Protocol C4671034

AN INTERVENTIONAL EFFICACY AND SAFETY, PHASE 2, RANDOMIZED, DOUBLE-BLIND, 3-ARM STUDY TO INVESTIGATE NIRMATRELVIR/RITONAVIR IN NONHOSPITALIZED PARTICIPANTS AT LEAST 12 YEARS OF AGE WITH SYMPTOMATIC COVID-19 WHO ARE IMMUNOCOMPROMISED

Statistical Analysis Plan (SAP)

Version: 1.0

Date: 28 Apr 2023

Version: 2.0

Date: 03-AUG-2023

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 28 Apr 2023	Original	N/A	SAP Original Version
2 30 Jun 2023	Original	To add subgroup analysis of primary endpoint by symptoms onset and provide clarification in section 6 of the SAP	• Section 4: Exclude site 1001 from all efficacy analysis. • Section 4 was amended to delete the paragraph about multiple enrollers as it is not applicable. • Section 6.1.1 was modified to add statistical methodology for primary endpoint. • Section 6.1.2: added sensitivity analysis of primary endpoint excluding all participants from site 1030. • Section 6.2.16 modified to add censoring method and definition signs and symptoms alleviation/resolution for duration of signs and symptoms endpoint. • Section 6.3 modified to add subgroup analysis of primary endpoint as follows: Duration since first symptom (<= 5 days, > 5 days <=30, >30) • Section 6.3 was modified to remove the subgroup analysis of primary endpoint by baseline serology (positive, negative) as it is not applicable in this study.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			Appendix 1 - Summary of Efficacy Analyses was modified to provide clarification on statistical method**.**

2. INTRODUCTION

Patients with COVID-19 who are immunocompromised are at increased risk of progressing to severe illness due to prolonged infection, limited contribution by the immune system in clearing the infection, and increased potential for viral resistance. Emergence of variants that are resistant to available treatment also puts the wider population at risk. Patients who are immunocompromised may benefit from extended treatment durations. The purpose of the study is to evaluate the efficacy and safety of nirmatrelvir/ritonavir 5, 10, and 15-day dosing durations for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age and weigh ≥40 kg who are immunocompromised (main study population).

In addition, this study will also evaluate the efficacy and safety of a second treatment course of nirmatrelvir/ritonavir (5-, 10-, or 15-days) in an additional population of nonhospitalized symptomatic participants who are immunocompromised with a rebound in COVID-19 within 14 days following completion of an initial 5-day treatment course of nirmatrelvir/ritonavir (population with rebound).

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4671034.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not Applicable.

2.2. Study Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To describe the effect of nirmatrelvir/ritonavir on viral RNA levels in NP swabs over time for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44.	• The proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44 in nonhospitalized, symptomatic patients ≥12 years of age with COVID-19 who are immunocompromised. This will be estimated without regard to study treatment discontinuation and considering participants receiving non-study antiviral or monoclonal antibody therapy post-baseline for the treatment of COVID-19 as not achieving sustained NP swab SARS-CoV-2 RNA <LLOQ.
Secondary:	**Secondary:**	**Secondary:**
• To describe the effect of nirmatrelvir/ritonavir treatment duration on the rate of sustained virologic clearance in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Time to first NP swab SARS-CoV-2 RNA<LLOQ (<2.0 $\log_{10}$ copies/mL) for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline. • Time to sustained NP swab SARS-CoV-2 RNA <LLOQ (<2.0 $\log_{10}$ copies/mL) through Day 44 for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline.	• Not applicable.
• To describe the effect of nirmatrelvir/ritonavir on viral clearance for the treatment of COVID-19 in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Proportion of participants with SARS-CoV-2 RNA <LLOQ in plasma over time. • Proportion of participants with SARS-CoV-2 RNA level in NP swabs <2.0 $\log_{10}$ copies/mL at each study visit through Day 44. • Change from baseline in SARS-CoV-2 RNA level in NP swabs and in plasma over time. • Rebound in SARS-CoV-2 RNA level in NP swabs at follow up (ie, any study visit after end of treatment through Day 44) that is defined as a half (0.5) $\log_{10}$ copies/mL increase or greater in SARS-CoV-2 RNA level relative to end of treatment SARS-CoV-2 RNA level based on treatment regimen, with a follow-up viral RNA level ≥2.5 $\log_{10}$ copies/mL.	• Not applicable.
• To describe the safety and tolerability of nirmatrelvir/ritonavir for the treatment of COVID-19 in	• Incidence of TEAEs. • Incidence of SAEs and AEs leading to discontinuations.	• Not applicable.

Objectives	Endpoints	Estimands
nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.		
• To describe the effect of nirmatrelvir/ritonavir on hospitalization and all-cause mortality in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Proportion of participants with COVID-19-related hospitalization >24 hours, or death from any cause through Day 28. • Proportion of participants with death (all cause) through Week 24.	• Not applicable.
• To describe COVID-19 related healthcare resource utilization in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised and treated with nirmatrelvir/ritonavir.	• Proportion of participants with COVID-19-related hospitalization of any duration. • Proportion of participants with COVID-19-related ICU admission of any duration. • Proportion of participants requiring invasive mechanical ventilation or ECMO. • Number of days in hospital and ICU stay in participants with COVID-19-related hospitalization. • Number of COVID-19-related medical visits through Day 44 and through Week 24.	• Not applicable.
• To evaluate nirmatrelvir/ritonavir for the duration and severity of signs and symptoms in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Duration of each targeted COVID-19 signs/symptoms. • Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 44.	• Not applicable.
• To determine the PK of nirmatrelvir/ritonavir in nonhospitalized symptomatic participants ≥12 years of age with COVID-19 who are immunocompromised.	• Nirmatrelvir and ritonavir PK in plasma and whole blood (if feasible).	• Not applicable.

