Phase 2a trial in UC, with a statistically significant proportion of patients (38.2%) achieving the primary endpoint of endoscopic improvement (Mayo endoscopic subscore = 0 or 1). Notably in the Phase 2a anti-TL1A study, transcriptomic analysis of inflamed biopsies taken at Week 14 of treatment revealed significant reduction in pro-inflammatory pathways in responders but no significant reduction in Th1 and Th17 inflammatory pathways in non responders, suggesting residual, unattenuated IL-12 and IL-23 inflammatory tone in affected non-responder tissues. The clinical efficacy demonstrated with [redacted] monotherapies highlights the importance of targeting [redacted] for IBD, while leaving room for improvement in rates of clinical response and remission. Based on overlapping and distinct biology of [redacted], PF-07261271 is expected to deliver therapeutic efficacy [redacted], and an acceptable benefit-risk profile.

Protocol Title:

A Phase 1, Randomized, Double-Blind, Sponsor Open, Placebo-Controlled, Dose Escalating Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Intravenous and Multiple Subcutaneous and Intravenous Doses of PF-07261271 in Healthy Participants.

Brief Title: A Phase 1 Study to Evaluate the Safety, Tolerability, PK, and PD of PF-07261271 in Healthy Participants.

Regulatory Agency Identification Number(s):

US IND Number:	162,077
EudraCT Number:	NA
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C4631001
Phase:	1

Rationale:

This is the first time PF-07261271 will be given to humans. The purpose of the study is to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of escalating single and multiple doses of PF-07261271 in healthy participants.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of PF-07261271, following single and multiple doses in healthy adult participants.	• Incidence and severity of TEAEs, SAEs. • Change from baseline in vital signs (BP, PR, and temperature measurements). • Change from baseline in clinical laboratory values (chemistry and hematology including coagulation panel). • Change from baseline in ECG parameters (heart rate, QT, QTc, PR, and QRS intervals).
Secondary:	**Secondary:**

• To characterize the serum exposure of PF-07261271, following single and multiple doses in healthy adult participants.	• PF-07261271 PK parameters as data permit:
	  • Part A (SAD-IV Infusion Dosing): AUC_{last}, AUC_{inf}, C_{max}, T_{max}, and $t_{½}$;
	  • Part B (MD-SC Dosing) or MD cohorts: AUC_{tau}, C_{max}, T_{max}, and $t_{½}$.

• To evaluate the immunogenicity profile of PF-07261271 following single and multiple doses in healthy adult participants.	• Incidence of the development of ADA and, if appropriate, NAb against PF-07261271 following single and multiple doses.

Overall Design:

This is an FIH randomized, double-blind, sponsor-open, placebo-controlled study of the safety, tolerability, PK, and PD following single escalating and multiple doses of PF-07261271 that will be conducted in healthy adult participants (see Figure 1).

Number of Participants:

Approximately 51 participants will be enrolled in the study.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

Age and Sex:

1. Participants aged 18 to 65 years (or the minimum age of consent in accordance with local regulations) at screening.

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, vital sign assessments, laboratory tests, and 12-lead ECGs.

Other Inclusion Criteria:

3. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

Informed Consent:

4. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Additional criterion for optional Japanese cohort only:

5. Participants who have four Japanese biological grandparents born in Japan.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

3. Recent exposure to live or attenuated vaccines within 28 days of the screening visit.

4. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention.

Prior/Concurrent Clinical Study Experience:

5. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 halflives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

6. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

7. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate- age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third- degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the uncorrected QT interval is >450 ms, this interval should be rate-corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

8. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

   - AST **or** ALT level ≥1.5 × ULN;
   - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

Other Exclusion Criteria:

9. History of drug or alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit, or 3 ounces (90 mL) of wine).

    - A positive urine drug test. A positive test for cannabinoid-based compounds (eg, THC, CBD, etc) will not be considered exclusionary.

    - Participants with >20 cigarettes per day intake or more than 30 pack years.

10. History of sensitivity to heparin or heparin-induced thrombocytopenia.

Study Arms and Duration:

The study has 2 phases: a SAD phase, Part A, and a MD phase, Part B.

Part A (SAD phase):

Within approximately 35 days of the initial screening visit, eligible participants for the single ascending dose period will be enrolled and randomized to receive a single IV infusion of PF-07261271 or placebo. In order to mitigate any unanticipated acute safety risks within the SAD cohorts, sentinel dosing will be implemented in all SAD cohorts (ie, cohorts where the dose being tested is the highest administered in the study to date).

As illustrated in Figure 1, healthy participants in Part A will be randomized sequentially into 4 single dose cohorts (Cohorts 1-4). Participants will be admitted into the CRU the day before dosing and may be required to stay confined in the CRU up to Day 5. For Cohorts 1-4, 7 (an optional SAD cohort), and 8 (an optional Japanese cohort), the final follow-up visit will be determined based on safety and PK data emerging from previous cohort(s).

During the SAD period, escalation to subsequent dose levels will only occur if the sponsor and investigator's review of the available safety and PK data for the previous cohorts suggest that the next dose is likely to have acceptable safety and tolerability. Doses in Part A may be adjusted depending upon the actual exposure of PF-07261271 observed in humans at lower doses. If, based on the observed data, the projected group mean C_{max} for the subsequent dose is >[CCI] µg/mL or the projected group mean [CCI] >[CCI] µg•hr/mL, the prespecified exposure limits prespecified, that dose will not be explored.

In addition, an optional cohort of healthy Japanese participants (Cohort 8, n=5) may be enrolled to receive a single IV or SC dose of PF-07261271 or placebo (active:placebo=4:1). This cohort may be enrolled at the discretion of the sponsor following demonstration that the dose planned for the Japan cohort was safe and well tolerated in a previous cohort.

Part B (MD phase):

One multiple SC dose cohort and 1 optional multiple dose cohort (SC or IV) in healthy participants are planned. Initiation of the first multiple doses cohort (Cohort 5) will occur following sponsor and investigator's review of available safety and PK from a SAD dose level that provides higher exposures ([CCI] and C_{max}) than projected for Cohort 5 after [CCI] repeat doses in addition to the accumulated safety and PK from the previous SAD cohorts. The starting dose of [CCI] mg for the initial multiple dose cohort may be adjusted, based on emerging safety and PK data from the single dose cohorts. Doses and/or dosing regimens planned may be modified based on emerging data from earlier single and multiple dose cohorts. If the exposures in the subsequent dose is projected to exceed the prespecified exposure limits, after repeat doses, that dose will not be explored.

Healthy participants who are enrolled into the multiple dose cohorts (Cohorts 5 and 6) will be randomized 6:2 to receive PF-07261271 or placebo [CCI]. Participants will be confined to the CRU starting on the day prior to dosing up to 5 days after the first dose of study intervention administration and 48 hours [CCI]. The final follow-up visit will be determined based on safety and PK data emerging from previous SAD and MD cohort(s), which may be earlier or later than Day 471 (±7 days).

Intervention Name	**PF-07261271**	**Placebo**
Arm Name (group of participants receiving a specific treatment or no treatment)	Experimental: intravenous, various single doses administered to various cohorts Experimental: subcutaneous, various multiple doses administered to various cohorts	Placebo: intravenous Placebo: subcutaneous
Unit Dose Strength(s)	PF-07261271 [CCI] mg/mL vial when reconstituted	Liquid in vial
Route of Administration	IV SC	IV SC
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP

Study Arm(s)				
Arm Title	Experimental: intravenous, various single doses administered to various cohorts	Experimental: subcutaneous, intravenous, various multiple doses administered to various cohorts	Placebo: intravenous	Placebo: subcutaneous, intravenous
Arm Type	Experimental	Experimental	Placebo	Placebo
Arm Description	Participants in various cohorts will receive single doses of PF-07261271 according to schema on Day 1	Participants in various cohorts will receive repeat doses of PF-07261271 according to schema [redacted]	Participants in various cohorts will receive single doses of placebo according to schema on Day 1	Participants in various cohorts will receive repeat doses of placebo according to schema [redacted]

Statistical Methods:

All participants who receive at least 1 dose of study intervention (safety population) will be included in the safety analyses. All safety data will be summarized through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations.

Methodology for summarization and statistical analyses of the data collected in this study is outlined in this protocol and further detailed in the 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.

No interim analysis is planned.

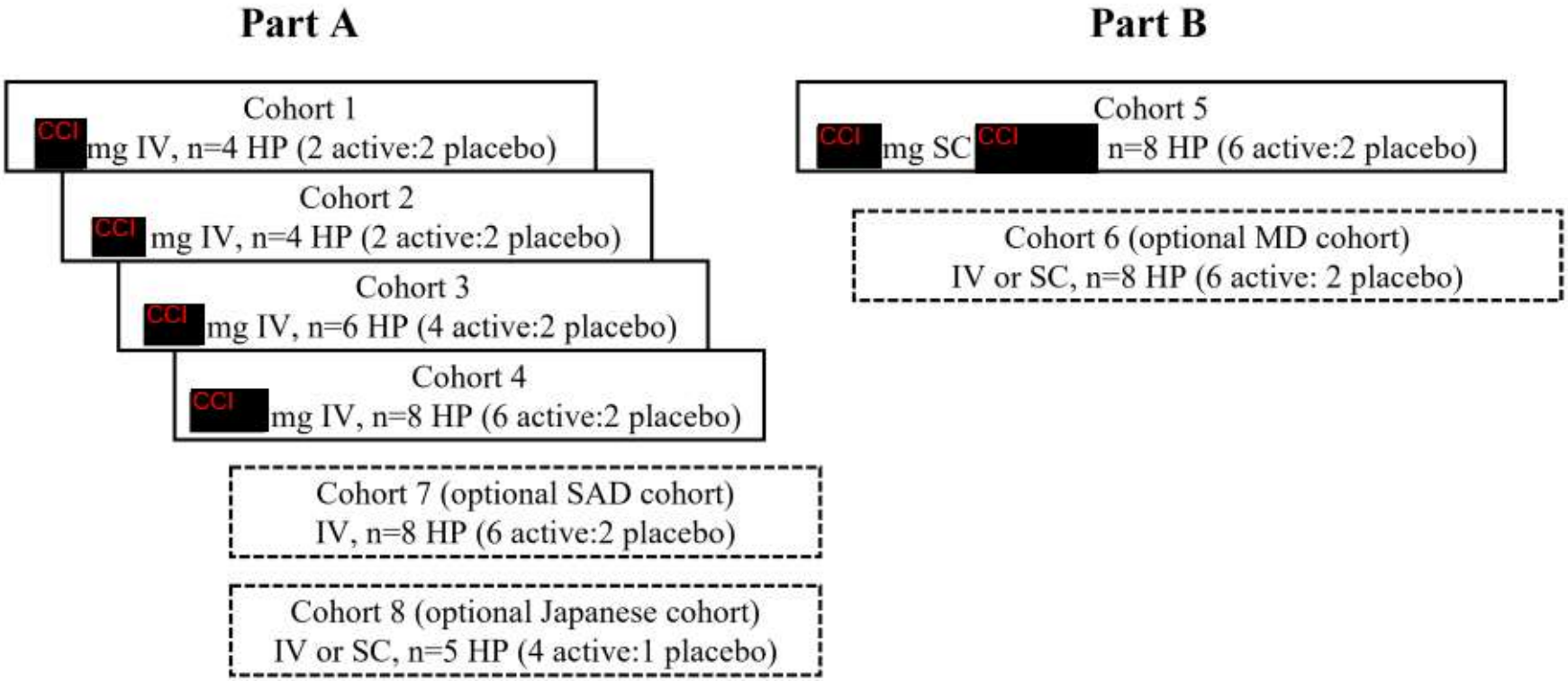
Ethical Considerations:

No clinical benefit is anticipated for healthy participants. However, participants may benefit society by contributing to the process of developing new therapies in an area of unmet need. Additionally, participants will benefit from medical evaluations/assessments associated with study procedures (eg, physical exam, ECG, labs, etc).

The risks involved are similar to risks with other large molecule therapeutics. Given the measures taken to minimize risk and burden related to diagnostic, and monitoring procedures to healthy participants, the overall potential benefit/risk of PF-07261271 is considered to be favorable.

1.2. Schema

Figure 1. C4631001 Study Design



Doses shown are planned doses and may be modified based on emerging data from previous cohorts. Cohort 7 is an optional SAD cohort with dose to be determined based on emerging data from previous SAD cohorts. Cohort 6 is an optional MD cohort with doses, route, and frequency to be determined by emerging data from SAD and MD cohorts. Cohort 8 is an optional cohort that will be conducted in Japanese healthy participants with dose and route of administration to be determined based on emerging data from previous cohorts.

1.3. Schedule of Activities

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.

