Protocol *C4671010*

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 MODERATE HEPATIC IMPAIRMENT AND HEALTHY PARTICIPANTS WITH NORMAL HEPATIC FUNCTION

Statistical Analysis Plan (SAP)

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SAP Author: PPD
(PPD , Mumbai)

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
Final	November 29, 2021	PPD	Not Applicable

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/ritonavir is intended for short-term (eg, 5 day) use, in patients with COVID-19, some of whom may have some degree of impaired hepatic function. The purpose of this study is to estimate the effect of hepatic 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 hepatic impairment.

2.1. Study Design

This is a Phase 1, non-randomized, open-label study to investigate the effect of hepatic impairment on the plasma PK, safety and tolerability of a single oral dose of PF-07321332 in combination with the PK boosting agent ritonavir in approximately 16 participants. The study will be conducted in adult participants with stable, moderate hepatic impairment and a control group of participants with normal hepatic function.

Enrollment will be in a staged manner such that participants with hepatic impairment (Cohort 2) will begin enrollment first. Participants without hepatic impairment (Cohort 1) will begin recruitment towards the end of Cohort 2 or earlier, at the sponsor's discretion such that the enrollment in both cohorts may overlap. Participants in Cohort 1 will match the average demographics (at a minimum, age and weight; gender and race as much as practically possible) of participants in Cohort 2.

All participants in both cohorts will provide informed consent and undergo Screening evaluations to determine their eligibility. Categorization of participants into hepatic impairment cohort, Cohort 2, will be done based on Child-Pugh scores.

Participants who prematurely discontinue for non-safety related reasons may be replaced, at the discretion of the PI and sponsor study team.

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.

Table 1. Hepatic Function Categories Based on Child-Pugh Score

Cohort	*Description*	*Child-Pugh Score*	*Number of Participants*
1	*Without hepatic impairment*	*Not Applicable*	*8*
2	*Moderate hepatic impairment*	*Class B (7 to 9 points)*	*8*

2.2. Study Objectives

2.2.1. Primary Objective

- *To compare the PK of PF-07321332, following a single oral dose administration of PF-07321332 pharmacokinetically boosted with ritonavir in adult participants with moderate hepatic impairment and age and body weight-matched participants without hepatic impairment.*

2.2.2. Secondary Objective

- *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 moderate hepatic impairment and in healthy participants with normal hepatic function.*

CCI

[redacted]

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 Set

"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.

5.2. Pharmacokinetic (PK) Analysis Set

5.2.1. Concentration Analysis Set

The PK concentration population is defined as all participants assigned to investigational product and treated who have at least 1 concentration measured.

5.2.2. Parameter Analysis Set

The PK parameter analysis population is defined as all participants assigned to investigational product and treated who have at least 1 of the PK parameters of primary interest measured.

5.3. Pharmacodynamic Analysis Set

None.

5.4. 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.

5.5. Other Analysis Sets

None.

5.6. Treatment Misallocations

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

5.7. Protocol Deviations

Subjects 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 subjects 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

Any events occurring following start of treatment (of PF-07321332) or increasing in severity will be counted as treatment emergent.

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

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

- *adverse events,*
- *laboratory data.*

6.3. Other Endpoints

6.3.1. PK Endpoints

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

Table 2. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	PF-07321332	CCI [redacted]
AUC_{inf}*	ln	A, D	CCI [redacted]
AUC_{last}	ln	A, D	CCI [redacted]
CCI [redacted]	[redacted]	[redacted]	CCI [redacted]
C_{max}	ln	A, D	[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, NA=not applicable, CCI [redacted] *=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 subject'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 subject discontinues).

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular hepatic function group 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 subject 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

The effect of the hepatic impairment on PK parameters will be assessed by constructing 90% confidence intervals around the estimated difference between each of the Test (impaired groups) and the Reference (normal hepatic function group) using a one-way ANOVA model based on natural log transformed data and assuming unequal variances.

8.2. Statistical Analyses

One-way ANOVA will be used to compare the natural log transformed AUC_{last}, AUC_{inf} (if data permit) and C_{max} for PF-07321332 between Cohort 2 with moderate hepatic impairment (Test) and Cohort 1 with normal hepatic function (Reference). 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.

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

Residuals from the models 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.

The following PK parameters will be summarized by analyte and hepatic function group as applicable:

Table 3. PK Parameters to be Summarized Descriptively by Group

Parameter	Summary Statistics
CCI, AUC_{last}, AUC_{inf}, C_{max}, CCI [redacted]	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
CCI	[redacted]
[redacted]	[redacted]

Supporting data from the estimation of t½ and AUC_{inf} will be listed by group: 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 CCI [redacted] (where applicable) concentrations will include:

- A listing of all concentrations sorted by hepatic function group (present in heading), subject id 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 hepatic function 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 hepatic function group (all hepatic function groups on the same plot per scale, based on the summary of concentrations by hepatic function group and time postdose).

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

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

- CCI [redacted].

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

8.3. Safety Analysis

A set of summary tables split by hepatic function group will be produced to evaluate any potential risk associated with the safety and toleration of administering PF-07321332.

8.3.1. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by hepatic function group.

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 Subjects' in accordance with the sponsor reporting standards by cohort.

8.3.3. Discontinuation(s)

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by hepatic function group.

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 hepatic function group.

8.3.5. Laboratory Data

The baseline measurement is the last planned predose measurement.

For each planned timepoint, baseline values and change from baseline values within each hepatic function group will be summarized with descriptive statistics (using sponsor default standards).

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

8.3.6. Vital Signs Data

Supine blood pressure and pulse rate will be measured at the time points as mentioned in the schedule of activities in the protocol.

The baseline measurement is the last planned predose measurement.

Vital Signs data will be databased and available upon request.

8.3.7. ECG Data

The baseline measurement is the last planned predose measurement.

ECG data will be databased and available upon request.

8.3.8. COVID-19 Data

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

8.3.9. Other Safety Data

None.

8.3.10. Concomitant Treatments

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

8.3.11. Screening and Other Special Purpose Data

If such data will be brought in-house, then it will not be listed.

9. REFERENCES

None.

10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

An example of the PROC GLM code is provided below:

```
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 -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 = Normal (Reference);  */;
```