2.2.1. Primary Estimand(s)

The primary estimand, reported separately for the main study population and the population with rebound, is the proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44 in nonhospitalized symptomatic patients ≥12 years of age with COVID-19 who are immunocompromised. This will be estimated without regard to study treatment discontinuation and considering participants receiving non-study antiviral or monoclonal antibody therapy post-baseline for the treatment of COVID-19 as not achieving sustained NP swab SARS-CoV-2 RNA <LLOQ.

2.2.2. Secondary Estimand(s)

Not Applicable.

2.3. Study Design

This Phase 2, randomized, double-blind, study will evaluate the efficacy and safety of nirmatrelvir/ritonavir (5-, 10-, and 15-day dosing durations) for the treatment of COVID-19 in approximately 150 nonhospitalized symptomatic participants aged at least 12 years and weigh ≥40 kg who are immunocompromised (main study population). In addition, this study will also evaluate the efficacy and safety of a second treatment course of nirmatrelvir/ritonavir (5-, 10-, or 15-days) in an additional population of nonhospitalized symptomatic participants who are immunocompromised with a rebound in COVID-19 within 14 days following completion of an initial 5-day treatment course of nirmatrelvir/ritonavir (population with rebound).

Participants in the additional population with rebound will be recruited during the enrollment phase for the main study population. Enrollment of the population with rebound will stop after the main study population is fully enrolled or after 50 participants in the population with rebound have been enrolled, whichever occurs sooner.

Eligible participants (main study population and additional population with rebound) for this study will be randomly assigned (1:1:1) to receive:

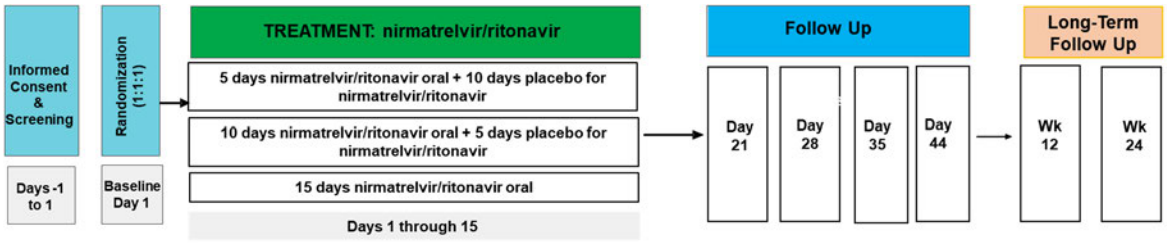
- nirmatrelvir plus ritonavir orally q12h for 5 days followed by placebo for nirmatrelvir plus ritonavir q12h for 10 days; or
- nirmatrelvir plus ritonavir orally q12h for 10 days followed by placebo for nirmatrelvir plus ritonavir q12h for 5 days; or
- nirmatrelvir plus ritonavir orally q12h for 15 days.

Participants will be screened on the same day as randomization or 1 calendar day before randomization. For the main study population, enrollment of participants considered immunocompromised based solely on receiving corticosteroids or TNF blockers will be capped at approximately 25%. Enrollment of participants considered immunocompromised based solely on receiving corticosteroids or TNF blockers in the additional population with rebound will not be capped.

For the main study population, randomization will be stratified by those who are considered immunocompromised solely based on corticosteroids or TNF blocker use (yes/no; see Protocol Section 10.9.4 Point #4). Randomization for the population with rebound will not be stratified by those who are considered immunocompromised solely based on corticosteroids or TNF blocker use.

The total study duration is up to 24 weeks, including study intervention administration through Day 15 or Day 16, safety assessments through Day 44, efficacy assessments through Week 24, and long-term follow-up at Weeks 12 and 24.

Figure 1. C4671034 Study Design



Analyses will be conducted after the main study population is fully enrolled and have completed the Day 44 visit regardless of the number of randomized participants in the population with rebound. There will be 2 analysis time points for reporting the results of this study. The primary analysis will be performed after all participants in the main study population have completed the Day 44 visit. The follow-up analysis will be performed after all participants in the main study population have completed the Week 24 visit. In addition, both analyses (primary and follow-up) will include separate results for the main study population and the additional population with rebound.

An independent E-DMC will review unblinded data to ensure the safety of participants on an ongoing basis throughout the duration of the study.

2.4. Sample Size Determination

Up to approximately 200 participants will be enrolled in this study.

The study will randomize approximately 150 participants in a 1:1:1 randomization ratio, resulting in approximately 50 participants in each treatment arm (main study population). In addition, the study will also enroll up to 50 additional nonhospitalized symptomatic participants (in a 1:1:1 randomization ratio) who are immunocompromised with a rebound in COVID-19 within 14 days following completion of an initial 5-day treatment course of nirmatrelvir/ritonavir (population with rebound).

Analyses will be conducted after the main study population is fully enrolled and have completed the Day 44 visit regardless of the number of randomized participants in the population with rebound. There will be 2 analysis time points for reporting the results of this study. The primary analysis will be performed after all participants in the main study population have completed the Day 44 visit. The follow-up analysis will be performed after all participants in the main study population have completed the Week 24 visit. In addition, both analyses (primary and follow-up) will include separate results for the main study population and the additional population with rebound.

As no formal hypothesis testing will be performed for this study, no power calculation was carried out to assess the number of participants required for each treatment arm. For the main study population, the goal of the primary analysis is to estimate the treatment effect for each duration of nirmatrelvir/ritonavir. The smaller numbers of participants in these groups will be reflected in the precision of the estimate of the primary endpoint. Table 2 displays which effect sizes would be excluded based on the expected width of the confidence interval around

the estimate of the proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44 with a sample size of 50.

