Protocol C4671042

AN INTERVENTIONAL, EFFICACY AND SAFETY, PHASE 2, RANDOMIZED, DOUBLE-BLIND, 2-ARM STUDY TO INVESTIGATE A REPEAT 5-DAY COURSE OF NIRMATRELVIR/RITONAVIR COMPARED TO PLACEBO/ritonavir IN PARTICIPANTS AT LEAST 12 YEARS OF AGE WITH REBOUND OF COVID-19 SYMPTOMS AND RAPID ANTIGEN TEST POSITIVITY

Statistical Analysis Plan
(SAP)

Version: 2

Date: 12 Oct 2023

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
Version 1/ 30 Sep 2022	Protocol amendment 1 16 Sep 2022	Original SAP	N/A
Version 2/ 12 Oct 2023	Protocol amendment 4 29 Jun 2023	Protocol amendment 4 changes, regulatory feedback and other clarification	• Updated the analysis populations in Section 2.2, 4, 5.1, 6.1, 6.2 and 6.3 for primary, secondary and relevant tertiary/exploratory obejective/estimand/endpoints to align with protocol change. • Updated Section 2.4 sample size to align with protocol change. • Added site exclusion for efficacy related analysis sets in Section 4. • Added secondary analyses for primary and sencondary endpoints in Section 6.1 and 6.2 to align with protocol change. Updated the multiplicity adjustment acordingly in Section 5.1. • Removed the analysis details for infectious titer by TCID50 and by virus recovery in Section 3.4, 4 and 6.3. These analyses will be specified in virology analysis plan. • Add analysis details for potential covariates in Section 6.2.1 and 6.2.2 • Added analysis details for time to sustained NP Swab SARS-CoV-2 RNA below the LLOQ in Section 6.3.5. • Added two alternative definitions/analyses of rebound in Section 6.3.6. • Added other analysis for the concordance of rapid antigen and RT-PCR test results in Section 6.3.12. • Added additional subgroups analyses in Sectoin 6.4. • Updated Appendix 1 to align with the analysis updates/changes in SAP main body. • Updated the handling of multiple measurements on the same day for lab data in Appendix 2.1.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			• Added Appendix 4 for Participant-Reported COVID-19-Related Signs and Symptoms • Editorial change throughout the document.

2. INTRODUCTION

Nirmatrelvir, a potent and selective SARS-CoV-2 3CL orally administered protease inhibitor, is being investigated in participants with rebound of COVID-19 symptoms and rapid antigen test positivity.

The purpose of this study is to evaluate the efficacy, safety and tolerability of a second 5-day treatment course of nirmatrelvir/ritonavir in participants with a rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks (14 days) following completion of an initial 5-day treatment course.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4671042.

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 compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on viral RNA level in NP swabs in participants with mild-to-moderate COVID-19.	• The change in viral SARS-CoV-2 RNA level as measured in NP swabs from baseline to Day 5.	• The difference in mean change of SARS-CoV-2 RNA level in NP swabs from baseline to Day 5 between nirmatrelvir/ritonavir and placebo/ritonavir group in participants with a rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course ,who have a positive viral RNA NP swab test result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.

Objectives	Endpoints	Estimands
Secondary:	**Secondary:**	**Secondary:**
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on the duration of viral shedding.	• Time to 2 consecutive negative rapid antigen test results obtained at least 24 (-2) h apart through Day 28.	• The hazard ratio for time to 2 consecutive negative rapid antigen test results obtained at least 24 (-2) h apart through Day 28 between nirmatrelvir/ritonavir and placebo/ritonavir group in participants with rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course, who have a positive viral RNA NP swab test result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on the duration and severity of signs and symptoms in participants with mild-to-moderate COVID-19.	• Time (days) to sustained alleviation of all targeted signs and symptoms through Day 28 where sustained alleviation is defined as the first of 2 consecutive days when any symptoms scored as moderate or severe at baseline are scored as mild or absent and any symptoms scored as mild or absent at baseline are scored as absent.	• The hazard ratio for time to sustained alleviation of all targeted signs and symptoms through Day 28 between nirmatrelvir/ritonavir and placebo/ritonavir group in participants with rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course, who have a positive viral RNA NP swab test result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.
• To describe the safety and tolerability of nirmatrelvir/ritonavir in participants with mild-to-moderate COVID-19.	• Incidence of TEAEs. Incidence of SAEs and AEs leading to discontinuation.	• Not applicable.
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on viral RNA level in NP swabs in participants with mild-to-moderate COVID-19.	• Proportion of participants with SARS-CoV-2 RNA in NP swab below the LLOQ on Days 3, 5, 10, 15, 21, 28, and 34. • Proportion of participants with sustained NP swab SARS-CoV-2 RNA below the LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 5 through Day 34. • Proportion of participants with SARS-CoV-2 RNA in NP swabs below the LLOQ (defined as	• Not applicable.

