Protocol C4611001

A PHASE 1B, 2-PART, DOUBLE-BLIND, PLACEBO-CONTROLLED, SPONSOR-OPEN STUDY, TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SINGLE ASCENDING (24-HOUR, PART 1) AND MULTIPLE ASCENDING (120-HOUR, PART 2) INTRAVENOUS INFUSIONS OF PF-07304814 IN HOSPITALIZED PARTICIPANTS WITH COVID-19

Statistical Analysis Plan
(SAP)

Version: **2.0**

Date: 29 Jun 2021

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1.0 25 Aug 2020	Original 04 Aug 2020	N/A	N/A
2.0 29 June 2021	PACL 1 17 Sep 2020 Protocol Amendment 1 21 Sep 2020 PACL 2 08 Oct 2020 Protocol Amendment 2 16 Oct 2020 Protocol Amendment 3 05 Nov 2020 PACL 3 06 Nov 2020 Protocol Amendment 4 15 Dec 2020 PACL 4 11 Feb 2021 PACL 5 01 Apr 2021	Ongoing data review	• General – text taken directly from protocol made to be consistent with changes in protocol amendment 4 since the original protocol. • Sections 3.1.3 and 3.1.4 - clarified both planned and unplanned measurements will be included in the maximum increase from baseline. • Section 3.1.4 – clarified baseline calculation. Removed wording around QTcF to be derived for all participants. Only centrally read data used. • Section 3.2 – removed PK parameters to be consistent with protocol amendment 4 although original PK parameters can be calculated for 500mg (in Cohort 1 as more timepoints). Added T_{max} for Part 2: MAD. Removed reference to urine as only collected in Part 1: SAD Cohort 2 which was not conducted • Section 3.3.2 – added exploratory biomarkers from protocol to be included in the CSR. • Section 5.2 – added the screening and early termination will be included in the summaries. • Section 5.3 – added cytokine data for BLQ values • Section 6 – placebo in Part 1: SAD will be reported separately by Cohort. If doses have been repeated, data will be pooled unless otherwise specified. • Section 6.1.2 – added listing of the most clinical significant laboratory test abnormalities.

			• Sections 6.1.3 and 6.1.4 – placebo in Part 1: SAD will be reported separately by Cohort. • Section 6.1.5 – clarified algorithm for oxygen use. • Section 6.2 – removed PK parameters to be consistent with protocol amendment 4 although original PK parameters can be calculated for 500mg (in Cohort 1 as more timepoints). Added T_{max} for Part 2: MAD. Removed reference to urine as only collected in Part 1: SAD Cohort 2 which was not conducted. Remove dose normalized plot for Part 1: SAD and replaced with C_{ss} for Part 2: MAD. • Section 6.3.1 – clarified which outputs are for absolute and change from baseline • Section 6.3.2 – added exploratory biomarkers from protocol to be included in the CSR. Added individual absolute plots for cytokines. Separate listings for biomarkers, coagulation markers, cytokines and serology. C C I [redacted]

2. INTRODUCTION

PF-07304814 is a phosphate prodrug of PF-00835231, a potent and selective inhibitor of the SARS-CoV-2 3CL protease, that is being developed as a continuous IV infusion for the treatment of patients hospitalized with COVID-19.