When the proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ from Day 15 through Day 44 ranges from 0.1 to 0.5, Table 2 displays the precision (width of the confidence interval) for the respective proportion to be estimated with a sample size of 50. That is, the width of the 95% CI does not exceed 14%.

Table 2. Width of 95% CI for the Proportion of Participants with Sustained NP Swab SARS-CoV-2 RNA <LLOQ

Nirmatrelvir/Ritonavir (n=50)	
Proportion of Participants With Sustained Viral RNA level <LLOQ	**Width of CI**
0.1	0.083
0.2	0.111
0.3	0.127
0.4	0.136
0.5	0.139

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The primary endpoint, summarized separately for the main study population and the population with rebound, is the proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44.

Sustained is defined as NP swab SARS-CoV-2 RNA level not ≥2.0 $\log_{10}$ copies/mL at any study visit (through Day 44) following the first study visit where the participant's NP swab SARS-CoV-2 RNA <LLOQ.

3.2. Secondary Endpoint(s)

Secondary endpoints include:

- Time to first NP swab SARS-CoV-2 RNA<LLOQ (<2.0 $\log_{10}$ copies/mL) for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline.
- Time to sustained NP swab SARS-CoV-2 RNA <LLOQ (<2.0 $\log_{10}$ copies/mL) through Day 44 for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline.
- Proportion of participants with SARS-CoV-2 RNA <LLOQ in plasma over time.

- Proportion of participants with SARS-CoV-2 RNA level in NP swabs <2.0 $\log_{10}$ copies/mL at each study visit through Day 44.
- Change from baseline in SARS-CoV-2 RNA level in NP swabs and in plasma over time.
- Rebound in SARS-CoV-2 RNA level in NP swabs at follow up (ie, any study visit after end of treatment through Day 44) that is defined as a half (0.5) $\log_{10}$ copies/mL increase or greater in SARS-CoV-2 RNA level relative to end of treatment SARS-CoV-2 RNA level based on treatment regimen, with a follow-up viral RNA level ≥2.5 $\log_{10}$ copies/mL.
- Incidence of TEAEs.
- Incidence of SAEs and AEs leading to discontinuations.
- Proportion of participants with COVID-19-related hospitalization >24 hours, or death from any cause through Day 28.
- Proportion of participants with death (all cause) through Week 24.
- Proportion of participants with COVID-19-related hospitalization of any duration.
- Proportion of participants with COVID-19-related ICU admission of any duration.
- Proportion of participants requiring invasive mechanical ventilation or ECMO.
- Number of days in hospital and ICU stay in participants with COVID-19-related hospitalization.
- Number of COVID-19-related medical visits through Day 44 and through Week 24.
- Duration of each targeted COVID-19 signs/symptoms.
- Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 44.
- Nirmatrelvir and ritonavir PK in plasma and whole blood (if feasible).

3.3. Other Endpoint(s)

Not applicable for this study.

3.4. Baseline Variables

For viral load data from NP swabs, the baseline window is set up according to study days of Day -2 to Day 1. Only results for samples collected within up to 1 hour post start of dosing will be treated as baseline data. This implies that if there is any issue with the Baseline (Day

1) measurement (eg, missing, undetectable, taken >1 hour post dose), then the screening measurement, if available, will be utilized as the baseline value. If the screening measurement is not available and the Day 1 measurement is undetectable and taken ≤1 hour post dose, then the baseline will be considered undetectable. If the screening measurement is not available and the Day 1 measurement is missing or taken >1 hour post dose, then the baseline will be considered missing.

For viral load data from plasma samples, the baseline window will be Day -2 to Day 1, but only results for samples collected within up to 1 hour post start of dosing will be treated as baseline.

For laboratory assessments, COVID-19 signs and symptoms, and vital signs, the baseline window will be Day -2 to Day 1, without any consideration to the time factor.

The following baseline variables will be used in efficacy analysis summarization. See below a list of derived baseline variables:

- eGFR/eCrCl (POC value) categories: Normal (≥90), Mild Impairment (≥60 to <90), Moderate Impairment (≥30 to <60), and Severe Impairment (<30).
- Participants considered immunocompromised based solely on receiving corticosteroids or TNF blockers (yes/no)

3.5. Safety Endpoints

The safety endpoints of this study are:

- Incidence of TEAEs.
- Incidence of SAEs and AEs leading to discontinuations.

Clinical Data Interchange Standards Consortium (CDISC) and Pfizer Standards (CaPS) will be used for the analysis of standard safety data.

3.5.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a study participant administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event started on or after the study medication start date. Since time of AE is not collected, AEs that begin on day 1, even if prior to study treatment start, will be considered TEAE.

3.5.2. Laboratory Data

Laboratory data includes hematology, chemistry, and other safety tests. To determine if there are any clinically significant laboratory abnormalities, the hematological and clinical biochemistry and other safety tests will be assessed against the criteria specified in the Pfizer

reporting standards. This assessment will take into account whether each participant's baseline test results are within or outside the laboratory reference range for a particular laboratory parameter.

3.5.3. Vital Signs

Vital sign measurements, including temperature, pulse rate, respiratory rate, oxygen saturation level, and blood pressure.

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

For purposes of analysis, the following analysis sets are defined (excluding participants from Site 1001 from all efficacy analyses):

Participant Analysis Set	Description
Full analysis set (FAS)	All participants randomly assigned to study intervention.
Evaluable analysis set/Safety Analysis Set (SAS)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.

The evaluable analysis set will be the primary analysis set for evaluating the primary estimand.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

No formal hypothesis testing will be performed for this study.