Objectives	Endpoints	Estimands
	<2.0 log_{10} copies/mL) on both Days 5 and 10. • The change in SARS-CoV-2 RNA level in NP swabs from baseline to Days 3, 10, 15, 21, 28, and 34. • Time to sustained NP swab SARS-CoV-2 RNA below the LLOQ (defined as <2.0 log_{10} copies/mL) and remains below the LLOQ through Day 34 for participants with NP swab SARS-CoV-2 RNA greater than or equal to the LLOQ at baseline. • Rebound in SARS-CoV-2 RNA level in NP swabs at follow-up (ie, any study visit from Day 10 to through Day 34, defined as a half (0.5) log_{10} copies/mL increase or greater in SARS-CoV-2 RNA level relative to SARS-CoV-2 RNA level on Day 5 and with a follow-up viral RNA level ≥2.5 log_{10} copies/mL.	
• To compare the effect of nirmatrelvir/ritonavir on the rate of cell culture infectious virus over time in participants with mild-to-moderate COVID-19	In participants with detectable viral titers at baseline by TCID50: • Time to negative infectious titer by TCID50. • Change in TCID50 from baseline to Days 3, 5, 10, 15, 21, 28, and 34. • Proportion of participants with negative infectious titer by TCID50 on Days 3, 5, 10, 15, 21, 28, and 34. In participants with positive viral titers at baseline by virus recovery: • Time to negative infectious titer by virus recovery. • Proportion of participants with negative infectious titer by virus recovery on Days 3, 5, 10, 15, 21, 28, and 34.	• Not applicable
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on viral concentration in plasma in participants with mild-to-moderate COVID-19.	• Change from baseline in SARS-CoV-2 viral RNA level in plasma, over time.	• Not applicable.

Objectives	Endpoints	Estimands
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on COVID-19-related hospitalization and all-cause mortality in participants with mild-to-moderate COVID-19.	• Proportion of participants with COVID-19-related hospitalization >24h or death from any cause through Day 28.	• Not applicable.
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on COVID-19-related healthcare resource utilization in participants with mild-to-moderate COVID-19.	• Number of COVID-19-related medical visits through Day 34.	• Not applicable.
• To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on the duration and severity of signs and symptoms in participants with mild-to-moderate COVID-19.	• Time (days) to sustained resolution of all targeted signs and symptoms through Day 28 where sustained resolution is defined as the first of two consecutive days when all targeted COVID-19 symptoms are scored as absent.	• Not applicable

2.2.1. Primary Estimand(s)

The primary estimand is the difference in mean change of SARS-CoV-2 RNA level in NP swabs from baseline to Day 5 between nirmatrelvir/ritonavir and placebo/ritonavir group in patients with a rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course, who have a positive viral RNA NP swab test result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.

2.2.2. Secondary Estimand(s)

Estimands for the secondary endpoints are:

- The hazard ratio for time to 2 consecutive negative rapid antigen test results obtained at least 24 (-2) h apart through Day 28 between nirmatrelvir/ritonavir and placebo/ritonavir group in participants with rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course, who have a positive viral RNA NP swabtest result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.

- The hazard ratio for time to sustained alleviation of all targeted signs and symptoms through Day 28 between nirmatrelvir/ritonavir and placebo/ritonavir group in participants with rebound in COVID-19 symptoms and a positive rapid antigen test within 2 weeks following completion of an initial 5-day treatment course, who have a positive viral RNA NP swabtest result at baseline. This will be estimated without regard to study treatment discontinuation and without regard to prohibited therapies.

2.3. Study Design

This Phase 2, randomized, double-blind, placebo-controlled study will evaluate the efficacy and safety of a repeat 5-day treatment course of nirmatrelvir/ritonavir or placebo/ritonavir for the treatment of mild-to-moderate COVID-19. Participants must have written documentation, such as an electronic health record, medical record, or prescription receipt of treatment with nirmatrelvir/ritonavir (verbal assertion of treatment is not acceptable) with patient-reported 100% compliance (ie, completed a 5 day course of nirmatrelvir/ritonavir). They must have experienced alleviation or resolution in COVID-19 signs/symptoms followed by a worsening (rebound) of signs/symptoms along with a positive rapid antigen test after completing an initial 5-day course of nirmatrelvir/ritonavir.

The onset of rebound in COVID-19 symptoms along with evidence of SARS-CoV-2 infection must occur within 2 weeks (14 days) after completion of an initial 5-day course of nirmatrelvir/ritonavir. A 2-week time-period for rebound symptoms and SARS-CoV-2 infection was selected to enroll a population that has a presumptive recurrence of the same viral illness and not a new SARS-CoV-2 infection. Symptom burden including alleviation, resolution and worsening (rebound) to qualify for the study is based on the judgment of both the participant along with investigator judgment.

Eligible participants for this study will be randomly assigned (2:1 allocation of active to placebo) to receive:

- nirmatrelvir plus ritonavir orally q12h for 5 days; or
- placebo plus ritonavir orally q12h for 5 days.

Randomization will be stratified by geographic region.

Participants will be screened within 24 hours before randomization.

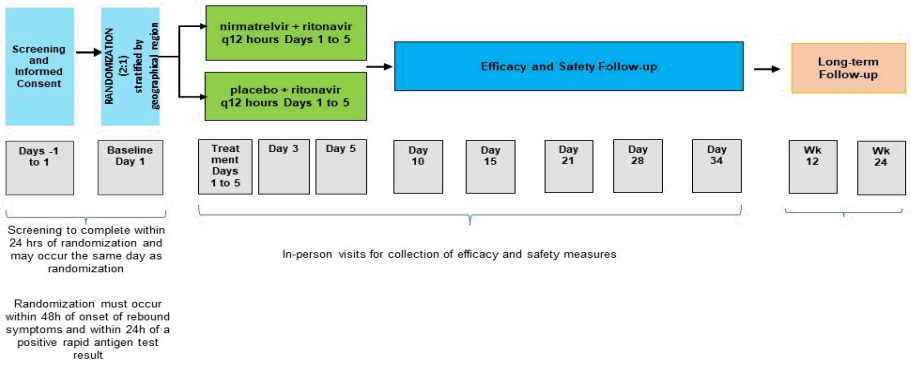
Participants must be randomized within 48 hours from the onset of the rebound COVID-19 symptoms and must be randomized within 24 hours of a positive baseline rapid antigen test. The total study duration is up to 24 weeks, including study intervention administration through Day 5 or Day 6, efficacy and safety assessments through Day 34, and long-term follow up at Weeks 12 and 24.