Table 1. Study Schedule of Assessment for Single Ascending Doses (Part A) in Healthy Participants (Cohorts 1-4 and 7) and Optional Japanese Cohort (Cohort 8) From Screening Through Day 15

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Clinical Confinement											Outpatient Visit		Early Discontinuation (before Day 15)	Notes
Days Relative to Day 1	Day -35 to Day -2	Day -1	Day 1							Day 2	Day 3	Day 4	Day 5	Day 8 (±1 day)	Day 15 (±2 days)		• All screening should be done ≤35 days before the first dose. • Day relative to start of study intervention (Day 1).
Hours After Dose			-2 h to -5 min	0 h	EoI	2 h	4 h	8 h	12 h	24 h	48 h	72 h	96 h				• Collect EoI and 2-hour procedures as close to collection time as possible. All other time point procedures should be within ±10% of collection time (ie, 4 hours ±24 minutes, etc).
Informed consent	X																• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
CRU confinement		X	→	→	→	→	→	→	→	→	→	→	X				• See Section 4.1.1 regarding potential CCI discharge.
Randomization		X															• Randomization may be performed on Day -1, or prior to Day 1 dosing.
Inclusion/exclusion criteria	X	X															
Medical/medication history	X																

Table 1. Study Schedule of Assessment for Single Ascending Doses (Part A) in Healthy Participants (Cohorts 1-4 and 7) and Optional Japanese Cohort (Cohort 8) From Screening Through Day 15

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Clinical Confinement												Outpatient Visit		Early Discontinuation (before Day 15)	Notes
Days Relative to Day 1	Day -35 to Day -2	Day -1	Day 1							Day 2	Day 3	Day 4	Day 5	Day 8 (±1 day)	Day 15 (±2 days)		• All screening should be done ≤35 days before the first dose. • Day relative to start of study intervention (Day 1).
Hours After Dose			-2 h to -5 min	0 h	EoI	2 h	4 h	8 h	12 h	24 h	48 h	72 h	96 h				• Collect EoI and 2-hour procedures as close to collection time as possible. All other time point procedures should be within ±10% of collection time (ie, 4 hours ±24 minutes, etc).
History of drug, alcohol, and tobacco use	X																
Demography	X																
Physical exam	X	X									X				X	X	• Full physical exam may be done at screening or deferred to Day -1. If done at screening, brief exam will be done on Day -1. A brief or full physical exam may be done, at the discretion of the investigator, at any visit.
Height, body weight	X																
12-Lead ECG	X		X		X	X		X	X	X			X		X	X	• During clinical confinement, ECGs will be collected in triplicate approximately 2-4 minutes apart at all time points. At the Day 1 predose time period, triplicate ECGs will be collected 3 times (eg, at -2 h, -1.5 h and -1 h). Single ECGs will be collected at all other designated visits.
Blood pressure, pulse rate, and temperature	X		X		X			X		X			X		X	X	• Supine blood pressure. • Temperature check for COVID-19 may be done daily during confinement or per site policy.
Respiratory rate			X		X			X									
Contraception check	X	X											X	X	X	X	
Prior/concomitant medication	X	X	→	→	→	→	→	→	→	→	→	→	→	X	X	X	
COVID-19 questionnaire	X	X															• Per local site procedure.

Table 1. Study Schedule of Assessment for Single Ascending Doses (Part A) in Healthy Participants (Cohorts 1-4 and 7) and Optional Japanese Cohort (Cohort 8) From Screening Through Day 15

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Clinical Confinement												Outpatient Visit		Early Discontinuation (before Day 15)	Notes
Days Relative to Day 1	Day -35 to Day -2	Day -1	Day 1							Day 2	Day 3	Day 4	Day 5	Day 8 (±1 day)	Day 15 (±2 days)		• All screening should be done ≤35 days before the first dose. • Day relative to start of study intervention (Day 1).
Hours After Dose			-2 h to -5 min	0 h	EoI	2 h	4 h	8 h	12 h	24 h	48 h	72 h	96 h				• Collect EoI and 2-hour procedures as close to collection time as possible. All other time point procedures should be within ±10% of collection time (ie, 4 hours ±24 minutes, etc).
COVID-19 testing	X	X															• Additional COVID-19 testing may be performed per local site practice, see Section 8.3.5.
CCI																	
Infusion/injection site reaction assessment			X		X	X	X	X	X	X	X	X	X			X	
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	• See Section 8.4.3 for follow-up AE and SAE assessments.
Safety laboratory assessments	X	X								X			X	X	X	X	• See Appendix 2.
Pregnancy test (WOCBP only)	X	X													X	X	• Serum pregnancy test required at Screening, see Section 8.3.6.
Serum FSH	X																• FSH test for female participants with no menses for 12 consecutive months <60 years of age to confirm postmenopausal status (see Section 10.4.3).
Urine drug test	X																• Minimum requirement for drug screening includes cocaine, opiates/opioids, benzodiazepines, and amphetamines.
HIV, HBsAg, HBcAb, HBsAb, HCVAb, and QuantiFERON TB Gold	X																

Table 1. Study Schedule of Assessment for Single Ascending Doses (Part A) in Healthy Participants (Cohorts 1-4 and 7) and Optional Japanese Cohort (Cohort 8) From Screening Through Day 15

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Clinical Confinement											Outpatient Visit		Early Discontinuation (before Day 15)	Notes
Days Relative to Day 1	Day -35 to Day -2	Day -1	Day 1							Day 2	Day 3	Day 4	Day 5	Day 8 (±1 day)	Day 15 (±2 days)		• All screening should be done ≤35 days before the first dose. • Day relative to start of study intervention (Day 1).
Hours After Dose			-2 h to -5 min	0 h	EoI	2 h	4 h	8 h	12 h	24 h	48 h	72 h	96 h				• Collect EoI and 2-hour procedures as close to collection time as possible. All other time point procedures should be within ±10% of collection time (ie, 4 hours ±24 minutes, etc).
Retained Research Sample for Genetics (Prep D1)		X															• Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.
Retained Research Sample for Biomarkers (Prep B1.5)			X												X	X	
Retained Research Sample for Biomarkers (Prep B2.5)			X												X	X	
Retained Research Samples for Biomarkers (Prep R1)			X												X	X	
Pharmacokinetic blood sampling			X		X	X	X	X	X	X	X		X	X	X	X	• Post-dose collection time points are calculated from start of infusion time (See Section 8.5 for additional details on PK sampling).
Immunogenicity (ADA, NAb)			X											X	X	X	
CCI																	

Table 2. Study Schedule of Assessment for Follow-up Visits in Single Ascending Doses (Part A) in Healthy Participants (Cohorts 1-4 and 7) and Optional Japanese Cohort (Cohort 8) From Day 32 Until Discharge

Visit Identifier Abbreviations used in this table may be found in Appendix 10.											Early Discontinuation (through Day 451)	Notes
Days Relative to Day 1	**Day 32**	**Day 46**	**Day 61**	**Day 91**	**Day 181**	**Day 211 and 241**	**Day 271**	**Day 301 and 331**	**Day 361**	**Day 451**		• No activities are planned for Days 16-31. • Day relative to start of study intervention (Day 1). • Visits from Day 32 through Day 361 may be completed as home visits. Telehealth visits may occur under extenuating circumstances. • If the emerging data project that half-life is longer than approximately 85 day, participants will be asked to return for additional follow-up visit(s) at up to 3-month intervals beyond the last follow-up visit until 1 of the discharge criteria in Section 4.1.1 is met.
Visit Window	**±3 days**	**±5 days**	**±5 days**	**±5 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**		
Physical exam	X		X	X	X		X		X	X	X	• Full physical examination is required at discharge. A brief or full physical examination may be performed at any visit, at the discretion of the investigator.
12-Lead ECG	X		X	X	X		X		X	X	X	• Single ECGs will be collected.
Blood pressure and pulse rate	X	X	X	X	X		X		X	X	X	• Supine blood pressure.
Body weight							X			X	X	
Contraception check	X	X	X	X	X	X	X	X	X	X	X	
Prior/concomitant medication	X	→	→	→	→	→	→	→	→	→	X	
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	X	• See Section 8.4.3 for follow-up AE and SAE assessments.
Safety laboratory	X	X	X	X	X		X		X	X	X	• See Appendix 2. • Safety labs for additional follow-up visits may be done at the discretion of the investigator.
Pregnancy test (WOCBP only)	X		X	X	X		X		X	X	X	
Retained Research Samples for Biomarkers (Prep B1.5)										X	X	
Retained Research Samples for Biomarkers (Prep B2.5)										X	X	

Table 2. Study Schedule of Assessment for Follow-up Visits in Single Ascending Doses (Part A) in Healthy Participants (Cohorts 1-4 and 7) and Optional Japanese Cohort (Cohort 8) From Day 32 Until Discharge

Visit Identifier Abbreviations used in this table may be found in Appendix 10.											Early Discontinuation (through Day 451)	Notes
Days Relative to Day 1	Day 32	Day 46	Day 61	Day 91	Day 181	Day 211 and 241	Day 271	Day 301 and 331	Day 361	Day 451		• No activities are planned for Days 16-31. • Day relative to start of study intervention (Day 1). • Visits from Day 32 through Day 361 may be completed as home visits. Telehealth visits may occur under extenuating circumstances. • If the emerging data project that half-life is longer than approximately 85 day, participants will be asked to return for additional follow-up visit(s) at up to 3-month intervals beyond the last follow-up visit until 1 of the discharge criteria in Section 4.1.1 is met.
Visit Window	±3 days	±5 days	±5 days	±5 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days		
Retained Research Samples for Biomarkers (Prep R1)										X	X	
Pharmacokinetic blood sampling	X	X	X	X	X	X	X	X	X	X	X	
Immunogenicity (ADA, NAb)	X	X	X	X	X	X	X	X	X	X	X	
CCI												
Dischage from study										X		• Follow-up visit schedule may be changed based on emerging safety, PK, and biomarker data from previous cohorts. See Section 4.1.1. For the final study visit, Day 451 activities should be performed as described in the table.

Table 3. Study Schedule of Assessment for Multiple Doses (Part B) in Healthy Participants (Cohorts 5 and 6) From Screening Through Day 15 (CCI)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Clinical Confinement											Outpatient Visit		Early Discontinuation (before Day 15)	Notes
Days Relative to Day 1	Day -35 to Day -2	Day -1	Day 1							Day 2	Day 3	Day 4	Day 5	Day 8	Day 15		• All screening should be done ≤35 days before the first dose. • Day relative to start of study intervention (Day 1).
Hours After Dose			-2 h to -5 min	0 h	1 h	2 h	4 h	8 h	12 h	24 h	48 h	72 h	96 h	±1 days	±2 days		• All procedures at 1- and 2-hour time points, should be completed within ±15 minutes. All other time point procedures should be within ±10% of collection time (ie, 4 hours ±24 minutes, etc).
Informed consent	X																• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
CRU confinement		X	→	→	→	→	→	→	→	→	→	→	X				• See Section 4.1.2 regarding potential CCI discharge.
Randomization		X															• Randomization may be performed Day -1, or prior to Day 1 dosing.
Inclusion/exclusion criteria	X	X															
Medical/medication history	X																
History of drug, alcohol, and tobacco use	X																
Demography	X																
Physical exam	X	X									X			X	X	X	• Full physical exam may be done at screening or deferred to Day -1. If done at screening, brief exam will be done on Day -1. A brief or full physical exam may be done, at the discretion of the investigator, at any visit.
Height, body weight	X																
12-Lead ECG	X		X		X	X		X	X	X			X	X	X	X	• During clinical confinement, ECGs will be collected in triplicate approximately 2-4 minutes apart at all time points. At the Day 1 predose time period, triplicate ECGs will be collected 3 times (eg, at -2 h, -1.5 h and -1 h). Single ECGs will be collected at all other designated visits.

Table 3. Study Schedule of Assessment for Multiple Doses (Part B) in Healthy Participants (Cohorts 5 and 6) From Screening Through Day 15 (CCI)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Clinical Confinement											Outpatient Visit		Early Discontinuation (before Day 15)	Notes
Days Relative to Day 1	Day -35 to Day -2	Day -1	Day 1							Day 2	Day 3	Day 4	Day 5	Day 8	Day 15		• All screening should be done ≤35 days before the first dose. • Day relative to start of study intervention (Day 1).
Hours After Dose			-2 h to -5 min	0 h	1 h	2 h	4 h	8 h	12 h	24 h	48 h	72 h	96 h	±1 days	±2 days		• All procedures at 1- and 2-hour time points, should be completed within ±15 minutes. All other time point procedures should be within ±10% of collection time (ie, 4 hours ±24 minutes, etc).
Blood pressure, pulse rate, and temperature	X		X		X			X		X			X	X	X	X	• Supine blood pressure. Temperature check for COVID-19 may be done daily during confinement or per site policy.
Respiratory rate			X		X			X									
Contraception check	X	X											X	X	X	X	
Prior/concomitant medication	X	X	→	→	→	→	→	→	→	→	→	→	→	X	X	X	
COVID-19 questionnaire	X	X															• Per local site procedure.
COVID-19 testing	X	X															• Additional COVID-19 testing may be performed per local site practice, see Section 8.3.5.
CCI																	
Infusion/injection site reaction assessment			X		X	X	X	X	X	X	X	X	X			X	
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	• See Section 8.4.3 for follow-up AE and SAE assessments.
Safety laboratory assessments	X	X								X			X	X	X	X	• See Appendix 2.
Pregnancy test (WOCBP only)	X	X														X	• A serum pregnancy test is required at Screening, see Section 8.3.6.
Serum FSH	X																• FSH test for female participants with no menses for 12 consecutive months <60 years of age to confirm postmenopausal status (see Section 10.4.3).
Urine drug testing	X																• Minimum requirement for drug screening includes cocaine, opiates/opioids, benzodiazepines, and amphetamines.