5.2. General Methods

All data will be presented by treatment group. Descriptive statistics will be provided for all endpoints.

The number of participants screened, randomized to the double-blind treatment phase, completing the study drug administration, and completing the study will be summarized from the FAS. The reason for all discontinuations will be summarized by treatment group.

Baseline demographic and other characteristics will be tabulated for the FAS and summarized by treatment group. Quantitative variables will be described by standard descriptive statistics (mean, standard deviation, median and range), and qualitative variables will be summarized by frequency tables with number and proportion in each category (with the corresponding sample sizes).

5.2.1. Analyses for Binary Endpoints

For binary endpoints (eg, proportion of participants with SARS-CoV-2 RNA <LLOQ in plasma over time, proportion of participants with COVID-19-related hospitalization >24 hours, or death from any cause through Day 28, etc), proportion of participants with the event will be summarized for each group.

5.2.2. Analyses for Continuous Endpoints

For continuous endpoints, (eg, change from baseline in SARS-CoV-2 RNA level in NP swabs and in plasma over time), results and/or changes from baseline over time, as applicable will be summarized with descriptive statistics (mean, SD, etc).

5.2.3. Analyses for Time-to-Event Endpoints

For time-to-event endpoints (eg, time to first NP swab SARS-CoV-2 RNA<LLOQ [<2.0 $\log_{10}$ copies/mL] for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline), Kaplan-Meier analysis where tabular summaries of the Kaplan-Meier curves providing the median and quartiles, will be provided for each treatment group. In addition, the Kaplan-Meier curves will be presented graphically.

5.3. Methods to Manage Missing Data

For SARS-CoV-2 RNA data, samples producing a result of <LLOQ or undetectable will not be considered missing, but rather will be imputed using values of 1.7 [$\log_{10}(50)$] or 0.0 $\log_{10}$ copies/mL, respectively. Missing SARS-CoV-2 RNA data will not be imputed.

As all analyses are descriptive, missing endpoint data will result in a summary where the N for that endpoint (and time point) is smaller than the total N of the corresponding analysis set. No imputation of the missing data will be performed.

For safety data, missing and partial dates will be programmatically handled according to Pfizer standards.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

The primary endpoint, summarized separately for the main study population and the population with rebound, is the proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44.

Sustained is defined as NP swab SARS-CoV-2 RNA level not ≥2.0 $\log_{10}$ copies/mL at any study visit (through Day 44) following the first study visit where the participant's NP swab SARS-CoV-2 RNA <LLOQ.

6.1.1. Main Analysis

The primary descriptive analysis will summarize, separately for the main study population and the population with rebound, the number and proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 15 through Day 44 for each treatment arm in the Evaluable Analysis Set and FAS. Participants

receiving non-study antiviral or monoclonal antibody therapy post-baseline (between randomization and Day 44 visit) for the treatment of COVID-19 will be considered as not achieving sustained NP swab SARS-CoV-2 RNA <LLOQ in the primary analysis.

As viral load measurements from NP swabs are taken on Days 15, 21, 28, 35, and 44 during the time interval from Day 15 to Day 44, all of the measurements that are non-missing must be <LLOQ (including undetectable), and the Day 15, Day 44, and no more than one of the Day 21, 28, and 35 measurements can be missing in order for the event to be considered sustained.

In addition, 95% CIs for the proportion of participants with sustained NP swab SARS-CoV-2 RNA <LLOQ from Day 15 through Day 44 for each treatment arm will be calculated using binomial distribution normal approximation. The difference in proportions for the primary endpoint and associated 95% CI will be calculated for each pairwise comparison of the treatment arms.

6.1.2. Sensitivity/Supplementary Analyses

Supplemental analyses will be performed for the primary efficacy endpoint:

1. An analysis of the primary endpoint will be conducted excluding data after the date of non-study antiviral or monoclonal antibody start for participants that received non-study antiviral or monoclonal antibody therapy post-baseline (between randomization and Day 44) for the treatment of COVID-19.

2. An analysis of the primary endpoint will be conducted to include all NP swab SARS-CoV-2 RNA data regardless of whether participants received non-study antiviral or mAb treatment post-baseline (between randomization and Day 44) for the treatment of COVID-19.

3. An analysis of the primary endpoint will be conducted where participants with baseline SARS-CoV-2 RNA level <LLOQ will be excluded.

4. An analysis of the primary endpoint will be conducted where participants who do not meet the protocol-defined immunocompromised criteria will be excluded.

5. An analysis of the primary endpoint will be conducted excluding participants from site 1030.

6.2. Secondary Endpoint(s)

6.2.1. Time to first NP swab SARS-CoV-2 RNA<LLOQ (<2.0 $\log_{10}$ copies/mL) for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline

6.2.1.1. Main Analysis

Time (days) to first NP swab SARS-CoV-2 RNA<LLOQ (<2.0 $\log_{10}$ copies/mL) will be evaluated for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline. The first day of NP swab SARS-CoV-2 RNA<LLOQ will be considered the First Event Date. Time

(days) to first NP swab SARS-CoV-2 RNA<LLOQ will be calculated as (First Event Date) – (First Dose Date) +1.

There are limitations to the timing of the first event date as NP viral RNA is generally only captured at in-person scheduled visits during the study.

The Day 44 visit day is the last possible day the NP swab SARS-CoV-2 RNA<LLOQ can be achieved.

For a participant that either completes the Day 44 visit of the study or discontinues from the study before the Day 44 visit without NP swab SARS-CoV-2 RNA<LLOQ (censored), censoring date will be at the last date on which NP swab SARS-CoV-2 RNA is assessed, and time will be calculated as (Censoring Date) – (First Dose Date) +1 or the Day 44 visit whichever occurs first.

