Protocol C4671006

A PHASE 2/3, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF 2 REGIMENS OF ORALLY ADMINISTERED PF-07321332/RITONAVIR IN PREVENTING SYMPTOMATIC SARS-COV-2 INFECTION IN ADULT HOUSEHOLD CONTACTS OF AN INDIVIDUAL WITH SYMPTOMATIC COVID-19

Statistical Analysis Plan (SAP)

Version: **3**

Date: **15 Apr 2022**

[redacted]

[redacted]

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
Version 1/ 9 Sep, 2021	Protocol amendment 1	Original SAP	NA
Version 2/ 23 Feb 2022	Protocol amendment 2	Protocol amendment 2 changes, FDA request and other clarification	• Updated Section 2.1, 3.1, 3.2, 5,1, 5.2, 6.1 and 6.2 to include rapid antigen test in the definition of confirmed SARS-CoV-2 infection for the primary objective/estimand/endpoint and relevant secondary obejective/estimand/endpoints. • Updated Section 2.1, 3.2 and 6.2 to include viral titers assessment in participants with a positive RT-PCR result at baseline as the secondary objective/endpoint and the corresponding analysis method. • Updated Section 2.3 sample size to reflect the adjustment of the relative risk reduction and the placebo event rate. • Updated Section 4 on mITT related analysis sets. • Added more information in Section 5.2 for region combination due to limited number of participants enrolled in Brazil and the description of analysis model in general. • Added the method of handling missing data for symptomatic and asymptomatic infection in Section 5.3. • Updated/added more information for the primary efficacy analysis in Section 6.1.1.1 including the endpoint defnition, the handling of model convergence, and the clarification of handling intercurrent events, and subgroup analyses. • Added more sensitivity analyses in Section 6.1.1.2. • Updated the definition of Asymptomatic infection through Day 14 in Section 6.2.5 to align with symptomatic infection defintion. • Added more details for the analysis of sense of taste and sense of smell in Section 6.2.9. • Added more details for PK analysis in Section 6.2.11.

			• Updated/added more analyses for viral titer in Section 6.2.13. • Added subgroup analyses in Section 6.4. • Medical history was moved from safety endpoint Section 3.6 and Section 6.6 to baseline and demo characteristics Section 6.5. • Updated the visit window for baseline in Section 3.4 and Appendix 2.1 and Add the handling of multiple measurements on the same day in Appendix 2.1. CCI [redacted] • Updated Section 7.1 for the timing of the planned interim analysis from 45% to 70% of enrolment and corresponding alpha levels. • Updated references in Section 8. • Updated Appendix 1 to align with the analysis updates/changes in SAP main body. • Clarified in Appendix 4 for the definition of the presence of risk factor/increased risk of severe COVID-19 illness. • Added the list of pre-specified AESI in Section 6.6.1 and Appendix 6.
Version 3/ 15 Apr 2022	Protocol amendment 2	FDA feedback and other update/ clarification	• Updated/added more information for analysis sets in Section 4 including mITT3 population definition, SAS treatment group assigment, handling of data cleaning and duplicate enrollment for efficacy and safety analyses. • Added sensitivity analyses in Section 6.1.1.2 for primary endpoint and in Section 6.2.3, 6.2.7 and 6.2.8 for secondary endpoints. • Added additional efficacy endpoints and/or analyses for mITT1 and mITT3 populations CC CCI [redacted] in Section CC 6.2.7, CC and 6.4. • Added more information on handling of model convergence and updated age subgroup categories in Section 6.4. • Clarified and added more details/summary on baseline and other summary in Section 6.5. • Clarified vital sign analysis in Section 6.6.3.

			• Add the statement of Interim analysis completion in Section 7.1. • Updated Appendix 1 to align with the analysis updates/changes in SAP main body. • Add the handling of multiple measurements on the same day for vital sign and lab data in Appendix 2.1. • Editorial changes/clarification in Section 5.2.6, Section 6.2.13 and Section 6.2.15.

2. INTRODUCTION

PF-07321332, a potent and selective SARS-CoV-2 3CL protease inhibitor, is being investigated as oral antiviral postexposure prophylaxis for adult household contacts of an individual with symptomatic COVID-19.

The purpose of this study is to evaluate the efficacy and safety of PF-07321332/ritonavir as postexposure prophylaxis for adult household contacts of an individual with symptomatic COVID-19.

2.1. Study Objectives, Endpoints, and Estimands

Primary Efficacy Objective:

To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in preventing symptomatic RT-PCR or rapid antigen test- confirmed SARS-CoV-2 infection in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.

Secondary Objective:

To describe the safety and tolerability of 5-day and 10-day regimens of PF-07321332/ritonavir relative to placebo in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.

To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in preventing symptomatic RT-PCR or rapid antigen test- confirmed SARS-CoV-2 infection in adult participants who have a negative RT-PCR result at baseline, who are at increased risk of severe COVID-19 illness, and who are household contacts of an individual with symptomatic COVID-19.

To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in preventing SARS-CoV-2 infection in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.

To compare the efficacy of 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the duration and severity of COVID-19 related signs and symptoms in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.

To determine the PK of PF-07321332 in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.

To describe all-cause mortality in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.

To describe the viral load in nasal samples over time in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.

To describe hospitalizations in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.

To describe COVID-19 related medical visits in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.

2.1.1. Primary Estimand

The risk reduction between 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the proportion of individuals who develop symptomatic RT-PCR or rapid antigen test- confirmed SARS-CoV-2 infection through Day 14 in adults who have a negative RT-PCR result at baseline and are household contacts of an individual with symptomatic COVID-19. This will be estimated without regard to adherence to randomized treatment.

2.1.2. Secondary Estimand

The risk reduction between 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the proportion of individuals who develop symptomatic RT-PCR or rapid antigen test- confirmed SARS-CoV-2 infection through Day 14 in adults who have a negative RT-PCR result at baseline, who are at increased risk of severe COVID-19 illness, and who are household contacts of an individual with symptomatic COVID-19. This will be estimated without regard to adherence to randomized treatment.

Symptomatic RT-PCR or rapid antigen test- confirmed infection through Day 14 is considered the main clinical outcome measure so estimands for the measure in targeted populations are presented. Estimands for the other outcome measures/populations are considered supportive of the main outcome measures and are not presented.