Table 3. Study Schedule of Assessment for Multiple Doses (Part B) in Healthy Participants (Cohorts 5 and 6) From Screening Through Day 15 (CCI)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Clinical Confinement											Outpatient Visit		Early Discontinuation (before Day 15)	Notes
Days Relative to Day 1	Day -35 to Day -2	Day -1	Day 1						Day 2	Day 3	Day 4	Day 5	Day 8	Day 15		• All screening should be done ≤35 days before the first dose. • Day relative to start of study intervention (Day 1). • All procedures at 1- and 2-hour time points, should be completed within ±15 minutes. All other time point procedures should be within ±10% of collection time (ie, 4 hours ±24 minutes, etc).
Hours After Dose			-2 h to -5 min	0 h	1 h	2 h	4 h	8 h	12 h	24 h	48 h	72 h	96 h	±1 days	±2 days		
HIV, HBsAg, HBcAb, HBsAb, HCVAb and QuantiFERON TB Gold	X															
Retained Research Sample for Genetics (Prep D1)		X	X													• Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. Prep D1 sample may be collected on Day -1, or prior to Day 1 dosing.
Retained Research Samples for Biomarkers (Prep B1.5)			X											X	X	
Retained Research Samples for Biomarkers (Prep B2.5)			X											X	X	
Retained Research Samples for Biomarkers (Prep R1)			X											X	X	
Pharmacokinetic blood sampling for SC cohorts			X						X		X		X	X	X	X	
Pharmacokinetic blood sampling for IV cohorts			X		X	X	X		X		X		X	X	X	X	• CCI [redacted]
Immunogenicity (ADA, NAb)			X											X	X	X	

Table 3. Study Schedule of Assessment for Multiple Doses (Part B) in Healthy Participants (Cohorts 5 and 6) From Screening Through Day 15 (CCI)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Clinical Confinement											Outpatient Visit		Early Discontinuation (before Day 15)	Notes
Days Relative to Day 1	Day -35 to Day -2	Day -1	Day 1							Day 2	Day 3	Day 4	Day 5	Day 8	Day 15		• All screening should be done ≤35 days before the first dose. • Day relative to start of study intervention (Day 1). • All procedures at 1- and 2-hour time points, should be completed within ±15 minutes. All other time point procedures should be within ±10% of collection time (ie, 4 hours ±24 minutes, etc).
Hours After Dose			-2 h to -5 min	0 h	1 h	2 h	4 h	8 h	12 h	24 h	48 h	72 h	96 h	±1 days	±2 days		
CCI																	

Table 4. Study Schedule of Assessment for Multiple Doses (Part B) in Healthy Participants (Cohorts 5 and 6) From Day 28 Through Day 36 (CCI)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Clinical Confinement										Outpatient Visit	Early Discontination (between Day 28 and Day 36)	Notes
Days Relative to Day 1	Day 28	Day 29							Day 30	Day 31	Day 36±3 days		• No activities are planned for CCI . • Day relative to start of study intervention (Day 1).
Hours After Dose		-2 h to -5 min	0 h	1 h	2 h	4 h	8 h	12 h	24 h	48 h			• All procedures at 1- and 2-hour time points, should be completed within ±15 minutes. All other time point procedures should be within ±10% of collection time (ie, 4 hours ±24 minutes, etc).
CRU confinement	X	→	→	→	→	→	→	→	→	X			
Physical exam	X									X		X	• Full or brief physical examination may be done at CCI at the discretion of the investigator. A physical examination may be performed, at the discretion of the investigator, at any visit.
12-lead ECG		X		X	X		X	X	X		X	X	• During clinical confinement, ECGs will be collected in triplicate approximately 2-4 minutes apart at all time points. Single ECGs will be collected at all other designated visits.
Body weight	X												
Blood pressure, pulse rate, and temperature		X		X			X		X		X	X	• Supine blood pressure. • Temperature check for COVID-19 may be done daily during confinement or per site policy.
Contraception check	X										X	X	
Prior/concomitant medication	X	→	→	→	→	→	→	→	→	→	→	X	
COVID-19 questionnaire	X												• Per local site procedure.
COVID-19 testing	X												• Additional COVID-19 testing may be performed per local site practice, see Section 8.3.5.
CCI													
Infusion/injection site reaction assessment		X		X	X	X	X	X	X	X		X	
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	X	• See Section 8.4.3 for follow-up AE and SAE assessments.
Safety laboratory	X								X	X	X	X	• See Appendix 2.
Pregnancy test (WOCBP only)	X										X	X	

Table 4. Study Schedule of Assessment for Multiple Doses (Part B) in Healthy Participants (Cohorts 5 and 6) From Day 28 Through Day 36 (CCI)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Clinical Confinement									Outpatient Visit	Early Discontination (between Day 28 and Day 36)	Notes
Days Relative to Day 1	Day 28	Day 29						Day 30	Day 31	Day 36±3 days		• No activities are planned for CCI . • Day relative to start of study intervention (Day 1). • All procedures at 1- and 2-hour time points, should be completed within ±15 minutes. All other time point procedures should be within ±10% of collection time (ie, 4 hours ±24 minutes, etc).
Hours After Dose		-2 h to -5 min	0 h	1 h	2 h	4 h	8 h	12 h	24 h	48 h			
Urine drug test	X											• Minimum requirement for drug screening includes cocaine, opiates/opioids, benzodiazepines, and amphetamines.
Retained Research Samples for Biomarkers (Prep B1.5)											X	
Retained Research Samples for Biomarkers (Prep B2.5)											X	
Retained Research Samples for Biomarkers (Prep R1)											X	
Pharmacokinetic blood sampling for SC cohorts		X						X		X	X	X	
Pharmacokinetic blood sampling for IV cohorts		X		X	X	X		X		X	X	X	• CCI [redacted]
Immunogenicity (ADA, NAb)		X									X	
CCI [redacted]												

Table 5. Schedule of Activities in Part B (MD Cohort 5) and Optional MD Cohort (Cohort 6) From Day 51 Until Discharge

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Follow-up Visits											Early Discontinuation (through Day 471)	Notes
Days Relative to Day 1	Day 51	Day 66	Day 81	Day 111	Day 171	Day 201	Day 231 and 261	Day 291	Day 321 and 351	Day 381	Day 471		• No activities are planned for Days 36-50. • Day relative to start of study intervention (Day 1). • Visits from Day 51 through Day 381 may be completed as home visits. Telehealth visits may occur under extenuating circumstances. • Participants may also be required to attend additional follow-up visits if the emerging data project that half-life is longer than approximately 85 days. Under these circumstances, participants will be asked to return for additional follow-up visit(s) at up to 3-month intervals beyond the last follow-up visit to cover until 1 of the discharge criteria in Section 4.1.2 is met.
Visit Window	±3 days	±5 days	±5 days	±5 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days		
Physical examination	X		X	X		X		X		X	X	X	• Full physical examination is required at discharge. A brief or full physical examination may be performed at any visit, at the discretion of the investigator.
Blood pressure and pulse rate	X	X	X	X		X		X		X	X	X	
Body weight								X			X	X	
Single 12-lead ECG	X		X	X		X		X		X	X		
Safety laboratory	X	X	X	X		X		X		X	X	X	• See Appendix 2. • Safety labs for additional follow-up visits may be done at the discretion of the investigator for cohorts currently in the study.
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	
Immunogenicity (ADA, NAb)	X	X	X	X	X	X	X	X	X	X	X	X	
CCI													
Retained research samples for biomarkers (Prep B2.5)											X	X	
Retained research samples for biomarkers (Prep R1)											X	X	

Table 5. Schedule of Activities in Part B (MD Cohort 5) and Optional MD Cohort (Cohort 6) From Day 51 Until Discharge

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Follow-up Visits											Early Discontinuation (through Day 471)	Notes
Days Relative to Day 1	Day 51	Day 66	Day 81	Day 111	Day 171	Day 201	Day 231 and 261	Day 291	Day 321 and 351	Day 381	Day 471		• No activities are planned for Days 36-50. • Day relative to start of study intervention (Day 1). • Visits from Day 51 through Day 381 may be completed as home visits. Telehealth visits may occur under extenuating circumstances. • Participants may also be required to attend additional follow-up visits if the emerging data project that half-life is longer than approximately 85 days. Under these circumstances, participants will be asked to return for additional follow-up visit(s) at up to 3-month intervals beyond the last follow-up visit to cover until 1 of the discharge criteria in Section 4.1.2 is met.
Visit Window	±3 days	±5 days	±5 days	±5 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days		
Retained research samples for biomarkers (Prep B1.5)											X	X	
Contraception check	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test (WOCBP only)		X	X	X		X		X		X	X	X	
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	X	• See Section 8.4.3 for follow-up AE and SAE assessments.
Concomitant medications	X	→	→	→	→	→	→	→	→	→	→	X	
Discharge from study											X		• Follow-up visit schedule may be changed based on emerging safety, PK, and biomarker data from previous cohorts. See Section 4.1.2. For the final study visit, Day 471 activities should be performed as described in the table.

2. INTRODUCTION

PF-07261271 is a recombinant humanized [redacted] antibody that combines [redacted], and [redacted] and is currently being developed for treatment of patients with moderate to severe IBD.

2.1. Study Rationale

This is the first time PF-07261271 will be given to humans. The purpose of the study is to evaluate the safety, tolerability, PK, and PD of escalating single and multiple doses of PF-07261271 in healthy participants.

2.2. Background

IBD is a chronic relapsing inflammatory illness of the intestine[1] with an age-standardized prevalence rate of 84.3 per 100,000 population, affecting 6.8 million people globally.[2] IBD is categorized into two different disorders: CD and UC. Commonly reported symptoms of IBD include diarrhea, fatigue, abdominal pain and cramping, unintended weight loss and blood in stool.[3] Treatment for mild to moderate IBD consists of mesalamine, corticosteroids, and immunosuppressants to manage induction and maintenance of remission.[4] For moderate to severe IBD, the first line treatment has been anti-TNFα antibody therapy for over 15 years.[5] Rates of failure to achieve remission with anti-TNFα therapy is high, with up to 30% of patients who experience primary non-response and up to 46% of patients who lose response over time.[6] Additional second line immune-targeted therapies are also in use for moderate to severe IBD including antibodies anti-p40 ustekinumab[7,8] and anti-α4β7 integrin vedolizumab[9,10] approved for both UC and CD. Small molecule Janus kinase inhibitors, tofacitinib[11] and upadacitinib[12], and S1PR modulator ozanimod[13] are also approved for use in UC. Despite a growing number of treatment options for IBD, rates of remission in induction trials are still less than 50%,[14] highlighting the high unmet need for safe and effective therapeutics that target the range of underlying disease mechanisms to drive improved efficacy.

p40 is a shared subunit of the heterodimeric pro-inflammatory cytokines IL-12 and IL-23, which activate Th1 and Th17 inflammatory pathways, respectively.[15,16,17,18] Signaling mediators of both IL-12 and IL-23 pathways are strongly associated with IBD at the genetic level[19], and transcripts of IL-12 and IL-23 are significantly upregulated in inflamed IBD mucosal tissue.[20,21,22] The anti-p40 antibody ustekinumab (Stelara®), which blocks both IL-12 and IL-23, has demonstrated efficacy in the treatment of both UC and CD.[7,8] Despite its activity, there is still room for improvement in the rates of clinical response during induction with ustekinumab and durable remission with maintenance treatment.[7,8]

TL1A, a member of the TNF superfamily, is a cytokine expressed under inflammatory conditions and can synergize with IL-12 and IL-23 to enhance Th1 and Th17 inflammation[23,24] TL1A can also promote cytokine production in memory T cells independently of IL-12 and IL-23[25] and is described to promote intestinal fibrosis[26,27,28] and induce epithelial damage responses.[29,30] Genome wide association studies point to genetic links to TL1A and IBD susceptibility[31,32,33,34,35] and TL1A expression is elevated in inflamed

IBD tissues.[36,37] The anti-TL1A antibody PF-06480605 was shown to be safe and efficacious in a Phase 2a trial in UC,[38] with a statistically significant proportion of patients (38.2%) achieving the primary end point of endoscopic improvement (Mayo endoscopic subscore = 0 or 1) (NCT02840721).[38] Notably in the Phase 2a anti-TL1A study, transcriptomic analysis of inflamed biopsies taken at Week 14 of treatment revealed significant reduction in pro-inflammatory pathways in responders, but no significant reduction in Th1 and Th17 inflammatory pathways in non responders, suggesting residual, unattenuated IL-12 and IL-23 inflammatory tone in affected non-responder tissues.[39]

The clinical efficacy demonstrated with CCI monotherapies highlights the importance of targeting CCI for IBD, while leaving room for improvement in rates of clinical response and remission. PF-07261271 is an CCI is a biotherapeutic combining high affinity human binding domains against CCI. The PF-07261271 CCI was engineered to minimize effector function and extend in vivo half-life to provide a potent and dose-convenient treatment for IBD. Based on overlapping and distinct biology of CCI, PF-07261271 is expected to deliver therapeutic efficacy CCI, and an acceptable benefit-risk profile.