Participants are eligible if they are at least 12 years of age (and weigh ≥40 kg at screening) and they must have at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19. However, participants who are immunocompromised are excluded from this study as they may have prolonged viral shedding due to their immunocompromised state. Participants will be eligible for enrollment irrespective of COVID-19 vaccination/boosted status (except for time course restrictions listed in the exclusion criteria).

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

The study schematic is provided in Figure 1.

Figure 1. Study Schema



2.4. Sample Size Determination

The study will enroll approximately 411 participants.

The sample size calculation is based on the primary efficacy endpoint as the change in viral RNA level from baseline to Day 5 as measured in NP swabs in the mITT analysis set. Assuming a SD of 1.8 (based on EPIC-HR, NCT04960202), a sample size of approximately 315 evaluable participants (210 participants in nirmatrelvir/ritonavir group and 105 participants in placebo/ritonavir group) is expected to provide 90% power to detect a difference of 0.7 $\log_{10}$ copies/mL in viral RNA between groups using a 2-sided 0.05 alpha level test. Assuming approximately 10% of participants will have a negative viral RNA result at baseline, and assuming a non-evaluable rate of 15%, approximately 411 participants will be randomized in the study to achieve approximately 315 participants evaluable for the primary efficacy endpoint.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- The primary endpoint is the change in viral SARS-CoV-2 RNA level as measured in NP swabs from baseline to Day 5.

3.2. Secondary Endpoint(s)

- Time to 2 consecutive negative rapid antigen test results obtained at least 24 (-2) h apart through Day 28.

- Time (days) to sustained alleviation of all targeted signs and symptoms through Day 28 where sustained alleviation is defined as the first of 2 consecutive days when any symptoms scored as moderate or severe at baseline are scored as mild or absent and any symptoms scored as mild or absent at baseline are scored as absent.

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

3.3. Tertiary/Exploratory Endpoint(s)

- Proportion of participants with SARS-CoV-2 RNA in NP swab below the LLOQ on Days 3, 5, 10, 15, 21, 28, and 34.

- Proportion of participants with sustained NP swab SARS-CoV-2 RNA below the LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 5 through Day 34.

- Proportion of participants with SARS-CoV-2 RNA in NP swabs below the LLOQ (defined as <2.0 $\log_{10}$ copies/mL) on both Days 5 and 10.

- The change in SARS-CoV-2 RNA level in NP swabs from baseline to Days 3, 10, 15, 21, 28, and 34.

- Time to sustained NP swab SARS-CoV-2 RNA below the LLOQ (defined as <2.0 $\log_{10}$ copies/mL) and remains below the LLOQ through Day 34 for participants with NP swab SARS-CoV-2 RNA greater than or equal to the LLOQ at baseline.

- Rebound in SARS-CoV-2 RNA level in NP swabs at follow-up (ie, any study visit from Day 10 to through Day 34, defined as a half (0.5) $\log_{10}$ copies/mL increase or greater in SARS-CoV-2 RNA level relative to SARS-CoV-2 RNA level on Day 5 and with a follow-up viral RNA level ≥2.5 $\log_{10}$ copies/mL.

- Time to negative infectious titer by TCID50 in participants with detectable viral titers at baseline by TCID50.

- Change in TCID50 from baseline to Days 3, 5, 10, 15, 21, 28, and 34 in participants with detectable viral titers at baseline by TCID50.

- Proportion of participants with negative infectious titer by TCID50 on Days 3, 5, 10, 15, 21, 28, and 34 in participants with detectable viral titers at baseline by TCID50.

- Time to negative infectious titer by virus recovery in participants with positive viral titers at baseline by virus recovery.

- Proportion of participants with negative infectious titer by virus recovery on Days 3, 5, 10, 15, 21, 28, and 34 in participants with positive viral titers at baseline by virus recovery.

- Change from baseline in SARS-CoV-2 viral RNA level in plasma, over time.
- Proportion of participants with COVID-19-related hospitalization >24h or death from any cause through Day 28.
- Number of COVID-19-related medical visits through Day 34.
- Time (days) to sustained resolution of all targeted signs and symptoms through Day 28 where sustained resolution is defined as the first of two consecutive days when all targeted COVID-19 symptoms are scored as absent.

3.4. Baseline Variables

Baseline visit (Day 1) will be defined as the latest measurement between Day -1 and Day 1.

For viral load data from NP swabs, viral load data from plasma samples, the baseline window will be Day -1 to Day 1, but post-dose samples that are collected within 1 hour post start of dosing will be treated as baseline.

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

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 AE is considered a treatment-emergent adverse event (TEAE) if the event started on or after the study medication start date and time.

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 chemistry 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 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.