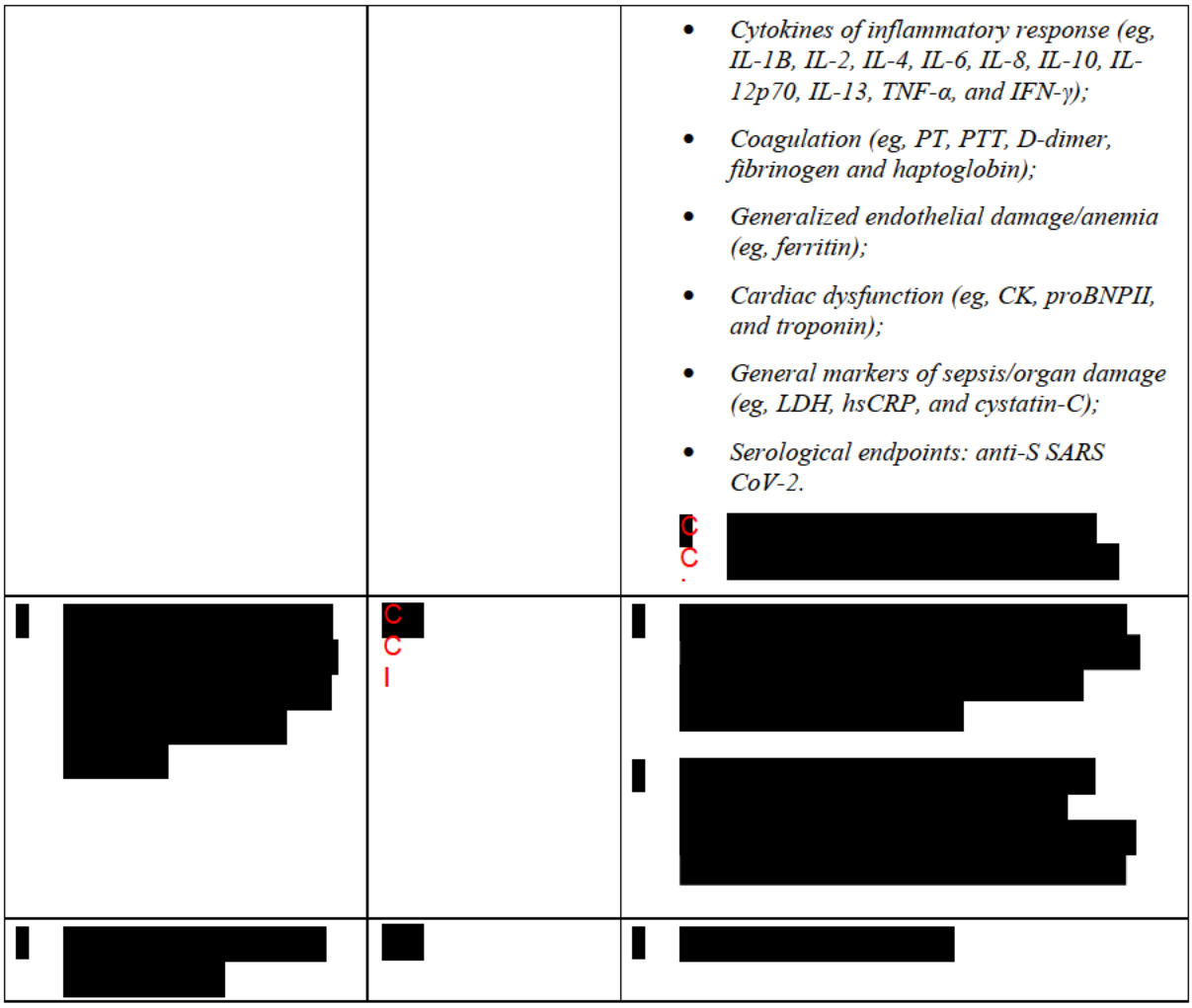
The current study is the first clinical administration with PF-07304814. It is designed as a 2-part study in hospitalized COVID-19 patients as a randomized, double-blind, sponsor-open, parallel group, placebo-controlled trial. Part 1 is to evaluate safety, tolerability, PK and markers of clinical activity of escalating doses of PF-07304814 given as 24-hour IV infusions. Part 2 is to evaluate safety, tolerability, PK and markers of clinical activity with escalating dose of PF-07304814 given as 120-hour IV infusions.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4611001. 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. Study Objectives, Endpoints, and Estimands

There are no estimands for this study.