2.2.1. CCI

2.2.1.1. CCI

CCI

CCI [redacted]

2.2.1.2. CCI [redacted]

2.2.1.3. CCI [redacted]

2.2.1.4. CCI [redacted]

2.2.1.5. CCI [redacted]

2.2.1.6. CCI [redacted]

2.2.2. CCI [redacted]

2.2.3. CCI [redacted]

2.2.4. Nonclinical Safety

The nonclinical toxicology package for PF-07261271 included a 13-week repeat-dose GLP toxicity study in cynomolgus monkeys, which is the only pharmacologically-relevant species. PF-07261271 administration at doses up to CCI mg/kg by IV injection every 2 weeks produced no adverse effects. The CCI mg/kg/dose (IV) exposure in monkeys at the NOAEL corresponds to 17× and 13× the predicted human C_{max} and C_{av}, respectively, at a dose of CCI mg administered IV CCI, a dose predicted to have a clinical effect and target coverage >99%.

Additional studies conducted to support nonclinical development, including a tissue cross-reactivity study and in vitro immunotoxicity C1q and FcγR binding assays, did not identify specific human risks.

Further details of the nonclinical safety program are provided in the current Investigator's Brochure.

2.2.5. Clinical Overview

PF-07261271 has not been administered to humans. Therefore, there are no clinical safety data with this molecule. However, clinical data indicate that inhibition of IL-12/IL-23 signaling (with the mAb ustekinumab) and TL1A signaling (with PF-06480605) is generally well-tolerated. IL-12/IL-23 signaling with the mAb ustekinumb has an acceptable safety profile in patients with Crohn's disease, ulcerative colitis, plaque psoriasis, and psoriatic arthritis and TL1A signaling (with PF-06480605) has an acceptable safety profile in patients with ulcerative colitis.

2.3. Benefit/Risk Assessment

Study C4631001 is the first time that PF-07261271 will be administered to humans. For healthy participants participating in this single ascending and multiple dose study, no clinical benefit is expected. The purpose of the study is to provide the basis for further clinical development of PF-07261271 as a potential new, pharmacological agent for the treatment of participants with IBD. As of the date of this protocol, no specific human risks have been identified; postulated risks based on nonclinical studies are summarized in Section 2.2.4. The

clinical impact of these potential risks will be minimized through the proposed cautious dose-escalation process wherein higher doses of PF-07261271 will be administered only after lower doses have been found to be well tolerated with an acceptable safety profile. In addition, this study includes standard, intensive, inpatient monitoring of the participants following administration of the study intervention. In light of the anticipated risks and risk mitigations, the overall potential benefit-risk profile of PF-07261271 is expected to be favorable.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07261271 may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-07261271 and Placebo		
Potential for anaphylaxis, infusion reactions, and injection site reactions.	As a protein therapeutic, there is a theoretical potential for immunotoxicity. The potential for PF-07261271 to induce significant antibody responses and for such antibody responses, should they occur, to cause clinically significant sequelae has been assessed based on the physical characteristics of PF-07261271, the planned clinical indication, and the design characteristics of the FIH study C4631001. The overall risk of immunogenicity is projected to be moderate.	Participants will be observed closely for signs and symptoms of infusion reactions and anaphylaxis using standard clinical monitoring, specifically for targeted AEs. Infusion of the study intervention will be interrupted and the rate reduced should mild infusion reactions be observed. If the reactions persist, the infusion will be stopped and the participant observed until stable. In the event of more severe infusion reactions or anaphylaxis, the infusion will be stopped and no re-challenge will be performed. All anaphylactic reactions will be assessed by Sampson's criteria. For SC administration of study treatment, injection site reactions will be monitored, and injection sites rotated.
Risk of infection	All therapeutics designed to reduce inflammation have the potential risk of immune suppression that could result in serious infection.	Participants will be screened and excluded if they have active or latent infections. They will be monitored for evidence of infection with laboratory testing and AE surveillance.
Study Procedures		
Extravasation of PF-07261271 and hematomas may occur after IV dosing.	In some cohorts, PF-07261271 will be administered intravenously.	Skilled nurses or phlebotomists will insert indwelling catheters for infusion and ensure that they are correctly placed in a vein. The infusion site will be monitored for development of hematomas and extravasation. In the event of an issue, the infusion will be interrupted and the catheters will be replaced.
Other		
The COVID-19 pandemic may pose risks to study participation.	Participants may have increased risk of SARS-CoV-2 infection by undergoing a study procedure at a study facility.	Inclusion of COVID-19 specific screening procedures and assessments according to the Schedule of Activities.

2.3.2. Benefit Assessment

No clinical benefit is anticipated for healthy participants. However, participants may benefit society by contributing to the process of developing new therapies in an area of unmet need. Additionally, participants will benefit from medical evaluations/assessments associated with study procedures (eg, physical exam, ECG, labs, etc).

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with PF-07261271 are justified by the anticipated benefits that may be afforded to participants with IBD.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of PF-07261271, following single and multiple doses in healthy adult participants.	• Incidence and severity of TEAEs, SAEs. • Change from baseline in vital signs (BP, PR, and temperature measurements). • Change from baseline in clinical laboratory values (chemistry and hematology including coagulation panel). • Change from baseline in ECG parameters (heart rate, QT, QTc, PR, and QRS intervals).
Secondary:	**Secondary:**

• To characterize the serum exposure of PF-07261271, following single and multiple doses in healthy adult participants.	• PF-07261271 PK parameters as data permit:
	  • Part A (SAD-IV Infusion Dosing): AUC_{last}, AUC_{inf}, C_{max}, T_{max}, and $t_{½}$;
	  • Part B (MD-SC Dosing) or MD cohorts: AUC_{tau}, C_{max}, T_{max}, and $t_{½}$.

• To evaluate the immunogenicity profile of PF-07261271 following single and multiple doses in healthy adult participants.	• Incidence of the development of ADA and, if appropriate, NAb against PF-07261271 following single and multiple doses.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To characterize further the PK profile of PF-07261271 following a single and multiple doses in healthy adult participants.	• PF-07261271 PK parameters, as data permit: CCI [redacted]
• To evaluate the effects of PF-07261271 on exploratory PD biomarkers.	• Change from baseline in blood levels of exploratory PD biomarkers: • Serum proteins: CCI [redacted]

4. STUDY DESIGN

4.1. Overall Design

This is an FIH randomized, double-blind, sponsor-open, placebo-controlled study of the safety, tolerability, PK, and PD following SAD and MD of PF-07261271 that will be conducted in healthy adult participants (see Figure 1).

Up to approximately 51 participants will be enrolled into the study. This will include up to approximately 35 healthy participants (including 5 optional Japanese participants, and 8 participants in the optional SAD cohort) in Part A, and up to approximately 16 healthy participants (including 8 participants in the optional MD cohort) in Part B.

4.1.1. Part A: Single Ascending Doses in Healthy Participants

Approximately 35 healthy adult participants will be enrolled at 1 or more sites into the proposed cohorts listed below. Participants may only participate in 1 cohort.

Participants in the single dose cohorts will be randomized sequentially as follows:

- Cohort 1 (n=4): PF-07261271 CCI mg (n=2) or placebo (n=2), IV;
- Cohort 2 (n= 4): PF-07261271 CCI mg (n=2) or placebo (n=2), IV;
- Cohort 3 (n=6): PF-07261271 CCI mg (n=4) or placebo (n=2), IV;
- Cohort 4 (n=8): PF-07261271 CCI mg (n=6) or placebo (n=2), IV.

An optional dose cohort may be added based on emerging PK and safety/tolerability data. This cohort (Cohort 7) will be randomized as follows:

- Cohort 7 (n=8): single PF-07261271 dose (n=6) or placebo (n=2), IV.

An optional cohort of Japanese participants may be included in the study at the discretion of the sponsor. This cohort (Cohort 8) will be randomized as follows:

- Cohort 8 (n=5): PF-07261271 at dose tested in the sequence above that is determined to be safe and well-tolerated based on emerging data from preceding cohorts (n=4) or placebo (n=1), IV or SC.

Within approximately 35 days of successful completion of the screening process, eligible participants will be randomized to receive a single IV infusion of PF-07261271 or placebo. In order to mitigate any unanticipated acute safety risks within the SAD cohorts, sentinel dosing will be implemented in all SAD cohorts (ie, cohorts where the dose being tested is the highest administered in the study to date). For sentinel dosing, the first 2 participants (1 active:1 placebo) will be dosed and monitored for at least 24 hours to assess safety and tolerability prior to dosing the remaining participants in the cohort. If the dose level for the first 2 sentinel participants is determined to have an acceptable safety and tolerability profile, as judged by the investigator, the remaining participants within the cohort will be dosed.

Single dose cohorts will be enrolled sequentially in a dose escalating fashion starting from the lowest proposed dose ([redacted] mg).

For Cohorts 1-2, if a single participant dosed with active drug meets 1 of the dose escalation stopping criteria mentioned in Section 6.6.1, based on a discussion between sponsor and investigators, 4 more participants may be added to the cohort (2 active:2 placebo). If a cohort is extended with 4 additional participants as described above, dose escalation stopping decisions (Section 6.6.1) will be based on the data from all 4 participants receiving active study intervention.

During Part A (SAD) of the study, escalation to subsequent dose levels will occur following the sponsor and investigator's review of available safety and PK data through study Day 15 for the immediately previous cohort (and emerging clinical and PK data from all enrolled cohorts). Dosing in this part may be adjusted depending upon the actual exposure of PF-07261271 observed in humans at lower doses. If, based on the observed data, the subsequent dose projected group mean C_{max} or [redacted] (data permitting) are higher than the PK exposure limit in humans of [redacted] µg/mL or [redacted] µg•hr/mL, respectively (determined as $1/10^{th}$ of the mean exposures observed at NOAEL in the 3-month cynomolgus monkey toxicity study) that dose will not be explored.

Participants will be admitted into the CRU approximately 1 day prior to dosing and may be required to stay overnight in the study center through completion of Day 5 evaluations as per the SoA. Participants may be discharged after Day 3 procedures have been completed and before Day 5, at the investigator's discretion to accommodate participant scheduling and if considered safe to do so. In this case, Day 5 activities will be conducted as an outpatient. Day 4 activities will be performed only if participants are not discharged after Day 3 procedures. For Cohorts 1-4, 7 and 8, the final follow-up visit will be determined based on safety and PK data emerging from previous cohort(s), which may be earlier than Day 451 (±7 days). The final follow-up visit will be based on at least 1 of the following criteria:

- approximately ≥5 times the observed half-life, OR
- of sufficient duration to have projected exposures decrease below ADA drug tolerance levels, OR
- to a level of exposure at which clinically significant pharmacologic effects on immune function is unlikely (eg, $<IC_{80}$).

Based on emerging data from previous and ongoing single dose cohorts, doses planned may be modified and other doses may be explored in additional cohorts. If the exposures in the subsequent dose is projected to exceed the exposure limits pre-specified, that dose will not be explored.

4.1.2. Part B: Multiple Doses in Healthy Participants

One multiple SC dose cohort of PF-07261271 (CCI mg) and 1 optional multiple dose cohort in healthy participants are planned. Participants in the multiple dose cohorts, will be randomized as follows:

- Cohort 5 (n=8): PF-07261271 CCI mg (n=6) or placebo (n=2), SC CCI ;
- Optional Cohort 6 (n=8): Multiple dose active (n=6) or placebo (n=2), IV or SC.

Initiation of the first multiple dose (Cohort 5) will occur following the sponsor and investigator's review of available safety and PK from a SAD dose level that provides higher exposures than projected for Cohort 5 after CCI repeat doses in addition to the accumulated safety from the previous SAD cohorts. The starting dose of CCI mg for the initial multiple dose cohort may be adjusted, based on emerging safety and PK data from the single dose cohorts. Progression to the next multiple dose may proceed after review of:

- Safety/tolerability data through Day 15 and PK data through Day 8 of the single dose that is no lower than the planned SC dose in next MD cohort;
- Cumulative safety and PK data from the previous single dose cohorts;
- Safety/tolerability and PK data through Day 36 (8 days following the second dose) of the ongoing MD cohort.

If, based on the observed data, projected group mean C_{max} or CCI at the subsequent MD dose level is >CCI µg/mL or >CCI µg/mL respectively following the second dose, that dose will not be explored.

An optional second MD cohort may be enrolled for further investigation of multiple doses as needed in light of emerging safety and PK data. The dose, frequency, and route of administration (IV or SC) for this cohort will be determined following a review of the cumulative safety and PK data from the single dose cohorts and at least through CCI of the CCI mg MD cohort.

Participants will be confined to the CRU starting on the day prior to dosing and through at least CCI
Participants may remain confined in CRU longer at the discretion of the investigator. Participants will return for outpatient visits per the SoA, with the final follow-up visit to be determined based on safety and PK data emerging from previous SAD and MD cohort(s), which may be earlier or later than Day 471 (±7 days). The final follow-up visits will be based on at least 1 of the following criteria:

- approximately ≥5 times the observed half-life, OR
- of sufficient duration to have projected exposures decrease below ADA drug tolerance levels, OR

- to a level of exposure at which clinically significant pharmacologic effects on immune function is unlikely (eg, $<IC_{80}$).

Based on emerging PK data, additional samples may be added to ensure PK is adequately characterized. Based on emerging data from previous and ongoing single and multiple dose cohorts, doses planned may be modified and other doses and/or dosing regimens (eg, Q4W) may be explored in separate cohorts. If the exposures in the subsequent dose are projected to exceed the pre-specified exposure limits, after repeat doses, that dose will not be explored.

