Protocol C4631001

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

Statistical Analysis Plan
(SAP)

Version: 2

Date: 08 Nov 2023

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 22 Sep 2022	Original 23 Jun 2022	N/A	N/A
2 08 Nov 2023	Protocol Amendment 2 18 Oct 2023	To be consistent with Protocol Amendment 2	Section 6.4. Modified the language of PD biomarkers.

2. INTRODUCTION

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

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.

IBD is a chronic relapsing inflammatory illness of the intestine with an age-standardized prevalence rate of 84.3 per 100,000 population, affecting 6.8 million people globally. 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. Treatment for mild to moderate IBD consists of mesalamine, corticosteroids, and immunosuppressants to manage induction and maintenance of remission. For moderate to severe IBD, the first line treatment has been anti-TNFα antibody therapy for over 15 years. 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. Additional second line immune-targeted therapies are also in use for moderate to severe IBD including antibodies anti-p40 ustekinumab, and anti-α4β7 integrin vedolizumab, approved for both UC and CD. Small molecule Janus kinase inhibitors, tofacitinib and upadacitinib, and S1PR modulator ozanimod 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%, highlighting the high unmet need for safe and effective therapeutics that target the range of underlying disease mechanisms to drive improved efficacy.

The clinical efficacy demonstrated with CCI [redacted] *monotherapies highlights the importance of targeting* CCI [redacted] *for IBD, while leaving room for improvement in rates of clinical response and remission. PF-07261271 is an* CCI [redacted] *is a biotherapeutic combining high affinity human binding domains against* CCI [redacted]. *The PF-07261271* CCI [redacted] *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.*

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4631001. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

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 $t_{½}$.*

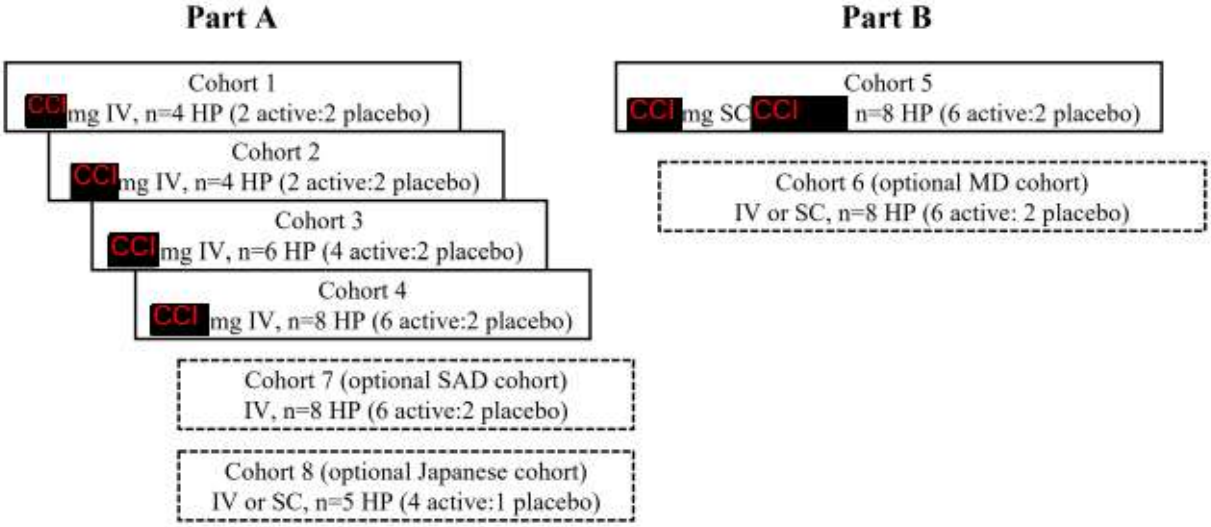
• *To evaluate the immunogenicity profile of PF-07261271 following single and multiple doses in healthy adult participants.*	• *Incidence of the development of ADA and, if appropriate, NAb against PF-07261271 following single and multiple doses.*
Tertiary/Exploratory:	*Tertiary/Exploratory:*
• *To characterize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

2.3. Study Design

This is an FIH within-cohort randomized, participant- and investigator-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.

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.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s): Safety Endpoints

The primary endpoints include:

- 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).

The following data are considered in standard safety summaries (see protocol for collection days, baseline assessment, and list of parameters):

- AEs;
- Safety laboratory tests;
- Vital signs (BP, PR, and temperature measurements);
- ECG.