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• *To assess the safety and tolerability following single and multiple ascending doses of PF-07304814 in hospitalized participants with COVID-19.*	*N/A*	• *Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs (including infusion site reactions).* • *Frequency and magnitude of abnormal laboratory findings.* • *Changes from baseline in vital sign measurements, pulse oximetry/SpO_2, and 12-lead ECG parameters.*
Secondary:	***Secondary:***	***Secondary:***
• *To evaluate the plasma PK of PF-07304814 and PF-00835231 and urinary PK of PF-00835231 following single and multiple ascending doses in hospitalized participants with COVID-19.*	*N/A*	***Part 1: SAD*** • *PF-07304814 (prodrug) and PF-00835231 (active moiety) plasma PK: C_{24} (end of infusion), and C_{24} (dn).* • *PF-00835231 urinary PK parameters: Ae, Ae%.* ***Part 2: MAD*** • *PF-07304814 (prodrug) and PF-00835231 (active moiety) plasma PK: C_{120} (end of infusion), C_{max}, $C_{ss}$and $t_{½}$.*
Tertiary/Exploratory:	***Tertiary/Exploratory:***	***Tertiary/Exploratory:***
[redacted]	C C I	[redacted]
• *Measurement of SARS-CoV-2 viral load (by RT-PCR) and, if feasible, molecular analysis in nasopharyngeal swab and saliva samples over time.*	*N/A*	• *SARS-CoV-2 viral load (RT-PCR) and, if feasible, molecular analysis in nasopharyngeal swab and saliva (at Screening, Days 1, 2, 3 and 6 for **Part 1: SAD**, and at Screening and Days 1, 3, 6, 7, 10, 14 and last follow-up for **Part 2: MAD**).*
• *Measurement of exploratory biomarkers.*	*N/A*	• *Change from baseline in biomarkers (on Days 1, 2, 3 and 6 for **Part 1: SAD**, and Days 1, 3, 6, 7, 10, 14 and last follow-up for **Part 2: MAD**) may include:*



- *Cytokines of inflammatory response (eg, IL-1B, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-α, and IFN-γ);*
- *Coagulation (eg, PT, PTT, D-dimer, fibrinogen and haptoglobin);*
- *Generalized endothelial damage/anemia (eg, ferritin);*
- *Cardiac dysfunction (eg, CK, proBNPII, and troponin);*
- *General markers of sepsis/organ damage (eg, LDH, hsCRP, and cystatin-C);*
- *Serological endpoints: anti-S SARS CoV-2.*

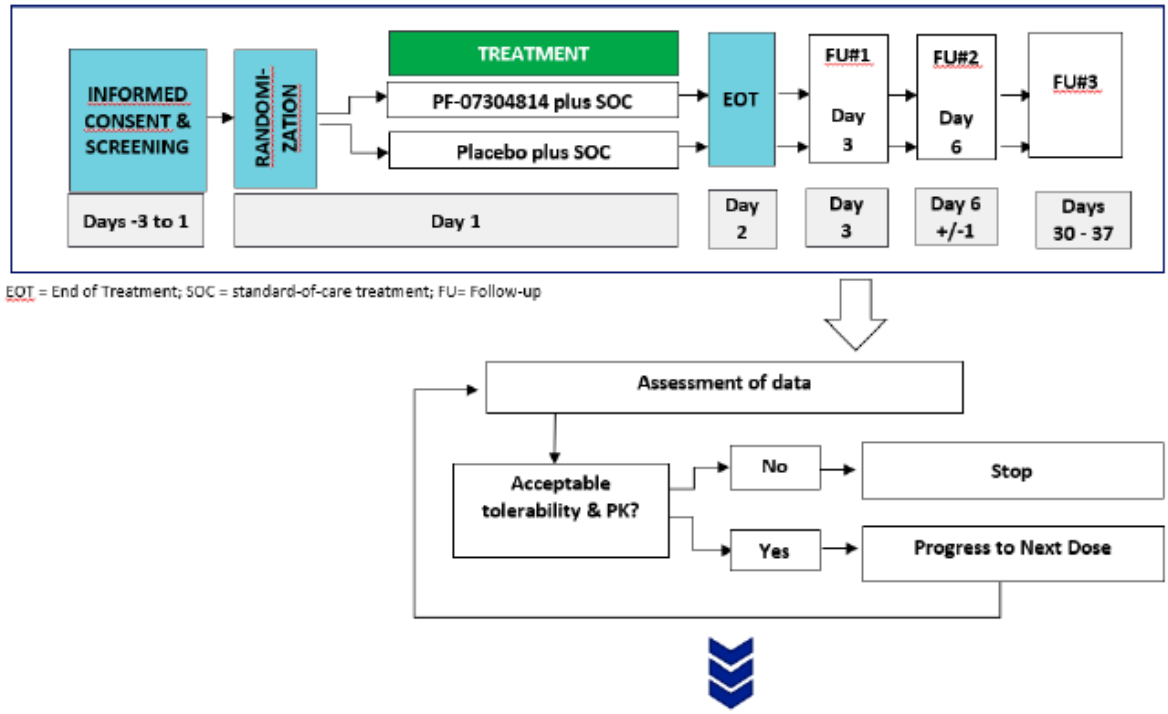
2.2. Study Design

This is a First-In-Human Phase 1b study to evaluate the safety, tolerability and PK of PF-07304814 in participants who are hospitalized for treatment of COVID-19. The participants will be receiving SoC therapy for the treatment of mild, moderate, or severe COVID-19, but will not be eligible if they require mechanical ventilation or ECMO at screening or baseline. All participants will have a confirmed positive test for SARS-CoV-2 and onset of symptoms withing 15 days of Screening. For inclusion into ***Part 2: MAD*** *of the study, participants will be required to have had a positive test for SARS-CoV-2 within 72 hours prior to Screening.*

