Protocol *C4671036*

A Phase 1, Open-Label, Randomized, Single Dose, Crossover Study to Estimate the Relative Bioavailability of Nirmatrelvir (PF-07321332)/Ritonavir Oral Powder in 3 Different Food Delivery Vehicles Relative to the Nirmatrelvir/Ritonavir Commercial Tablets Under Fasted Conditions and the Effect of Food on Relative Bioavailability of Nirmatrelvir (PF-07321332) /Ritonavir Oral Powder in Healthy Adult Participants

Statistical Analysis Plan
(SAP)

Version: 1

Date: 08 Sep 2022

[redacted]

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

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 / 08 Sep 2022	Original 19 Jul 2022	N/A	N/A

2. INTRODUCTION

Nirmatrelvir a potent and selective inhibitor of the SARS-CoV-2 M^{pro} is being developed as an oral treatment of COVID-19. Ritonavir is a strong CYP3A4 inhibitor being used to inhibit the metabolism of nirmatrelvir in order to increase plasma concentrations of nirmatrelvir to values that are sufficient to suppress viral replication through the entire dosing interval.

The purpose of this study is to estimate the rBA of nirmatrelvir/ritonavir oral powder in 3 different food vehicles relative to the Paxlovid® tablets under fasted condition, and to estimate the effect of food on the rBA of the nirmatrelvir/ritonavir oral powder formulation in healthy adult participants. The study will also assess the safety, tolerability, and palatability of nirmatrelvir/ritonavir oral powder in healthy adult participants.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4671036.

2.1. Modifications to the Analysis Plan Described in the Protocol

None.

2.2. Study Objectives and Endpoints

Objectives	***Endpoints***
Primary:	***Primary:***
• *To estimate the rBA of the nirmatrelvir/ritonavir* CCI [redacted] *oral powder mixed with water compared to the nirmatrelvir/ritonavir* CCI [redacted] *commercial tablets under fasted conditions.*	• *The test/reference ratios for AUC_{inf} (if data permits), AUC_{last}, and C_{max} of nirmatrelvir and ritonavir.*

Objectives	***Endpoints***
• *To estimate the rBA of the nirmatrelvir/ritonavir* CCI [redacted] *oral powder mixed with infant formula compared to the nirmatrelvir/ritonavir* CCI [redacted] *commercial tablets under fasted conditions.* • *To estimate the rBA of the nirmatrelvir/ritonavir* CCI [redacted] *oral powder mixed with vanilla pudding compared to the nirmatrelvir/ritonavir* CCI [redacted] *commercial tablets under fasted conditions.* • *To estimate the rBA of the nirmatrelvir/ritonavir* CCI [redacted] *oral powder mixed with vanilla pudding under fed conditions compared to the nirmatrelvir/ritonavir* CCI [redacted] *commercial tablets under fasted conditions.*	
Secondary:	***Secondary:***
• *To estimate the effect of food on the rBA of the nirmatrelvir/ritonavir* CCI [redacted] *oral powder mixed with vanilla pudding.* • *To evaluate the safety and tolerability of nirmatrelvir/ritonavir in healthy participants.* • *To assess the palatability of nirmatrelvir/ritonavir oral powder mixed with water/ infant formula/ vanilla pudding.*	• *The test/reference ratios for AUC_{inf} (if data permits), AUC_{last}, and C_{max} of nirmatrelvir and ritonavir.* • *Assessment of TEAEs, clinical laboratory abnormalities, vital signs, PEs, and 12 lead ECGs.* • *Assessment of palatability via questionnaire: mouth feel, bitterness, tongue/mouth burn, throat burn and overall liking.*
CCI [redacted]	[redacted]
[redacted]	[redacted]

Objectives	*Endpoints*
CCI [redacted]	[redacted]

2.3. Study Design

This is a Phase 1, open-label, single dose, randomized, crossover study in healthy adult participants to estimate rBA of nirmatrelvir/ritonavir CCI [redacted] *oral powder mixed with 3 different food vehicles (Test formulations) compared to the nirmatrelvir/ritonavir* CCI [redacted] *commercial tablets (Reference formulation) under fasted conditions, and to estimate the effect of food on the rBA of the nirmatrelvir/ritonavir oral powder formulation mixed with vanilla pudding. The study will also assess the safety, tolerability, and palatability of nirmatrelvir/ritonavir in healthy adult participants.*

Approximately 12 adult healthy male and/or female participants will be enrolled and randomized to 1 of 6 possible treatment sequences. 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 sequence 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: Single oral dose of nirmatrelvir/ritonavir* CCI [redacted] *tablets under fasted condition*
- *Treatment B: Single oral dose of nirmatrelvir/ritonavir* CCI [redacted] *oral powder mixed in water under fasted condition*
- *Treatment C: Single oral dose of nirmatrelvir/ritonavir* CCI [redacted] *oral powder mixed in infant formula under fasted condition*
- *Treatment D: Single oral dose of nirmatrelvir/ritonavir* CCI [redacted] *oral powder mixed in vanilla pudding under fasted condition*
- *Treatment E: Single oral dose of nirmatrelvir/ritonavir* CCI [redacted] *oral powder mixed in vanilla pudding under fed condition*

Participants will be randomly assigned to 1 of 6 sequences as shown below in Table 2. 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 nirmatrelvir 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 2. Randomized Treatment Sequences

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

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

The primary endpoints are the test/reference ratios for AUC_{inf} (if data permits), AUC_{last}, and C_{max} of nirmatrelvir and ritonavir. Treatment A will be the Reference treatment while Treatments B, C, D, E will be the Test treatments.

3.2. Secondary Endpoints

The secondary endpoints are the following:

- The test/reference ratios for AUC_{inf} (if data permits), AUC_{last}, and C_{max} of nirmatrelvir and ritonavir, where Treatment D will be the Reference treatment while Treatment E will be the Test treatment.
- Safety and tolerability data, discussed in Section 3.5.
- Palatability data, collected using the sponsor-provided questionnaire. The scores for each attribute (mouth feel, bitterness, tongue/mouth burn, throat burn, overall liking) will be derived by measuring the length (using a scale with gradations of at least 0.1 cm) of the "x" marked by the participant relative to the "good trait".

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Other exploratory endpoints include the test/reference ratios for AUC_{inf} (if data permits), AUC_{last}, and C_{max} of nirmatrelvir and ritonavir, where Treatment B will be the Reference treatment while Treatments C and D will be the Test treatments.

3.4. Baseline Variables

Baseline characteristics will be collected according to the schedule of activities (SoA) as specified in the protocol.

3.5. Safety Endpoints

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

- adverse events (AE)
- laboratory data
- vital signs data
- electrocardiogram (ECG) results

3.5.1. Adverse Events

Any adverse events occurring following start of treatment will be considered as treatment emergent adverse event (TEAE). Events that occur during follow-up within the lag time of up to 28 days after the last of nirmatrelvir/ritonavir dose will be counted as treatment emergent and attributed to the last treatment taken. Events that occur during the washout period (up to 28 days from the last treatment) between study periods will be counted as treatment emergent and attributed to the previous treatment taken. The time period for collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent.

3.5.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol. 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 not take into account whether each participants's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

The baseline measurement is the predose measurement on Day -1.

3.5.3. Vital Signs

Supine blood pressure (BP) and pulse rate (PR) will be measured at times specified in the SoA given in the protocol.

For each period, the baseline measurement is the predose measurement on Day 1.

3.5.4. Electrocardiograms

QT interval, QTcF, PR, QRS and heart rate (HR) will be recorded at each assessment time indicated in the SoA given in the protocol. QTcF will be derived using Fridericia's heart rate correction formula:

$$QTcF = QT / (RR)^{(1/3)} \text{ where } RR = 60/HR \text{ (if not provided)}$$

The baseline measurement is the predose measurement on Period 1 Day 1.

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 releasing the database and classifications will be documented per standard operating procedures.

Participant Analysis Set	***Description***
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.*
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.*
PK Concentration Set	*All participants who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported.*
PK Parameter 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. GENERAL METHODOLOGY AND CONVENTIONS

Final analysis will be performed after study participant data set release following last participant last visit.

5.1. Hypotheses and Decision Rules

No statistical hypothesis will be tested in this study.

5.2. General Methods

5.2.1. Analyses for Binary/Categorical Endpoints

For binary or categorical variables, number of participants, numbers and percentages of participants meeting the categorical criteria will be presented in accordance with the Clinical Data Interchange Standards Consortium and Pfizer Standards (CaPS).

5.2.2. Analyses for Continuous Endpoints

For continuous variables, the data will be summarized using the number of participants, mean, median, standard deviation (SD), minimum, and maximum in accordance with the CaPS. For appropriate PK parameters, geometric mean and geometric coefficient of variation (%CV) will also be summarized.

5.3. Methods to Manage Missing Data

5.3.1. Pharmacokinetic Data

Methods to handle missing PK data are described below.

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.).

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.

An anomalous concentration value is one that, after verification of bioanalytical validity, is grossly inconsistent with other concentration data from the same individual or from other participants. For example, a BLQ concentration that is between quantifiable values from the same dose is considered as anomalous. Anomalous concentration values may be excluded from PK analysis at the discretion of the PK analyst.

PK 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 not be presented for a particular treatment group if more than 50% of the data are NC. For statistical analyses, PK parameters coded as NC will also be set to missing.

If an individual participant has a known biased estimate of a PK parameter (due for example to dosing error or an unexpected event such as vomiting before all the compound is adequately absorbed from the gastrointestinal tract), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses. For instance, if a participant has a vomiting event post dose that is within a duration of time that is 2-times the derived median T_{max} for the population for the administered treatment, then the

pharmacokineticist should consider the exclusion of the PK concentration data collected following the initial vomiting event in that treatment period and the PK parameter data reported for that treatment period from the datasets used to calculate summary statistics or statistical analyses.

