Protocol *C4671011*

A PHASE 1, NON-RANDOMIZED, OPEN-LABEL STUDY TO ASSESS THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF PF-07321332 BOOSTED WITH RITONAVIR IN ADULT PARTICIPANTS WITH RENAL IMPAIRMENT AND IN HEALTHY PARTICIPANTS WITH NORMAL RENAL FUNCTION

Statistical Analysis Plan (SAP)

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

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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.

The purpose of this study is to characterize the effect of renal impairment on the plasma PK of PF-07321332/ritonavir. Findings from this study will be used to develop dosing recommendations so that the dose and/or dosing interval may be adjusted appropriately in the presence of renal disease.

2.1. Study Design

This is a Phase 1, non-randomized, open-label, 2-part study to investigate the effect of renal impairment on the plasma and urine (if applicable) PK, safety and tolerability of a single oral dose of PF-07321332 in combination with the PK boosting agent ritonavir in approximately 32 participants. Part 1 will be conducted in approximately 24 adult male and female participants with stable mild or moderate renal impairment and a control group of participants with normal renal function. Part 2 will be conducted in approximately 8 adult male and female participants with stable severe renal impairment. A staged approach, as outlined in detail below, will be followed in the study.

Participants will be selected and categorized into normal renal function or renal impairment groups based on their eGFR as shown in table below:

Table 1. Renal Function Categories by eGFR Ranges

Cohort	***Renal Impairment[a]***	***Estimated eGFR[b](mL/min)***	***Number of Participants***
1	*Moderate Renal Impairment*	*≥30 to <60*	***8***
2	*Mild Renal Impairment*	*60 – 89*	***8***
3	*None (Normal))*	*≥90*	*8*
4	*Severe Renal Impairment*	*<30 and not requiring dialysis*	*8*

a. Stages of renal impairment are based on Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Chronic Kidney Disease (CKD).

b. Estimate of eGFR based on CKD-EPI formula. The average of the 2 screening eGFR value will be used for group assignment.

Part 1: *Approximately 24 participants will be enrolled in Part 1; approximately 8 participants with moderate renal impairment (Cohort 1), approximately 8 with mild renal impairment (Cohort 2), and approximately 8 with normal renal function (Cohort 3), to ensure at least 6 evaluable participants in each group. Participants from the moderate renal impairment group (Cohort 1) will be recruited first. Enrollment into the mild renal impairment group (Cohort 2) will initiate, if necessary, after preliminary analysis of PK and safety data from at least 2 participants with moderate renal impairment have been reviewed. The healthy participants (Cohort 3) will be recruited later such that each participant's age is within ±10 years and weight is within ±15 kg of the mean of the groups of participants with renal impairment group. Care will be taken when recruiting the healthy participants such that the entire group is not of substantially different age or of substantially different body weight than the moderate renally impaired participants. Approval from the sponsor must be obtained* ***before*** *proceeding with dosing healthy participants with normal renal function.*

Participants with stable mild and moderate renal impairment and control participants with normal renal function will receive a single 100 mg dose of PF-07321332 administered orally in combination with the PK boosting agent ritonavir administered as a 100 mg dose at -12, 0, 12, and 24 hours relative to PF-07321332 dosing.

If there are participants who withdraw or discontinue treatment from the normal or mild or moderate renal impairment groups and who are considered to be non-evaluable with respect to the primary PK objective, additional participants can be enrolled at the discretion of the sponsor.

Part 2: *The decision to conduct Part 2 will be made based on results from Part 1. Enrollment into Part 2 will not commence until preliminary analysis of PK and safety data from at least 2 participants with moderate renal impairment have been reviewed. Approximately 8 participants with severe (Cohort 4) renal impairment will be enrolled to ensure at least 6 evaluable participants in each group. As in Part 1, renal impairment classification will be based on eGFR. Participants will receive a single 100 mg dose of PF-07321332 administered orally in combination with the PK boosting agent ritonavir administered as a 100 mg dose at -12, 0, 12, and 24 hours relative to PF-07321332 dosing.*

For both Parts 1 and 2*: All participants in both normal and renal impairment groups will provide informed consent and undergo Screening evaluations to determine their eligibility. Participants will be selected and categorized into normal renal function or renal impairment groups based on their eGFR (using the CKD-EPI equation).*

Eligible participants will be admitted to the CRU on Day -1 (at least 12 hours prior to the dosing of PF-07321332 on Day 1) and will be confined in the CRU until Day 3. On the evening of Day -1, participants will receive a single 100 mg dose of ritonavir (-12 hour relative to PF-07321332 dosing). On the morning of Day 1, the participants will receive a single dose of 100 mg PF-07321332 with a 100 mg dose of ritonavir after a fast of at least 10 hours. Ritonavir, 100 mg, will continue to be dosed at 12 and 24 hours post PF-07321332 dosing to ensure maintenance of the PK boosting effect. Serial blood and

urine samples at specified intervals will be collected up to 48 hours post-dose for plasma and urine PK assessments.

Safety assessments will be performed during Screening, on Day -1 prior to dosing, and on Day 3. Physical examinations, vital sign measurements, and clinical laboratory tests will be conducted, and AEs will be monitored to assess safety. The total participation time (eg, CRU confinement time for study procedures) for each participant in this study is approximately 3 nights/4 days (excluding screening & Follow-Up contact).

A safety follow-up call will be made to participants 28 to 35 days from administration of the dose of study intervention.

Number of Participants

Approximately 32 participants may be enrolled to study intervention.

Note: "Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity 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.

Intervention Groups and Duration

Each enrolled participant will receive a single 100 mg dose of PF-07321332 administered orally in combination with the PK boosting agent ritonavir administered as a 100 mg dose at -12, 0, 12, and 24 hours relative to PF-07321332 dosing.

The total planned duration of participation, from the Screening visit to the last Follow-up phone call, is approximately up to 9 weeks.

Calculation of eGFR

The following CKD-EPI equation will be used to calculate eGFR ($S_{cr,\ std}$ denotes serum creatinine measured with a standardized assay for serum creatinine):

If female and SCr is ≤0.7 mg/dL:

$$eGFR\ (mL/min/1.73\ m^2) = 144 \times (S_{Cr,\ std}/0.7)^{-0.329} \times 0.993^{age}\ (\times 1.159, \text{if Black})$$

If female and SCr is >0.7 mg/dL:

$$eGFR\ (mL/min/1.73\ m^2) = 144 \times (S_{Cr,\ std}/0.7)^{-1.209} \times 0.993^{age}\ (\times 1.159, \text{if Black})$$

If male and SCr is ≤0.9 mg/dL:

$$eGFR\ (mL/min/1.73\ m^2) = 141 \times (S_{Cr,\ std}/0.9)^{-0.411} \times 0.993^{age}\ (\times 1.159, \text{if Black})$$

If male and SCr is >0.9 mg/dL:

$$GFR\ (mL/min/1.73\ m^2) = 141 \times (S_{Cr,\ std}/0.9)^{-1.209} \times 0.993^{age}\ (\times 1.159, \text{if Black})$$

Note that the value of eGFR, which is directly obtained from the laboratory or calculated using the equation above, is generally normalized to an average body size of 1.73 m^2 for diagnosis, prognosis and treatment of renal disease. In terms of clearance of renally filtered drugs (including secreted drugs), renal elimination capacity is related to absolute GFR in mL/min. To use the CKD-EPI-derived, BSA-adjusted value of eGFR to obtain absolute GFR (mL/min) for renal disease classification or participant assignment into different renal disease groups, this value should be multiplied by the individual participant's BSA (ie, measured BSA/1.73 m^2). The BSA of an individual can be calculated by the following formula as described below:

$$BSA = (Weight^{0.425} \times Height^{0.725}) \times 0.007184$$

In summary, GFR in mL/min calculated as below will be used for renal impairment group placement:

Step 1: Obtain the CKD-EPI-derived eGFR:

Step 2: Convert the CKD-EPI-derived, BSA-adjusted eGFR obtained above to absolute GFR (mL/min) for eligibility assessment using the following equation:

- *eGFR (mL/min) = eGFR (mL/min/1.73m^2) × participant's BSA, where BSA is calculated as BSA = $(Weight^{0.425} \times Height^{0.725}) \times 0.007184$.*

CL_{CR} will also be estimated from a spot serum creatinine measurement using the following C-G equation:

$$CL_{CR}\ (mL/min) = \frac{(140 - age\ [years]) \times total\ body\ weight\ (kg) \times (0.85\ for\ females)}{72 \times serum\ creatinine\ (mg/dL)}$$

Note that eGFR calculated by the CKD-EPI equation will be used for categorization of degrees of renal impairment. Nevertheless, renal function will be estimated using both C-G and CKD-EPI equations in this study and dose recommendations will be made using both C-G and CKD-EPI equations.

To be enrolled into the study, participant must demonstrate stable renal function, with ≤25% change based upon screening S1 eGFR and screening S2 eGFR (calculated by the CKD-EPI equation). The S2 eGFR assessment should be performed between 3 to 14 days after the S1 eGFR assessment. The average of these 2 eGFR values will be used for group placement based on the renal function classification category.

- *If the renal function stability criterion is met and the renal function classification category remains the same between S1 eGFR and the average of the S1 and S2 eGFRs, participant will be eligible for enrollment.*
- *If the renal function stability criterion is not met, participant will be screen failed.*
- *If the renal function stability criterion is met but the renal function classification category changes between S1 eGFR and the average of the S1 and S2 eGFRs, the eGFR measurement at Day -1 will also be used to determine the appropriate group classification category using an average of all 3 eGFR values, to determine whether the participant will be eligible for enrollment.*

Please see Table 2 below regarding demonstration of stable renal function:

Table 2. Criteria to Establish Stable Renal Function

Renal function Measurement	***eGFR (mL/min)***	***Criterion for stability***
S1	*G1*	*N/A*
S2 (Within 3 to 14 days after S1)	*G2*	*D=|G2-G1|×100/G1[a]* *If D ≤25%; stable* *If D >25%; not stable*

a. Parenthesis of | | represents absolute values.

2.2. Study Objectives

2.2.1. Primary Objectives

- ***Part 1****: To evaluate the effect of mild (if applicable) and moderate renal impairment on the PK of PF-07321332, following a single oral dose administration of PF-07321332 pharmacokinetically boosted with ritonavir.*
- ***Part 2****: To evaluate the effect of severe renal impairment on the PK of PF-07321332, following a single oral dose administration of PF-07321332 pharmacokinetically boosted with ritonavir.*

2.2.2. Secondary Objectives

- *To evaluate the safety and tolerability of PF-07321332 and ritonavir, following a single oral dose administration of PF-07321332 pharmacokinetically boosted with ritonavir, in participants with renal impairment and in healthy participants with normal renal function.*

- *To characterize* additional *PK parameters of PF-07321332 following a single oral dose of PF-07321332 pharmacokinetically boosted with ritonavir by renal function.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No formal interim analysis will be conducted for this study. However, 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 statistical hypothesis will be tested in this study.

4.2. Statistical Decision Rules

There are no statistical decision rules.

5. ANALYSIS SETS

5.1. Pharmacokinetic (PK) Analysis Set

5.1.1. Concentration Analysis Set

The PK concentration population will be defined as all participants treated in whom at least 1 plasma concentration value is reported.

5.1.2. Parameter Analysis Set

The PK parameter analysis population is defined as all participants dosed who have at least 1 of the PK parameters of primary interest.

5.2. Pharmacodynamic Analysis Set

None.

5.3. 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.

5.4. Other Analysis Sets

None.

5.5. 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.

5.6. 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.

5.6.1. 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.

5.6.2. 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

Any events occurring following start of treatment or increasing in severity will be counted as treatment emergent.

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 assessments (see protocol for collection days and list of parameters):

- *adverse events,*
- *laboratory data,*
- *vital signs data,*
- *ECG results.*

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of PF-07321332 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) from the concentration-time data using standard noncompartmental methods:

Table 3. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	PF-07321332
AUC_{last}	ln	A, D
AUC_{inf}*	ln	A, D
C_{max}	ln	A, D
C_{12}	R	D
C_{24}	R	D
T_{max}	R	D
$t_{1/2}$*	R	D
CL/F*	R	D
V_z/F*	R	D

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

If urine samples are need to be analyzed, the following urine PK parameters (Table 4) will be calculated for PF-07321332 (as data permit):

Table 4. Urine PK Parameters

PK Parameter	Analysis Scale	PF-07321332
Ae_{48}	R	D
Ae_{48}%	R	D
CL_r	R	D

Key: D=displayed with descriptive statistics, R=raw (untransformed).

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

8.2. Statistical Analyses

ANOVA will be used to compare the natural log transformed AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated) and C_{max} for PF-07321332 between normal renal function group (Reference) and each impaired renal function group separately as applicable (Test). 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 the adjusted geometric means (Test/Reference) and 90% CIs for the ratios. If substantial differences in demographic characteristics between healthy and impaired participants are observed, weight and age may be explored as covariates.

Box and whisker plots for individual participant parameters (AUC_{inf} and C_{max}) will be constructed by renal function group and overlaid with geometric means.

For summary statistics and median/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.

Linear regression will be used to analyze the potential relationship between appropriate PK parameters (CL/F or CL_r, and V_z/F) and renal function (eGFR). Estimates of the slope and, intercept, together with their precision (90% CI), and the coefficient of determination will be obtained from the model.

Plots of PK parameters (CL/F or CL_r, and V_z/F) versus renal function (eGFR) will be constructed. A regression line and 90% confidence region for the PK parameters and eGFR will be included if appropriate. Vertical lines for the renal function group cut-off values will also be presented on the plots. Different symbols will be used to identify participants from different renal function groups.

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 5. PK Parameters to be Summarized Descriptively by Cohort

Parameter	Summary Statistics
AUC_{inf}, AUC_{last}, C_{max}, C_{12}, C_{24}, $t_{1/2}$, CL/F, V_z/F	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.
T_{max}	N, median, minimum, maximum.

Supporting data from the estimation of $t_{½}$, AUC_{inf} will be listed by Cohort: 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, period 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 cohort 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 cohort (all cohorts on the same plot per scale, based on the summary of concentrations by cohort and time postdose).

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

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

- A listing of all urine concentration intervals sorted by renal function group (present in heading), participant ID and nominal collection duration postdose.

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 cohort 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 cohort.

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

8.3.2. Demographic and Clinical Examination Data

A breakdown 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 cohort.

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 cohort.

8.3.5. Laboratory Data

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

8.3.6. Vital Signs Data

Supine blood pressure, pulse rate, respiratory rate and oral temperature will be measured at the protocol specified timepoints.

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

8.3.7. ECG Data

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

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

The screening data with the exception of demography and lab creatine data will not be brought in-house, and therefore will not be listed.

CCI

9. REFERENCES

None.

10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

- **An example of the PROC Mixed code is provided below for ANOVA:**

```
proc mixed data = tab.pk covtest alpha=0.1;
        class group;
        model l&var = group / S covb alpha=0.1 CL DDFM=KR;
        repeated/type=un subject=subjid group=group R;
        lsmeans group;
        estimate 'Moderate vs Normal'        group 1 0 -1 0;
        estimate 'Mild vs Normal'            group 0 1 -1 0;
        estimate 'Severe vs Normal'          group 0 0 -1 1;
        ods output lsmeans = lsmeans&var;
        ods output solutionf = solution&var;
run;

/* Letter assignments for group within the estimate statement above are as follows;

A = Moderate (Test);
B = Mild (Test);
C = Normal (Reference);
D = Severe (Test) */;
```

- **Linear Regression Example code (Relationship between PK parameters (CL/F or CL_r and V_z/F) and renal function (eGFR):**

```
Proc glm data=tab.pk
class trt;
model &var= trt  &var1/ solution clparm alpha=0.1;
ods 'FitStatistics' out=Rsq&var;
ods 'Modelanaova' out=tst&var;
ods 'Parameterestimates' out=pe&var;
run;

Notes:

&var   = [CL/F or CLr] /  Vz/F
&var1 = eGFR
```