3.1.1. Adverse Events

An adverse event (AE) is considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first dosing day and time/start time, if collected, but before the end of the last follow-up date, will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date. If an AE starts on the same day as the first dose date, it will be considered treatment emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset which was occurred before the first treatment dosing.

3.1.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol. See Protocol Appendix 2 for the list of clinical safety laboratory tests to be performed.

To determine if there are any clinically significant laboratory abnormalities, the hematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will not take into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

The baseline will be the last pre-dose measurement.

3.1.3. Vital Signs

Supine blood pressure, pulse rate, temperature and respiratory rate will be measured at times specified in the SoA given in the protocol.

The baseline will be the last pre-dose measurement.

3.1.4. ECG

Standard 12 lead ECGs should be collected at times specified in the SoA section of the protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex.

Triplicate 12 lead ECGs will be obtained approximately 2 to 4 minutes apart during clinical confinement; the average of three triplicate ECG measurements collected at Day 1 predose will serve as each participant's time controlled baseline QTcF value. This baseline definition will be applied to other ECG parameters.

3.2. Secondary Endpoint(s)

3.2.1. Pharmacokinetic Endpoints

- PF-07261271 PK parameters as data permit:
  - Part A (SAD-IV or SC Infusion Dosing): AUC_{last}, AUC_{inf}, C_{max}, T_{max}, and $t_{½}$;
  - Part B (MD-IV or SC Dosing) or MD cohorts: AUC_{tau}, C_{max}, T_{max}, and $t_{½}$.

The PK parameters to be assessed, their definition, and method of determination are detailed in Table 2. Actual PK sampling times will be used in the derivation of PK parameters. Some of these PK parameters are exploratory endpoints and are described in Section 3.3.

Table 2. 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		

Table 2. Serum PK Parameters

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[a]	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.

Part B: MD

Parameter	Study Day Relative to Day 1	Definition	Method of Determination
AUC_{tau}	1, CCI	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
CCI			
C_{max}	1, CCI	Maximum serum concentration.	Observed directly from the data
CCI			
T_{max}	1, CCI	Time for C_{max}.	Observed directly from data
CCI			

Table 2. Serum PK Parameters

Parameter		Definition	Method of Determination
$t_{½}$[a]	CCI	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
CCI			

a. If data permits.

3.2.2. Immunogenicity

- Incidence of the development of ADA and, if appropriate, NAb against PF-07261271 following single and multiple doses.

3.3. Tertiary/Exploratory Endpoint(s)

- PF-07261271 PK parameters, as data permit:

CCI

The PK parameters to be assessed, their definition, and method of determination are detailed in Table 2.

- CCI
- Change from baseline in blood levels of exploratory PD biomarkers:
  - Serum proteins: CCI

The baseline will be the last pre-dose measurement.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Participant Analysis Set	Description	Applicable Analysis (for additional information refer to Section 6)
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.	Safety analysis/ Primary endpoint
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.	PK analysis
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.	PD analysis

4.1. Treatment Misallocations

All analyses will be performed on an "as-treated" basis and will not include data from participants who are randomized but not treated.

If a participant takes a treatment that is not consistent with the treatment they are randomized to, then they will be reported under the treatment that they actually receive for all safety, PK and pharmacodynamic analyses, where applicable.

4.2. Protocol Deviations

Participants who experience events that may affect their PK profile may be excluded from the PK analysis. At the discretion of the pharmacokineticist, a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed prior to database closure.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

No formal hypothesis testing will be performed in this study.

5.2. General Methods

Descriptive analyses will be performed. Some measures will be summarized using graphical representations, where appropriate.

5.2.1. Analyses for Continuous Endpoints

For continuous variables, the data will be summarized using the number of participants, mean, median, standard deviation, minimum, and maximum in accordance with current Pfizer's data and reporting standards. For appropriate PK parameters, geometric mean and geometric coefficient of variation (geocv%) will also be summarized.

5.2.2. Analyses for Categorical Endpoints

For categorical or ordinal variables, number of participants, numbers and percentages of participants meeting the categorical criteria will be supplied in accordance with current Pfizer's data and reporting standards.

5.3. Methods to Manage Missing Data

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

Methods to handle missing PK data are described below.

Concentrations Below the Limit of Quantification:

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ" where LLQ will be replaced with the value for the lower limit of quantification).