Population	Description
Full analysis set (FAS)	All participants randomly assigned to study intervention.
Safety analysis set (SAS)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they received.
mITT	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and who have a positive viral RNA NP swab test result ($\geq$ 2.0 $\log_{10}$ copies/mL) at baseline. Participants will be analyzed according to the study intervention they were randomized.
Per protocol (PP)	All participants in the mITT analysis set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint. Protocol deviations will be reviewed to generate the list of participants with significant deviations to be excluded from the PP analysis set. The PP exclusion criteria will be finalized prior to breaking the blind.
mITT1	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and who have a positive rapid antigen test result at baseline. Participants will be analyzed according to the study intervention they were randomized.

The primary analysis set for efficacy will be the mITT. mTT1 will be used for relevant efficacy endpoints. Safety Analysis Set (SAS) will be used in the analyses of the safety data.

All participants from CCI will be excluded from the efficacy analyses due to GCP issues.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The primary hypothesis is to test whether or not there is a difference in mean change of viral RNA level in NP swabs from baseline to Day 5 between nirmatrelvir/ritonavir and the placebo/ritonavir group:

Null hypothesis: H_0 $\mu_{\text{nirmatrelvir/ritonavir}} - \mu_{placebo/ritonavir} = 0$

Alternative hypothesis: H_a $\mu_{\text{nirmatrelvir/ritonavir}} - \mu_{placebo/ritonavir} \neq 0$

Where $\mu_{\text{nirmatrelvir/ritonavir}}$ and $\mu_{\text{placebo/ritonavir}}$ are mean change of viral RNA level ($\log_{10}$ copies/mL) in NP swabs from baseline to Day 5 for nirmatrelvir/ritonavir and placebo/ritonavir groups.

The overall Type I error rate across the primary and key secondary efficacy endpoints will be controlled at alpha = 0.05. Following the positive test of the primary efficacy endpoint in the primary analysis set (mITT), the secondary analysis for the primary efficacy endpoint using the mITT1 analysis set will be tested.

Following the positive test of the secondary analysis,, the following key secondary efficacy endpoints will be tested using Hochberg method:[1]

- Time to 2 consecutive negative rapid antigen test results obtained at least 24 (-2)h apart through Day 28 in the mITT analysis set.

- Time (days) to sustained alleviation of all targeted signs and symptoms through Day 28 where sustained alleviation is defined as the first of two consecutive days when any symptoms scored as moderate or severe at baseline are scored as mild or absent and any symptoms scored as mild or absent at baseline are scored as absent in the mITT analysis set.

5.2. General Methods

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 and qualitative variables will be summarized by frequency tables with number and proportion in each category.

5.2.1. Analyses for Binary Endpoints

For binary endpoints, the proportion of participants with the event will be summarized for each group. Where appropriate, logistic regression will be utilized to estimate the odds ratio and its corresponding 95% confidence interval.

5.2.2. Analyses for Continuous Endpoints

For continuous endpoints, descriptive statistics will be provided by treatment group. Where appropriate, analysis of covariance (ANCOVA) or mixed model for repeated measures (MMRM) analysis will be utilized.

5.2.3. Analyses for Categorical Endpoints

For categorical endpoints, the number and proportion of participants for each category will be summarized for treatment group.

5.2.4. Analyses for Time-to-Event Endpoints

For time-to-event endpoints, a Cox proportional hazard regression model will be performed and the estimate of the hazard ratio, its confidence interval and p-value will be provided. In addition, time-to-event endpoints will be summarized graphically using Kaplan-Meier plots for each treatment group.

5.3. Methods to Manage Missing Data

Missing viral load will not be imputed in general. MMRM will be used to analyze viral load data to handle Missing at Random (MAR), and it allows for inclusion of participants with partial longitudinal data in the analysis.

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 efficacy endpoint is the change in viral SARS-CoV-2 RNA level from baseline to Day 5 as measured in NP swabs.

6.1.1. Main Analysis

The primary analysis for mean change in SARS-CoV-2 RNA level from baseline will be performed using a MMRM. The analysis will include the fixed effects of treatment, geographic region, baseline viral RNA level, visit, and treatment-by-visit interaction. An unstructured (co)variance structure will be used to model the within-participant variability. The LS means and treatment difference for each visit will be calculated and presented with their corresponding 95% CIs. The primary comparison for treatment effect will be the difference in LS means and 95% CI at Day 5. The primary analysis will be performed using mITT analysis set.

The secondary analysis for primary endpoint will be performed using the mITT1 analysis set. In the analysis, samples with result "<LLOQ" will be imputed as 1.7 $\log_{10}$ copies/mL, and samples with result "undetectable" will be imputed as 0.0 $\log_{10}$ copies/mL.

6.1.2. Sensitivity/Supplementary Analyses

Supplementary Analysis:

- A supplementary analysis of the primary endpoint will be conducted using MMRM in PP analysis set.

6.2. Secondary Endpoint(s)

6.2.1. Time to 2 Consecutive Negative Rapid Antigen Test Results Obtained at least 24(-2)h Apart through Day 28

The event of 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart through Day 28 is defined as achieving two consecutive non-missing rapid antigen test with negative results through Day 28, where the two tests are at least 22 hours and at most 7 days apart. For the event of 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart through Day 28, the date of the first negative rapid antigen test result will be considered the First Event Date.

Time to 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart for the purpose of this study is defined as:

- For a participant achieving the event, time to event will be calculated as (First Event Date) – (First Dose Date) +1.

- For a participant not achieving the event (censored), censoring date will be at the last date of rapid antigen test measurement, and time will be calculated as (Censoring Date) – (First Dose Date) +1 or Day 27 whichever occurs first (Day 27 is the last possible day to achieve 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart through Day 28).