4.2. Scientific Rationale for Study Design

Study C4631001 represents the first time PF-07261271 will be administered to humans and hence will employ an escalating dose design initially using single doses and then, once the safety and tolerability of higher single doses has been demonstrated, repeat doses.

Part A (SAD phase) of Study C4631001 will be initiated with a starting dose of CCI mg estimated to have sufficient safety margin (see Justification for Dose, Section 4.3) with dose escalation continuing up to the maximum planned dose as long as projected exposures do not meet any stopping criteria. Part B (MD phase) of the study will be initiated once adequate safety data are available from a higher dose in the SAD phase of the study (see Section 4.1.2). An optional MD cohort is planned to study additional dose levels in case of lower than projected bioavailability and accumulation or SC related safety signals. Study C4631001 uses a placebo-controlled, blinded design to minimize bias which is justified in this early clinical study to provide a reference for safety and tolerability.

The study will be conducted in healthy participants (as defined by the inclusion/exclusion criteria) in order to establish the safety, tolerability, and PK profile of PF-07261271 prior to exposure in patient populations. Although healthy participants can derive no potential benefit from exposure to PF-07261271, there is extensive experience with inhibitors of the cytokines targeted by PF-07261271 that suggests that PF-07261271 will be well-tolerated and have an acceptable safety profile in healthy participants.

PF-07261271 is designed to inhibit sTL1A, IL-12, and IL-23 cytokines, and is expected to bind these cytokines at the site of action. To understand target engagement, total levels of CCI if feasible will be measured.

Both adult male and female participants (including WOCBP) are eligible for enrollment into the study. Since human reproductive safety data are not available for PF-07261271, female participants must either be confirmed to be of non-childbearing potential or, if of childbearing potential, to be using at least 1 form of highly effective method of contraception as detailed in Appendix 4. As an additional safety measure, WOCBP will be required to have a negative pregnancy test prior to randomization and at pre-specified visits per the SoA (including before each repeat dose in the MD cohorts), and contraception checks will be performed at all outpatient visits.

No barrier method of contraception (eg, condom) is warranted for male participants as the potential exposure to PF-07261271 via semen to partners of male participants is anticipated

to be very low. The calculated safety margin between the estimated maternal exposure due to seminal transfer at maximum dose/exposure proposed in human and the MABEL of PF-07261271 is in excess of 10,000-fold. Additionally, PF-07261271 does not have genotoxicity concerns.

Healthy Japanese participants may be enrolled in a separate, optional cohort to provide a preliminary characterization of the safety, tolerability, PK, and PD profile of PF-07261271, to support potential inclusion of Japanese patients in future studies.

Risks to study participants will be minimized by cautious dose escalation in an inpatient setting, with careful assessment and ongoing review of emerging safety data. Additionally, sentinel dosing will be implemented in all SAD cohorts (ie, cohorts where the dose being tested is the highest administered dose in the study to date). Together, the implementation of sentinel dosing in SAD cohorts and the dose escalation rules (Section 6.6.1) are expected to minimize risk to study participants while providing key safety and tolerability information.

Since all mAbs have a potential for immunogenicity, all participants will be monitored closely for signs and symptoms of immunogenicity, including infusion reactions and anaphylaxis. Blood samples will be collected for measurement of ADA in all participants. Samples determined to be positive for ADA may be further characterized for NAbs. If emerging data suggests ADA and/or NAb levels are still significantly associated with any safety concerns present at the last scheduled visits in MD cohorts, additional follow-up visit(s) with ADA/NAb assessment may be required in the next cohorts.

Since this molecule is designed to reduce inflammation, there is a potential risk of infection due to immune suppression. All participants will be screened and excluded if they have active or latent infections, and monitored for evidence of infection with laboratory testing and AE surveillance.

Participants who discontinue prior to completion of the study for other than safety reasons may be replaced, at the discretion of the investigator and sponsor.

For all other cohorts in Parts A and B, the final follow-up visit will be determined based on safety and PK data emerging from previous cohort(s) based on one of the criteria detailed in Sections 4.1.1 and 4.1.2.

4.2.1. Choice of Contraception/Barrier Requirements

Studies to evaluate the developmental toxicity of PF-07261271 have not been conducted. Therefore, the use of a highly effective method of contraception for WOCBP is required (see Appendix 4).

4.2.2. Collection of Retained Research Samples

Retained Research Samples will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

Doses presented are projected based on nonclinical data and may be modified based on emerging safety, tolerability, and PK data.

4.3.1. Prediction of Human PK

PF-07261271 has been engineered for extended half-life in a manner similar to PF-06817024 (ClinicalTrials.gov Identifier: NCT02743871), an anti-IL-33 mAb that has already been studied in humans, and it is expected to have similar PK properties. PK simulations for PF-07261271 assume a 2-compartment PK with the following parameters: CCI [redacted] Based on these parameters, the half-life is projected to be approximately CCI [redacted] days.

4.3.2. Dose Justification for SAD and MD Cohorts

The pathogenic cytokines mediated by TL1A and p40 (IL-12/IL-23) are expressed in inflammatory/disease conditions[20,21,22,36,50] and do not play any key role in maintaining vital functions as demonstrated by cytokine knock-out animal models.[51,52] Therefore, moderate to complete suppression of these cytokines simultaneously over an extended period of time are expected to be safe with no untoward effects in healthy participants where the levels of both TL1A and p40 are not upregulated. This is consistent with clinical experience with the mAbs targeting TL1A (PF-06480605) and p40 (ustekinumab) where existing clinical data support an overall well-tolerated safety profile in healthy participants and IBD patients. Specifically, the anti-TL1A antibody PF-06480605 was shown to be safe and efficacious in the Phase 2a trial in UC[38] (NCT02840721) where participants received 500 mg PF-06480605 every 2 weeks for a total of 7 doses. The PF-06480605 population PK/PD model predicted serum CCI [redacted] throughout the dosing interval for this regimen. Additionally, regular blinded safety review of the ongoing 52 week Phase 2b Study B7541007[53] (NCT04090411) CCI [redacted]

Since its first approval in 2009 to treat psoriasis, ustekinumab (Stelara®) has been extensively studied and is approved for UC, CD, psoriatic arthritis, and plaque psoriasis with a favorable safety profile.[54] Stelara® was safe and well-tolerated even when co-administered with immunomodulators, such as 6-MP, AZA, and MTX. At the approved dosing regimen for UC and CD (90 mg SC dose 8 weeks after 390 mg IV induction dose, and 90 mg SC Q8W thereafter), the Stelara® model predicted p40 target CCI [redacted] in the serum for at least 1 year. No adverse events were observed when patients with moderate-to-severe CD were followed for 49 weeks (range, 8-114 weeks) in a retrospective and prospective cohort study of real world effectiveness outcomes where the 390 mg IV induction followed by 90 mg SC Q4W dosing regimen was evaluated.[55] CCI [redacted]

The nonclinical safety profile of PF-07261271 which simultaneously target the TL1A and p40 cytokines has been adequately characterized to support progression into human clinical studies. There were no PF-0726127-related adverse effects or target organs of toxicity that were identified following CCI of PF-07261271 in a pivotal 3-month cynomolgus monkey toxicity study. The NOAEL was defined as the highest dose tested, CCI mg/kg Q2W (IV). In this study, the C_{max}, CCI and CCI exposure limit for dose escalation are set to be CCI, respectively, determined as the 1/10th of the mean exposures observed at NOAEL in the monkey toxicity study.

Both TL1A and IL-12/IL-23 are precedent mechanisms with favorable safety profiles for mAb targeting these cytokines as detailed above. Thus, a starting dose of PF-07261271 of CCI mg IV is also supported by adequate safety margins. The predicted PF-07261271 safety margins for C_{max} and CCI at the CCI mg single dose are approximately 154- and 167-fold, respectively, below the pre-defined PK exposure limits at 1/10th the NOAEL exposure (Table 7).

The PK/PD model of PF-07261271 suggests that the CCI serum inhibition at CCI dosing is expected to be 34% and 99%, respectively. At Week 52 following CCI mg dose of PF-07261271, the CCI target coverage in the serum are 1.7% and 1.1%, respectively, indicating that both cytokines are almost at their baseline levels.

CCI

The highest proposed IV-infusion dose of CCI mg is estimated to provide an exposure margin of 4.6- and 5.0-fold for C_{max} and CCI, relative to the exposure limits. CCI single dose is predicted to be CCI respectively, thereby assuring an adequate test of pharmacology. The serum p40 and TL1A target coverage at Week 52 are approximately CCI respectively.

The CCI mg SC dose administered CCI was selected for the planned MD cohort with C_{max} and CCI safety margins that are 34- and 27-fold below the pre-defined exposure limits, respectively (Table 8).

For the optional cohort(s), the predicted exposures for the selected dose which could exceed CCI mg IV, if needed, will be no greater than the pre-defined exposure limits (refer to Sections 4.1.1 and 4.1.2).

Table 8. Projected Exposures and Safety Margins Following Repeat SC Doses of PF-07261271

Dose	C_{max}[a] (µg/mL)	CCI[a] (µg/mL)	SM_C_{max}[b] (folds)	SM_C_{av}[b] (folds)
CCI mg SC CCI	CCI			

a. C_{max} and CCI values after the second SC dose are presented in the table.
b. SM is calculated relative the exposure limit (C_{max}=CCI µg/mL and C_{av}=CCI µg/mL) calculated as 1/10th of the NOAEL exposures.

4.4. End of Study Definition

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

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit as shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. Use of a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, and race, and ethnicity. 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. Participants aged 18 to 65 years (or the minimum age of consent in accordance with local regulations) at screening.

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

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, vital sign assessments, laboratory tests, and 12-lead ECGs.

Other Inclusion Criteria:

3. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

4. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Additional criterion for optional Japanese cohort only:

5. Participants who have four Japanese biological grandparents born in Japan.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

    - History of HIV infection; infection with hepatitis B, or hepatitis C viruses according to protocol-specific testing algorithm.

        - For hepatitis B, participants will undergo testing for HBsAg and HBcAb. Participants who are HBsAg positive will not be eligible for this study. Participants who are HBsAg negative but HBcAb positive will be reflex tested for HBsAb. Please refer to Appendix 2 for testing algorithm and reflex testing.

        - For hepatitis C, all participants will undergo testing for HCVAb during screening. Participants who are HCVAb positive will be reflex-tested for HCV RNA. Participants who are HCVAb and HCV RNA positive are not eligible for the study.

    - Evidence of active, latent, or inadequately treated infection with Mycobacterium TB.

        - If a participant previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multidrug resistant TB infections are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, TB tests

do not need to be obtained. Details of previous course of therapy (eg, medication(s) used, dose, duration of therapy) should be documented in the source documentation.

- Any malignancies or history of malignancies with the exception of adequately treated or excised non-metastic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ.

- History of any lymphoproliferative disorder such as EBV related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic or lymphoid tissue disease.

2. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

    - History of febrile illness within 5 days prior to the first dose of investigational product.

    - Significant trauma or major surgery within 1 month of the first dose of study drug.

Prior/Concomitant Therapy:

3. Recent exposure to live or attenuated vaccines within 28 days of the screening visit.

4. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.9 Prior and Concomitant Therapy for additional details).

5. Current use of any prohibited concomitant medication(s). Refer to Section 6.9 Prior and Concomitant Therapy.

Prior/Concurrent Clinical Study Experience:

6. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 halflives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

7. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg

(diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

8. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate- age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third- degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the uncorrected QT interval is >450 ms, this interval should be rate-corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

9. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

   - AST **or** ALT level ≥1.5 × ULN;
   - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

Other Exclusion Criteria:

10. History of drug or alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit, or 3 ounces (90 mL) of wine).

    - A positive urine drug test. A positive test for cannabinoid-based compounds (eg, THC, CBD, etc) will not be considered exclusionary.
    - Participants with >20 cigarettes a day intake or more than 30 pack years.

11. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 30 days prior to screening.

12. History of sensitivity to heparin or heparin-induced thrombocytopenia.

13. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

14. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

The following requirements apply ONLY while participants are confined in CRU:

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations. Water is permitted without restriction.
- Noncaffeinated drinks may be consumed with meals and the evening snack.
- Breakfast must be completed post baseline safety measurements (eg, vitals, ECG, etc).
- Lunch will be provided approximately 4 hours after dosing.
- Dinner will be provided approximately 9 to 10 hours after dosing.
- An evening snack may be permitted.
- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing and within 2 hours prior to vital sign/ECG measurements on all other days of confinement at the CRU and outpatient visits. .

- Participants will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol during clinical confinement at the CRU. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Smoking may be allowed according to CRU practices. Smoking will not be permitted during frequent sampling procedures, and will not be permitted within 2 hours prior to any vital sign or ECG assessments. Smoking will also not be permitted 2 hours before and 2 hours following any dose of study intervention.

5.3.4. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted;

- Participants will be confined to the procedure room for the first hour after dosing on Day 1 for close monitoring after infusion completesAfter this, participants may be ambulatory during the ECG monitoring period, but should not engage in strenuous activities. If equipment does not allow ambulation, appropriate accommodations will be made by the investigator site to facilitate continuous monitoring (eg, bedside urinals should be provided to accommodate participants' excretory needs).

5.3.5. Other Restrictions

Blood donations are to be limited to approximately 1 pint (500 mL) once every 3 months, 3 months after all doses are completed for the participant.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened based on investigator's discretion if there was a reasonable cause for failure (eg, use of prohibited concomitant medications that was not washed out, etc). Participants who met the criteria for participation during screening but fell outside screening window, may be rescreened.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and noninvestigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to PF-07261271 and placebo administered either intravenously or subcutaneously.

6.1. Study Intervention(s) Administered

Table 9. Study Intervention(s)

Intervention Name	PF-07261271	Placebo
Type	biologic	placebo
Dose Formulation	PF-07261271 powder for solution for injection vial (single use only)	Placebo Solution for Injection Vial (single use only)
Unit Dose Strength(s)	CCI mg/vial	NA
Dosage Level(s)	IV: CCI mg[a] SC: CCI mg	NA
Route of Administration	IV SC	IV SC
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.

a. Doses upto CCI mg can be supported if needed.

Table 10. Study Arm(s)

Arm Title	Experimental: intravenous, subcutaneous, various single doses administered to various cohorts	Experimental: subcutaneous, intravenous, various multiple doses administered to various cohorts	Placebo: intravenous, subcutaneous	Placebo: subcutaneous, intravenous
Arm Type	Experimental	Experimental	Placebo	Placebo
Arm Description	Participants in various cohorts will receive single doses of PF-07261271 according to schema on Day 1	Participants in various cohorts will receive repeat doses of PF-07261271 according to schema CCI	Participants in various cohorts will receive single doses of placebo according to schema on Day 1	Participants in various cohorts will receive repeat doses of placebo according to schema CCI
Associated Intervention Labels	PF-07261271	PF-07261271	Placebo	Placebo

PF-07261271 will be provided by Pfizer as powder for solution for injection at the CRU.

Placebo will be provided by Pfizer as solution for injection at the CRU.

PF-07261271 will be supplied by Pfizer as sterile vials.

Placebo sterile vials will also be provided.

PF-07261271 and placebo sterile vials will be supplied as individual vials, which are labeled according to local regulatory requirements, for constitution/reconstitution and subsequent unit dosing as appropriate.

6.1.1. Administration

PF-07261271 and placebo will be administered IV or SC.

Part A: Participants will receive study intervention (start time of infusion) at approximately 0800 hours (±3 hours). For planned IV dosing (Cohorts 1-4, 7, and 8), study intervention will be administered as an intravenous infusion over [redacted]. Details on infusion/injection volumes and rates will be provided in the IP manual, which may supersede the descriptions in the protocol. In the case of mild infusion reactions, at the discretion of the investigator, the infusion may be interrupted and restarted at a slower infusion rate not to exceed a total administration duration of [redacted]. The start and stop time of the infusion will be recorded in source document and CRF. Time 0 is the time when the study intervention infusion begins. The exact injection volume (for IV injections), infusion rate, and the volume infused will be recorded.

Part B: For Cohort 5, study intervention is planned to be administered SC at approximately 0800 hours (±3 hours). Cohort 6 is optional and may be administered either SC or IV. SC injections can be administered in the abdomen, thigh, back of arms or as outlined in the IP manual. The preferred body location for the SC injection is the abdomen. If abdominal injections are not possible, arm or thigh locations may also be used. The total dose volume may be divided into an appropriate number of syringes for administration according to local site practice. Where multiple SC injections may be required to make up the total SC dose, it is preferable to administer each of the SC injections in the same body location but spaced slightly apart. Signs of infection/inflammation in the injection area after discharge should be reported immediately to the investigator. Further details on administration including injection volumes and sites will be provided in the IP manual.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

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

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to the labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. See the IPM for storage conditions of the study intervention once reconstituted and/or diluted.

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. All destruction must be adequately documented. 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.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IPM.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

See the IPM for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

PF-07261271 and placebo are CCI [redacted].

PF-07261271 and placebo will be prepared by qualified unblinded site personnel according to the IPM. Study intervention will be administered in a blinded fashion to the participant by blinded site personnel.

6.3. Assignment to Study Invervention

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

Study intervention will be dispensed at the study visits summarized in the SoA. Study intervention will be masked as per IP Manual to help maintain the blind. For cohorts requiring SC administration, unblinded site staff who have no other responsibilities may be required.

For all SAD and MD cohorts, healthy participants will be randomized within cohort after screening to receive either PF-07261271 or placebo. Participants will receive the same blinded treatment assignment (ie, the same dose level of PF-07261271 or placebo) throughout, in MD cohorts.

- The randomization ratio for Cohorts 1-2 will be 1:1 (PF-07261271:placebo).
- The randomization ratio for Cohorts 3 will be 2:1 (PF-07261271:placebo).
- The randomization ratio for Cohorts 4 and 7 in Part A and Cohorts 5-6 in Part B will be 3:1 (PF-07261271:placebo).
- The randomization ratio for Japanese cohort (Cohort 8), will be 4:1 (PF-07261271:placebo), if conducted.

6.4. Blinding

This is an double-blind (sponsor-unblinded) study.

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to participants' assigned study intervention.

Participants will be assigned to receive study intervention according to the assigned treatment group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

In order to maintain this blind, site staff responsible for receiving, storing, dispensing, and preparing the study intervention will be unblinded, while site staff administering the study intervention will be blinded.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.4.3. Blinding of the Sponsor

Sponsor staff not directly involved in the conduct of the study may be unblinded to participants' assigned study intervention as needed to support study activities.

6.4.4. Breaking the Blind

The method for breaking the blind in this study will be manual. A sealed envelope that contains the study intervention assignment(s) for each participant will be provided to the investigator. The sealed envelope will be retained by the investigator (or representative) in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the study medical monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF/DCT.

Once the study is complete, all envelopes (sealed and opened) must be inventoried and retained until authorization for destruction has been provided.

Blood specimens will be obtained from all participants for PK analysis to maintain the study blind at the investigator site. Only the investigator site staff and blinded study monitor, if assigned, will be blinded to study treatment. Other Pfizer personnel will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data; and provide information necessary to potentially alter the dose-escalation sequence. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for the study has been completed. Specimens from participants randomized to placebo will not be routinely analyzed. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer unblinded personnel and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required dosage Preparation Record located in the IPM. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

6.6. Dose Modification

The decision to proceed to the next dose level of study intervention will be made by the study team and the investigators based on safety, tolerability, and preliminary PK and/or PD data obtained at the prior dose level, as described in Section 4.1. Provided no safety concerns or AEs suggesting that the limits of tolerability have been reached in the current or preceding cohorts, dose escalation may proceed if safety and PK data are available from all participants from Cohorts 1 and 2, at least 5 of 6 participants in Cohort 3, and at least 7 of 8 participants in Cohorts 4-6.

The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety, PK, and PD findings at a given dose level or to add cohorts to evaluate additional dose levels. The study procedures for these additional participant(s)/cohort(s) will be the same as that described for other study participants/cohorts.

6.6.1. Dose Escalation and Stopping Rules

Dose escalation stopping rules will be used to determine whether the maximal tolerated dose has been attained. Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability have been reached. This decision will be made after a discussion takes place between the sponsor study team and the investigator. The sponsor study team may not overrule the investigator's decision to stop dose escalation. If dose escalation is stopped because of any of these criteria, additional cohorts may receive the same or lower doses of the study intervention.

The dose escalation will be terminated based on the following criteria:

- If 50% or more of the participants receiving active drug at a given dose level (but not participants receiving placebo) develop similar clinically significant laboratory, ECG, or vital sign abnormalities, in the same organ class, indicating dose-limiting intolerance.

- Severe nonserious AEs, considered as, at least, possibly related to study intervention administration, in 2 participants at a given dose level (but not participants receiving placebo), independent of within or not within the same system organ class, indicating dose-limiting intolerance.

- Dosing will be paused for any SAE that occurs in a participant receiving active treatment until causality is fully assessed by the PI and sponsor. Dosing may resume if the SAE is determined to be not drug-related by the PI and sponsor. If the SAE is determined to be either drug-related or unknown, either dosing will cease or the SAE will be evaluated by the sponsor's protocol review committee (or similar review group), which is independent of the study team and investigators. If the protocol review committee determines that dosing may resume, a plan that mitigates risks to participants with the resumption of dosing will be implemented. Such a plan could include a revision of inclusion/exclusion criteria, repeating or reducing the dose, or adding appropriate safety monitoring.

- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the study team and the investigator.

- Other findings that, at the discretion of the study team and investigator, indicate that dose escalation should be halted.

- If, at any dose level, the average exposure reaches or exceeds the PK stopping limits, C_{max} of [redacted] µg/mL or [redacted] of [redacted] µg•hr/mL.

- If, based on the observed data, the group mean C_{max} or AUC (based on total serum concentration) of the next planned dose is projected to exceed the escalation limits, that dose will not be explored. Modified doses may be explored if they are not expected to exceed PK stopping criteria.

Progression to the next dose will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data.

6.7. Continued Access to Study Intervention After the End of the Study

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

6.8. Treatment of Overdose

For this study, any dose of PF-07261271 greater than the maximum dose within a 24-hour time period ±12 hours will be considered an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.

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

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

5. Obtain a blood sample for PK analysis within 28 days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a casebycase basis).

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

6.9. Prior and Concomitant Therapy

6.9.1. Permitted During the Study

The following concomitant therapies are permitted during the study:

- Non-medicated emollient, creams, and sunscreen.
- Vitamins, minerals, and purified food substances of standard potency are allowed in amounts not known to be associated with adverse effects (such as hypervitaminosis).
- Acetaminophen may be used intermittently (not to exceed 2.5 g/day).
- OTC formulations (including but not limited to herbal supplements, syrups, suspensions, medicated creams, analgesics, antipyretics, antacids, etc) believed to not have any effect on drug metabolism or affect the primary endpoints of the study may be permitted on a case-by-case basis following approval by the investigator.
- Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).
- Some prescription medications may be permitted during the study on a case-by-case basis after investigator and sponsor approval.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 35 days before the first dose of study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

Unless a prohibited medication or treatment, participants may be administered any other medications necessary for the treatment of concomitant medical disorders as deemed necessary by the treating physician. Following Day 1 up to 3 months post first dose, the addition of concomitant medications or any change in the dosage should be limited to those considered medically essential.

6.9.2. Prohibited During the Study

Participants are required to discontinue and avoid using certain medications and treatments. Participants should be instructed at each visit to contact the study site investigator promptly if there are any intended changes or additions to concomitant medications. Prohibited medications during the study include:

- Oral and parenteral corticosteroids within 4 weeks prior to the first dose of study intervention.
- Current or anticipated use of protein therapeutics including but not limited to CCI targeted therapies within 6 months of the first dose of study intervention.
- Herbal medications with presumed anti-inflammatory properties, or that are known to have an effect on drug metabolism (eg, St. John's Wort) must be discontinued at least 7 days or 5 half-lives (whichever is longer) before the first dose of study intervention.
- Oral and parenteral anti-infectives within 2 weeks or 5 half-lives (whichever is longer) before the first dose of study intervention.
- Herbal and prescription medications for treatment of chronic diseases including but not limited to hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease.
- Any other investigational drug(s) within 4 weeks of the first dose of study intervention or 5 half-lives (whichever is longer), or at any time during the study.

A protocol deviation is to be completed for any participant that takes a prohibited treatment or medication during the study and the sponsor is to be notified.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- Any participant, who develops Grade 2 or higher AEs for cardiac and blood/bone marrow categories and Grade 3 or higher AEs in all other categories according to

criteria defined in CTCAE (version 5), will be discontinued from treatment and followed until resolution of the AE(s);

- If a participant experiences symptoms typical of an allergic reaction (see Section 7.1.6 for temporary discontinuation and rechallenge in Part B), the study drug administration should be discontinued immediately and permanently;
- ECG changes (see Section 7.1.2);
- Unacceptable toxicity as judged by the investigator;
- Pregnancy.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for 5 half-lives after last dose. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.1.1. Liver Injury

A participant who meets the criteria as described in Appendix 6 will be withdrawn from study intervention (if in MD cohort).

7.1.2. ECG Changes

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

- QTcF >500 ms.
- Change from baseline: QTcF >60 ms.

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

7.1.3. Potential Cases of Acute Kidney Injury

Abnormal values in SCr concurrent with presence or absence of increase in BUN that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in SCr level relative to the participant's own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 µmol/L] in SCr relative to the participant's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 µmol/L), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 healthy participants in a given treatment arm are noted to have 2 *consecutive* SCr results of ≥0.3 mg/dL (or ≥26.5 µmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.1.4. Pregnancy

Pregnancy tests are conducted as per SoA and dosing of study intervention will occur only in the presence of a negative pregnancy test. If a participant is confirmed to be pregnant (see Section 8.3.6) during any visit, further dosing with study intervention (if in the MD cohorts) will be discontinued immediately and permanently.

Section 8.4.5.1 Exposure During Pregnancy describes the follow-up activities if a participant meets the EDP criteria.

7.1.5. COVID-19

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

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

7.1.6. Temporary Discontinuation

If a participant experiences symptoms typical of infusion reactions (eg, lightheadedness, nausea, chills, fever) or mild immunogenicity reactions, the study intervention infusion should be stopped. At the discretion of the investigator, the infusion can be restarted at a

slower rate if symptoms are resolved within 1 hour after the stop of infusion. If symptoms return, then the study intervention administration should be discontinued immediately and permanently.

In the event that there is an infusion interruption, the entire duration of drug infusion, from the initial start of infusion to the completion of infusion, should not exceed 3 hours. The start and stop time of the infusion and the infusion rate and amount of volume infused in the event of an interruption will be recorded. Participants will receive appropriate treatment at the discretion of the investigator.

For MD cohorts, if participants miss the scheduled second dosing visit window (approximately a week), this will be considered a temporary study drug interruption and a protocol deviation. Participants will be contacted and further dosing decisions will be based on discussions between investigators and sponsor.

Participants in multiple dose cohorts who may have had mild/moderate injection site reaction(s), may receive the second scheduled dose of study intervention at the discretion of the investigator.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following:

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

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/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

If a participant withdraws from the study, they 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 Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them 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 study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant 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 attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether 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, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative 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.

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.

Participants will be screened within 35 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 35 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require recollection of banked biospecimens.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, retained research samples, may be used without repeat collection, as appropriate.

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 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 they have 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.

Safety/laboratory/analyte results that have been collected for the purposes of this study and could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

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 675 to 870 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 56 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

8.1.1. Telehealth Visits

Telehealth visits may be used to assess participant safety and collect data points (see SoA notes). Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit (see the SoA):

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

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

8.1.2. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit (see the SoA):

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.
- Perform physical examination, vital signs, weight, and ECG collection as required by SoA.
- Blood and/or urine sample collection as required by SoA which may include but not limited to:
  - Safety laboratory samples;
  - PK and immunogenicity samples;
  - Exploratory biomarker samples;

- Pregnancy testing;
- Retained research samples.

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

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

8.2. Efficacy Assessments

As this is a healthy participant study, efficacy assessments are not applicable.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant -reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Pulse Rate

Supine BP will be measured as per SoA with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same

arm (preferably the dominant arm) will be used throughout the study. BP should not be taken from the arm with an intravenous infusion. Participants should be instructed not to speak during measurements.

If a single measurement is >140 mm Hg systolic and/or >90 mm Hg diastolic, the BP assessment should be repeated two more times (approximately two minutes apart), and the average of the three BP values recorded in the CRF and noted in the source document.

The same properly sized and calibrated BP cuff should be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2.2. Respiratory Rate

Respiratory rate will be measured after approximately 5 minutes of rest in a supine position by observing and counting the respirations of the participant for 30 seconds and multiplying by 2. When BP is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before BP measurement. Post-dose respiratory rate measurements to be done at the investigator's discretion.

8.3.2.3. Temperature

Temperature will be measured by either oral, tympanic, or temporal artery method, it is preferred for the same method to be used consistently throughout the study. No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement.

8.3.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart at all time points during clinical confinement; the average of the triplicate ECG measurements collected

at each nominal time point on Day 1 will serve as each participant's time-controlled baseline QTcF value.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any postdose QTcF interval is increased by ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG. If either of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF value get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF values do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

ECG values of potential clinical concern are listed in Appendix 8.

8.3.4. 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. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that 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 significant and abnormal during participation in the study or within 90 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study 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.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing results conducted prior to dosing must be in alignment with Section 5.2 Exclusion Criterion 10 for participants to receive study intervention.

8.3.5. COVID-19 Testing

The testing for COVID-19 will be performed as per SoA and may be performed at each outpatient visit per local site regulations. For participants admitted for CRU confinement, a subsequent COVID-19 test may be performed per local site procedures or if they develop COVID-19 like symptoms. Testing may be completed per local site practice.

8.3.6. Pregnancy Testing

A serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study intervention. 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 IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3.6.1. At-Home Pregnancy Testing

If a participant requiring pregnancy testing cannot visit a local laboratory, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

8.3.7. Infusion and Injection Site Reaction and Anaphylaxis Assessment

Participants will be monitored for signs of any infusion or injection site reactions, including but not limited to erythema, swelling, bruising, pain, or pruritus at times specified in the SoA.

Any signs or symptoms related to either an infusion or injection site reaction should be treated according to the investigator's standard of care and reported as AEs. All anaphylactic reactions will be assessed by the Pfizer clinical team according to Sampson's criteria (Appendix 9).

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

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 the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

8.4.1. 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 undergoing any study -related procedure and/or receiving study intervention), through and including a minimum of approximately 5 half-lives or until their exposures are below LLOQ after the last administration of the study intervention.

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and theyconsider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious Aes and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be 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.

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

8.4.2. 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.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or 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 provided in Appendix 3.

8.4.4. 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 toward the safety of participants and the safety of a study intervention under clinical investigation are met.

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

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.

- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:

  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

  - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, 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. Details of the pregnancy will be collected after the start of study intervention and until at least 5 terminal half-lives after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the 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.

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).

Abnormal pregnancy outcomes are considered SAEs. 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 including miscarriage and missed abortion should be reported as an SAE;
- 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 study intervention.

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.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so 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.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure 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 about the occupational exposure 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 must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;

- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

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.

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 the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

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

8.5. Pharmacokinetics

Blood samples will be collected for measurement of serum concentrations of PF-07261271 as specified in the SoA. If a participant is suspected to be experiencing an immune-related event, the unscheduled blood samples should be collected for concentration of PF-07261271 within 3 days of the event and sampling time and date should be documented. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, and if needed, additional PK samples may be taken at times specified by Pfizer, provided the total blood volume taken during the study does not exceed 550 mL during any period of 56 consecutive days. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Post-dose sample collection time points are calculated from start of infusion time. For infusions that take longer than CCI, the EOI CCI PK sample should be taken at the end of infusion. Post-dose samples collected up to and including 2.5 hours and which are within 15 mins of nominal time will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF/DCT. Samples collected between 2.5 -10 hours and which are within 10% of the nominal time will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF/DCT. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF/DCT. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows. If a scheduled blood sample

collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, participant, and sponsor.

Samples will be used to evaluate the PK of PF-02761271. Samples collected for analyses of PF-07261271 serum concentration may also be used to evaluate safety or other aspects related to concerns arising during or after the study, and/or evaluation of the bioanalytical method, or for other internal exploratory purposes and are not reported in the CSR.

Samples collected for measurement of serum concentrations of PF-02761271 will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Drug concentration information that would unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

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

Retained Research Samples may be used for research related to the study intervention(s), and IBD or other inflammatory conditions. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

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

8.7. Biomarkers

Collection of samples for biomarker research is also part of this study.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- Serum for [redacted];
- Serum for [redacted]

8.7.1. Specified Gene Expression (RNA) Research

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

8.7.2. Specified Protein Research

Specified protein research is not included in this study.

8.7.2.1. [redacted]

A 8.5-mL blood sample will be collected to provide serum for measurement of total levels of [redacted] The sample(s) will be analyzed for exploratory research.

8.7.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.4. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study from all participants for exploratory research relating to the drug response in diseases of inflammation. If not collected on the designated day, collect at the next available time point when biospecimens are being collected in conjunction with a participant's visit:

- Prep B2.5 (serum collection optimized for biomarker/proteomic/metabolomic analysis): A 6-mL blood biospecimen will be collected at times specified in the SoA section of the protocol.
- Prep R1 (PAXGene whole-blood collection optimized for RNA analysis): A 2.5-mL blood biospecimen will be collected at times specified in the SoA section of the protocol.
- Prep B1.5 (plasma collection optimized for biomarker/proteomics analysis): A 6-mL blood biospecimen will be collected at times specified in the SoA section of the protocol.

Retained Research Samples will be collected as local regulations and IRB/ECs allow according to the SoA.

Retained Research Samples may be used for research related to PF-07261271 and IBD or other inflammatory conditions. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

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

8.8. Immunogenicity Assessments

Blood samples will be collected for determination of ADA and NAb as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for determination of ADA and NAb may also be used for additional characterization of the immune response and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will be used for internal exploratory purposes and not reported in the CSR.

Genetic analyses will not be performed on these blood samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples determined to be positive for ADA may be further characterized for neutralization activity .

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Immunogenicity information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.9. 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 the 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. Statistical Hypothesis

No statistical hypothesis will be tested for this study.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization/assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Full analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.
Safety analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK population	The PK concentration population will be defined as all randomized participants who received at least 1 dose of PF-07261271 and in whom at least 1 serum concentration value is reported.
PK parameters	The PK parameter analysis population will be defined as all randomized participants who received at least 1 dose of PF-07261271 and who have at least 1 of the PK parameters of interest calculated.
PD analysis set	All randomized participants who received at least 1 dose of PF-07261271 and who have baseline and at least 1 post-dose assessment.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe 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.

9.3.1. Primary Endpoint(s) Analysis

The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive at least 1 dose of study intervention (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include:

- TEAEs and SAEs;
- Withdrawals from active treatment due to AEs;
- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials;
- Safety laboratory tests (eg, hematology [including coagulation panel], chemistry and urinalysis);
- ECG (HR, QT, QTc, PR, and QRS intervals) changes from baseline;
- Vital signs (BP, pulse rate and temperature).

Changes from baseline on laboratory data and vital signs will be additionally summarized. Participant listings will also be produced for these safety endpoints.

AEs, ECGs, BP, pulse rate, temperature, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.3.1.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters HR, QT interval, QTc interval, PR interval, and QRS intervals will be summarized by treatment and time. The frequency of uncorrected QT values above 500 ms will be tabulated.

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

Safety QTcF Assessment

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

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

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 ms, but the mean of the triplicates is not >500 ms, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-ms value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 ms will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 ms. Changes from baseline will be defined as the change between the postdose QTcF value and the average of the predose triplicate values on Day 1.

In addition, an attempt will be made to explore and characterize the relationship between serum concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship will be examined.

9.3.2. Secondary Endpoint(s) Analysis

Immunogenicity and PK parameters are secondary endpoints. The PK parameters to be assessed, their definition, and method of determination are detailed in Section 9.3.2.1. Actual PK sampling times will be used in the derivation of PK parameters.

Incidence of the development of ADA and, if appropriate, NAb against PF-07261271 following single and multiple doses may be summarized by dose and presented in tabular form or graphically.

9.3.2.1. Pharmacokinetic Analysis

Actual PK sampling times will be used in the derivation of PK parameters. The serum concentration of PF-07261271 will be listed and descriptively summarized by nominal PK

sampling time and treatment group. Individual participant, mean, and median profiles of the serum concentration-time data will be plotted by treatment group using actual (for individual) and nominal (for median) times respectively. Mean and median profiles will be presented on both linear and log scales.

Table 11. Serum PK Parameters

Parameter	Definition	Method of Determination
Part A: SAD		
AUC_{last}	Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (C_{last}).	Linear/Log trapezoidal method
CCI		
AUC_{inf}[a]	Area under the serum concentration time-profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis
CCI		
C_{max}	Maximum serum concentration	Observed directly from data
CCI		

Parameter	Definition	Method of Determination
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[a]	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the loglinear -concentration time- curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression
CL/F and CCI[a]	Apparent clearance for SC dosing (CL/F) and systemic clearance for IV dosing (CL)	$Dose/AUC_{inf}$
V_{ss}[a]	Volume of distribution at steady state (IV dosing)	CL×MRT
V_z/F	Apparent volume of distribution during the terminal phase (SC dosing)	$Dose/AUC_{inf} \times k_{el}$
MRT[a]	Mean residence time	$AUMC_{inf}/AUC_{inf}$, where $AUMC_{inf}$ is the area under the first moment curve from time zero to infinity.

Table 11. Serum PK Parameters

Part B: MD			
Parameter	**Study Day Relative to Day 1**	**Definition**	**Method of Determination**
AUC_{tau}	1, [redacted]	Area under the concentration time profile from time zero to time tau (τ), the dosing interval, where tau=672 hours for Q4W dosing.	Linear/Log trapezoidal method
[redacted]			
C_{max}	1, [redacted]	Maximum serum concentration.	Observed directly from the data
[redacted]			
T_{max}	1, [redacted]	Time for C_{max}.	Observed directly from data
[redacted]			
$t_{½}$[a]	[redacted]	Terminal elimination half-life.	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the loglinear-concentration time-curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression
[redacted]			

a. If data permits.

The PK parameters in Table 11 will be summarized descriptively by treatment group and dosing day in healthy participants in accordance with Pfizer data standards. Summary statistics will also include the geometric mean and coefficient of variation for all parameters except T_{max} (median, min - max range) and $t_{½}$ (arithmetic mean ± SD).

Where data permit, dose normalized (to a 1 mg dose) C_{max}, AUC_{inf}, AUC_{last} and/or AUC_{tau}, will be plotted against dose and administration route and day, as appropriate for single dose and multiple doses. The plot will include individual participant values and the geometric means for each dose. These plots will be used to help understand the relationship between the PK parameters and dose and/or administration route.

The PK data from the optional Japanese cohort will be summarized separately, if conducted.

9.3.3. Tertiary/Exploratory Endpoint(s) Analysis

All of the exploratory endpoints including, but not limited, to PD biomarkers (eg, [redacted]), may be summarized by dose and presented separately

by each time point presented in tabular form or graphically. In addition, some of these endpoints may be analyzed longitudinally to study the effect over time. Participant level exploratory endpoints may also be summarized by treatment. For immunogenicity, effect of positive ADA and neutralizing immune response on safety, tolerability, PD and PK may be assessed, if appropriate. These data and any subsequent analyses, if performed, may or may not be reported in the CSR.

9.3.4. Other Analyses

Pharmacogenomic or biomarker data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4. Interim Analyses

No interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

9.5. Sample Size Determination

The sample size for this study is not based on any statistical considerations and is determined on the need to minimize first exposure to humans of a new chemical entity and the requirement to provide adequate safety and tolerability assessment at each dose.

A sufficient number of participants will be screened to achieve 4 participants to be randomized in each of the first 2 cohorts (Cohorts 1-2), 6 participants in the next cohort (Cohort 3) and 8 participants in the remaining cohorts, except Cohort 8. Cohort 8 will only screen a sufficient number of participants to randomize 5 Japanese participants.

For Cohorts 1 and 2 participants will be randomly assigned to PF-07261271 or placebo in a ratio of 1:1. For Cohort 3, a randomization ratio of 2:1 will be used. A randomization ratio of 4:1 is planned for the Japanese cohort (Cohort 8) and 3:1 for the remaining cohorts in the study.

A total of approximately 30 participants will be randomized (without optional Cohorts 6-8) or up to 51 (with 3 optional cohorts) will be enrolled into the study.

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 CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, 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 study intervention, 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 the ICH GCP guidelines 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 the investigator'srepresentative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

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

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

The investigator further must ensure that each study participant is fully informed about theirright to access and correct theirpersonal data and to withdraw consent for the processing of theirpersonal 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 on which 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 IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

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

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

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.

Particpants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will 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 participants 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 their actual identity and medical record ID. 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.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.6. 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 EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its 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 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. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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.

10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and 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, including definition of study-critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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.

10.1.8. 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 eCRF that are 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.

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

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

The sponsor or designee will perform monitoring 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 guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. 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 sponsor or designee/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 the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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.

10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.11. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the CTMS.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is tobe used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

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

At screening, HbsAg and HbcAb will be tested:

a. If both tests are negative, the participant is eligible for study inclusion;

b. If HbsAg is positive, the participant must be excluded from participation in the study;

c. If HbsAg is negative and HbcAb is positive, HbsAb reflex testing is required:

   i. If HbsAb is negative, the participant must be excluded from participation in the study;

   ii. If HbsAb is positive, the participant is eligible for study inclusion.

Table 12. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs) **Coagulation** PT/INR/aPTT	BUN and creatinine CystatinC and eGFR[g] Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	<u>Local dipstick:</u> pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase <u>Laboratory:</u> Microscopy and culture[a]	COVID-19 testing (may be completed locally) Urine drug tests <u>At screening:</u> • FSH[b] • Urine drug screening[c] • Pregnancy test (β-Hcg)[d] • HBsAg, HBcAb, HBsAb • Hepatitis C antibody[e] • QuantiFERON-TB Gold/Gold Plus/T-SPOT[f] • HIV For suspected DILI: AST/ALT T bili, direct and indirect bili Total bile acids, GGT Total protein, albumin CK PT, INR Acetaminophen/paracetamol or protein adduct levels Hepatitis serology (even if screening negative)

a. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
b. For confirmation of postmenopausal status only.
c. The minimum requirement for drug screening includes cocane, opiates/opioids, benzodiazepines, and amphetamines.
d. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-Hcg for female participants of childbearing potential.
e. HCVAb positive results will be reflex tested for HCV RNA.
f. Local QuantiFERON or T-SPOT can be completed with sponsor approval if QuantiFERON-TB result is indeterminate or believed to be a false positive and participant has no clinical signs or symptoms consistent with TB.
g. Scr-based eGFR will be used for standard kidney safety monitoring and Scr-Scys eGFR for reflex testing if Scr increase is confirmed after baseline.

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.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. Upon completion of the study, these retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

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

10.3.1. Definition of AE

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

Events Meeting 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. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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 an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
b. Results in death
c. 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.
d. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (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.

e. Results in persistent or significant 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
f. Is a congenital anomaly/birth defect
g. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.
h. Other situations: • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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 During the Active Collection Period

AE and SAE Recording/Reporting
The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2)

nonserious Aes; and (3) exposure to the study intervention 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 study intervention under study during pregnancy or breastfeeding	All Aes/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** Aes or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or 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 or 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 or 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 or SAE.

Assessment of Intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- 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.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have 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 theiropinion 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 study intervention caused the event, then the event will be handled as "related to study intervention" 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 providers.
- 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 submitted documents.
- 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 DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT 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 DCT 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 the 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, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, 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 and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥10,000-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

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 definition in Section 10.4.3).

  OR

- Is a WOCBP and agrees to use a highly effective contraceptive method (failure rate of <1% per year) during the intervention period and for at least 5 terminal half-lives after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective, user-dependent method is chosen, she agrees to concurrently use an effective barrier method of contraception. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;

- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy.

For individuals with permanent infertility due to a 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 no menses for 12 months without an alternative medical cause. In addition:

  A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.

  A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

<u>Highly Effective Methods That Have Low User Dependency</u>

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.

5. Vasectomized partner:

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

Highly Effective Methods That Are User Dependent

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

    - Oral + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral + barrier*
    - Injectable + barrier*

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 study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

- Male or female condom, with or without spermicide;
- Cervical cap, diaphragm or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.
- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-07261271 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
    - Retained samples will be stored indefinitely or for another period as per local requirements.
    - Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.
    - Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili 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** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili 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 T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/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/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or 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, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to estimate glomerular filtration rate [Scr-based eGFR] or creatinine clearance [eCrCl]). Baseline and postbaseline serum Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations[56]

2021 CKD-EPI Scr Only	Scr *(mg/dL)*	Scys *(mg/L)*	Recommended eGFR Equation
Female	if ≤ 0.7	NA	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	NA	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	NA	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	NA	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr *(mg/dL)***	**Scys *(mg/L)***	**Recommended eGFR Equation**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to KDIGO criteria.

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute) or by ≥60 ms 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 PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as SAEs

• QTcF prolongation >500 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex>120 ms).
• New-onset right bundle branch block (QRS complex>120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants 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 participants 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 (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and

monomorphic/polymorphic ventricular tachycardia (HR >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 SAEs

- 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.

10.9. Appendix 9: Clinical Criteria for Diagnosing Anaphylaxis Guidance[57]

Anaphylaxis is highly likely when any <u>one</u> of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lipstongue-uvula): AND AT LEAST ONE OF THE FOLLOWING a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia). b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula). b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia). c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence). d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*. b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
Abs	absolute
ADA	anti-drug antibodies
ADL	activity/activities of daily living
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
CCI [redacted]	
AUC_{inf}	area under the serum concentration-time curve from time 0 extrapolated to infinite time
CCI [redacted]	
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
CCI [redacted]	
AUC_{tau}	area under the concentration-time curve at steady state over the dosing interval (τ), where tau=672 hours for Q4W dosing.
CCI [redacted]	
$AUMC_{inf}$	the area under the first moment curve from time 0 to infinity
AV	atrioventricular
AxMP	auxiliary medicinal product
β-Hcg	β-human chorionic gonadotropin
BBS	Biospecimen Banking System
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C1q	complement component 1q
CCI [redacted]	
CBD	cannabidiol
CD	Crohn's Disease
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CCI [redacted]	

Abbreviation	Term
CL/F	apparent clearance of drug from serum
C_{last}	the last quantifiable concentration
C_{last}*	the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis
C_{max}	maximum observed concentration
CCI	
CO_2	carbon dioxide
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CTMS	Clinical Trial Management System
CCI	
CYP	cytochrome P450
DcR3	decoy receptor 3
DCT	data collection tool
DILI	drug-induced liver injury
CCI	
EBV	Epstein Barr virus
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCrCl	creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EoI	end of infusion
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clincal Trials (European Clinical Trials Database)
CCI	
Fc	fragment of the immunoglobulin that is encoded by constant (c) genes
FcγR	Fc gamma receptor

Abbreviation	Term
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HP	healthy participant(s)
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
CCI /IC_{80}	CCI % or 80% inhibitive concentration
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IgG1	Immunoglobulin G1
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug
INF-γ	interferon gamma
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IV	intravenous(ly)
k_a	first-order absorption rate constant
CCI	[redacted]
k_{el}	first-order elimination rate constant
KDIGO	Kidney Disease Improving Global Outcomes
LBBB	left bundle branch block
LFT	liver function test
LLOQ	lower limit of quantification
mAb	monoclonal antibody
MABEL	minimum anticipated biological effect level
MD/md	multiple doses
MQI	medically qualified individual

Abbreviation	Term
MRT	mean residence time
NA	not applicable
NAb	neutralizing antibodies
CCI	[redacted]
NIMP	non-investigational medicinal product
NOAEL	no observed adverse effect level
OTC	over-the-counter
PD	pharmacodynamic(s)
PEF	peak expiratory flow
PK	pharmacokinetic(s)
PR	pulse rate
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
CCI	[redacted]
Q	inter-compartmental clearance
Q2W	every 2 weeks
Q4W	every 4 weeks
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
S1PR	Sphingosine-1-phosphate receptor
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
Scr	serum creatinine
Scys	serum cystatin C
SD	standard deviation
SM	safety margin(s)
SoA	schedule of activities
SOP	standard operating procedure
CCI	[redacted]
SRSD	single reference safety document
STAT3/STAT4	signal transducer and activator of transcription 3/4
sTL1A	soluble TL1A
SUSAR	Suspected Unexpected Serious Adverse Reaction
T bili	total bilirubin
$t_{½}$	terminal phase half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event

Abbreviation	Term
Th1/Th17	type 1/17 helper T cells
THC	tetrahydrocannabinol
TK	toxicokinetic(s)
TL1A	tumor necrosis factor-like cytokine 1A
T_{max}	time to reach C_{max}
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
V_c	central volume of distribution
V_p	peripheral volume of distribution
V_{ss}	steady-state volume of distribution
V_z	volume of distribution for extravascular dosing
V_z/F	apparent volume of distribution for extravascular dosing
WBC	white blood cell
WOCBP	woman/women of childbearing potential

10.11. Appendix 11: Protocol Amendment History

Amendment 1 (02 March 2023)

Overall Rationale for the Amendment: The protocol was amended to add single eligibility criterion for optional Japanese cohort and to clarify aspects of the protocol.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 Synopsis; Inclusion Criteria Section 5.1. Inclusion Criteria	Added inclusion criteria for optional Japanese cohort.	To clarify eligibility criteria for optional Japanese cohort.	Substantial
Section 1.1 Synopsis; Overall Design Section 4.1. Overall Design	Replaced " This is an FIH within-cohort randomized, participant- and investigator-blind, sponsor-open, placebo-controlled study…" with "This is an FIH randomized, double-blind, sponsor-open, placebo-controlled study…".	To be consistent with the protocol title.	Nonsubstantial
Section 1.3, SoA, Tables 1, 3, and 4 Section 8.3.3. Electrocardiograms	Added "at all time points" to emphasize that all ECGs will be done in triplicate during clinical confinement.	To clarify ECG requirements.	Nonsubstantial
Section 1.3, SoA, Tables 1, 3, and 4	Added "Post-dose collection time points are calculated from start of infusion time (See Section 8.5 for additional details on PK sampling)".	To clarify PK sampling time points.	Nonsubstantial
Section 1.3, SoA, Table 2	Updated early discontinuation window to "through Day 451".	Administrative error.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.3, SoA, Table 3	Included option to collect Prep D1 sample at Day -1 for the multiple dose cohorts 5 and 6.	To provide flexibility and more time for all required sample collection on Day 1.	Nonsubstantial
Section 1.3, SoA, Table 3	Added Day 15 time point for CCI [redacted] sample collection for the multiple dose cohorts 5 and 6.	To be consistent with sample collection time points for single ascending dose cohorts.	Nonsubstantial
Section 1.3, SoA, Table 5	Updated early discontinuation window to 'through Day 471'.	Administrative error.	Nonsubstantial
Section 1.3, SoA, Table 5	Replaced "Vital signs' with 'Blood pressure and pulse rate". Removed bullet point under 'Notes' section.	To clarify that temperature will not be collected during the follow-up period.	Nonsubstantial
Section 6.1.1. Administration	Added additional instructions for SC administration.	To provide additional instructions when multiple SC injections are required per dose.	Nonsubstantial
Section 6.1.1. Administration	Deleted 'manual' that was inadvertently repeated.	Administrative error.	Nonsubstantial
Section 8.3.3. Electrocardiograms Section 9.3.1.1. Electrocardiogram Analyses	Deleted reference to Day -1 time point.	ECGs are not required at Day -1.	Nonsubstantial
Section 8.5. Pharmacokinetics	Rephrased instructions on PK collection time points.	To clarify pharmacokinetics sampling time points.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 8.7.4. Retained Research Samples	Deleted paragraph referencing the optional component of sampling banking.	To be in alignment with the current consent document (ICD version date: 13 September 2022). Sample banking is not optional.	Nonsubstantial
Section 10.2, Appendix 2, Table 12	Added local QuantiFERON as an option for repeat TB testing.	To provide flexibility on testing options.	Nonsubstantial
Section 10.2, Appendix 2, Table 12	Added footnote to clarify that Scr-based eGFR will be used for standard kidney safety monitoring and Scr-Scys eGFR will be used for reflex testing only.	To clarify eGFR calculations used in this protocol.	Nonsubstantial

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