This is a 2-part study in up to a total of approximately 72 participants on Standard of Care *(SoC) with the intervention such that approximately 72 evaluable participants complete the study. It is a randomized, double-blind, sponsor-open, parallel group, placebo-controlled trial.* ***Part 1: SAD*** *is to evaluate safety, tolerability, and PK of escalating doses of PF-07304814 given as 24-hour IV infusions. Two planned and 3 optional cohorts with 8 participants/cohort will be included in* ***Part 1. Part 2: MAD*** *is to evaluate safety, tolerability,*

and PK with multiple ascending doses of PF-07304814 given as 120-hour IV infusions. Two planned and 2 optional cohorts with 8 participants/cohort will be included in ***Part 2****.*

Figure 1. Part 1: SAD (24-h Continuous IV Infusion)



Precautionary ***sentinel*** *dosing will be used in each dose-escalating cohort in Part 1. A small cohort of 2 participants (1 receiving PF-07304814 and 1 receiving placebo) will be dosed prior to the remainder of the cohort.*

Cohorts of 8 participants each who meet the eligibility criteria will be enrolled. The 2 sentinel participants will be randomized in a ratio of 1 (PF-07304814): 1 (placebo), while the remaining 6 participants will be randomized in a ratio of 5 (PF-07304814):1 (placebo).

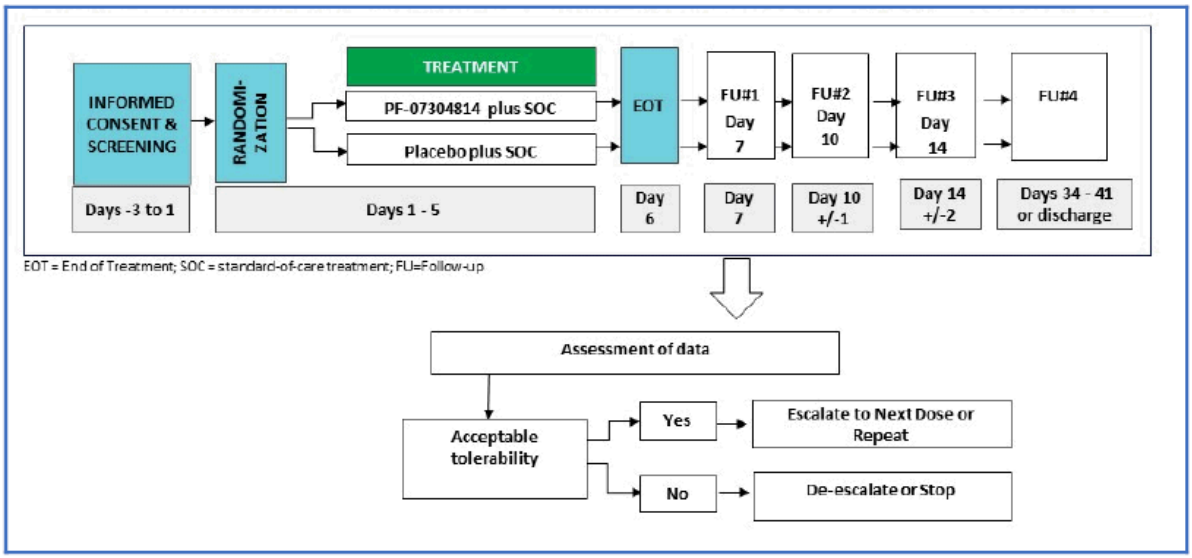
All participants will follow the study procedures as outlined in Schedule of Activities (*SoA). They will be required to stay in hospital from at a minimum, Day 1, pre-dose (at least 2 hours) through completion of Day 3 evaluations (Follow-up 1). Participants will then return for Day 6 (Follow-up 2) activities and a planned final follow-up visit per the SoA on Day 30-37 (Follow-up 3) for a total of approximately 4-5 weeks study participation from first dose to follow-up, excluding screening.*

Participants who discontinue for reasons other than drug-related safety events during the trial may be replaced at the discretion of the Sponsor and investigator.