2.2. Study Design

This Phase 2/3, randomized, double-blind, double-dummy, placebo-controlled study will compare the efficacy of 2 regimens of PF 07321332/ritonavir versus placebo in approximately 2880 participants who have a negative screening SARS-CoV-2 rapid antigen test result and are asymptomatic household contacts of individuals who are symptomatic and recently tested positive for SARS-CoV-2 (index case: defined as patient with symptomatic COVID-19). Index cases may be participants in Phase 2/3 safety and efficacy studies of PF-07321332/ritonavir (C4671002 and C4671005), but this is not required. Eligible participants for this study will be randomly assigned (1:1:1) within 96 hours after collection of the index case's first positive SARS-CoV-2 test to receive:

- *PF-07321332/ritonavir q12h for 5 days followed by matching placebo q12h for 5 days; or*
- *PF-07321332/ritonavir q12h for 10 days; or*
- *Matching placebo for PF-07321332/ritonavir q12h for 10 days.*

Randomization will be stratified based on the presence of risk factors associated with severe COVID-19 illness and geographic region at screening. Throughout the study period, provision will be made to allow study visits to be conducted at a participant's home or at another nonclinic location approved by the investigator where possible when participants are unwilling or unable to attend a clinic visit at the investigational site.

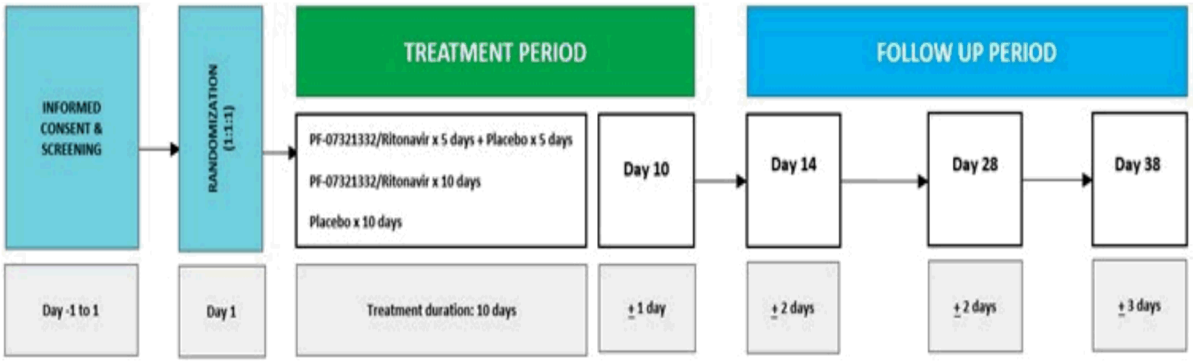
Participants will be screened within 24h before randomization. The total duration of the study is up to 42 days and includes screening, study intervention through Day 10, efficacy assessments through Day 14, and a safety follow-up period through Day 38 [±3 days].

An independent E-DMC will review unblinded data to ensure the safety of participants on an ongoing basis throughout the duration of the study. In addition to up to weekly reviews of safety data, the E-DMC will review the following:

- *Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 150 participants have completed Day 10 of the study, at which point enrollment will be paused pending E-DMC review of the safety data. After review of the sentinel cohort, the frequency of safety reviews may be reduced subsequently based on E-DMC recommendations.*
- *Interim analysis: An interim analysis will be conducted for efficacy, futility, and sample size re-estimation and reviewed by an E-DMC after a prespecified accrual of participants (ie, before or at approximately 70% participants have complete the Day 14 assessments with a minimum number of 24 participants having symptomatic infection [mITT analysis set]).*

Subsequent to the planned interim analysis, there will be a single analysis for reporting the results of this study after all participants have had their last study visit. The study schematic is provided in Figure 1.

Figure 1. C4671006 Study Design



2.3. Sample Size Determination

Based on the results from Study C4671005, which showed PF-07321332/ritonavir treatment significantly reduced the risk of hospitalization or death from any cause by 89% compared with placebo in nonhospitalized symptomatic adult participants with COVID-19 who were at increased risk of progression to severe disease when they were treated within 3 days of symptom onset, and the high relative risk reduction (approximately 80%) observed in Regeneron REGEN-COV post-exposure prophylaxis study, the risk reduction between PF-07321332/ritonavir group versus placebo group is assumed to be 70%. The symptomatic infection rate assumption in the placebo group is adjusted to 4% based on the observed seropositivity rate in this study and the impact of seropositivity on the incidence of primary endpoint events in the REGEN-COV post-exposure prophylaxis study where the incidence of symptomatic infection was 2% in participants who were seropositive and 8% in those who were seronegative.[1] As of January 2022, a large percentage of participants were observed to be seropositive. Based on a 2% placebo event rate for participants who were seropositive and 8% placebo rate for participants who were seronegative observed in the REGEN-COV postexposure prophylaxis study[1] the expected placebo rate across the 2 groups is estimated to be approximately 3%. In addition, based upon emerging epidemiology data for the Omicron variant,[2,3] which suggests higher infectivity than with prior variants, the placebo rate is adjusted to be 4%.

Among baseline RT-PCR negative participants, assuming a 4% symptomatic infection rate in the placebo group, a 70% reduction in symptomatic infection (1.2% symptomatic infection rate) in the PF-07321332/ritonavir group (5-day and 10-day regimen), a sample size of 821 participants per group (2463 participants total) will provide approximately 90% power for each comparison between 5-day and 10-day regimens of PF-07321332/ritonavir group versus placebo group under a 2-sided type-1 error rate of 5%. Assuming approximately 5% of participants with negative rapid antigen test result at screening will have a positive RT-PCR result at baseline, and assuming an approximately 10% dropout rate, the total sample size for this study will be approximately 2880 participants.

