Protocol *C4671039*

A PHASE I, MULTIPLE DOSE, OPEN-LABEL PHARMACOKINETIC STUDY OF NIRMATRELVIR/RITONAVIR IN HEALTHY LACTATING WOMEN

Statistical Analysis Plan (SAP)

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
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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 (also referred as nirmatrelvir) is a potent and selective inhibitor of the SARS CoV-2 3CL protease that is approved for the treatment of mild-to-moderate COVID 19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Ritonavir is a strong CYP3A4 inhibitor used to inhibit the metabolism of PF-07321332 in order to increase plasma concentrations of PF-07321332. In a Phase 3 randomized, controlled trial, nirmatrelvir/ritonavir (300 mg/100 mg BID for 5 days) administered to unvaccinated outpatients infected with SARS-CoV-2 showed an 89.1% relative risk reduction in Covid 19–related hospitalization or death.

2.1. Study Design

This is an open-label, PK, multiple-dose study in 8 healthy lactating females who are actively breastfeeding and are documented PCR negative for COVID-19 infection at the time of enrollment to determine the amount of nirmatrelvir and ritonavir secreted in breast milk following multiple BID oral dosing in lactating women. In the event that participants withdraw or are unable to express breast milk during a collection interval, additional participants may be recruited.

Participants will not be permitted to breastfeed their infant from the evening of the day prior to the first dose and for 72 hours (3 days) after the Day 2 dose. Participants must have a plan for feeding the infant during the time when the infant cannot breastfeed. Though not a study requirement, participants may wish to express sufficient breast milk in advance of the study to cover the duration when breastfeeding is not permitted (ie, when nursing is restricted during study participation).

Participants on Day 1 will receive one dose of nirmatrelvir/ritonavir in the morning and 1 dose in the evening and finally 1 dose of nirmatrelvir/ritonavir in the morning of Day 2. There will not be any dietary restrictions associated with dosing. After the Day 2 dose there will be collections of breast milk and plasma over 48 hours to characterize the PK of nirmatrelvir and ritonavir in this population.

Potential participants will be screened within 28 days prior to study treatment (Days -28 to Day 2). All participants who meet the eligibility criteria check into the CRU on Day -1 at a time convenient to the participant and the CRU and receive the Day 1 and Day 2 doses every 12 hours and reside at the CRU until the morning of Day 4 (ie, 48 hours after the Day 2, morning dose).

Participants will be discharged from the CRU on the morning of Day 4 (48 hours after the Day 2 dose) and may begin to breastfeed their infant 72 hours (3 days) after the Day 2 dose. Participants must confirm that they will not breastfeed their infant from the evening of the day prior to the first dose and for 72 hours after the last dose and conform to the study protocol.

2.2. Study Objectives

2.2.1. Primary Objectives

To evaluate amount of nirmatrelvir secreted in human breast milk following multiple oral BID dosing with nirmatrelvir/ritonavir.

2.2.2. Secondary Objectives

- *To determine ritonavir concentrations in human breast milk following multiple oral BID dosing with nirmatrelvir/ritonavir.*
- *To characterize plasma PK parameters of nirmatrelvir and ritonavir following multiple oral BID doses with nirmatrelvir/ritonavir in lactating women.*
- *Estimate the infant daily dose that would result from nirmatrelvir and ritonavir secretion in breast milk following multiple oral BID doses with nirmatrelvir/ritonavir.*
- *To characterize the safety and tolerability of nirmatrelvir and ritonavir in lactating women.*

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.

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. Pharmacokinetic (PK) Analysis Set

5.1.1. Concentration Analysis Set

The PK concentration population is defined as all participants randomly assigned to study intervention and who take at least 1 dose of nirmatrelvir/ritonavir and in whom at least 1 concentration value is reported.

5.1.2. Parameter Analysis Set

The PK parameter analysis population is defined as all participants assigned to study intervention and who take at least 1 dose of nirmatrelvir/ritonavir and in whom at least 1 of the PK parameters of interest is reported.

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, PK and pharmacodynamic 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 pharmacokinetics 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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the Investigator or other healthcare providers (clinical signs, test results, etc.).

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. The algorithm will not consider any events that started prior to the first dose date.

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 data and summarized and/or listed where appropriate (see protocol for collection days and list of parameters):

- *Physical examinations data,*
- *laboratory data,*
- *vital signs data,*
- *ECG results,*
- *Pregnancy Testing,*
- *Nursing mother questionnaire.*

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 and Ritonavir (if possible) from the concentration-time data using standard noncompartmental methods:

Table 1. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	PF-07321332 and Ritonavir
Plasma and Breast Milk		
AUC_{tau}	ln	A, D
AUC_{last}	ln	A, D
C_{max}	ln	A, D
C_{av}	ln	A, D
T_{max}	R	D
$t_{1/2}$*	R	D
Plasma Only		
C_{min}	ln	A, D
CL/F	ln	A, D
V_z/F	ln	A, D
Breast Milk Only		
Ae_{tbm}	ln	A, D
Ae_{tbm}%	ln	A, D
CL_{bm}	ln	A, D
*		
Ae_{24bm}	ln	A, D
$MPAUC_{tau}$	ln	A, D
MPC_{max}	ln	A, D
BWNID	ln	A, D
BWNMD	ln	A, D
BWNIDPCM	ln	A, 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 the actual sampling time is missing, nominal times may be used if appropriate.

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

Concentrations for nirmatrelvir and ritonavir in plasma and breast milk will be listed. Plasma and breast milk concentrations will be listed and summarized descriptively by nominal PK sampling time, respectively. PK parameters for breast milk and plasma will be listed and summarized using descriptive statistics utilizing all participants for whom a valid PK parameter can be calculated and reported.

Individual participant and summary profiles (mean and median plots) concentration time data will be plotted by analyte 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. Plots of AUC_{tau}, C_{max}, and C_{av} will be presented for each analyte comparing the PK parameters in breast milk versus those in plasma.

For AUC_{tau}, C_{max}, and C_{av} plots, these parameters will be plotted by body fluid for each analyte (plasma and breast milk PK parameters on 1 plot).

Table 2. PK Parameters to be Summarized Descriptively by Treatment.

Parameter	Summary Statistics
AUC_{last}, AUC_{tau}, C_{max}, C_{min}, C_{av}, CL/F, V_z/F, Ae_{rbm}, Ae_{rbm}%, CL_{bm}, Ae_{24bm}, $MPAUC_{tau}$, MPC_{max}, BWNID, BWNMD, BWNIDPCM	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.

Presentations for PF-07321332 and ritonavir concentrations will include:

Individual participant and summary profiles (mean and median plots) concentration time data will be plotted by analyte with both plasma and milk data on one plot 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. Plots of AUC_{tau}, C_{max}, and C_{av} will be presented for each analyte comparing the PK parameters in breast milk versus those in plasma on one plot.

8.3. Safety Analysis

All safety analyses will be performed on the safety population.

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

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 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 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

Blood pressure, pulse rate and temperature will be measured at the specified timepoints as detailed in schedule of activities of protocol.

The baseline measurement is the predose measurement.

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

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

8.3.7. ECG Data

The baseline measurement is the predose measurement.

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

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

8.3.8. Other Safety Data

Participants will be checked for recent exposure to positive case, COVID-19 related signs and symptoms. Participants will be tested for COVID-19 infection by PCR prior to being admitted to the clinic for confinement and a subsequent COVID-19 test may be performed if they develop COVID-19 like symptoms. Additional testing may be required by local regulations or by the Principal Investigator.

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

These data will not be brought in-house, and therefore will not be listed.

9. REFERENCES

None.

10. APPENDICES

None.