Three optional cohorts may be added to further explore the dose range based on emerging safety, tolerability and PK assessments. If dose progression is further explored in ***Part 1*** *of*

the study, the predicted exposures for both PF-00835231 and PF-07304814 will not exceed the agreed PK stopping limit with competent regulatory authorities.

Figure 2. Part 2: MAD (120-h Continuous IV Infusion)



Progression to Part 2 will occur if safety, tolerability, and PK data from the Part 1 24-h infusion cohorts as well as those from study C4611007 are determined to be supportive and acceptable by competent regulatory authorities. The dose progression will be based on emerging PK, safety and tolerability data and will not exceed the exposure limits agreed with competent authorities.

Cohorts of 8 participants each who meet the eligibility criteria will be enrolled and randomized in a ratio of 6 PF-07304814:2 placebo. All participants will follow the study procedures as outlined in SoA. They will be required to stay in hospital from at a minimum, Day 1, pre-dose through completion of Day 7 evaluations (Follow-up 1). Participants will then return for Day 10 (Follow-up 2) and Day 14 (Follow-up 3) activities and a final planned follow-up (Follow-up 4) visit per the SoA on Days 34-41 for a total of approximately 5-6 weeks study participation from the start of dosing to follow-up, excluding screening.

Participants who discontinue for reasons other than drug-related safety events during the trial may be replaced at the discretion of the Sponsor and investigator.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Adverse Events

An adverse event 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 study will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date.

A 3-tier approach for summarizing AEs will not be used due to the low number of participants planned to be recruited.

Infusion site reactions are being assessed as part of AEs.

3.1.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol.

Baseline will be the last pre-dose measurement.

To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

3.1.3. Vital Signs

Single supine blood pressure and pulse measurements will be taken at times detailed in the SoA given in the protocol.

Baseline will be defined as the last pre-dose measurement.

The following vital signs endpoints will be determined:

- Change from baseline in supine systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate.
- The maximum decrease from baseline over all measurements taken post-dose for supine systolic and diastolic blood pressures and respiratory rate.
- The maximum increase from baseline over all measurements taken post-dose for supine pulse rate and temperature.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each post-dose measurement (both planned and unplanned) to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

Similarly, the maximum decrease from baseline will be determined by selecting the minimum value of the changes from baseline. In cases where a participant does not show a decrease, the minimum increase should be taken.

3.1.4. ECG

Only centrally read ECG data will be used.

A single 12-lead ECG will be obtained on all participants at screening.

12-lead ECGs will be recorded in triplicate on all subjects at times detailed in the SoA given in the protocol. The QT, heart rate, QTcF, PR and QRS will be recorded at each assessment time.

The average of the triplicate readings collected at each assessment time will be calculated for each ECG parameter. Baseline will be defined as the average (if possible) of the triplicate pre-dose recordings on Day 1.

The following ECG endpoints will be determined:

- Change from baseline in QT interval, heart rate, QTcF interval, PR interval, and QRS complex.
- The maximum absolute value (post-dose) will be calculated for QTcF, PR and QRS
- The maximum increase from baseline over all measurements taken post-dose will be calculated for QTcF.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each post-dose measurement (both planned and unplanned) to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

3.1.5. Pulse Oximetry/SpO2

Pulse oximetry/SpO2 will be taken at times detailed in the SoA given in the protocol.

The following pulse oximetry endpoints will be determined:

- Change from baseline in pulse oximetry/SpO2

Baseline will be defined as the last pre-dose measurement.

3.2. Secondary Endpoint(s)

Blood samples for PK analysis of PF-07304814 and PF-00835231 will be taken according to the SoA given in the protocol. Urine PK was only planned to be collected in Part 1: SAD Cohort 2 and as this was not conducted, has been removed from the SAP.

Plasma PK parameters of PF-07304814 and PF-00835231 will be derived (if data permit) from the concentration-time data using standard noncompartmental methods following 24h infusion (see Table 2) or 120h (see Table 3) infusions. .

Table 2. Noncompartmental PK Parameters for Part 1: SAD

Parameter	SAD Dose	Analysis Scale	PF-07304814	PF-00835231
AUC_{last}	500mg only	ln	D	D
AUC_{inf}*	500mg only	ln	D	D
C_{24}	All	ln	D	D
C_{ss}	500mg only	ln	D	D
C_{max}	500mg only	ln	D	D
$t_{1/2}$*	500mg only	R	D	D
CL*	500mg only	ln	D	
V_{ss}*	500mg only	ln	D	

Key: D=displayed with descriptive statistics,
ln=natural-log transformed, R=raw (untransformed),
*=if data permits, dn = normalized to a 1mg PF-07304814 dose

Table 3. Noncompartmental PK Parameters for Part 2: MAD

Parameter	Analysis Scale	PF-07304814	PF-00835231
C_{120}	ln	D	D
C_{max}	ln	D	D
C_{ss}	ln	D	D
Tmax	R	D	D
$t_{1/2}$*	R	D	D
C_{120} (dn)	ln	D	D
C_{ss} (dn)	ln	D	D

Key: D=displayed with descriptive statistics,
ln=natural-log transformed, R=raw (untransformed),
*=if data permits, dn = normalized to a 1mg PF-07304814 dose

3.3. Other Endpoint(s)

3.3.1. SARS-CoV-2 Viral Load

Nasopharyngeal swab and saliva samples will be collected according to the SoA given in the protocol.

Baseline will be the last pre-dose measurement.

The following viral load endpoints will be determined and reported as separate endpoints:

- Change from baseline in nasophargyngeal swab and saliva viral load

3.3.2. Biomarkers

Exploratory biomarkers will be collected according to the SoA given in the protocol.

Baseline will be the last pre-dose measurement.

The following biomarker endpoints will be determined:

- Change from baseline in blood hs-CRP, LDH, Ferritin, WBC, Monocytes, Haptoglobin, Procalcitonin, Neutrophils and Creatine Kinase
- Change from baseline in coagulation markers D-dimer, PT, aPTT and Fibrinogen
- Change from baseline in cytokines of inflammatory response

Reactive and Non-Reactive IgG will be collected according to the SoA given in the protocol.

All other exploratory biomarkers will be used for internal exploratory purposes and will not be included in the CSR but reported in a separate addendum.

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3.4. Baseline Variables

N/A.

3.5. Safety Endpoints

See Section 3.1 for details.

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.

Population	Description
Enrolled/Randomly assigned to study intervention	*"Enrolled" means a participant's, or his/her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. 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.*
Evaluable	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention* for the given part of the study (**Part 1: SAD** or **Part 2: MAD**).
Safety	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention* for the given part of the study (**Part 1: SAD** or **Part 2: MAD**). *Participants will be analyzed according to the product they actually received.*
PK Concentration Set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported for the given part of the study (**Part 1: SAD** or **Part 2: MAD**).*
PK Parameter Set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest are reported for the given part of the study (**Part 1: SAD** or **Part 2MAD**).*
Biomarker Analysis Set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the biomarkers of interest are reported for the given part of the study (**Part 1: SAD** or **Part 2: MAD**).*

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis testing planned for this study and no statistical decision rules will be applied.

5.2. General Methods

Unless otherwise stated, all summaries and plots will be presented by treatment. Screening and Early Termination will be included in the summaries.

5.2.1. Analyses for Continuous Endpoints

Continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation, median, minimum and maximum values.

Log transformed continuous variables will be presented using summary statistics: number of observations, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

5.2.2. Analyses for Categorical Endpoints

Categorical variables will be presented using summary statistics: number of observations and percentages.

5.3. Methods to Manage Missing Data

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

In all PK 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 (LLQ).

For PK summary tables and plots of mean/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/statistician.

For listing of viral load and cytokine data, BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification (LLQ). For summaries and plots BLQ values will be replaced with the value for the lower limit of quantification (LLQ).

6. ANALYSES AND SUMMARIES

Separate tables will be produced for **Part 1: SAD** and **Part 2: MAD** unless otherwise specified. Listings will include both Part 1: SAD and Part 2: MAD unless otherwise specified. Placebo will be reported separately by Cohort for **Part 1: SAD**. If doses have been repeated, data will be pooled unless otherwise specified.

6.1. Primary Endpoint(s)

6.1.1. Adverse Events

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

6.1.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. Baseline is as defined in Section 3.1.2.

A listing of the most clinically significant laboratory test abnormalities, by participant will be produced. The listing will include the baseline value, most abnormal value and the final value.

6.1.3. Vital Signs

Absolute values and changes from baseline in supine systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate will be summarized by treatment and time post-dose, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.1.3.

Mean changes from baseline for supine systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate will be plotted against time post-dose. On each plot there will be 1 line for each treatment. Data from all cohorts will be plotted on the same figure usingseparate lines for each placebo for Part 1: SAD and a single line for the pooled placebo for Part 2: MAD . Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum decrease from baseline for supine systolic and diastolic blood pressures and respiratory rate and maximum increase from baseline for supine pulse rate and temperature will be summarized by treatment, according to sponsor reporting standards.

Maximum absolute values and changes from baseline for supine vital signs will also be summarized descriptively by treatment using categories as defined in Appendix 1. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post-dose timepoints will be counted in these categorical summaries.

6.1.4. ECG

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by treatment and time post-dose using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.1.4.

Mean changes from baseline in QT, heart rate and QTcF will be plotted against time postdose. On each plot there will be 1 line for each treatment. Data from all cohorts will be plotted on the same figureusing separate lines for each placebo for Part 1: SAD and a single line for the pooled placebo for Part 2: MAD . Corresponding individual plots of changes from baseline will also be produced for each treatment.

Changes from baseline in QTcF will also be plotted separately against drug concentrations (separate plots for PF-07304814 and PF-00835231). This will be a scatter plot for all observations where QTcF and drug concentration are recorded. Placebo data will also be included (with drug concentration set to zero). Different symbols will be used for each treatment.

Maximum increase from baseline for QTcF will be summarized by treatment, according to sponsor reporting standards.

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by treatment using categories as defined in Appendix 1 (for QTcF these correspond to the Pfizer Guidance in Section 8). Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries.

Listings of participants with any single post-dose value >500msec will also be produced for QTcF.

6.1.5. Pulse Oximetry/SpO2

Absolute values and changes from baseline in pulse oximetry/SpO2 will be summarized by treatment and time post-dose. Baseline is as defined in Section 3.1.5.

Numbers and percentages of participants meeting the categorical criteria as defined in Appendix 1 will be provided. All planned and unplanned post-dose timepoints will be counted in these categorical summaries.

All tables above will have three columns per treatment based on whether the participant is receiving oxygen CCI [redacted] throughout, at somepoint during the study or never received. Days 2 to 6 will be used i.e. Days 2, 3 & 6 for Part 1: SAD and Days 2, 3, 4, 5 & 6 for Part 2: MAD and any unplanned readings between Day 2 and Day 6 will be used (where collected).

6.2. Secondary Endpoint(s)

To assess the pharmacokinetics of PF-07304814 and PF-00835231, the PK parameters detailed in Section 3.2 will be listed and summarized for participants in the PK analysis set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3. Each PK parameter will be summarized byanalyte and dose. Each summary will include the set of summary statistics as specified in Table 4 for the **Part 1: SAD** part and Table 5 for the **Part 2: MAD** part respectively.

Table 4. PK Parameters to be Summarized Descriptively for Part 1: SAD

Parameter	Dose	Summary Statistics
C_{24}	All doses	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
AUC_{last}, AUC_{inf}, C_{24}, C_{ss}, C_{max}, CL and V_{ss}	500mg only	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
$t_{1/2}$,	500mg only	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

Table 5. PK Parameters to be Summarized Descriptively for Part 2: MAD

Parameter	Summary Statistics
C_{120}, C_{max}, T_{max}, C_{ss}, C_{120} (dn) and C_{ss} (dn)	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

There will be one summary table for each analyte presenting all PK parameters. This will include data from all cohorts and will be presented by dose.

To assess the relationship between the PK parameters and dose, dose normalized C_{120} and C_{ss} (**Part 2: MAD**) of PF-07304814 and PF-00835231 will be plotted against dose (using a logarithmic scale), and 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. Dose normalized C_{120} and C_{ss} (**Part 2: MAD**) for both analytes will be listed along with other individual PK parameters.

Supporting data from the estimation of t½ will be listed by analyte and dose 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}. These data may be included in the CSR.

Presentations for PF-07304814 and PF-00835231 concentrations will be presented by analyte using participants in the PK concentration analysis set (as defined in Section 4) will include:

- a listing of all concentrations sorted by participant ID, dose and nominal time post-dose. 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 dose and nominal time post-dose, 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.
- individual concentration-time plots by dose (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each dose per scale).
- median concentrations-time plots (on both linear and semi-log scales) against nominal time post-dose by dose (all doses on the same plot per scale, based on the summary of concentrations by dose and time post-dose).
- mean concentrations-time plots (on both linear and semi-log scales) against nominal time post-dose by dose (all doses on the same plot per scale, based on the summary of concentrations by dose and time post-dose).

The scale used for the x-axis (time) of these plots will be decided on review of the data, and will depend on how long PF-07304814 and PF-00835231 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.

6.3. Other Endpoint(s)

6.3.1. SARS-CoV-2 Viral Load

Absolute and changes from baseline in nasopharyngeal swab and saliva viral load will be summarized by treatment and time post-dose. Baseline is as defined in Section 3.3.1.

Individual and mean plots will be produced for absolute and changes from baseline in nasopharyngeal swab and saliva viral load by treatment.

The percentage of participants who have viral load detectable at baseline and undetectable (<BLQ for both nasopharyngeal swab and saliva) at 24 hours after the end of the infusion (i.e. at the FU #1 visit) will be produced by treatment.

6.3.2. Biomarkers

Absolute and changes from baseline in blood hs-CRP, LDH, Ferritin, WBC, Monocytes, Haptoglobin, Procalcitonin, Neutrophils and Creatine Kinase will be summarized by treatment and time post-dose. Baseline is as defined in Section 3.3.2.

Absolute and changes from baseline in coagulation markers (D-dimer, PT, aPTT) and Fibrinogen will be summarized by treatment and time post-dose. Baseline is as defined in Section 3.3.2.

Absolute and changes from baseline in cytokines of inflammatory response will be summarized by treatment and time post-dose. Baseline is as defined in Section 3.3.2.

Individual and mean changes from baseline plots will be produced by treatment. For cytokines - individual absolute plots will also be produced.

The percentage of participants with Reactive and Non-Reactive IgG will be summarized by treatment.

Listings of biomarkers, coagulation markers, cytokines and serology will be produced separately to the laboratory listing.

CCI [redacted]

6.4. Subset Analyses

No subset analyses will be performed.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Study Conduct and Participant Disposition

Participant evaluation groups will show participant disposition for each phase of the study (screening, treatment and follow-up) and will additionally show which participants were analysed for PK, biomarker as well as for safety. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment. Data will be reported in accordance with the sponsor reporting standards.

6.5.2. Demographic Data

Demographic data (age, gender, race, ethnicity, weight, body mass index and height) will be summarised by treatment and overall (if applicable) in accordance with the sponsor reporting standards.

6.5.3. Significant Medical History

Significant medical history will be summarized by treatment and overall.

6.5.4. Study Treatment Exposure

For **Part 2: MAD**, a summary table of infusion duration will be presented by treatment and overall

6.5.5. Concomitant Medications and Nondrug Treatments

All prior and concomitant medication(s) as well as non-drug treatment(s) will be reported according to current sponsor reporting standards.

6.6. Safety Summaries and Analyses

See Section 6.1 for details.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. However, as this is a sponsor-open study, the sponsor will conduct unblinded reviews of the safety and PK data during the course of the study along with the IRC for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development. Unblinded results will be reviewed by a designated limited number of sponsor colleagues within the study team.

An independent IRC will assess whether it is safe to proceed to continued dosing after a small sentinel cohort of 2 participants within each dose-escalating cohort or if it is safe to dose-escalate to the next dose level within Part 1.

7.2. Interim Analyses and Summaries

N/A

8. REFERENCES

Pfizer Guidance for Evaluation of QT / QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs; Members of the Cardiovascular Safety & Advisory Council (CVSAC); January 26, 2018

APPENDICES

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

Categories for QTcF

Absolute value of QTcF (msec)	>450 and ≤480	>480 and ≤500	>500
Increase from baseline in QTcF (msec)	>30 and ≤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 & Pulse Oximetry

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
Standing pulse rate (bpm)	min. <40	max. >140
Pulse oximetry/SpO2 (%)	<94	