Participants who are hospitalized for the treatment of COVID-19 or die from any cause during the 28-day period will be classified as not achieving the event and will be censored at Day 27.

Cox proportional hazard model analyses will be used for time to 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart in mITT analysis set. Cox proportional hazard model will include treatment, geographic region, baseline viral load (< 4 or ≥ 4) and time since the last vaccination (≤ 6 months, > 6 months or unvaccinated) as appropriate. The treatment group comparison will be presented as the estimate of the hazard ratio, 95% CI and p-value. In addition, time to 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart will be summarized graphically using Kaplan-Meier plots for each of the treatment groups in mITT analysis set.

The log-rank test will be performed as additional analysis to compare the treatment group using mITT analysis set.

Similar analyses for time to 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart will also be performed in the mITT1 analysis set.

6.2.2. Time (days) to Sustained Alleviation of All Targeted Signs and Symptoms through Day 28

Sustained alleviation of all targeted COVID-19 signs/symptoms is defined as the event occurring on the first of 2 consecutive days when all symptoms scored as moderate or severe at study entry are scored as mild or absent AND all symptoms scored mild or absent at study entry are scored as absent. The first day of the 2 consecutive-day period will be considered the First Event Date.

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

Day 27 is the last possible day that symptom alleviation can be achieved (definition includes data from the subsequent day) and Day 28 is the last day participants report their daily signs and symptoms.

The time to sustained symptom alleviation for the purpose of this study is defined as:

- For a participant with sustained symptom alleviation, time to event will be calculated as (First Event Date) – (First Dose Date) +1.

- For a participant that either completes Day 28 of the study or discontinues from the study before Day 28 without sustained symptom alleviation(censored), censoring date will be at the last date on which symptom alleviation is assessed, and time will be calculated as (Censoring Date) – (First Dose Date) +1 or Day 27 whichever occurs first.

Participants who are hospitalized for the treatment of COVID-19 or die from any cause during the 28-day period will be classified as not achieving sustained symptom alleviation and will be censored at Day 27.

Cox proportional hazard model analyses will be used for time to sustained symptom alleviation in mITT analysis set. Cox proportional hazard model will include treatment, geographic region baseline viral load (< 4 or ≥ 4) and time since the last vaccination (≤ 6 months, > 6 months or unvaccinated) as appropriate. The treatment group comparison will be presented as the estimate of the hazard ratio, 95% CI and p-value. In addition, time to sustained symptom alleviation will be summarized graphically using Kaplan-Meier plots for each of the treatment groups in mITT analysis set.

Similar analyses for time to sustained symptom alleviation will also be performed in the mITT1 analysis set.

6.2.3. Incidence of Treatment Emergent Adverse Events (TEAEs); Incidence of SAEs and AEs Leading to Discontinuation

The incidence of TEAEs will be summarized by treatment group, by System Organ Class (SOC) and preferred term (PT) using the SAS.

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

6.3. Tertiary/Exploratory Endpoints

6.3.1. Proportion of Participants with SARS-CoV-2 RNA in NP Swab below the LLOQ on Days 3, 5, 10, 15, 21, 28, and 34

The number and proportion of participants with SARS-CoV-2 RNA level in NP swabs <2.0 $\log_{10}$ copies/mL at 3, 5, 10, 15, 21, 28, and 34 will be summarized by treatment group. The analysis will be done using mITT analysis set.

6.3.2. Proportion of Participants with Sustained NP Swab SARS-CoV-2 RNA below the LLOQ (defined as <2.0 $\log_{10}$ copies/mL) from Day 5 through Day 34

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 5 through Day 34 will summarized by treatment group using mITT analysis set.

Sustained SARS-CoV-2 RNA below the LLOQ from Day 5 through Day 34 is defined as having all non-missing measurements from Day 5 to Day 34 below the LLOQ and no more than 3 visits with missing SARS-CoV-2 RNA levels (scheduled collection on Days 5, 10, 15, 21, 28 and 34).

6.3.3. Proportion of Participants with SARS-CoV-2 RNA in NP Swabs below the LLOQ (defined as <2.0 $\log_{10}$ copies/mL) on both Days 5 and 10

The number and proportion of participants with SARS-CoV-2 RNA in NP swabs below the LLOQ (defined as <2.0 $\log_{10}$ copies/mL) on both Days 5 and 10 will be summarized by treatment group. The analysis will be done using mITT analysis set.

6.3.4. Change in SARS-CoV-2 RNA Level in NP Swabs from Baseline to Days 3, 10, 15, 21, 28, and 34

Change in SARS-CoV-2 RNA level in NP swabs from baseline to Days 3, 10, 15, 21, 28, and 34 will be analyzed similarly to the primary endpoint using MMRM model in the mITT analysis set. The LS means and treatment difference for each visit will be calculated and presented with their corresponding 95% CIs.

6.3.5. Time to Sustained NP Swab SARS-CoV-2 RNA below the LLOQ (defined as <2.0 log_{10} copies/mL) and Remains below the LLOQ through Day 34 for Participants with NP Swab SARS-CoV-2 RNA Greater than or Equal to the LLOQ at Baseline

Time to sustained NP swab SARS-CoV-2 RNA below the LLOQ (defined as <2.0 log_{10} copies/mL) and remains below the LLOQ through Day 34 will be summarized graphically using Kaplan-Meier plots for each of the treatment groups. The analyses will be done similary as in Section 6.2.2 using the mITT analysis set, which includes participants with baseline viral load ≥ LLOQ.

Sustained is defined as NP swab SARS-CoV-2 RNA level not ≥2.0 log_{10} copies/mL at any study visit (through Day 34) following the first study visit where the participant's NP swab SARS-CoV-2 RNA <LLOQ.

Let *t* represent the study day t between Day 5 and 28 visit inclusive for which there is a measurement of SARS-CoV-2 RNA level.
Then a sustained event will correspond to the first possible value of *t* to satisfy the following criteria:

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

b) At least one SARS-CoV-2 RNA measurement is <LLOQ after Day t

c) All available (non-missing) SARS-CoV-2 RNA measurements between Day *t* and Day 34 visit are <LLOQ

d) No more than 50% missingness between Day *t* and Day 34 are missing.

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

The Day 28 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* ≤ the Day 28 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 34 visit, and time will be calculated as (Censoring Date) – (First Dose Date) +1.

6.3.6. Rebound in SARS-CoV-2 RNA Level in NP Swabs at Follow-up ie, Any Study Visit from Day 10 to through Day 34, Defined as a Half (0.5) Log_{10} Copies/mL Increase or Greater in SARS-CoV-2 RNA Level Relative to SARS-CoV-2 RNA Level on Day 5 and with a Follow-up Viral RNA Level ≥2.5 Log_{10} Copies/mL

The number and proportion of participants with rebound in SARS-CoV-2 RNA level in NP swabs up at follow-up will be summarized by treatment group. The analyses will be done using mITT analysis set.

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 Day 5 through Day 34) that is defined as a half (0.5) log_{10} copies/mL increase or greater in SARS-CoV-2 RNA level relative to SARS-CoV-2 RNA level on Day 5, 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 Day 5 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 SARS-CoV-2 RNA level based on Day 5, 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 SARS-CoV-2 RNA measurement on DAY 5 and at least one non-missing measurement among after Day 5 visit through the Day 34 visit (or through the Day 28 visit for the second alternative definition of rebound analysis).

6.3.7. Endpoints Related to Infectious Titer

The analyses for the following endpoionts related to infectious titer will be specified in virology analysis plan.

- Time to negative infectious titer by TCID50 in participants with detectable viral titers at baseline by TCID50.

- Change in TCID50 from baseline to Days 3, 5, 10, 15, 21, 28, and 34 in participants with detectable viral titers at baseline by TCID50.

- Proportion of participants with negative infectious titer by TCID50 on Days 3, 5, 10, 15, 21, 28, and 34 in participants with detectable viral titers at baseline by TCID50.

- Time to negative infectious titer by virus recovery in participants with positive viral titers at baseline by virus recovery.

- Proportion of participants with negative infectious titer by virus recovery on Days 3, 5, 10, 15, 21, 28, and 34 in participants with positive viral titers at baseline by virus recovery.

6.3.8. Change from Baseline in SARS-CoV-2 Viral RNA Level in Plasma, Over Time

Change from baseline in SARS-CoV-2 viral RNA level in plasma, over time will be analyzed similar to the primary endpoint using MMRM model in mITT analysis set. The LS means and treatment difference for each visit will be calculated and presented with their corresponding 95% CIs.

6.3.9. Proportion of Participants with COVID-19-related Hospitalization >24h or Death from Any Cause through Day 28

The number and proportion of participants with COVID-19-related hospitalization >24h or death from any cause through Day 28 will be summarized by treatment group. The analyses will be done using the mITT analysis set.

6.3.10. Number of COVID-19-related Medical Visits through Day 34

Number of COVID-19-related medical visits through Day 34 will be summarized by treatment group descriptively (n, mean, standard deviation, median, min, max). The analysis will be done using the mITT analysis set.

6.3.11. Time (days) to Sustained Resolution of All Targeted Signs and Symptoms through Day 28

Sustained resolution of all targeted COVID-19 signs/symptoms is defined as the event occurring on the first of 2 consecutive days when all targeted COVID-19 symptoms are scored as absent. The first day of the 2 consecutive-day period will be considered the First Event Date.

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

Day 27 is the last possible day that symptom resolution can be achieved (definition includes data from the subsequent day) and Day 28 is the last day participants report their daily signs and symptoms.

The time to sustained symptom resolution for the purpose of this study is defined as:

- For a participant with sustained symptom resolution, time to event will be calculated as (First Event Date) – (First Dose Date) +1.

- For a participant that either completes Day 28 of the study or discontinues from the study before Day 28 without sustained symptom resolution (censored), censoring date will be at the last date on which symptom resolution is assessed, and time will be calculated as (Censoring Date) – (First Dose Date) +1 or Day 27 whichever occurs first.

Participants who are hospitalized for the treatment of COVID-19 or die from any cause during the 28-day period will be classified as not achieving sustained symptom resolution and will be censored at day 27.

Time to sustained symptom resolution will be analyzed similarly as in Section 6.2.2.

6.3.12. Other analyses

For the rapid antigen test and NP swab SARS-CoV-2 RNA/RT-PCR test that are collected on the same study day, the corcordance analysis will be performed at each visit, across post-baseline visits and across all visits for the each treatment group and overall/combined treatment group in mITT1 analysis set. Kappa statistic will be provided as a measurement of agreement between rapid antgen test and RT-PCR for across post-baseline visits and across all visits.

6.4. Subset Analyses

Subgroup analyses of the primary endpoint (if data permitted) will include:

- Age group (<18, 18 to <60, ≥60) and (<65, ≥65);
- Gender;
- Race;
- Ethincity;
- BMI category (<25, 25 to <30, ≥30);
- Baseline viral load (<7 $\log_{10}$ copies/mL, ≥7 $\log_{10}$ copies/mL; <4 $\log_{10}$ copies/mL, ≥4 $\log_{10}$ copies/mL);
- Geographic region (US, Ex-US) .

A forest plot will display confidence intervals across subgroups.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline and Other Characteristics Summaries

The baseline and demographic characteristics will be summarized by treatment group within the FAS and other analysis set as appropriate. This will include age, gender, race, height, and baseline weight, etc. Other characteristics including household characteristics will also be summarized by treatment group within the FAS.

6.5.2. Study Conduct and Participant Disposition

Study conduct and participant disposition will be summarized within the FAS. The number of participants randomized, treated, completing and discontinuing from the study, 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.

6.5.3. Study Treatment Exposure

Duration of treatment will be summarized within the SAS.

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 participant is considered compliant if between 80% and 115% of the planned number of doses is received. The compliance will be summarized in the following categories: <80%, 80% to 115%, and >115% by the number and percentage of participants in each treatment group.

6.5.4. Prior and Concomitant Medications

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

6.6. Safety Summaries and Analyses

Standard summary tables and listings will be generated in accordance with CDISC and CaPS for safety reporting for the following parameters: AEs, laboratory parameters, and vital signs.

6.6.1. Adverse Events

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

6.6.2. Laboratory Data

Laboratory values and the corresponding changes from baseline will be summarized with descriptive statistics by treatment group in the SAS. Laboratory data will be reported in accordance with CDISC and CaPS for safety reporting.

6.6.3. Vital Signs

Vital sign data and the corresponding changes from baseline will be descriptively summarized by treatment within the SAS. Vital sign data will be reported in accordance with CDISC and CaPS.

7. INTERIM ANALYSES

7.1. Interim Analyses and Summaries

No formal interim analysis is planned for this study. However, the sponsor may conduct unblinded reviews of the data during the course of the study if requested by regulatory authorities including in the support of regulatory submissions. Should an unblinded review be requested, details of the unblinding plan will be described in a SAP and a separate data unblinding document.

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 E-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. In addition, the E-DMC may monitor the baseline SARS-CoV-2 RNA levels to ensure the population is consistent with the study design assumptions. 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 safety data, to regulatory authorities and investigators, as appropriate.

8. REFERENCES

1. Benjamini Y, & Hochberg, Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. . Journal of the Royal Statistical Society. 1995;57:289–300.

APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Change in viral SARS-CoV-2 RNA level as measured in NP swabs from baseline to Day 5	Primary	mITT	All data collected will be included regardless of study treatment discontinuation and prohibited therapies. MMRM method to take account of missing at random.	MMRM
Change in viral SARS-CoV-2 RNA level as measured in NP swabs from baseline to Day 5	Secondary	mITT1	All data collected will be included regardless of study treatment discontinuation and prohibited therapies. MMRM method to take account of missing at random.	MMRM
Change in viral SARS-CoV-2 RNA level as measured in NP swabs from baseline to Day 5	Supplementary	PP	MMRM method to take account of missing at random.	MMRM
Change in viral SARS-CoV-2 RNA level as measured in NP swabs from baseline to Day 5	Subgroup analyses for the primary endpoint	mITT	All data collected will be included regardless of study treatment discontinuation and prohibited therapies. MMRM method to take account of missing at random. Subgroups defined in Section 6.4	MMRM

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Time to 2 consecutive negative rapid antigen test results obtained at least 24(-2)h apart through Day 28	Secondary	mITT mITT1	All data collected will be included regardless of study treatment discontinuation and prohibited therapies. Missing data will not be imputed.	Cox proportional hazard model; KM curves; Log-rank test
Time (days) to sustained alleviation of all targeted signs and symptoms through Day 28	Secondary	mITT mITT1	All data collected will be included regardless of study treatment discontinuation and prohibited therapies. Missing data will not be imputed.	Cox proportional hazard model; KM curves
Proportion of participants with SARS-CoV-2 RNA in NP swab below the LLOQ on Days 3, 5, 10, 15, 21, 28, and 34	Exploratory	mITT	Missing data will not be imputed.	Descriptive summary
Proportion of participants with sustained NP swab SARS-CoV-2 RNA below the LLOQ (defined as <2.0 log10 copies/mL) from Day 5 through Day 34	Exploratory	mITT	Missing data will not be imputed.	Descriptive summary
Proportion of participants with SARS-CoV-2 RNA in NP swabs below the LLOQ (defined as <2.0 log10 copies/mL) on both Days 5 and 10	Exploratory	mITT	Missing data will not be imputed.	Descriptive summary

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Change in SARS-CoV-2 RNA level in NP swabs from baseline to Days 3, 10, 15, 21, 28, and 34	Exploratory	mITT	MMRM method to take account of missing at random.	MMRM
Time to sustained NP swab SARS-CoV-2 RNA below the LLOQ (defined as <2.0 log10 copies/mL) and remains below the LLOQ through Day 34	Exploratory	mITT	Missing data will not be imputed.	Cox proportional hazard model; KM curves
Rebound in SARS-CoV-2 RNA level in NP swabs at follow-up (ie, any study visit after Day 5 to through Day 34, defined as a half (0.5) log10 copies/mL increase or greater in SARS CoV-2 RNA level relative to SARS-CoV-2 RNA level on Day 5 and with a follow-up viral RNA level ≥2.5 log10 copies/mL	Exploratory	mITT	Missing data will not be imputed.	Descriptive summary