5.3.2. Safety Data

Missing values in standard summaries of AEs, laboratory data, vital signs, and ECGs will be imputed according to CaPS.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

For the estimation of rBA of nirmatrelvir/ritonavir oral powder in 3 different food delivery vehicles relative to the nirmatrelvir/ritonavir commercial tablets, *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% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Treatment A will be the Reference treatment while Treatments B, C, D and E will be the Test treatments.*

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 CSR. 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.

6.2. Secondary Endpoints

For the secondary endpoints on the assessment of food effect, same analyses as in the primary endpoints will be used, but with Treatment D as the Reference treatment and Treatment E as the Test treatment.

Analyses and summaries of safety data are described in Section 6.6.

For the taste assessment of the study, the data used in the analysis will be transcribed and rescaled to a score from 0 to 100 from the raw measurements on the questionnaire. The sensory attributes (mouthfeel, bitterness, tongue/mouth burn, throat burn, overall liking) from the taste questionnaires will be listed and descriptively summarized by treatment, and question across participants. Summary statistics (mean and 90% CI) will be calculated for the various questions. Radar plots for each of 4 time points, summarizing all attributes for each treatment will be generated. Boxplots of each attribute will be plotted against the time points.

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[redacted]	[redacted]
[redacted]	[redacted]

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6.4. Subset Analyses

There are no planned subset analyses.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Demographic Summaries

Demographic characteristics (age, gender, ethnicity, race, weight, height and body mass index) will be summarized for enrolled population in accordance with the CaPS.

6.5.2. Study Conduct and Participant Disposition

Participants evaluation groups will show end of study participant disposition. Frequency counts will be supplied for participant discontinuation(s) by treatment. Data will be reported in accordance with the CaPS.

6.5.3. Study Treatment Exposure

Study treatment exposure will be listed.

6.5.4. Concomitant Medications and Nondrug Treatments

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

6.6. Safety Summaries and Analyses

All safety analyses will be performed on the Safety Analysis Set.

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

6.6.1. Adverse Events

Adverse events will be reported in accordance with the CaPS.

Participant discontinuations due to adverse events will be detailed by treatment. Data will be reported in accordance with the CaPS.

6.6.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the CaPS.

6.6.3. Vital Signs

Vital sign data will be databased and available upon request.

6.6.4. Electrocardiograms

ECG data will be databased and available upon request.

7. INTERIM ANALYSES

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 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.

APPENDICES

Appendix 1. SAS Code for Analyses

An example of the PROC MIXED code is provided below:

For primary objectives:

```
proc mixed data=tab.pk;
        class seq period trt participant;
        model l&var=seq period trt/ ddfm=KR;
        random participant(seq) /subject=participant(seq);
        lsmeans trt;
        estimate 'B vs A' trt -1 1 0 0 0  /cl alpha=0.1;
        estimate 'C vs A' trt -1 0 1 0 0  /cl alpha=0.1;
        estimate 'D vs A' trt -1 0 0 1 0  /cl alpha=0.1;
        estimate 'E vs A' trt -1 0 0 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: Single oral dose of nirmatrelvir/ritonavir CCI [redacted] tablets under fasted condition (Reference);
B: Single oral dose of nirmatrelvir/ritonavir CCI [redacted] oral powder mixed in water under fasted condition (Test);
C: Single oral dose of nirmatrelvir/ritonavir CCI [redacted] oral powder mixed in infant formula under fasted condition (Test);
D: Single oral dose of nirmatrelvir/ritonavir CCI [redacted] oral powder mixed in vanilla pudding under fasted condition (Test);
E: Single oral dose of nirmatrelvir/ritonavir CCI [redacted] oral powder mixed in vanilla pudding under fed condition (Test)    */
```

For secondary objective:

```
proc mixed data=tab.pk;
where trt in ("D", "E");
        class seq period trt participant;
        model l&var= seq period trt / ddfm=KR;
        random participant(seq) / subject=participant(seq);
        lsmeans trt;
        estimate 'E vs D' trt -1  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;
D: Single oral dose of nirmatrelvir/ritonavir CCI [redacted] oral powder mixed in vanilla
pudding under fasted condition (Reference);
E: Single oral dose of nirmatrelvir/ritonavir CCI [redacted] oral powder mixed in vanilla
pudding under fed condition (Test)    */
```

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Appendix 2. List of Abbreviations

Abbreviation	Term
%CV	coefficient of variation
AE	adverse event
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from 0 to time of last measurable concentration
BLQ	below the limit of quantitation
BP	blood pressure
CaPS	Clinical Data Interchange Standards Consortium and Pfizer Standards
CI	confidence interval
C_{last}	estimated plasma concentration at the last quantifiable time point estimated form the log-linear regression analysis
C_{max}	maximum observed plasma concentration
CSR	clinical study report
ECG	electrocardiogram
HR	heart rate
k_{el}	the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve
LLQ	lower limit of quantitation
mg	milligram
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
PK	pharmacokinetic(s)
PR	pulse rate
QRS	Combination of Q-, R- and S- wave on an electrocardiogram representing ventricular depolarization
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
RR	respiratory rate
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
C[redacted] CI	[redacted]
TEAE	treatment emergent adverse event
CCI	[redacted]