Time to NP swab SARS-CoV-2 RNA<LLOQ will be summarized graphically using Kaplan-Meier plots for each of the treatment groups in main study population.

6.2.2. Time to sustained NP swab SARS-CoV-2 RNA <LLOQ (<2.0 $\log_{10}$ copies/mL) through Day 44 for participants with NP swab SARS-CoV-2 RNA ≥LLOQ at baseline

Time (days) to sustained NP swab SARS-CoV-2 RNA<LLOQ (<2.0 $\log_{10}$ copies/mL) will be evaluated. Sustained is defined as NP swab SARS-CoV-2 RNA level not ≥2.0 $\log_{10}$ copies/mL at any study visit (through Day 44) following the first study visit where the participant's NP swab SARS-CoV-2 RNA <LLOQ.

Let *t* represent the number of days between 5 and 35 inclusive for which there is a protocol-specified measurement of SARS-CoV-2 RNA level on Day *t*.
Then a sustained event will correspond to the first possible value of *t* to satisfy the following criteria:

a) The Day 44 SARS-CoV-2 RNA level is <LLOQ

b) The Day *t* SARS-CoV-2 RNA level is <LLOQ

c) All available (non-missing) protocol-specified SARS-CoV-2 RNA measurements between Day *t* and Day 44 are <LLOQ

d) No more than one of the protocol-specified SARS-CoV-2 RNA measurements between Day *t* and Day 44 are missing.

There are limitations to the timing of the first event date as NP viral RNA is generally only captured at in-person scheduled visits during the study.

The Day 35 visit is the last possible day the sustained NP swab SARS-CoV-2 RNA<LLOQ can be achieved.

The time to the sustained event is defined as:

- For a participant with sustained event at Day *t*, the First Event Date is the date of the Day *t* measurement, and time to event will be calculated as (First Event Date) – (First Dose Date) +1.

- For a participant for which no possible value of $t \leq$ the 35 visit satisfies the criteria for a sustained event (censored), censoring date will be the date of the last available protocol-specified SARS-CoV-2 RNA measurement other than Day 44, and time will be calculated as (Censoring Date) – (First Dose Date) +1.

Time to sustained NP swab SARS-CoV-2 RNA<LLOQ will be summarized graphically using Kaplan-Meier plots for each of the treatment groups in main study population.

6.2.3. Proportion of participants with SARS-CoV-2 RNA <LLOQ in plasma over time.

- The proportion of participants with SARS-CoV-2 RNA <LLOQ as measured in plasma will be summarized at each study visit through week 24 for each treatment arm. In addition, 95% CIs for the proportion of participants with SARS-CoV-2 RNA <LLOQ in plasma at each study visit will be calculated for each treatment arm.

6.2.4. Proportion of participants with SARS-CoV-2 RNA level in NP swabs <2.0 $\log_{10}$ copies/mL at each study visit

The proportion of participants with SARS-CoV-2 RNA < 2.0 $\log_{10}$ copies/mL as measured by NP swab will be summarized at each study visit through Week 24 for each treatment arm. In addition, 95% CIs for the proportion of participants with SARS-CoV-2 RNA <2.0 $\log_{10}$ copies/mL as measured by NP swabs at each study visit will be calculated for each treatment arm.

6.2.5. Change from baseline in SARSCoV-2 RNA level in NP swabs and in plasma over time.

Descriptive statistics by treatment group for the change from baseline to each study visit (Day 5, 10, 15, 21, 28, 35, 44) will be provided. Participants are excluded from the analysis for reasons of Not Detected, Zero or Missing baseline and/or post-baseline viral load results.

6.2.6. Rebound in SARS-CoV-2 RNA level in NP swabs

Rebound in SARS-CoV-2 RNA level in NP swabs at follow up (ie, any study visit after end of active treatment through Day 44) that is defined as a half (0.5) $\log_{10}$ copies/mL increase or greater in SARS-CoV-2 RNA level relative to end of active treatment SARS-CoV-2 RNA level based on treatment regimen, with a follow-up viral RNA level $\geq$2.5 $\log_{10}$ copies/mL.

In addition, two alternative definitions of rebound will also be evaluated:

- Rebound that is defined as: SARS-CoV-2 RNA level in NP swabs at follow up (ie, any study visit after end of active treatment through Day 44) that is defined as a half (0.5) $\log_{10}$ copies/mL increase or greater in SARS-CoV-2 RNA level

relative to end of active treatment SARS-CoV-2 RNA level based on treatment regimen, with a follow-up viral RNA level ≥**3.0** $\log_{10}$ copies/mL.

- Rebound that is defined as: SARS-CoV-2 RNA level in NP swabs at follow up (ie, any study visit after end of active treatment through **Day 28**) that is defined as a half (0.5) $\log_{10}$ copies/mL increase or greater in SARS-CoV-2 RNA level relative to end of active treatment SARS-CoV-2 RNA level based on treatment regimen, with a follow-up viral RNA level ≥3.0 $\log_{10}$ copies/mL.

The rebound analyses will be restricted to those participants with non-missing end of active treatment SARS-CoV-2 RNA measurement and at least one non-missing measurement among the study visits after end of treatment through the Day 44 visit (or through the Day 28 visit for the second alternative definition of rebound analysis).

6.2.7. Incidence of TEAEs

- The incidence of TEAEs will be summarized by treatment group, by SOC and PT using the Safety Analysis Set.

6.2.8. Incidence of SAEs and AEs leading to discontinuations

The incidence of SAEs and AEs leading to discontinuation will be summarized by treatment group using the safety analysis set.