Study enrollment will stop once approximately 2463 participants are evaluable and at least 34 participants had symptomatic infection for the primary analysis. However, enrollment may continue until the 70% interim analysis has been completed.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

- *Proportion of participants who develop a symptomatic, RT-PCR or rapid antigen test- confirmed SARS-CoV-2 infection through Day 14 for participants who have a negative RT-PCR result at baseline.*

3.2. Secondary Endpoint(s)

- *Incidence of treatment emergent adverse events (TEAEs).*
- *Incidence of Serious Adverse Events (SAEs) and Adverse Events (AEs) leading to discontinuations.*
- *Proportion of participants with symptomatic, RT-PCR or rapid antigen test- confirmed SARS-CoV-2 infection through Day 14 for participants who have a negative RT-PCR result at baseline and who are at increased risk of severe COVID-19 illness.*
- *Proportion of participants with COVID-19 related hospitalization or death from any cause by Day 28 for participants who have a negative RT-PCR result at baseline and who are at increased risk of severe COVID-19 illness.*
- *Proportion of participants with asymptomatic RT-PCR or rapid antigen test- confirmed SARS-CoV-2 infection through Day 14 for participants who have a negative RT-PCR result at baseline.*
- *Time to RT-PCR or rapid antigen test- confirmed SARS-CoV-2 infection through Day 14 for participants who have a negative RT-PCR result at baseline.*
- *Proportion of participants with symptomatic RT-PCR or rapid antigen test- confirmed SARS-CoV-2 infection through Day 14 for participants who have a positive RT-PCR result at baseline.*
- *Proportion of participants with symptomatic RT-PCR or rapid antigen test- confirmed SARS-CoV-2 infection through Day 14 for participants who have a negative or positive RT-PCR result at baseline.*
- *Proportion of participants with no, mild, moderate, or severe signs and symptoms attributed to COVID-19 through Day 28 for participants who have a negative RT-PCR result at baseline.*
- *Number of days of symptomatic SARS-CoV-2 infection through Day 28 for participants who have a negative RT-PCR result at baseline.*

- *PF-07321332 PK in plasma and whole blood (if feasible).*
- *Proportion of participants with death (all-cause) through Day 38 for participants who have a negative RT-PCR result at baseline.*
- *Viral titers measured via RT-PCR in nasal swabs over time for participants who have a negative RT-PCR result at baseline.*
- *Viral titers measured via RT-PCR in nasal swabs over time for participants who have a positive RT-PCR result at baseline.*
- *Number of days of hospital and ICU stay in participants with COVID-19-related hospitalization through Day 28 for participants who have a negative RT-PCR result at baseline.*
- *Number of COVID-19 related medical visits through Day 28 for participants who have a negative RT-PCR result at baseline.*

3.4. Baseline Variables

Baseline visit (Day 1) will be defined as the latest measurement between Day -2 and Day 1.

3.5. Stratification Variables

Randomization will be stratified based on the presence of risk factors associated with severe COVID-19 illness (Appendix 4) and geographic region at screening.

3.6. Safety Endpoints

The safety endpoints of this study are:

- Incidence of TEAEs;

- Incidence of SAEs and AEs leading to discontinuations;
- Laboratory assessments;
- Vital signs.

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

3.6.1. Adverse Events

An 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 TEAE if the event started on or after the study medication start date and time.

3.6.2. Laboratory Data

Laboratory data includes hemotology, 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.

3.6.3. Vital Signs

Vital signs measurements include temperature, pulse rate, respiratory rate, and blood pressure. Participants attending a COVID-19 Signs/Symptoms Onset visit will also have oxygen saturation measured.

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 regardless of whether or not study intervention was administered.
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 intervention they actually received. A randomized but not treated participant will be excluded from the safety analyses.

Population	Description
Modified Intent-To-Treat (mITT)	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and have a negative RT-PCR result at baseline. Participants will be analyzed according to the study intervention they were randomized.
Modified Intent-To-Treat (mITT1)	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and have a positive RT-PCR result at baseline. Participants will be analyzed according to the study intervention they were randomized.
Modified Intent-To-Treat (mITT2)	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and have a negative RT-PCR result at baseline and are at increased risk of severe COVID-19 illness (Appendix 4). Participants will be analyzed according to the study intervention they were randomized.
Modified Intent-To-Treat (mITT3)	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and have a negative, positive or missing RT-PCR result at baseline. Participants will be analyzed according to the study intervention they were randomized.
Per-Protocol (PP)	All participants in the mITT 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.

The primary population for efficacy analysis is mITT.

The primary population for safety analysis is SAS, where participants will be analyzed according to the intervention they actually received. If a participant receives PF-07321332 kit(s) (containing PF-07321332 or matching placebo) different from the kit(s) assigned by randomization, the participant will be analyzed according to the actually received kits. A participant who first receives matching placebo for PF-07321332 and then PF-07321332 will be analyzed as in 5-day treatment group.

For efficacy related analysis (mITT, mITT1, mITT2, mITT3 and PP), participants with data cleaned for reporting purposes will be included in the analysis. A sensitivity analysis for the primary endpoint will be performed in mITT population regardless of data cleaning level. For safety analysis (SAS), all safety data will be included regardless of data cleaning level.

For efficacy related analysis (mITT, mITT1, mITT2, mITT3 and PP), if a participant enters/is randomized into the study multiple times, the data associated with first randomization will be included in the analysis. Sensitivity analyses for the primary endpoint and secondary endpoints will be performed using all efficacy data by considering all randomized participants as independent participants. For safety analysis (SAS), all safety data will be included by considering all randomized participants as independent participants.

5. GENERAL METHODOLOGY AND CONVENTIONS

The final analysis will be performed after dataset release.

5.1. Hypotheses and Decision Rules

The primary hypothesis is to test, in participants who have a negative RT-PCR at baseline, whether or not the risk ratio between 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo in the proportion of participants who develop symptomatic RT-PCR or rapid antigen test-confirmed infection through Day 14 is equal to 1:

$$\left.\begin{array}{l} \text{Ho: } \pi_{\text{PF-7321332}} / \pi_{\text{placebo}} = 1 \\ \qquad \textit{versus} \\ \text{Ha: } \pi_{\text{PF-7321332}} / \pi_{\text{placebo}} \neq 1 \end{array}\right\}$$

Where $\pi_{\text{PF-7321332}}$ and π_{placebo} are the symptomatic infection rate through Day 14 for 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo groups in participants who have a negative RT-PCR result at baseline. The hypotheses will be tested at an overall significant level of 5% (2-sided).

5.2. General Methods

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

The number of participants 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 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, minimum, and maximum), and qualitative variables will be summarized by frequency tables with number and proportion in each category (with the corresponding sample sizes).

Due to limited number of participants enrolled in Brazil, Brazil region will be combined with rest of the World region when appropriate.

Unless otherwise specified, the analysis model will include the fixed effects of treatment, geographic regions and presence of risk factors associated with severe COVID-19 illness.

5.2.1. Multiplicity Adjustment

There will be 2 group comparisons for the primary endpoint: 5-day regimen of PF-07321332/ritonavir versus placebo groups and 10-day regimen of PF-07321332/ritonavir versus placebo groups. Multiplicity adjustment for the primary endpoint will be made for multiple comparisons using Hochberg method.[4]

Following the positive test of the primary endpoint, the following key secondary endpoint will be tested: proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in participants who have a negative RT-PCR result at baseline and who are at increased risk of severe COVID-19 illness.

If the primary endpoint is significant for both treatment groups, the key secondary endpoint will be tested at an overall level of 5% (2-sided) using Hochberg method to adjust for multiple comparisons for both treatment groups.

If one of PF-07321332/ritonavir regimens is discontinued, sequential testing will be performed in the remaining PF-07321332/ritonavir regimen in the order of primary endpoint and the key secondary endpoint.

5.2.2. Analyses for Binary Endpoints

For binary endpoints (ie, participants with or without symptomatic or asymptomatic infection), the proportion of participants with the event will be summarized for each group. Treatment comparison between the groups will be presented as the risk ratio/reduction of proportions with its 95% confidence intervals using a similar analysis method as the primary endpoint. For other binary endpoints, logistic regression model will be preformed when applicable.

5.2.3. Analyses for Continuous Endpoints

For continuous endpoints (ie, viral titer), descriptive statistics will be summarized for each group at each visit. The plot of mean over time will be generated when applicable.

5.2.4. Analyses for Categorical Endpoints

For categorical endpoints (ie, participants with no, mild, moderate or severe signs/symptoms attributed to COVID-19), proportion of participant for each category will be summarized for each group.

5.2.5. Analyses for Count Endpoints

For count endpoints (ie, number of COVID-19 related medical visits through Day 28), a negative-binomial regression model analysis will be performed using the log-total number of days of data collection as the participant offset variable.

5.2.6. Analyses for Time-to-Event Endpoints

For time-to-event endpoints, Kaplan-Meier analysis will provide tabular summaries of the Kaplan-Meier curves including the median, quartiles (if applicable)for each treatment group. In addition, the KM curves will be presented graphically. If significant covariates are identified, Cox proportional hazard model will be performed.

5.3. Methods to Manage Missing Data

For the primary endpoint/relevant secondary endpoints (symptomatic infection and asymptomtic infection through Day 14), if a participant has both RT-PCR and rapid antigen test results missing at Day 14, the participant is considered to have confirmed-infection at Day 14 if either RT-PCR or RAT test is positive at Day 15 or Day16 (if Day 15 missing).

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

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. Primary Endpoint/Estimand Analysis

6.1.1.1. Main Analysis

The primary endpoint is the proportion of participants who develop a symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 for participants who have a negative RT-PCR result at baseline in the mITT population.

For the primary efficacy analysis, GEE will be used to analyze the proportion of participants who develop a symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 for each treatment group. The analysis model will include the fixed effects of treatment, geographic regions and presence of risk factors associated with severe COVID-19 illness(Appendix 4). The compound symmetry variance-covariance structure will be used to account for the correlation among the participants associated with the same index case. If the covariance structure fails to converge, independent variance-covariance structure or generalized linear model assuming independence may be considered, whichever is applicable. The risk ratio between 5-day regimen of PF-07321332/ritonavir versus placebo group and 10-day regimen of PF-07321332/ritonavir versus placebo group and the corresponding 95% confidence intervals (CIs) will be calculated based on the GEE/generalized linear model using a log link function. Comparisons between the 5-day and 10-day regimens of PF-07321332/ritonavir versus placebo will be presented as risk reductions with 95% CIs, which are calculated as 1 minus the risk ratio.

A symptomatic infection event through Day 14 is defined as having any symptoms consistent with COVID-19 (Appendix 3 and FDA guidance[5]) within 14 days of an RT-PCR or rapid antigen test-confirmed infection through Day 14. Symptoms consistent with COVID-19 will be collected through self-reported participant diary. Multiplicity adjustment for primary endpoint will be made for multiple comparisons using Hochberg method.

Significance level will be determined using the O'Brien-Fleming approach at the interim analysis and the final analysis. The overall type I error rate is maintained at 5% (2-sided).

Handling of missing data is provided in Section 5.3. Handling of anticipated intercurrent events is provided below:

- Discontinuation of assigned treatment: Participants who discontinue assigned treatment will be handled similarly as the participants who complete assigned treatment.

- Use of an additional or alternative treatment: Treatment with additional or alternative treatments does not imply or infer that a participant has a symptomatic infection. Thus, participants with additional or alternative treatment will not be handled differently than those participants not receiving additional or alternative treatment.

- Termination event: COVID-19 related hospitalization or COVID-19 related death through Day 14will be considered as achieving the primary endpoint. COVID-19 related hospitalization or COVID-19 related death after Day 14 happening within 14 days of an RT-PCR or rapid antigen test-confirmed infection through Day 14 will be considered as achieving the primary endpoint.

Among participants with symptomatic infection through Day 14, participants will be grouped into symptomatic RT-PCR test confirmed infection and symptomatic rapid antigen test confirmed infection and summarized for each treatment group. Symptomatic RT-PCR test confirmed infection is defined as having symptomatic infection where infection is first confirmed by RT-PCR positivity. Symptomatic rapid antigen test confirmed infection is defined as having symptomatic infection where infection is first confirmed by rapid antigen test positivity. If infection is confirmed by RT-PCR test positivity and rapid antigen test positivity on the same day, participants will be assigned into symptomatic RT-PCR test confirmed infection group.

In addition, participants with symptomatic infection through Day 14 will be summarized by variant type for each treatment group if data available.

6.1.1.2. Sensitivity Analyses

The following sensitivity analyses will be performed for the primary efficacy endpoint:

- Using PP analysis set.

- Excluding all participants from Site [redacted].
- If a participant has received therapeutic monoclonal antibody or other treatment approved under EUA for SARS-CoV-2 and has positive RT-PCR or rapid antigen test through Day 14, the participant will be considered as achieving the primary endpoint.
- If a participant having SARS-CoV-2 Symptom on or before Day 14 and all RT-PCR or rapid antigen test are missing on or after the symptom day through Day 14, the participant is considered as achieving the primary endpoint.
- Using mITT population regardless of data cleaning level.
- Using mITT population by considering all randomized participants as independent participants.
- Symptomatic infection is based on an RT-PCR test-confirmed infection through Day 14.
- If meeting one of the following criteria, participants will be considered as achieving the primary endpoint:
    - Participants who report symptoms consistent with COVID-19 by Day 14 and are missing infection status for four or more days through Day 14;
    - Participants who have a positive RT-PCR or RAT result by Day 14 and are missing four or more daily symptom diary entries through Day 14;
    - Participants who are lost to follow-up through Day 14.

6.2. Secondary Endpoint(s)

6.2.1. Incidence of Treatment Emergent Adverse Events (TEAEs)

The incidence of TEAEs will be summarized by treatment group, by system organ class (SOC) and preferred term (PT) using the SAS population.

6.2.2. 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 SAS population.

6.2.3. Proportion of Participants with Symptomatic, RT-PCR or Rapid Antigen Test-confirmed SARS-CoV-2 Infection through Day 14 for Participants who have a Negative RT-PCR Result at Baseline and who are at Increased Risk of Severe COVID-19 Illness

The proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 who have a negative RT-PCR result at baseline and

who are at increased risk of severe COVID-19 illness will be analyzed using a similar analysis method as the primary endpoint. The analysis model will include the fixed effects of treatment and geographic regions. The analyses will be done using mITT2 population.

In addition, sensitivity analysis will be performed for mITT2 population by considering all randomized participants as independent participants.

6.2.4. Proportion of Participants with COVID-19 Related Hospitalization or Death from Any Cause by Day 28 for Participants who have a Negative RT-PCR Result at Baseline and who are at Increased Risk of Severe COVID-19 Illness

The proportion of participants with COVID-19 related hospitalization or death from any cause by Day 28 in participants who have a negative RT-PCR result at baseline will be summarized and analyzed using logistic regression model if applicable. The analyses will be done using mITT2 population.

6.2.5. Proportion of Participants with Asymptomatic RT-PCR or Rapid Antigen Test-confirmed SARS-CoV-2 Infection through Day 14 for Participants who have a Negative RT-PCR Result at Baseline

The proportion of participants with asymptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in participants who have a negative RT-PCR result at baseline will be analyzed using a similar analysis method as the primary endpoint. An asymptomatic infection event through Day 14 is defined as having no symptoms consistent with COVID-19 within 14 days of an RT-PCR or rapid antigen test-confirmed infection through Day 14. The analyses will be done using mITT population.

6.2.6. Time to RT-PCR or Rapid Antigen Test-confirmed SARS-CoV-2 Infection through Day 14 for Participants who have a Negative RT-PCR Result at Baseline

For this analysis, time to RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection will be measured from the first dose of study medication in days.

- For participants with RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection (event), time to event will be calculated as: (Event Date) – (First Dose Date) + 1.

- For participants that either completes Day 14 of study or discontinues from study before Day 14 without RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection (censored), censoring date will be calculated as (Censoring/last available RT-PCR or rapid antigen test Date) – (First Dose Date) +1 or Day 14 whichever occurs first.

Time to RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection will be summarized graphically using Kaplan-Meier plots for each of the treatment groups, the analyses will be done using mITT population.

If significant covariates are identified, Cox proportional hazard model will be performed using mITT population.where the estimate of the hazard ratio for treatment (each PF-07321332/ritonavir group vs Placebo), 95% CI and p-value will be provided.

6.2.7. Proportion of Participants with Symptomatic RT-PCR or Rapid Antigen Test-confirmed SARS-CoV-2 Infection through Day 14 for Participants who have a Positive RT-PCR Result at Baseline

The proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in participants who have a positive RT-PCR result at baseline will be analyzed using a similar analysis method as the primary endpoint in mITT1 population.

In addition, sensitivity analysis will be performed for mITT1 population by considering all randomized participants as independent participants.

6.2.8. Proportion of Participants with Symptomatic RT-PCR or Rapid Antigen Test-confirmed SARS-CoV-2 Infection through Day 14 for Participants who have a Negative or Positive RT-PCR Result at Baseline

The proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in participants who have a negative or positive RT-PCR result at baseline will be analyzed using a similar analysis method as the primary endpoint. The analyses will be done using mITT3 population.

In addition, sensitivity analysis will be performed for mITT3 population by considering all randomized participants as independent participants.

6.2.9. Proportion of Participants with No, Mild, Moderate or Severe Signs/symptoms Attributed to COVID-19 through Day 28 in Participants who have a Negative RT-PCR Result at Baseline

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. Vomiting and diarrhea rated on a 4-point frequency scale will be mapped to 4-point severity rating accordingly.

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.

Among the 12 sign/symptoms with 4 grading levels, the proportion of participants with no, mild, moderate or severe post-baseline signs/symptoms will be summarized for each treatment group by RT-PCR or rapid antigen test results during the study and by total. For

participants with multiple symptoms and severity, participants will be assigned to the severity category based on the maximum severity across symptoms. In addition, the proportion of participants with any severe post-baseline signs/symptoms attributed to COVID-19 through Day 28 will be summarized with number and percent of participants by treatment group. Treatment comparisons between between each PF-07321332/ritonavir group versus placebo group will be presented as odds ratios with 95% CI and P-value based on logistic regression model.

For the 2 signs/symptoms with 3 grading levels (ie, sense of taste and sense of smell), similar analyses will be provided based on 3 grading levels.

The analyses will be done using mITT population.

6.2.10. Number of Days of Symptomatic SARS-CoV-2 Infection through Day 28 for Participants who have a Negative RT-PCR Result at Baseline

The number of days of symptomatic SARS-CoV-2 infection through Day 28 in participants who have a negative RT-PCR result at baseline will be summarized using mITT population.

6.2.11. PF-07321332 Plasma PK in Plasma and Whole Blood (if feasible)

The PK analysis will be performed and summarized descriptively by GPD Clinical Pharmacology. PF-07321332/ritonavir plasma and blood (if feasible) PK concentrations will be descriptively summarized for each time point and treatment group.

6.2.12. Proportion of Participants with Death (all-cause) through Day 38 for Participants who have a Negative RT-PCR Result at Baseline

The proportion of participants with death (all-cause) through Day 38 will be summarized by treatment group using mITT population. Treatment comparisons between each PF-07321332/ritonavir group versus placebo group will be presented as odds ratios with 95% CIs and P-value based on logistic regression model (if data permit).

6.2.13. Viral Titers (quantitative RT-PCR) Measured in Nasal Swabs Over Time for Participants who have a Negative RT-PCR Result at Baseline

The viral load in nasal samples over time will be evaluated daily.Viral load data will be transformed to a Log10 bases scale. Viral load (Log10 base transformed) for each day will be summarized using mITT population. The proportion of RT-PCR positivity over time will also be summarized using the mITT population.

For participants with viral titer above the limit of detection (detectable) in the mITT population, viral load (Log10 base transformed) for will be summarized daily. The mean value over time will be plotted.

For participants with viral titer above the limit of detection (detectable) in the mITT population, peak viral load (Log10 base transformed) for will be summarized for each treatment group.

For participants with any positive RT-PCR test result (at or above the limit of quantification) in the mITT population, first positive viral load (Log10 base transformed) for will be summarized for each treatment group.

6.2.14. Viral Titers (quantitative RT-PCR) Measured in Nasal Swabs Over Time for Participants who have a Positive RT-PCR Result at Baseline

The viral load in nasal samples over time will be summarized daily for the mITT1 population. The mean value over time will be plotted.

6.2.15. Number of Days of Hospital and ICU Stay in Participants with COVID-19 Related Hospitalization through Day 28 for Participants who have a Negative RT-PCR Result at Baseline

The number of Days of hospitalizations/ICU visits through Day 28 will be summarized by each treatment group using mITT population.

6.2.16. Number of COVID-19 Related Medical Visits throught Day 28 for Participants who have a Negative RT-PCR Result at Baseline

The number of COVID-19 related medical visits through Day 28 visit will be summarized by each treatment group using mITT population. The endpoint will also be analyzed with a negative-binomial regression model, using the log-total number of days of data collection as the participant offset variable (if data permit). Treatment group comparison each PF-07321332/ritonavir group versus placebo group will be based on estimated rate of medical visits.

[redacted]

6.4. Subset Analyses

Subgroup analyses of the primary endpoint in mITT analysis set will include:

- By age group (18 to 44, 45 to 59 , and ≥60);
- Sex;
- Race;
- Geographic regions;
- Presence of risk factors associated with severe COVID-19 illness;
- Pre or post emergence of the omicron variant (Participant randomized before Dec 20 2021 vs on or after Dec 20 2021);
- Baseline serology status.

In addition, the subgroup analysis for pre or post emergence of the omicron variant will be performed for mITT1 and mITT3 population.

The analysis model for subgroup analyses including fixed effects and variance-covariance structure will be similar to the primary analysis. For subgroup analysis or analysis similar to primary analysis, if model fails to converge, the following fixed effects could be considered sequentially with different variance-covariance structure: 1) treatment and geographic regions 2) treatment and presence of risk factors associated with severe COVID-19 3) treatment.

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 index and 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 population. 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.

In addition, participants who were excluded from the PP analysis set will be listed with reasons.

6.5.3. Study Treatment Exposure

Duration of treatment and compliance will be summarized within 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.

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 SAS population in accordance with CDISC and CaPs.

6.5.5. Medical History

Medical history data will be displayed in listings by participant in accordance with the Pfizer Data Standards for safety reporting.

6.6. Safety Summaries and Analyses

Standard summary tables and listings will be generated using Pfizer's Clinical Data Analysis and Reporting System (CDARS) for the following parameters: AEs, laboratory data and vital signs.

6.6.1. Adverse Events

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by treatment group within SAS population. A list of pre-specified AESIs is provided in Appendix 6.

6.6.2. Laboratory Data

Descriptive statistics will be summarized by treatment group as well as mean change from baseline for laboratory parameters within SAS population.

All laboratory data will be reported in accordance with CDISC and CaPs for safety reporting.

6.6.3. Vital Signs

Vital sign measurements will be displayed in listings by participant for each sample collection date and time.

Vital sign data including temperature, pulse rate, respiratory rate, and blood pressure will be descriptively summarized by treatment group within SAS population and reported in accordance with the Pfizer Data Standards for safety reporting.

7. INTERIM ANALYSES

7.1. Interim Analyses and Summaries

An interim analysis will be conducted for efficacy, futility, and sample size re-estimation and reviewed by an independent E-DMC after a prespecified accrual of participants (ie, before or at approximately 70% overall participants have completed the Day 14 assessments with a minimum number of 24 participants having symptomatic infection [mITT analysis set]). The nominal significance level for the interim and final analyses is determined by means of the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary, with an overall two-sided type I error rate of 5%. O'Brien-Fleming approach provides relatively conservative stopping boundary for decision making, ie, the nominal level for interim analysis for efficacy and futility is 0.014 and 0.32, respectively. The nominal significance level for final analysis is 0.046. The actual stopping boundaries will depend on the exact number of participants included in the interim analysis.

At the predefined interim analysis, the sample size may be adjusted based on sample size re-estimation with maximum increase of 30%. A well-established method such as CHW[6] will be used to control the Type I error probability. Besides stopping a PF-07321332/ritonavir arm for safety or futility, a PF-07321332/ritonavir arm (5-day or 10-day regimen) may be discontinued based on overall evaluation of efficacy and safety profiles between the 2 arms.

Before any interim analysis is performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in a DMC charter.

The interim analysis was performed as planned above. The DMC recommendation was to continue study as designed.

7.2. Data Monitoring Committee

This study will use a 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 efficacy and 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, investigators, as appropriate.

8. REFERENCES

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9. 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 of participants who develop a symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 for participant who have a negative RT-PCR result at baseline.	Primary Efficacy analysis	mITT	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1. Missing data will be handled based on Section 5.3.	GEE/Generalized linear model Descriptive statistics
Proportion of participants who develop a symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 who have a negative RT-PCR result at baseline.	Sensitivity analysis for primary endpoint	PP	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1. Missing data will be handled based on Section 5.3.	GEE/Generalized linear model
Proportion of participants who develop a symptomatic, RT-PCR or rapid antigen	Sensitivity analysis for primary endpoint	mITT excluding Site 1483	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or	GEE/Generalized linear model

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
test-confirmed SARS-CoV-2 infection through Day 14 who have a negative RT-PCR result at baseline.			COVID-19-related death will be handled based on Section 6.1.1.1. Missing data will be handled based on Section 5.3.	
Proportion of participants who develop a symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 who have a negative RT-PCR result at baseline.	Sensitivity analysis for primary endpoint	mITT	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1. If a participant has received therapeutic monoclonal antibody or other treatment approved under EUA for SARS-CoV-2 and has positive RT-PCR or rapid antigen test through Day 14, the participant will be considered as achieving the primary endpoint. Missing data will be handled based on Section 5.3.	GEE/Generalized linear model

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Proportion of participants who develop a symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 who have a negative RT-PCR result at baseline.	Sensitivity analysis for primary endpoint	mITT	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1. Missing data will be handled based on Section 5.3. If a participant having SARS-CoV-2 Symptom on or before Day 14 and all RT-PCR or rapid antigen test are missing on or after the symptom day through Day 14, the participant is considered to achieve the primary endpoint.	GEE/Generalized linear model
Proportion of participants who develop a symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 who have a negative RT-PCR result at baseline.	Sensitivity analysis for primary endpoint	mITT regardless of data cleaning level	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1.	GEE/Generalized linear model

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
			Missing data will be handled based on Section 5.3.	
Proportion of participants who develop a symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 who have a negative RT-PCR result at baseline.	Sensitivity analysis for primary endpoint	mITT by considering all randomized participants as independent participants	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1. Missing data will be handled based on Section 5.3.	GEE/Generalized linear model
Proportion of participants who develop a symptomatic, RT-PCR confirmed SARS-CoV-2 infection through Day 14 who have a negative RT-PCR result at baseline.	Sensitivity analysis for primary endpoint	mITT	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1. Missing data will be handled based on Section 5.3 (RT-PCR data only). Symptomatic infection is based on an RT-PCR test-confirmed infection through Day 14.	GEE/Generalized linear model

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Proportion of participants who develop a symptomatic, RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 who have a negative RT-PCR result at baseline.	Sensitivity analysis for primary endpoint	mITT	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1. If meeting one of the following criteria, participants will be considered as achieving the primary endpoint: participants who report symptoms consistent with COVID-19 by Day 14 and are missing infection status for four or more days through Day 14; participants who have a positive RT-PCR or RAT result by Day 14 and are missing four or more daily symptom diary entries through Day 1; participants who are lost to follow-up through Day 14.	GEE/Generalized linear model
Proportion of participants who develop a symptomatic, RT-PCR or rapid antigen test-	Subgroup analyses for the primary endpoint	mITT	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or	GEE/Generalized linear model

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
confirmed SARS-CoV-2 infection through Day 14 who have a negative RT-PCR result at baseline.			COVID-19-related death will be handled based on Section 6.1.1.1. Missing data will be handled based on Section 5.3. Subset analysis define in Section 6.4.	
Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 for participant who have a negative RT-PCR result at baseline and who are at increased risk of severe COVID-19 illness.	Secondary analysis	mITT2	All data collected will be included. For Intercurrent event of COVID-19 related hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1. Missing data will be handled based on Section 5.3.	GEE/Generalized linear model
Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 for participant who have a	Sensitivity analysis for sencondary endpoint	mITT2 by considering all randomized participants as independent participants	All data collected will be included. For Intercurrent event of COVID-19 related hospitalization or COVID-19-related death, it will be handled based on Section 6.1.1.1.	GEE/Generalized linear model

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
negative RT-PCR result at baseline and who are at increased risk of severe COVID-19 illness.			Missing data will be handled based on Section 5.3.	
Proportion of participants with COVID-19 related hospitalization or death from any cause by Day 28 for participant who have a negative RT-PCR result at baseline and who are at increased risk of severe COVID-19 illness.	Secondary analysis	mITT2	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Descriptive statistics Logistic regression model if applicable
Proportion of participants with asymptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 for participants who have a negative RT-PCR result at baseline.	Secondary analysis	mITT	All data collected will be included regardless of intercurrent events. Missing data will be handled based on Section 5.3.	GEE/Generalized linear model
Time to RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection	Secondary analysis	mITT	All data collected will be included regardless of intercurrent events.	KM plot; Cox proportional hazard model as needed.

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
through Day 14 for participants who have a negative RT-PCR result at baseline.			Missing data will not be imputed.	
Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in participant who have a positive RT-PCR result at baseline.	Secondary analysis	mITT1	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1. Missing data will be handled based on Section 5.3.	GEE/Generalized linear model
Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in participant who have a positive RT-PCR result at baseline.	Sensitivity analysis for sencondary endpoint	mITT1 by considering all randomized participants as independent participants	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1. Missing data will be handled based on Section 5.3.	GEE/Generalized linear model
Proportion of participants with symptomatic RT-PCR or rapid antigen	Subgroup analyses on pre or post emergence	mITT1	All data collected will be included. Intercurrent event of COVID-19 related	GEE/Generalized linear model

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
test-confirmed SARS-CoV-2 infection through Day 14 in participant who have a positive RT-PCR result at baseline.	of the omicron variant for secondary endpoint		hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1. Missing data will be handled based on Section 5.3.	
Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in participant who have a negative or positive RT-PCR result at baseline.	Secondary analysis	mITT3	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1. Missing data will be handled based on Section 5.3.	GEE/Generalized linear model
Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in participant who have a negative or positive RT-PCR result at baseline.	Sensitivity analysis for sencondary endpoint	mITT3 by considering all randomized participants as independent participants	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1. Missing data will be handled based on Section 5.3.	GEE/Generalized linear model

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Proportion of participants with symptomatic RT-PCR or rapid antigen test-confirmed SARS-CoV-2 infection through Day 14 in participant who have a negative or positive RT-PCR result at baseline.	Subgroup analyses on pre or post emergence of the omicron variant for secondary endpoint	mITT3	All data collected will be included. Intercurrent event of COVID-19 related hospitalization or COVID-19-related death will be handled based on Section 6.1.1.1. Missing data will be handled based on Section 5.3.	GEE/Generalized linear model
Proportion of participants with no, mild, moderate, or severe signs and symptoms attributed to COVID-19 through Day 28 for participants who have a negative RT-PCR result at baseline.	Secondary analysis	mITT	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Descriptive statistics Logistic regression model
Number of days of symptomatic SARS-CoV-2 infection through Day 28 for participants who have a negative RT-PCR result at baseline.	Secondary analysis	mITT	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Descriptive statistics

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Proportion of participants with death (all-cause) through Day 38 for participants who have a negative RT-PCR result at baseline.	Secondary analysis	mITT	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Descriptive statistics Logistic regression model if applicable
Viral titers measured via RT-PCR in nasal swabs over time for participants who have a negative RT-PCR result at baseline.	Secondary analysis	mITT	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Descriptive statistics
Viral titers measured via RT-PCR in nasal swabs over time for participants who have a positive RT-PCR result at baseline.	Secondary analysis	mITT1	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Descriptive statistics
Number of days of hospital and ICU stay in participants with COVID-19-related hospitalization through Day 28 for participants who have a negative RT-PCR result at baseline.	Secondary analysis	mITT	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Descriptive statistics

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 28 for participants who have a negative RT-PCR result at baseline.	Secondary analysis	mITT	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Descriptive statistics negative binomial model
[redacted]				

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
[redacted]				

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Visit Windows in Reporting

For safety endpoints, the following table defines the visit label, target day and visit windows:

Visit Label	Target Day	Definition [Day window]
Baseline	Day 1	Day -2 to Day 1
Day 5	Day 5	Days 2 to Day 7
Day 10	Day 10	Days 8 to Day 11
Day 14	Day 14	days 12 to 26
Day 38	Day 38	days 27 and beyond

These visit windows may be revised for analysis and reporting purpose when deemed appropriate.

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

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

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

For viral load data collected daily, if there are multiple measurements on the same day, the extreme/the largest value will be used.

Appendix 3. Signs and Symptoms Consistent With COVID-19

Daily Sign and Symptom Collection	Exclusion Criterion #2	Daily Signs and Symptom Collection
Cough	X	X
Shortness of breath or difficulty breathing	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
Fatigue (low energy or tiredness)	X	X
Muscle or body aches	X	X
Diarrhea (loose or watery stools)	X	X
Nausea (feeling like you wanted to throw up)	X	X
Vomiting (throw up)	X	X
Headache	X	X
Sore throat	X	X
Stuffy or runny nose	X	X
Loss of smell	X	X
Loss of taste	X	X

Appendix 4. Risk Factors Associated With Severe COVID-19 Illness

- ≥60 years of age.
- BMI >25 kg/m^2.
- Current smoker (cigarette smoking within the past 30 days) and history of at least 100 lifetime cigarettes.
- Immunosuppressive disease (eg, bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications:
    - Has received corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days within 30 days prior to study entry;
    - Has received treatment with biologics (eg, infliximab, ustekinumab), immunomodulators (eg, methotrexate, 6MP, azathioprine), or cancer chemotherapy within 90 days prior to study entry;
    - HIV infection with CD4 cell count <200 mm^3 and a viral load less than 400 copies/mL.
- Chronic lung disease (if asthma, requires daily prescribed therapy).
- Known diagnosis of hypertension.
- CVD, defined as history of any of the following: myocardial infarction, stroke, TIA, HF, angina with prescribed nitroglycerin, CABG, PCI, carotid endarterectomy, and aortic bypass.
- Type 1 or Type 2 diabetes mellitus.
- CKD.
- Sickle cell disease.
- Neurodevelopmental disorders (eg, cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (eg, genetic or metabolic syndromes and severe congenital anomalies).
- Active cancer, other than localized skin cancer, including those requiring treatment as long as the treatment is not among the prohibited medications that must be administered/continued during the study period.
- Medical-related technological dependence (eg, CPAP [not related to COVID-19]).

If a participant meets at least one of the above criteria, the participant is considered as having the presence of risk factors associated with severe COVID-19 illness (increased risk of severe COVID-19 illness).

Appendix 5. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse events of special interest
CDARS	Clinical Data Analysis and Reporting System (of US Food and Drug Administration)
CDISC	Clinical Data Interchange Standards Consortium
CaPs	Clinical Data Interchange Standards Consortium and Pfizer Standards
CI	Confidence Interval
DMC	data monitoring committee
E-DMC	external data monitoring committee
FAS	full analysis set
FDA	Food and Drug Administration (United States)
GEE	Generalized estimating equation
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NA	not applicable
PK	pharmacokinetic(s)
PP	per-protocol
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SOP	standard operating procedure

Appendix 6. List of Pre-specified AESIs

Table Adverse Events of Special Interest

Category of Interest	Medra version 24 Criteria/Programming Details
Hemodynamic events	Arrhythmia related investigations, signs and symptoms (SMQ); Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) (SMQ); Bradycardia; Heart rate decreased; Heart rate abnormal; Maximum heart rate decreased;Tachycardia;Heart rate increased; Maximum heart rate increased;Hypertension;Hypotension
Inflammatory events	Hyperfibrinogenaemia; Prothrombin level abnormal; Prothrombin level increased; Prothrombin time prolonged; Prothrombin time abnormal; Thrombocytosis; Leukocytosis; White blood cell count increased; White blood cell count abnormal;Blood fibrinogen increased; Blood fibrinogen abnormal; Activated partial thromboplastin time prolonged; Activated partial thromboplastin time abnormal; Platelet count abnormal; Platelet count increased; Fibrin D dimer increased; Haptoglobin abnormal; Haptoglobin increased; Blood albumin abnormal; Protein total abnormal; Albumin globulin ratio abnormal; C-reactive protein abnormal; C-reactive protein increased; Neutrophilia; Neutrophil count abnormal; Lymphocytosis; Lymphocyte count abnormal; Eosinophilia; Eosinophil count abnormal; Monocytosis; Monocyte count abnormal
thyroid-related events	Blood thyroid stimulating hormone abnormal;Blood thyroid stimulating hormone increased;Thyroxine free abnormal; Thyroxine free increased; Thyroxine abnormal; Thyroxine increased