Protocol *C4671008*

A PHASE 1, OPEN-LABEL, RANDOMIZED, SINGLE-DOSE, CROSSOVER STUDY TO ESTIMATE THE RELATIVE BIOAVAILABILITY OF PF-07321332 FOLLOWING ORAL ADMINISTRATION OF 4 DIFFERENT FORMULATIONS RELATIVE TO THE COMMERCIAL TABLET FORMULATION IN HEALTHY ADULT PARTICIPANTS UNDER FASTED CONDITIONS

Statistical Analysis Plan (SAP)

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	March 11, 2022	PPD	Not Applicable

NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

None.

APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

PF-07321332 is a potent and selective inhibitor of the SARS-CoV-2 3CL protease that is currently being developed as an oral treatment of COVID-19. Ritonavir is a strong CYP3A4 inhibitor being used to inhibit the metabolism of PF-07321332 in order to increase plasma concentrations of PF-07321332 to values that are anticipated to be efficacious.

This study objective is to estimate the rBA of single doses of PF-07321332 300 mg slower dissolution tablet formulation and larger particle size tablet formulation with ritonavir 100 mg compared to a 300 mg doses of PF-07321332 commercial tablet formulation with ritonavir 100 mg. An additional objective of this study is to estimate the rBA of PF-07321332 300 mg doses SDD extemporaneous suspension formulation administered with and without ritonavir 100 mg compared to PF-07321332 300 mg doses commercial tablet formulation co administered with ritonavir 100 mg.

2.1. Study Design

This is a Phase 1, open-label, single-dose, randomized, crossover study in healthy adult participants to evaluate relative bioavailability of PF-07321332 slower dissolution tablet formulation (Test formulation 1) and larger particle size tablet formulation (Test formulation 2), compared to the PF-07321332 commercial tablet formulation (Reference formulation) under fasted conditions. An additional objective of this study is to estimate the rBA of PF-07321332 300 mg doses SDD extemporaneous suspension formulation administered with (Test formulation 3) and without (Test formulation 4) ritonavir 100 mg compared to PF-07321332 300 mg doses commercial tablet formulation administered with ritonavir 100 mg (Reference).

Approximately 12 healthy male and/or female participants will be enrolled and randomized to 1 of 6 possible treatment sequences to ensure at least 10 participants will complete the study. Participants who discontinue from the study for non-safety reasons may be replaced at the sponsor's discretion in collaboration with the Investigator. The replacement participant will receive the same treatment sequences as the participant who discontinued.

Each enrolled participant will participate in 5 study periods to receive 5 different treatments according to the sequence determined by randomization:

- *Treatment A: PF-07321332 300 mg (2 × 150 mg commercial tablets)/100 mg ritonavir.*
- *Treatment B: PF-07321332 300 mg (2 × 150 mg slower dissolution tablets)/100 mg ritonavir.*

- *Treatment C: PF-07321332 300 mg (2 × 150 mg large particle size tablets)/100 mg ritonavir.*
- *Treatment D: PF-07321332 300 mg (SDD suspension)/100 mg ritonavir.*
- *Treatment E: PF-07321332 300 mg (SDD suspension).*

Participants will be randomly assigned to 1 of 6 sequences as shown below in Table 1. Participants will be discharged on Day 4 of Period 5, following completion of all assessments. Between each treatment, a minimum of 4 days washout is proposed to minimize any residual PF-07321332 concentrations prior to start of the next treatment. The total planned duration of participation from the Screening visit to the last Follow-up phone call, is approximately 12 weeks.

Table 1. Study Schematic

Treatment Sequence	***Period 1***	***Period 2***	***Period 3***	***Period 4***	***Period 5***
Sequence 1 (N =2)	*Treatment A*	*Treatment B*	*Treatment C*	*Treatment D*	*Treatment E*
Sequence 2 (N =2)	*Treatment B*	*Treatment C*	*Treatment A*	*Treatment D*	*Treatment E*
Sequence 3 (N =2)	*Treatment C*	*Treatment A*	*Treatment B*	*Treatment D*	*Treatment E*
Sequence 4 (N =2)	*Treatment A*	*Treatment C*	*Treatment B*	*Treatment E*	*Treatment D*
Sequence 5 (N =2)	*Treatment B*	*Treatment A*	*Treatment C*	*Treatment E*	*Treatment D*
Sequence 6 (N =2)	*Treatment C*	*Treatment B*	*Treatment A*	*Treatment E*	*Treatment D*

2.2. Study Objectives

2.2.1. Primary Objectives

- *To estimate the rBA of the PF-07321332 slower dissolution tablet formulation (2 × 150 mg)/ritonavir 300/100 mg compared to the PF-07321332 commercial tablet formulation (2 × 150 mg) ritonavir 300/100 mg under fasted conditions.*
- *To estimate the rBA of the PF-07321332 larger particle size tablet formulation (2 × 150 mg)/ritonavir 300/100 mg compared to the PF-07321332 commercial tablet formulation (2 × 150 mg)/ritonavir 300/100 mg under fasted conditions.*
- *To estimate the rBA of the PF-07321332 SDD suspension formulation/ritonavir 300/100 mg compared to the PF-07321332 commercial tablet formulation (2 × 150 mg)/ritonavir 300/100 mg under fasted conditions.*
- *To estimate the rBA of the PF-07321332 SDD suspension formulation (300 mg) without ritonavir compared to the PF-07321332 commercial tablet formulation (2 × 150 mg)/ritonavir 300/100 mg under fasted conditions.*

2.2.2. Secondary Objective

- *To evaluate the safety and tolerability of PF-07321332/ritonavir in healthy participants.*

2.2.3. Tertiary/Exploratory Objectives

- *To characterize the PK of PF-07321332 after single oral doses of different formulations.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

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

Final analysis will follow the official database release. As this will be an open-label study, there is no formal unblinding of the randomization code.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No hypotheses are required.

4.2. Statistical Decision Rules

No decision rules are required.

5. ANALYSIS SETS

5.1. Enrolled/Randomly Assigned to Study Intervention

"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and 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. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

5.2. Pharmacokinetic (PK) Analysis Set

5.2.1. Concentration Analysis Set

All participants who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported.

5.2.2. Parameter Analysis Set

All participants who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of primary interest are reported.

5.3. Pharmacodynamic Analysis Set

None.

5.4. Safety Analysis Set

All participants who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

5.5. Other Analysis Sets

None.

5.6. 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, for example takes a treatment out of sequence or takes the same treatment twice, then they will be reported under the treatment that they actually receive for all safety, and PK analyses, where applicable.

5.7. Protocol Deviations

Participants who experience events that may affect their PK profile (eg lack of compliance with dosing) 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 to identify major and minor deviations prior to database closure.

5.7.1. Deviations Assessed Prior to Randomization

At Screening, the investigator will assess participants against the inclusion and exclusion criteria as set out in Sections 5.1 and 5.2 of the protocol.

5.7.2. Deviations Assessed Post-Randomization

A full list of protocol deviations for the study report will be compiled prior to database closure. Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

None.

6.2. Safety Endpoints

An adverse event will be 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 last dose plus the lag time (28 days) will be flagged as TEAEs.

Events that occur in a non-treatment period (for example, Washout or Follow-up) will be counted as treatment emergent and attributed to the previous treatment taken.

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

- *adverse events;*
- *laboratory data.*

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of PF- 07321332 and ritonavir will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for PF- 07321332 (if possible) and ritonavir from the concentration-time data using standard noncompartmental methods:

Table 2. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	PF- 07321332	Ritonavir
AUC_{inf}*	ln	A, D	D
AUC_{last}	ln	A, D	D
C_{max}	ln	A, D	D
T_{max}	R	D	D
$t_{1/2}$*	R	D	D
CL/F*	ln	D	D
V_z/F*	ln	D	D

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits.

6.3.2. PD Endpoints

None.

6.4. Covariates

None.

7. HANDLING OF MISSING VALUES

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

7.1. 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).

7.2. 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.

7.3. 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 treatment with ≥3 evaluable measurements. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing; and analyses will not be performed for a particular parameter if more than 50% of the data are NC.

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 in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

Precision of the estimate of PK parameters will be determined by constructing 90% confidence intervals around the estimated difference between the Test and Reference treatments using a mixed effects model based on natural log transformed data. The mixed effects model will be implemented using SAS Proc Mixed, with REML estimation method and Kenward-Roger degrees of freedom algorithm.

8.2. Statistical Analyses

Data for Treatments A, B, and C will be analyzed separately from data for Treatments D and E.

Natural log transformed AUC_{inf} (if data permits), AUC_{last} and C_{max} will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within a sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Treatment A will be the Reference treatment while Treatments B and C will be the Test treatments.

For the SDD formulations, natural log transformed AUC_{inf} (if data permits), AUC_{last} and C_{max} will be analyzed using a mixed effect model with sequence and treatment as fixed effects and participant within a sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Treatment A will be the Reference treatment while Treatments D and E will be the Test treatments.

PK parameters, including plasma AUC_{inf} (if data permits), AUC_{last}, C_{max}, and T_{max}, $t_{½}$ (if data permits) of PF-07321332 will be summarized descriptively by treatment. For AUC_{inf} (if data permits), AUC_{last} and C_{max}, a listing of the individual participant ratios (Test/Reference) will be provided. Box and whisker plots for AUC_{inf} (if data permits), AUC_{last} and C_{max}, will be plotted by treatment.

The plasma concentrations of PF-07321332 will be listed and descriptively summarized by nominal PK sampling time and treatment. Individual participant, as well as mean and median profiles of the plasma concentration time data will be plotted by treatment using actual (for individual) and nominal (for mean and median) times respectively. Mean and median profiles will be presented on both linear and semi-log scales.

For ritonavir, only the PK parameters summary table and individual listings will be reported.

Residuals from the model will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the clinical study report. If there are major deviations from normality or outliers then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

Table 3. PK Parameters to be Summarized Descriptively by Treatment

Parameter	Summary Statistics
AUC_{inf}, AUC_{last}, C_{max}, CL/F, V_z/F	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.

For AUC_{inf}, AUC_{last} and C_{max} a listing of the individual participant ratios (Test/Reference) will be provided.

Supporting data from the estimation of t½ and AUC_{inf} will be listed by analyte and treatment: 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- 07321332 concentrations will include:

- A listing of all concentrations sorted by participant ID, treatment 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 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 (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).

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

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

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.

8.3. Safety Analysis

A set of summary tables split by treatment will be produced to evaluate any potential risk associated with the safety and toleration of administering study treatments.

8.3.1. Treatment and Disposition of Participants

Participant evaluation groups will show end of study participant disposition and will show which participants were analyzed for pharmacokinetics, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for participant discontinuation(s) by treatment.

Data will be reported in accordance with the sponsor reporting standards.

8.3.2. Demographic and Clinical Examination Data

A break down of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by sex at birth and 'All Participants' in accordance with the sponsor reporting standards.

8.3.3. Discontinuation(s)

Participant discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by treatment.

Data will be reported in accordance with the sponsor reporting standards.

8.3.4. Adverse Events

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

8.3.5. Laboratory Data

Laboratory data will be listed in accordance with the sponsor reporting standards.

8.3.6. Vital Signs Data

Vital Signs data will be databased and available upon request.

8.3.7. ECG Data

ECG data will be databased and available upon request.

8.3.8. Other Safety Data

None.

8.3.9. Concomitant Treatments

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

8.3.10. Screening and Other Special Purpose Data

If these data will be brought in-house, then it will be listed.

9. REFERENCES

None.

10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

An example of the PROC MIXED code is provided below:

```
proc mixed data=tab.pk(where period <4);
        class seq period trt participant;
        model l&var=seq period trt/ ddfm=KR;
        random participant(seq);
        lsmeans trt;
        estimate 'B vs A' trt -1  1  0   /cl alpha=0.1;
        estimate 'C vs A' trt -1  0  1   /cl alpha=0.1;
        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

/* Letter assignments for treatments (trt) within the estimate statement above are as follows;

A = PF-07321332 300 mg (2 × 150 mg commercial tablets)/100 mg ritonavir (Reference);
B = PF-07321332 300 mg (2 × 150 mg slower dissolution tablets)/100 mg ritonavir (Test)
C = PF-07321332 300 mg (2 × 150 mg large particle size tablets)/100 mg Ritonavir (Test)
*/;

proc mixed data=tab.pk(where trt in (A,D,E);
        class seq trt participant;
        model l&var=seq trt/ ddfm=KR;
        random participant(seq);
        lsmeans trt;
        estimate 'D vs A' trt -1  1  0   /cl alpha=0.1;
        estimate 'E vs A' trt -1  0  1   /cl alpha=0.1;
        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

/* Letter assignments for treatments (trt) within the estimate statement above are as follows;

A = PF-07321332 300 mg (2 × 150 mg commercial tablets)/100 mg ritonavir (Reference)
D = PF-07321332 300 mg (SDD suspension)/ 100 mg ritonavir
E = PF-07321332 300 mg (SDD suspension) */;
```