6.2.9. Proportion of participants with COVID-19-related hospitalization >24 hours, or death from any cause through Day 28

The proportion of participants with COVID-19-related hospitalization >24 hours, or death from any cause through Day 28 will be summarized. The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study will be estimated for each treatment group using the Kaplan-Meier method to take account of losses to follow-up and summarized graphically for each treatment group.

For participants without an event who complete the Day 28 assessment, they will be censored at Day 28. For participants without an event who discontinue or are lost to follow-up before the Day 28 assessment, they will be censored at the last known date in the study.

6.2.10. Proportion of participants with death (all cause) through Week 24

The proportion of participants who died from any cause through Week 24 will be analyzed using the method specified in Section 6.2.9 and summarized for each treatment group. KM plots for each treatment group will also be provided. Participants without an event will be censored at the last known date in the study.

6.2.11. Proportion of participants with COVID-19-related hospitalization of any duration

The proportion of participants with COVID-19-related hospitalization of any duration will be analyzed using the method specified in Section 6.2.9 and summarized by treatment arm

through day 44 and through week 24. Participants without an event (at Day 44/Week 24) will be censored at that time or at the last known date in the study, whichever is later.

6.2.12. Proportion of participants with COVID-19-related ICU admission of any duration

The proportion of participants with COVID-19-related ICU admission of any duration will be analyzed using the method specified in Section 6.2.9 and summarized by treatment arm through day 44 and through week 24. Participants without an event (at Day 44/Week 24) will be censored at that time or at the last known date in the study, whichever is later.

6.2.13. Proportion of participants requiring invasive mechanical ventilation or ECMO

The proportion of participants requiring invasive mechanical ventilation or ECMO will be analyzed using the method specified in Section 6.2.9 and summarized by treatment arm through day 44 and through week 24. Participants without an event (at Day 44/Week 24) will be censored at that time or at the last known date in the study, whichever is later.

6.2.14. Number of days in hospital and ICU stay in participants with COVID-19-related hospitalization

The number of days of hospital stay and number of days of ICU stay in participants with COVID-19-related hospitalization will be summarized through Day 44 and through Week 24 by treatment group using descriptive statistics (ie, mean, median, range).

6.2.15. Number of COVID-19-related medical visits through Day 44 and through Week 24

The number of COVID-19-related medical visits through Day 44 and through Week 24 will be summarized by treatment group using descriptive statistics (ie, mean, median, range).

6.2.16. Duration of each targeted COVID-19 signs/symptoms

Duration of each targeted COVID -19 signs/symptoms is defined as (First Date when the symptom alleviated/resolved) – (First Dose Date) +1 for each participant with baseline severity of mild, moderate, or severe.

For a participant that either completes the Day 44 visit of the study or discontinues from the study before the Day 44 visit without alleviation/resolution of signs/symptoms (censored), censoring date will be at the date of discontinuation from the study or day 44 whichever comes first, and time will be calculated as (Censoring Date) – (First Dose Date) +1.

Symptoms Alleviation through day 44 of each targeted COVID-19 sign/symptom is defined as **the first time** when each targeted symptom scored as moderate or severe at study entry are scored as mild or absent AND a targeted symptom scored mild or absent at study entry are scored as absent.

Symptoms Resolution through day 44 of each targeted COVID-19 sign/symptom is defined as the first time when each targeted symptom scored as mild, moderate or severe at study entry are scored as absent.

For symptoms with no reported severity in baseline, the symptom will have to be absent in order to be counted as alleviated/resolved (missing severity at baseline will be treated as mild).

For duration of each targeted COVID19 sign/symptom, a Kaplan-Meier analysis providing the event rate, median and quartiles will be provided for each treatment arm.

6.2.17. Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 44

Participants will record a daily severity rating of their symptom severity over the past 24 hours based on a 4-point scale in which 0 is reported if no symptoms were present; 1 if mild; 2 if moderate; and 3 if severe.

Vomiting and diarrhea will each be rated on a 4-point frequency scale where 0 is reported for no occurrence, 1 for 1 to 2 times, 2 for 3 to 4 times, and 3 for 5 or greater. Sense of smell and sense of taste will each be rated on a 3-point Likert scale where 0 is reported if the sense of smell/taste was the same as usual, 1 if the sense of smell/taste was less than usual, and 2 for no sense of smell/taste.

The proportion of participants with any severe targeted signs/symptoms attributed to COVID-19 through Day 44 will be summarized by treatment group. A participant with severe score for any targeted symptoms post-baseline will be counted as severe. Additionally, the proportion of participants reporting the presence of each targeted sign and symptom that is mild, moderate, or severe categories over time will also be presented.

In addition, to understand the severity of signs/symptoms attributed to COVID-19, the following analysis will be performed:

1. Proportion of participants with any severe targeted signs/symptoms attributed to COVID-19 at DAY 1 (baseline).

2. Proportion of participants with any severe targeted signs/symptoms attributed to COVID-19 Day 2 to end of active study treatment (during treatment; treatment arm dependent).

3. Proportion of participants with any severe targeted signs/symptoms attributed to COVID-19 from end of active treatment to Day 44 (post treatment).

6.2.18. Nirmatrelvir and ritonavir PK in plasma and whole blood

Nirmatrelvir and ritonavir PK in plasma and whole blood (if feasible) will be performed and summarized by the PK/PD group.

6.2.19. Other Endpoint(s)

Not applicable for this study.

