Protocol *C4671023*

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

Statistical Analysis Plan (SAP)

Version: **1.0**

SAP Author: PPD
(PPD Pune)

Date: 28-SEP-2022

Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	September 28, 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

Nirmatrelvir is a potent and selective inhibitor of the SARS-CoV-2 M^{pro} 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 nirmatrelvir in order to increase plasma concentrations of nirmatrelvir to values that are efficacious.

The purpose of this study is to estimate the rBA of nirmatrelvir/ritonavir of 4 different FDC tablet formulations relative to the commercial tablet formulation under fasted conditions in healthy adult participants. CCI [redacted]

2.1. Study Design

This is a Phase 1, open label, single dose, randomized, crossover study in healthy adult participants to estimate rBA of nirmatrelvir/ritonavir 300/100 mg of 4 different FDC Test formulations compared to the nirmatrelvir/ritonavir 300/100 mg commercial tablets (Reference formulation) under fasted conditions. The study will also assess the safety and tolerability of nirmatrelvir/ritonavir FDC and commercial tablet formulations in healthy adult participants. CCI [redacted]

Approximately 15 healthy male and/or female participants will be enrolled and randomized to 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.

Healthy participants will be screened to determine eligibility within 28 days prior to study treatment. Medical history and results of PEs, vital signs, 12-lead ECGs, and clinical laboratory evaluations will determine eligibility. Eligible participants will be admitted to the PCRU on Day -1 and will be confined in the PCRU until discharge on Day 4 of Period 4.

On Day 1 of each period, participants will receive a single oral dose of study intervention nirmatrelvir/ritonavir 300/100 mg as per the randomization schedule. Study treatments will be administered with approximately 240 mL of ambient temperature water under fasted conditions (overnight fast and no food until 4 hours after dosing). Serial PK samples will be collected up to 72 hours post dose. Participants will be discharged from the PCRU on Day 4 of Period 4, following completion of all assessments.

If a participant has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the participant may be asked to remain in the PCRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow up.

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

Number of Participants

Approximately 15 healthy male and/or female participants will be enrolled and randomized to 1 of 5 possible treatment sequences to ensure at least 12 participants will complete the study.

Intervention Groups and Duration

The study will consist of 5 treatments. Each enrolled participant will participate in 4 study periods to receive 4 different treatments according to the sequence determined by randomization:

- *Treatment A: Single oral dose of nirmatrelvir/ritonavir 300 (2 × 150)/100 mg commercial tablets under fasted conditions (Reference).*
- *Treatment B: Single oral dose of nirmatrelvir/ritonavir 300/100 mg (2 × 150/50 mg) FDC tablets Test formulation 1 (low disintegrant) under fasted conditions (Test 1).*
- *Treatment C: Single oral dose of nirmatrelvir/ritonavir 300/100 mg (2 × 150/50 mg) FDC tablets Test formulation 2 (high disintegrant) under fasted conditions (Test 2).*
- *Treatment D: Single oral dose of nirmatrelvir/ritonavir 300/100 mg (2 × 150/50 mg) FDC tablets Test formulation 3 (high drug loading) under fasted conditions (Test 3).*
- *Treatment E: Single oral dose of nirmatrelvir/ritonavir 300/100 mg (3 × 100/33.3 mg) FDC tablets Test formulation 4 under fasted conditions (Test 4).*

Participants will be randomly assigned to 1 of 5 sequences as below:

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

Between each treatment, a minimum of 4 days washout is proposed to minimize any residual nirmatrelvir and ritonavir concentrations prior to start of the next treatment. Participants will be discharged on Day 4 of Period 4, following completion of all assessments.

The total planned duration of participation from the Screening visit to the last follow-up phone call, is approximately 12 weeks.

2.2. Study Objectives

2.2.1. Primary Objectives

- *To estimate the rBA of the nirmatrelvir/ritonavir 300/100 mg (2 × 150/50 mg) FDC tablets Test formulation 1 (low disintegrant) compared to the nirmatrelvir/ritonavir 300 (2 × 150)/100 mg commercial tablets under fasted conditions (reference).*

- *To estimate the rBA of the nirmatrelvir/ritonavir 300/100 mg (2 × 150/50 mg) FDC tablets Test formulation 2 (high disintegrant) compared to the nirmatrelvir/ritonavir 300 (2 × 150)/100 mg commercial tablets under fasted conditions (reference).*

- *To estimate the rBA of the nirmatrelvir/ritonavir 300/100 mg (2 × 150/50 mg) FDC tablets Test formulation 3 (high drug load) compared to the nirmatrelvir/ritonavir 300 (2 × 150)/100 mg commercial tablets under fasted conditions (reference).*

- *To estimate the rBA of the nirmatrelvir/ritonavir 300/100 mg (3 × 100/33.3 mg) FDC tablets Test formulation 4 compared to the nirmatrelvir/ritonavir 300 (2 × 150)/100 mg commercial tablets under fasted conditions (reference).*

2.2.2. Secondary Objectives

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

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [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

There are no statistical hypotheses for 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 analysis set is defined as all participants who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported.

5.1.2. Parameter Analysis Set

The PK parameter analysis set is defined as 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.

5.2. Pharmacodynamic Analysis Set

None.

5.3. 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.

5.4. Enrolled

"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization. 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.

5.5. 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 4.1 and 4.2 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

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

- adverse events,
- laboratory data,
- vital signs data,
- ECG results,
- Pregnancy Testing.

6.3. Other Endpoints

6.3.1. PK Endpoints

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

Plasma PK parameters of nirmatrelvir and ritonavir will be derived (as data permits) from the concentration-time data using standard noncompartmental methods as outlined in Table 1. *Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters*.

Table 1. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	nirmatrelvir and ritonavir
AUC_{last}	ln	A, D
AUC_{inf}*	ln	A, D
AUC_{12}	ln	D
C_{max}	ln	A, D
T_{max}	R	D
$t_{1/2}$*	R	D
CL/F*	ln	D
V_z/F*	ln	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

8.2. Statistical Analyses

For the primary objective, natural log transformed AUC_{inf} (if data permits), AUC_{last} and C_{max} for nirmatrelvir and ritonavir will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within 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.

PK parameters, including plasma AUC_{inf} (if data permits), AUC_{last}, C_{max}, CCI [redacted] (if data permits) of nirmatrelvir and ritonavir will be summarized descriptively by analyte and treatment. Box and whisker plots for AUC_{inf} (if data permits), AUC_{last}, and C_{max}, will be plotted by treatment.

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 2. PK Parameters to be Summarized Descriptively by Analyte and Treatment

Parameter	Summary Statistics
AUC_{inf}, AUC_{last}, AUC_{12}, C_{max}, CCI [redacted]	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
C [redacted] CI	[redacted]
[redacted]	[redacted]

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

Supporting data from the estimation of CCI AUC_{inf} or AUC_{last} 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 nirmatrelvir and ritonavir concentrations separately 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 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.

CCI [redacted]

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 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

The baseline is defined as measurement taken on Day -1 of Period 1.

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

8.3.6. Vital Signs Data

The baseline is defined as pre-dose measurement taken on Day 1 of each period.

Supine blood pressure, pulse rate and 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

The baseline is defined as pre-dose measurement taken on Day 1 of Period 1.

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

8.3.11. Banked Bio specimens

Banked bio specimens will be collected for the purpose of conducting research in future. This data will not be reported in the Clinical study report.

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;
    class seq period trt subject;
    model l&var= seq period trt / ddfm=KR;
    random subject(seq) / subject = subject(seq);
    lsmeans trt;
    estimate ' B vs A' trt  -1  1  0  0  0;
    estimate ' C vs A' trt  -1  0  1  0  0;
    estimate ' D vs A' trt  -1  0  0  1  0;
    estimate ' E vs A' trt  -1  0  0  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 300 (2 × 150)/100 mg commercial
    tablets under fasted conditions (Reference)

    B = Single oral dose of nirmatrelvir/ritonavir 300/100 mg (2 × 150/50 mg) FDC
    tablets Test formulation 1 (low disintegrant) under fasted conditions (Test 1)

    C = Single oral dose of nirmatrelvir/ritonavir 300/100 mg (2 × 150/50 mg) FDC
    tablets Test formulation 2 (high disintegrant) under fasted conditions (Test 2)

    D = Single oral dose of nirmatrelvir/ritonavir 300/100 mg (2 × 150/50 mg) FDC
    tablets Test formulation 3 (high drug loading) under fasted conditions (Test 3)

    E = Single oral dose of nirmatrelvir/ritonavir 300/100 mg (3 × 100/33.3 mg) FDC
    tablets Test formulation 4 under fasted conditions (Test 4) */;
```