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Rebound in SARS-CoV-2 RNA level in NP swabs at follow-up (ie, any study visit after Day 5 to through Day 34, defined as a half (0.5) log10 copies/mL increase or greater in SARS CoV-2 RNA level relative to SARS-CoV-2 RNA level on Day 5 and with a follow-up viral RNA level ≥3log10 copies/mL	Exploratory	mITT	Missing data will not be imputed.	Descriptive summary
Rebound in SARS-CoV-2 RNA level in NP swabs at follow-up (ie, any study visit after Day 5 to through Day 28, defined as a half (0.5) log10 copies/mL increase or greater in SARS CoV-2 RNA level relative to SARS-CoV-2 RNA level on Day 5 and with a follow-up viral RNA level ≥3log10 copies/mL	Exploratory	mITT	Missing data will not be imputed.	Descriptive summary
Change from baseline in SARS-CoV-2 viral RNA level in plasma, over time	Exploratory	mITT	MMRM method to take account of missing at random.	MMRM
Proportion of participants with COVID-19-related hospitalization	Exploratory	mITT	Missing data will not be imputed.	Descriptive summary

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
>24h or death from any cause through Day 28				
Number of COVID-19-related medical visits through Day 34	Exploratory	mITT	Missing data will not be imputed.	Descriptive summary
Time (days) to sustained resolution of all targeted signs and symptoms through Day	Exploratory	mITT mITT1	Missing data will not be imputed.	Cox proportional hazard model; KM curves
Corcordance analysis of RAT and SARS-CoV-2 viral RNA level in NP swabs	Other	mITT1	Missing data will not be imputed.	Descriptive summary

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 for viral RNA data and infectious titer data:

Visit Label	Target Day	Visit Window
Baseline (Day 1)	Day 1	Days -1 to 1
Day 3	Day 3	Days 2 to 4
Day 5	Day 5	Days 4 to 7
Day 10	Day 10	Days 8 to 12
Day 15	Day 15	Days 13 to 17
Day 21	Day 21	Days 18 to 24
Day 28	Day 28	Days 25 to 30
Day 34	Day 34	Days 31 to 37

The following table defines the visit windows and labels for vital sign data:

Visit Label	Target Day	Visit Window
Baseline (Day 1)	Day 1	Days -1 to 1
Day 3	Day 3	Days 2 to 4
Day 5	Day 5	Days 4 to 7
Day 10	Day 10	Days 8 to 21
Day 34	Day 34	Days 22 to 37

The following table defines the visit windows and labels for Lab data:

Visit Label	Target Day	Visit Window
Baseline (Day 1)	Day 1	Days -1 to 1
Day 5	Day 5	Days 2 to 19
Day 34	Day 34	Days 20 to 37

These visit windows will be applied to visit-wise summary and may be revised for analysis and reporting purpose when deemed appropriate.

For viral RNA data collected in NP swab or plasma, and vital sign data collected on study Day 4, it has falls into Day 3 visit and Day 5 visit due to an overlap between Day 3 and Day 5 visit windows, the decision made is to assign the window according to the nominal visit. If the nominal visit is “ET” visit, it will be assigned to Day 5 visit.

For lab data, if there are multiple measurements on the same day, the average will be used.

For vital sign data, if there are multiple measurements on the same day, the latest measurement will be used.

For viral RNA data collected in NP swab or plasma and infectious titer data, if there are multiple measurements on the same day, the largest value will be used.

For rapid antigen test data, if there are multiple measurements with negative and positive results on the same day, the positive result will be used.

If two or more measurements fall into the same visit window, keep the one closest to the Target Day. If two measurements are equal distance from the Target Day in absolute value, the later visit should be used.

Appendix 3. List of Abbreviations

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
CaPS	Clinical Data Interchange Standards Consortium and Pfizer Standards
CDARS	Clinical Data Analysis and Reporting System (of US Food and Drug Administration)
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
COVID-19	coronavirus disease 2019
DMC	data monitoring committee
E-DMC	external data monitoring committee
EPIC-HR	Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients
FAS	full analysis set
h	hour
LLOQ	lower limit of quantitation
LOD	limit of detection
LS	least-squares
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model with repeated measures
NCT	National Clinical Trial
NP	nasopharyngeal
PP	per-protocol
PT	preferred term
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
TCID50	Median Tissue Culture Infectious Dose
TEAE	treatment-emergent adverse event
US	United States
WHO	World Health Organization

Appendix 4. Participant-Reported COVID-19-Related Signs and Symptoms

Sign and Symptom Collection	Eligibility Criterion #5 Targeted (used for study entry)	Signs and Symptom Collection	Targeted Symptoms for Analysis
Cough	X	X	X
Shortness of breath or difficulty breathing	X	X	X
Fever (documented temperature >38˚C [100.4˚F]) or subjective fever (eg, feeling feverish)	X		
Feeling feverish		X	X
Chills or shivering	X	X	X
Fatigue (low energy or tiredness)	X	X	
Muscle or body aches	X	X	X
Diarrhea (loose or watery stools)	X	X	X
Nausea (feeling like you wanted to throw up)	X	X	X
Vomiting (throw up)	X	X	X
Headache	X	X	X
Sore throat	X	X	X
Stuffy or runny nose	X	X	X
Loss of smell	X	X	
Loss of taste	X	X	