6.3. Subset Analyses

Subgroup analysis will be performed for the main study population as numbers permit and results will be summarized only. Subgroup analyses of the primary endpoint will include:

- age group (<65, ≥65 and <18; ≥18);
- Sex (Male, Female);
- Race (White, Black or African American, Asian, Other);
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino);
- BMI category (<25, 25-29, ≥30);
- Immunocompromised Category (stratification factor*): Participants considered immunocompromised based solely on receiving corticosteroids or TNF blockers (yes/no)
- Baseline viral load defined as: $< 10^4$ copies/mL vs $\geq 10^4$ copies/mL
- Baseline viral load defined as: $< 10^7$ copies/mL vs $\geq 10^7$ copies/mL);
- Duration since first symptom (<= 5 days, > 5 days <= 30, >30)
- Vaccination status (unvaccinated or received last vaccination more than 6 months prior to randomization vs received last vaccination within 6 months prior to randomization)

    - *: Participants will be analyzed according to the category as determined by the CRF data and not according to the category selected at randomization (when different).

    - Subgroup analysis is not planned for the population with rebound, but may be performed if numbers permit.

6.4. Baseline and Other Summaries and Analyses

6.4.1. Baseline Summaries

The demographic characteristics will be summarized by treatment group within the FAS. This will include age, sex, race, ethnicity, baseline height, baseline weight, BMI, eGFR/eCrCl, renal function category, and region. Renal function will be based on the baseline eGFR/eCrCl (mL/min/1.73 m^2) using the following categories: Normal (≥90), Mild Impairment (≥60 to <90), Moderate Impairment (≥30 to <60), and Severe Impairment (<30).

All baseline disease characteristics, including COVID-19 disease (e.g., vaccination status, baseline serology, baseline viral load) and immunocompromised disease characteristics, will be summarized by treatment group within the FAS.

6.4.2. Study Conduct and Participant Disposition

Participant evaluation groups will be presented for all enrolled participants, and participant disposition will be summarized within the FAS population. The number of participants, treated, completing, and discontinuing by study phase, as well as the number of participants in each analysis set will be summarized by treatment group. For participants who did not complete the study, the reasons for withdrawal from the study will be presented.

6.4.3. Study Treatment Exposure

Duration of treatment will be summarized within the SAS population. The duration of treatment will be calculated as follows:

Duration of treatment = Date of last dose of study drug - date of first dose of study drug +1.

Compliance over the whole treatment period will be calculated as follows:

$$\text{Compliance} = \frac{\text{Actual Number of Doses Received}}{\text{Planned Number of Doses}} * 100$$

A subject is considered compliant if between 80% and 120% of the planned number of doses is received. Medication compliance will be summarized by treatment group. The compliance will be summarized in the following categories: $< 80\%$, $\geq 80\%$.

6.4.4. Concomitant Medications and Nondrug Treatments

The frequency of prior and concomitant medications will be summarized by treatment based on the WHO-drug coding dictionary within SAS population in accordance with Clinical Data Interchange Standards Consortium (CDISC) and Pfizer Standards (CaPS).

Concomitant medications of special interest will include anti-viral and mAb therapies (eg., remdesivir, dexamethasone, baricitinib, and tocilizumab). Prior medications of special interest will include molnupiravir, Evusheld, monoclonal antibodies, convalescent plasma, steroid treatment, and immunosuppressant medications (ie., medications that qualify the participant for the study).

6.5. Safety Summaries and Analyses

Standard summary tables and listings will be generated in accordance with Clinical Data Interchange Standards Consortium (CDISC) and Pfizer Standards (CaPS) for safety reporting for the following parameters: adverse events, lab parameters, vital signs, discontinuations from study, discontinuations from treatment, and treatment duration.

6.5.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is

generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation.

All adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by treatment group within SAS population.

6.5.2. Laboratory Data

Laboratory values and the corresponding changes from baseline will be summarized with descriptive statistics by treatment group over time in the SAS.

Laboratory shift tables from baseline utilizing central lab data will be presented for the following laboratory parameters at baseline: Liver function tests (ALT/AST), estimated glomerular filtration rate and Creatinine Clearance (derived using eGFR CKD EPI or Cockcroft-Gault Equation respectively), TSH, T4 (free), platelets, albumin, and total protein, and WBC.

All laboratory data will be reported in accordance with Clinical Data Interchange Standards Consortium (CDISC) and Pfizer Standards (CaPS) for safety reporting.

6.5.3. Vital Signs

The measurement taken immediately prior to start of study drug will be used as the baseline for calculating changes in vital signs. All vital sign data will be descriptively summarized by treatment group within SAS population and reported in accordance with the Pfizer Data Standards for safety reporting.

6.5.4. Electrocardiograms

Not Applicable.

7. INTERIM ANALYSES

7.1. Interim Analyses and Summaries

There is no interim analysis planned for this study.

7.2. Data Monitoring Committee

This study will use an E-DMC. The E-DMC is independent of the study team and includes only external members. The E-DMC charter describes the role of the DMC in more detail. The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of safety data to regulatory authorities or investigators, as appropriate.

8. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Proportion with sustained SARS-CoV-2 RNA < LLOQ from Day 15 to Day 44 (NP)	Primary	Evaluable, FAS	Intercurrent event: non-study anti-viral or mAb therapy – participant considered failure No imputation of missing data	Descriptive (n, %), 95% CI for proportion and the difference in proportion using binomial distribution normal approximation .
Proportion with sustained SARS-CoV-2 RNA < LLOQ from Day 15 to Day 44 (NP)	Supplementary	Evaluable	Intercurrent event: non-study anti-viral or mAb therapy – data excluded/considered missing No imputation of missing data	Descriptive (n, %), 95% CI for proportion and the difference in proportion using binomial distribution normal approximation
Proportion with sustained SARS-CoV-2 RNA < LLOQ from Day 15 to Day 44 (NP)	Supplementary	Evaluable	Intercurrent event: non-study anti-viral or mAb therapy – data included as is No imputation of missing data	Descriptive (n, %),95% CI for proportion and the difference in proportion using binomial distribution normal approximation
Proportion with sustained SARS-CoV-2 RNA < LLOQ from Day 15 to Day 44 (NP)	Supplementary	Evaluable	Participants with baseline SARS-CoV-2 RNA level <LLOQ will be excluded Intercurrent event: non-study anti-viral or mAb therapy – participant considered failure	Descriptive (n, %), 95% CI for proportion and the difference in proportion using binomial distribution