Deviations, Missing Concentrations and Anomalous Values:

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, no sample).
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

Pharmacokinetic Parameters:

Actual PK sampling times will be used in the derivation of PK parameters. If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a participant discontinues). In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥3 evaluable measurements.

If an individual participant has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed from the gastrointestinal tract), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s): Safety Summaries and Analyses

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.

6.1.1. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards.

Participant discontinuations due to adverse events will be detailed by treatment. Data will be reported in accordance with sponsor reporting standards.

Injection site reaction (ISR) and infusion related reaction (IRR) categories will not be summarized under adverse events reporting (see Section 6.1.2 and Section 6.1.3 for details).

6.1.2. Immune-based AEs

Immune-based adverse events will be summarized by visits. If ADA results are available, immune-based adverse events may be summarized by categories of ADA results (for example, by ADA positive, negative and not-tested categories). Immune-based adverse events will include ISR and IRR, and clinically evaluated results of anaphylaxis based on the Sampson's Criteria, and AEs based on the Anaphylactic Reaction Standardised MedDRA Query (SMQ), Angioedema SMQ, Hypersensitivity SMQ, cytokine storm, and delayed immune response.

6.1.3. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards.

6.1.4. Vital Signs

Supine blood pressure, pulse rate, temperature and respiratory rate will be measured at times specified in the SoA given in the protocol.

The following vital signs endpoints will be determined and summarized for each treatment group:

- Actual values, change from baseline in supine blood pressure and pulse rate over all measurements taken postdose.

The increase from baseline will be calculated by subtracting the baseline value from each postdose measurement to give the change from baseline for each participant. The maximum of these values over the duration of dosing will be reported as maximum increase from baseline, except where a participant does not show an increase. In such an instance, the minimum decrease will be reported.

Similarly, decrease from baseline will be calculated by subtracting each post-dose measurement from individual participant's baseline value. Maximum decrease from baseline will be reported as the minimum value of the changes from baseline. In cases where a participant does not show a decrease, the minimum increase will be reported.

Maximum absolute values and changes from baseline for vital signs will also be tabulated by treatment using categories as defined in Appendix 1.

6.1.5. Electrocardiograms

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 maximum absolute value (post-dose) and the maximum increase from baseline for QTcF, QT, heart rate, PR and QRS, will be determined over all measurements taken postdose and reported.

The increase from baseline will be calculated by first subtracting each post-dose measurement from individual participant's baseline to give the change from baseline.

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.

In addition, PR and QRS maximum values and maximum increases from baseline will also be tabulated by treatment using categories as defined in Appendix 1.

6.2. Pharmacokinetic Endpoints

All PK analysis will be performed on the PK analysis set (See Section 4).

The PK parameters in Table 2 will be summarized descriptively by treatment group in healthy participants in accordance with Pfizer data standards. Missing values will be handled as detailed in Section 5.3. The PK parameters will be calculated using standard non-compartmental methods. 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) as specified in the table below.

Table 3. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{last}, CCI, AUC_{inf}, CCI, C_{max}, CCI, AUC_{tau}, CCI, CCI, R_{ac}, $R_{ac,Cmax}$, CCI, CL/F, CCI, V_z/F, F, MRT, CCI	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

There will be two summary tables presenting all PK parameters for SAD and MD separately. They will include data from all cohorts and will be presented by treatment group. For the derivation of PK parameters, actual PK sampling times will be used.

The PK data from Japanese participants will be summarized separately.

The serum concentration of PF-07261271 will be listed and descriptively summarized by nominal PK sampling time and treatment group. Individual participant, mean (with SD), 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.

Where data permit, dose normalized (to a 1 mg dose) C_{max}, AUC_{inf}, AUC_{last} and/or AUC_{τ}, 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. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented and that data from all cohorts are presented on the plot but SAD, MD SC and/or MD IV will be identified with different symbols. The PK data from Japanese cohort will be summarized separately.

Supporting data from the estimation of t½ will be listed where applicable: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of k_{el}. This data may be included in the clinical study report.

Presentations for PF-07261271 concentrations will include:

- A listing of all concentrations sorted by participant ID, treatment group and nominal time postdose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by treatment group and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment group (all treatments on the same plot per scale, based on the summary of concentrations by treatment group and time postdose).

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment group (all treatments on the same plot per scale, based on the summary of concentrations by treatment group and time postdose).

- Individual concentration time plots by treatment group (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each dose per scale).

- Individual concentration time plots by participant (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each participant (containing all doses) per scale].

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long PF-07261271 concentration is quantifiable in the matrix.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual participant plots by time, the actual PK sampling time will be used.

Additional PK analyses may be performed if deemed appropriate.

6.3. Immunogenicity

All immunogenicity data analysis will be performed on the safety analysis set (See Section 4). The analysis of immunogenicity data will include:

- Incidences of ADAs and NAbs, both continuous (if data permit) and categorical (ie, positive or negative or not done), will be listed and summarized descriptively by treatment group and visit.

- Time to first ADA and NAb detection will be summarized by treatment group.

- If data permit, individual ADA and NAb titers for each participant will be plotted with PK concentration and PD target levels against time for each treatment group in the same plot.

- If data permit, the descriptive statistics of PK concentration and PK parameters will be summarized by visit and by ADA and NAb status (for example: positive, negative, not done) in each treatment group.

- If data permit, the descriptive statistics of PD target level will be summarized by visit and by ADA and Nab status in each treatment group.

- Summary statistics will be presented for the ADA and NAb for each participant. The table will also summaries the maximum assay result obtained post-baseline for each participant (if data permit). This analysis may not be included in the CSR.

6.4. PD Biomarkers

If data permit, PD biomarkers analysis for CCI [redacted] will be performed on the PD analysis set (See Section 4). These endpoints are considered exploratory and the results may not be included in the CSR.

The PD biomarkers data will be summarized as following:

- Absolute values, change from baseline and percent change from baseline will be summarized descriptively by treatment group and nominal time postdose.

Presentations for biomarker concentrations will also include:

- A listing of all target levels sorted by participant ID, treatment group and nominal time postdose. The listing will also include the actual times.

- Median target level time plots (on both linear and semi-log scales) against nominal time postdose by treatment group (all treatments on the same plot per scale, based on the summary of target levels by treatment group and time postdose).

- Mean target levels time plots (on both linear and semi-log scales) against nominal time postdose by treatment group (all treatments on the same plot per scale, based on the summary of target levels by treatment group and time postdose).

- Individual target level time plots by treatment group (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each dose per scale).

- Individual target level time plots by participant (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each participant (containing all doses) per scale].

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.

6.5. Subset Analyses

No subset analyses are planned.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

Baseline summary of demographic characteristics will be presented for safety population in accordance with the sponsor reporting standards.

6.6.2. Study Conduct and Participant Disposition

Participant discontinuations and temporary discontinuations will be detailed and summarized using safety population according to Pfizer standards.

6.6.3. Concomitant Medications and Nondrug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be reported in the listings.

7. 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.

APPENDICES

Appendix 1. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

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

Categories for PR and QRS

PR (ms)	max. ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max. ≥140	
QRS (ms) increase from baseline	≥50% increase	

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120

Measurements that fulfill these criteria are to be listed in the clinical study report.

Appendix 2. List of Abbreviations

Abbreviation	Term
Abs	absolute
ADA	anti-drug antibodies
AE	adverse event
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
BP	blood pressure
bpm	beats per minute
CCI [redacted]	
CD	Crohn's Disease
CCI [redacted]	
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 [redacted]	
CRF	case report form
CSR	Clinical Study Report
CCI [redacted]	
ECG	electrocardiogram
CCI [redacted]	
FIH	first-in-human
HP	healthy participant(s)
HR	heart rate
IBD	Inflammatory Bowel Disease
ID	identification
IgG1	Immunoglobulin G1

Abbreviation	Term
IL	interleukin
INF-γ	interferon gamma
IP	investigational product
ISR	injection site reaction
IV	intravenous(ly)
IRR	infusion related reaction
k_{el}	first-order elimination rate constant
MD/md	multiple doses
MRT	mean residence time
NA	not applicable
NAb	neutralizing antibodies
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR	pulse rate
CCI [redacted]	
Q4W	every 4 weeks
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
S1PR	Sphingosine-1-phosphate receptor
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SD	standard deviation
SoA	schedule of activities
CCI [redacted]	
$t_{½}$	terminal phase half-life
TEAE	treatment-emergent adverse event
CCI [redacted]	
T_{max}	time to reach C_{max}
TNF	tumor necrosis factor
UC	ulcerative colitis
CCI [redacted]	
V_z/F	apparent volume of distribution for extravascular dosing