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
			No imputation of missing data	normal approximation
Proportion with sustained SARS-CoV-2 RNA < LLOQ from Day 15 to Day 44 (NP)	Supplementary	Evaluable	Participants who do not meet the protocol-defined immunocompromised criteria will be excluded. Intercurrent event: non-study anti-viral or mAb therapy – participant considered failure No imputation of missing data	Descriptive (n, %), 95% CI for proportion and the difference in proportion using binomial distribution normal approximation
Time to first SARS-CoV-2 RNA < LLOQ (NP)	Secondary	Evaluable with BL ≥ LLOQ	No imputation for missing data	KM curves
Time to sustained SARS-CoV-2 RNA < LLOQ (NP)	Secondary	Evaluable with BL ≥ LLOQ	No imputation for missing data	KM curves
Proportion with SARS-CoV-2 RNA <LLOQ over time (plasma)	Secondary	Evaluable	Missing at timepoint imputed as not <LLOQ	Descriptive (n, %)
Proportion with SARS-CoV-2 RNA <LLOQ over time (NP)	Secondary	Evaluable	Missing at timepoint imputed as not <LLOQ	Descriptive (n, %)
Change from baseline in SARS-CoV-2 RNA level over time (NP & plasma)	Secondary	Evaluable	<LLOQ imputed as 1.7, post-BL undetectable imputed as 0.0, no imputation for missing data	Descriptive summary
Rebound in SARS-CoV-2 RNA up to Day 44 (NP) defined as a half $\log_{10}$ copies/mL increase or greater relative to EOT (active) with follow-up viral RNA level ≥2.5 $\log_{10}$ copies/mL	Secondary	Evaluable with EOT (active) and 1 post-EOT not missing	No imputation for missing data	Descriptive (n, %)

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Rebound in SARS-CoV-2 RNA up to Day 44 (NP) defined as a half log_{10} copies/mL increase or greater relative to EOT (active) with follow-up viral RNA level ≥**3.0** log_{10} copies/mL	Secondary	Evaluable with EOT (active) and 1 post-EOT not missing	No imputation for missing data	Descriptive (n, %)
Rebound in SARS-CoV-2 RNA up to Day **28** (NP) defined as a half log_{10} copies/mL increase or greater relative to EOT (active) with follow-up viral RNA level ≥**3.0** log_{10} copies/mL	Secondary	Evaluable with EOT (active) and 1 post-EOT not missing	No imputation for missing data	Descriptive (n, %)
Proportion with COVID-19-related hospitalization >24 hours, or death through Day 28	Secondary	Evaluable	Max censor time at Day 28	KM method
Proportion with death (all cause) through Week 24	Secondary	FAS	Max censor time at Week 24	KM method
Proportion with COVID-19-related hospitalization	Secondary	Evaluable	Max censor time at Day 44	KM method
Proportion with COVID-19-related ICU admission	Secondary	Evaluable	Max censor time at Day 44	KM method
Proportion requiring IMV or ECMO	Secondary	Evaluable	Max censor time at Day 44	KM method
Number of days in hospital and ICU stay	Secondary	Evaluable, participants with COVID-19-related hospitalization	In the absence of a specific record of a COVID-19-related hospitalization, participants will be considered to be out of hospital	Descriptive summary

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Number of COVID-19-related medical visits through Day 44 and through Week 24	Secondary	Evaluable	In the absence of a specific record of a COVID-19-related medical visit, participants will be considered to not have a COVID-19-related medical visit.	Descriptive summary
Duration of each targeted COVID-19 signs/symptoms	Secondary	Evaluable	No imputation for missing data	KM method
Proportion with severe signs/symptoms attributed to COVID-19	Secondary	Evaluable	No imputation for missing data	Descriptive (n, %)

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Visit Windows in Reporting

The following table defines the visit windows and labels to be used for reporting:

Visit Label	Target Day	Definition [Day window]
Baseline	1	Day -2 to Day 1
Day 5	5	Day 2 to Day 7
Day 10	10	Day 8 to Day 12
Day 15	15	Day 13 to Day 18
Day 21	21	Day 19 to Day 24
Day 28	28	Day 25 to Day 31
Day 35	35	Day 32 to Day 39
Day 44	44	Day 40 to Day 49
Week 12	84	Day 77 to Day 91
Week 24	168	Day 161 to Day 175

If multiple observations fall into the same window, choose the one closest to the visit and if equidistance, then choose the latter of the two. .

Appendix 3. List of Abbreviations

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
BL	Baseline
BMI	body mass index
CaPS	CDISC aligned Pfizer Standards
CDISC	Clinical Data Interchange Standard Consortium
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
ECMO	extracorporeal membrane oxygenation
E-DMC	external data monitoring committee
eGFR	estimated glomerular filtration rate
FAS	full analysis set
ICU	intensive care unit
IMV	invasive mechanical ventilation
IRC	internal review committee
KM	Kaplan-Meier
LLOQ	lower limit of quantitation
LS	least-squares
LSM	least-squares mean
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
MNAR	missing not at random
N/A	not applicable
NP	nasopharyngeal
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	preferred term
RAT	rapid antigen test
RNA	ribonucleic acid
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure

Abbreviation	Term
TEAE	treatment emergent adverse event
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary