Protocol C4671002

AN INTERVENTIONAL EFFICACY AND SAFETY, PHASE 2/3, DOUBLE-BLIND, 2-ARM STUDY TO INVESTIGATE ORALLY ADMINISTERED PF-07321332/RITONAVIR COMPARED WITH PLACEBO IN NONHOSPITALIZED SYMPTOMATIC ADULT PARTICIPANTS WITH COVID-19 WHO ARE AT LOW RISK OF PROGRESSING TO SEVERE ILLNESS

Statistical Analysis Plan (SAP)

Version: 1
Date: 18 AUG 2021

Version: 2
Date: 01 DEC 2021

Version: 3
Date: 16 DEC 2021

Version 4
Date: 14 JUL 2022

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1. VERSION HISTORY

Table 1 Summary of Changes

Version/ Date	Rationale	Specific Changes
V1/ 18AUG2021	Original SAP	No changes
V2/ 18OCT2021	Protocol Amendment 4 and other clarification	• Updated Section 2.1.2 to include estimand for COVID-19 related hospitalization or death from any cause. • Updated Section 3.2 to reorder secondary endpoints; moving COVID-19 related hospitalization or death from any cause up to second secondary endpoint. • Updated Section 3.4 with definition of baseline visit and baseline derived variables. • Added to Section 3.5 the definition of stratification variable geographical region and clarified stratification variables for mITT & mITT1 populations. • Updated Section 4 to clarify analyses population sets. • Updated Section 5.1 to include Covid-19 related hospitalization and death of any cause in the sequential testing. • Section 5.2.2 updated to clarify strata by analyses population sets. • Section 5.2.2 has been updated to add ANCOVA model for change from baseline to Day 5 of viral load data in addition to the MMRM model and added baseline serology as covariate in the model. • Section 5.1 has been updated to include the Covid 19 related hospitalization or death due to any cause as the second secondary endpoint in sequential testing. Furthermore, the following endpoints, proportion of subject with severe signs and symptoms and medical visits were removed from the sequential testing. • Section 6.1.1.2 has been updated to include a new sensitivity analysis. based on FDA request, a sensitivity analysis exclude participants from site 1488. • Section 6.1.1.2 updated to add sensitivity analysis for primary endpoint for participants who discontinued the study before Day 28 with events to be censored at Day 25. • Section 6.1.1.2 updated to add factors such as region, vaccination, baseline serology in the analysis model. • Added changes to Section 6.2.4 – added KM for proportions of hospitalizations/deaths. • Section 6.2.6 updated to add the plot of proportions for each targeted signs and symptom with severe category and

Version/ Date	Rationale	Specific Changes
		additional analysis of proportion of severe signs/symptoms in order to understand the severe signs/symptoms data. • Section 6.2.12 updated to clarify ANCOVA model for viral titer endpoint. • Section 6.2.12 updated to add the analysis for association between baseline viral load and primary endpoint based on the viral strains identified at baseline. • Section 6.2.14 updated to add "through Day 28" and removed the following text "if data permit, negative binomial model analysis". • Section 6.4 subset analysis section has been updated to include a subset analysis for viral load categories defined in section 3.4. • Section 6.4 updated to add subgroup analyses of first and second secondary endpoint by vaccination status. • Section 6.6 has been updated to add a subgroup analysis of AE and SAE by vaccination status (new Section 6.6.2). • Updated Appendix 1 to change the logistic regression to Kaplan-Meier method. • Updated visit window for efficacy endpoints to Appendix 2. • Added Appendix 5 with list of adverse events of special interest. • Section 8 updated to add Greenwood Formula reference.
V3/ 16DEC2021	According to FDA request	• Section 4 has been modified to update the mITT, mITT1 and mITT2 populations requested by FDA. • Section 6.2.12 has been updated to include nasopharyngeal (Y/N) in the model. • Section 6.2.12 has been updated to remove analysis of association between baseline viral variants and primary endpoint (as per virology meeting of 12/13/2021 this assessment was nor needed). • Section 3.5 updated to add Brazil to the rest of the world region. • Section 3.4, 6.6.5, Appendix 2. Appendix 3 has been updated to remove ECG. • General clarification in section 6.2.6, 6.2.12. • Section 6.2.8 updated to add the following: • Proportion of participants with any progression to worsening of targeted symptoms attributed to COVID 19 Day 2 to Day 6 (during treatment). Proportion of participants with any progression to worsening of targeted symptoms attributed to COVID 19 Day 7 to Day 28 (post treatment).

Version/ Date	Rationale	Specific Changes
		• Section 6.2.13 & 6.2.14 removed "through day 28" for the endpoint. • Appendix 1: Added change from baseline to day 5 ANCOVA model for viral titer.
V4/ 11JUL2022	Protocol Amendment 5	• Section 2.2, the total number of participant update from 1140 to 1980 and the section cleaned up to align with Protocol Amendment #5. • Section 2.2 , the following (Aside from ongoing E-DMC review of safety data mentioned above, the aforementioned reviews and formal interim analysis were performed as specified above.) was added to align with Protocol Amendment #5 and to indicate that IA, Proof-of-concept and sentinel cohort analysis has been already performed. • Section 2.3, sample size update to align with protocol amendment #5 • Section 3.3 updated to add persistent signs and symptoms of COVID-19 endpoint and long COVID-19 endpoint • Section 3.5 updated to add Russia, Slovakia, and Romania to EU region • Section 3.5 was updated to provide definition of vaccination subgroup/strata • Section 4 updated to specify mITT1 as the main population • Section 5.1 updated to remove the sequential testing as it is no longer applicable to Protocol Amendment #5. • Section 5.1 updated to specify COVID-19 related hospitalization and death to any cause, number of medical visits, number of days in ICU. • Section 5.2.1 updated to clarify binary endpoints • Section 5.2.2 updated to remove use of mITT population • Section 5.3 updated to remove the (BOCF) form imputation of missing value. • Section 6 update to re-arrange the secondary endpoint to align with Protocol Amendment #5 endpoints and removed use of mITT population • Section 6.2.7 updated to include additional analysis of severity of signs and symptoms of COVID-19 for individual targeted symptoms • Section 6.2.7 updated to include an expanded definition and analysis of severity of signs and symptoms

Version/ Date	Rationale	Specific Changes
		• Section 6.2.10 updated to include expanded definition and analysis of worsening of signs and symptoms • Section 6.3.1 added to include proportion of participants with persistent symptoms of COVID-19 at Week 12, Week 24 • Section 6.3.2 added to include long-term COVID-19 symptoms collected by telephone interviews at Week 12 and Week 24
V4 11JUL2022	Protocol Amendment 6	• At the first interim analysis, the IA did not meet primary endpoint objective and there is no remaining alpha for subsequent hypothesis tests. Thus, all further analysis will use nominal p-values for reporting. • The total study duration is up to 24 weeks, with study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow-up at Weeks 12 and 24. • Proportion of participants with death (all cause) through Week 24 and final visit. • Update sections 2.1, 2.1.1 and 2.1.2 to align with the Protocol Amendment 6 • Section 2.1.2, rearrange the order of the secondary estimands to align with secondary objectives. • Section 3.2 updated to re-arrange the secondary endpoints to be aligned with objective of the protocol amendment #6 • Section 3.5 updated to stratification of symptom onset. • Section 4 update mITT definition • Section 6 update to re-arrange the secondary endpoint to align with protocol amendment #6 endpoints and removed use of mITT population • Section 6.4 updated to change subset analysis criteria to align with PAS #6 • Appendix 1 updated to use mITT1 population set and added relevant analyses per plan.

For the entire document, text in *Italic* format will represent language copied directly from protocol.

2. INTRODUCTION

PF-07321332, a potent and selective SARS-CoV-2 3CL protease inhibitor, is being investigated as an oral antiviral treatment of COVID-19.

The purpose of this study is to evaluate the efficacy and safety of PF-07321332/ritonavir for the treatment of nonhospitalized, symptomatic adult participants with COVID-19 who are at low risk of progressing to severe illness.

The first interim analysis (IA) did not meet the primary endpoint objectives and *there is no remaining alpha for subsequent hypothesis tests. Thus, all further analysis will use nominal p-values for reporting.*

All data entered in the eCRF will be analyzed and additional subgroup analyses will be included in the final CSR.

2.1. Study Objectives, Endpoints, and Estimands

Primary Efficacy Objective:

To compare the efficacy of PF-07321332/ritonavir to placebo for the treatment of symptomatic COVID-19 in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.

Secondary Efficacy Objective:

To compare PF-07321332/ritonavir versus placebo for COVID-19-related hospitalization and all-cause mortality in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.

To compare PF-07321332/ritonavir versus placebo for COVID-19-related medical visits in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease

To compare PF-07321332/ritonavir to placebo for the duration and severity of signs and symptoms in nonhospitalized symptomatic adult participants with COVID-19 who are at low risk of progression to severe disease.

Secondary Safety Objective:

To describe the safety and tolerability of PF-07321332/ritonavir relative to placebo in the treatment of nonhospitalized symptomatic adult participants with COVID-19 who are at low risk of progression to severe disease.

Other Secondary Objectives:

To determine the PK of PF-07321332 in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.

To describe the viral load in nasal samples over time in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.

2.1.1. Primary Estimand

The difference in median time (days) to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 between PF-07321332/ritonavir and placebo in nonhospitalized adult patients with COVID-19 who are at low risk of progression to severe disease at baseline and were treated ≤5 days after COVID-19 symptom onset. This will be estimated irrespective of adherence to randomized treatment.

Because the study did not meet the primary endpoint based on the interim analysis at 45%, all hypothesis assessments are done with a nominal alpha.

2.1.2. Secondary Estimands

The estimands associated with the secondary objectives are as follows:

- *The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with COVID-19 who are at low risk of progression to severe disease and were treated ≤5 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.*

- *The difference in estimated rate of number of COVID-19-related medical visits through Day 28 in nonhospitalized adult patients with COVID--19 who are at low risk of progression to severe disease at baseline. This will be estimated irrespective of adherence to randomized treatment*

- *The difference in the estimated rate of number of days in hospital and ICU stay in patients with COVID-19-related hospitalization through Day 28 in nonhospitalized adult patients with COVID-19 who are at low risk of progression to severe disease and were treated ≤5 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.*

Estimands for the other outcome measures are not presented.

2.2. Study Design

This Phase 2/3, randomized, double-blind, placebo-controlled study in approximately 1980 symptomatic adult participants with COVID-19 who are at low risk of progressing to severe illness will determine the efficacy, safety, and tolerability of PF-07321332/ritonavir compared with placebo. Eligible participants with a confirmed diagnosis of SARS-CoV-2 infection will be randomized (1:1) to receive PF-07321332/ritonavir or placebo orally q12h

for 5 days (10 doses total). Randomization will be stratified by geographic region, by vaccination status and by COVID-19 symptom onset (≤3 days vs >3 to 5 days).

The total study duration is up to 24 weeks and includes a screening period of no more than 48 hours, administration of study intervention through Day 5 or Day 6, efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow up at Weeks 12 and 24.

An independent E-DMC will review unblinded data for this Study C4671002 to ensure the safety of participants throughout the duration of the study. In addition to up to weekly reviews of safety, the E-DMC will review the following:

- *Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 100 randomized participants have completed through Day 10. Whether enrollment is paused for this review will depend on the successful completion of the Study C4671005 sentinel cohort (after approximately the first 60 randomized participants have completed through Day 10). If the C4671005 sentinel cohort safety review has successfully completed and no clinically significant safety signals have been identified prior to enrollment of the first 100 participants in this Study C4671002, the study will continue without pause. Otherwise, enrollment of Study C4671002 will be paused pending the E-DMC review of safety data. After review of the sentinel cohort in this Study C4671002, the frequency of safety reviews may be reduced subsequently based on E-DMC recommendations.*

- *Proof-of-concept assessment: Viral load data when 25% (approximately 200 participants in the primary analysis set who were treated ≤3 days following COVID-19 symptoms onset) complete the Day 5 assessments. Enrollment will not be paused during review of these data but may be paused or stopped following E-DMC review.*

- *First interim analysis (45% planned enrollment through Protocol Amendment 4): A planned interim analysis for efficacy, futility and sample size reestimation was conducted after approximately 45% of participants completed the Day 28 assessments in the mITT analysis set.*

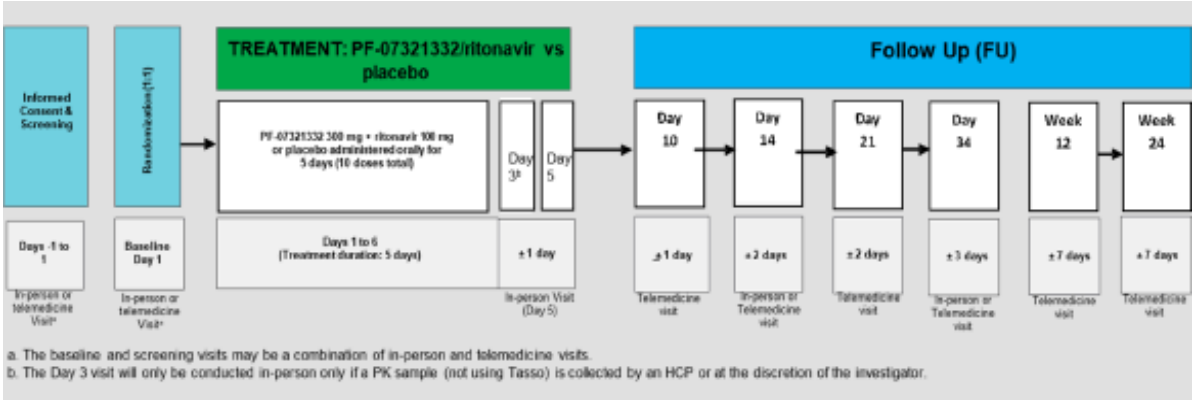
- *Second interim analysis (80% planned enrollment through Protocol Amendment 4): At the request of the E-DMC, a second interim analysis was conducted on 80% of enrolled participants without any adjustment to the alpha.*

- *Third Interim analysis (100% planned enrollment through Protocol Amendment 4)*: A third interim analysis was completed on enrolled participants who had risk factors for severe COVID-19 illness (ie, vaccinated against the SARS-CoV-2 virus) as well as participants who did not have risk factors for severe COVID-19 illness (ie, not vaccinated). Data from the study were required to support regulatory submissions thereby necessitating an interim analysis utilizing the 19 December 2021 dataset. This dataset had not been analyzed previously because the protocol was amended to increase the sample size and extend enrollment to assess the potential benefit of

participants at low risk of progression to severe COVID-19 in the clinically relevant endpoint of hospitalization or death (Protocol Amendment 5, 21 January 2022). The participants who were vaccinated were considered the high risk population and the unvaccinated participants were considered standard risk in the statistical analysis. This interim analysis was without any adjustment to the alpha.

Subsequent to the interim analyses above, there will be a final analysis for reporting the results of this study. The final study analysis will be performed after all participants have completed or otherwise withdrawn from the study. The study schematic is provided in Figure 1.

Figure 1. Schema



2.3. Sample Size Determination

The initial estimate of required sample size was based on the primary endpoint, the difference in time to sustained alleviation of all targeted COVID-19 associated signs/symptoms between participants who were treated ≤3 days after COVID-19 symptom onset with PF-07321332/ritonavir compared to placebo. The sample size is calculated based on a 2-sample test - parallel design – log-rank test, assuming a 90% power, 2-sided test at alpha = 0.05, approximate accrual rate of 30 participants per day, 2 days difference in the median days to sustained alleviation of all targeted COVID-19-associated symptoms (6 days for PF-07321332/ritonavir and 8 days for placebo ie, a 25% reduction in time to sustained alleviation of all targeted COVID-19 signs/symptoms) based on the Lilly - BLAZE-1[1] and assuming a 18% study discontinuation rate, the sample size of approximately 800 participants (approximately 515 events) will provide 90% power to detect that difference.

Allowing for approximately 30% of participants with COVID-19 symptom onset >3 days, a sample size of approximately 1140 participants will be enrolled for this study.

After the second interim analysis *(80% planned enrollment through Protocol Amendment 4), in order to improve estimation precision of the treatment effect in the clinically relevant key secondary endpoint of COVID-19-related hospitalization or death from any cause, the sample size has been adjusted to approximately 1880 participants. This adjustment will provide the required total number of 26 COVID-19-related hospitalizations or death from any cause, which will have approximately 90% conditional power (based on the interim data) such that the nominal 95% CI of the treatment group difference in the event rate does not include 0 when assuming that PF-7321332/ritonavir reduces the event rate by 70% or more relative to placebo.*

The sample size increase of 740 participants is based on the assumption of a 1.5% event rate for the targeted enrollment countries. The number of participants is approximately 1880 (1140 enrolled participants plus the 740 participants). Assuming a 5% premature study discontinuation rate, approximately 1980 participants will be enrolled in the study.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

- *Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28.*

3.2. Secondary Endpoint(s)

- *Incidence of treatment emergent adverse events (TEAEs).*
- *Incidence of SAEs and AEs leading to discontinuations.*

- *Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.*
- *Proportion of participants with death (all cause) through Week 24.*
- *Number of COVID-19 related medical visits through Day 28.*
- *Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization through Day 28.*
- *Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28.*
- *Time (days) to sustained resolution of all targeted COVID-19 signs/symptoms through Day 28.*
- *Duration of each targeted COVID-19 sign/symptom.*
- *Progression to a worsening status in 1 or more self-reported COVID-19-associated symptoms through Day 28.*
- *Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.*
- *PF-07321332 PK in plasma and whole blood (if feasible).*
- *Viral titers measured via RT-PCR in NP/nasal swabs over time.*

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- [redacted]
- [redacted]

3.4. Baseline Variables

Baseline visit (Day -2 to Day 1) will be defined as the latest measurement taken prior to start of study drug, within the baseline window as defined in Appendix 2.1.

For Viral Load data, Baseline visit is set up according to study days of Day -2 to Day 1. Only results that are within 1 hour post start of dosing will be treated as Baseline data.

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

The Baseline Viral Load data will be categorized as follows:

- Baseline Viral Load defined as: $<10^4$ copies/mL vs $\geq 10^4$ copies/mL.
- Baseline Viral Load defined as: $<10^7$ copies/mL vs $\geq 10^7$ copies/mL.
- Nasopharyngeal (Y/N).

3.5. Stratification Variables

Randomization was stratified by geographic region, by vaccination status and by COVID-19 symptom onset (≤3 days vs >3 to 5 days).

Vaccination status is defined as completely vaccinated (high risk) and not vaccinated (standard risk).

Geographical region is defined as follows:

- US region: country of the United States, including Puerto Rico.
- Europe region: countries of Bulgaria, Czech Republic, Hungary, Poland, Spain, Ukraine, Slovakia and Romania.
- Rest of the World region: countries of Argentina, Brazil, Colombia, Japan, Malaysia, Mexico, South Africa, Republic of Korea, Taiwan, Thailand, and Turkey.

Baseline and stratification variables defined above will be applied to the analyses depending on the analysis population used:

- mITT1 analysis will include: Baseline viral load, baseline serology status, geographic region, vaccination status and symptom onset days to first dose date (≤3 days, >3 days). Detail will be described in each endpoint if applied.

3.6. Safety Endpoints

The safety endpoints of this study are:

- Incidence of treatment emergent adverse events (TEAEs)
- Incidence of SAEs and AEs leading to discontinuation.

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 adverse event (AE) is any untoward medical occurrence in a study participant administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. An adverse event is considered a

Treatment-Emergent Adverse Event (TEAE) if the event started on or after the study medication start date and time.

3.6.2. Medical History

Medical history in addition to COVID-19 disease history and demographics will be collected at screening. Smoking status was collected for participants who enrolled under the original protocol (18 June 2021) or any of the first 4 amendments (02 July 2021; 19 July 2021; 03 August 2021; and 23 November 2021, respectively). Participants who enrolled under Protocol Amendment 5 (21 January 2022) were not eligible to participate in the study if they were smokers. Medication history of all prescription or nonprescription drugs (including vaccinations), and dietary and herbal supplements taken within 30 days prior to the planned first dose will be collected. General medical history will combine data collected before and after Protocol Amendment 5 (21 January 2022). Significant medical history collected under the original protocol and the first 4 amendments (ie, before Protocol Amendment 5, 21 Jan 2022) will be reported separately for the CSR.

3.6.3. Height and Weight

Height and weight will be measured and recorded at screening.

3.6.4. Laboratory Data

To determine if there are any clinically significant laboratory abnormalities, the hematological and clinical biochemistry and other safety tests will be assessed against the criteria specified in the Pfizer reporting standards. This assessment will take into account whether each participant's baseline test results are within or outside the laboratory reference range for particular laboratory parameter.

3.6.5. Vital Signs

Vital signs measure include 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 regardless of whether or not study intervention was administered.
Safety Analysis Set (SAS)	All participants who receive 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 with at least 1 postbaseline visit through Day 28 who were treated ≤3 days after COVID symptoms onset. Participants will be analyzed according to the study intervention to which they were randomized.
Modified Intent-To-Treat (mITT1)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they were randomized.
Per-Protocol (PP)	All participants in the mITT1 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.

Both the mITT1 and PP analysis sets will be used in the analyses of the primary efficacy endpoint, with the mITT1 being primary. For proportion of COVID-19 related hospitalization or death from any cause and all other efficacy endpoints, mITT1 will be used. The Safety Analysis Set will be used in the analyses of the safety data.

Multiple Enrollers:

If a participant enters/is randomized into Study C4671002 more than once or is enrolled in Study C4671002 and in 1 or 2 other Phase 2/3 nirmatrelvir/ritonavir studies:

(1) The primary and key secondary efficacy analyses will be performed by considering all enrolled participants (subject IDs) as independent participants.

(2) Sensitivity analyses for both the primary and key secondary endpoints will be performed using only data from a duplicate participant's first enrollment within this study and excluding data from a duplicate participant's subsequent enrollments.

5. GENERAL METHODOLOGY AND CONVENTIONS

The final analysis will be performed after dataset release.

5.1. Hypotheses and Decision Rules

The primary hypothesis to be tested is whether or not there is a difference in median time (days) to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 between PF-07321332/ritonavir and placebo. The statistical hypothesis is as follows:

- *The null hypothesis (H_0) is that there is no difference in median time to sustained alleviation of targeted symptoms of COVID-19 between PF-07321332/ritonavir and placebo.*

- *The alternative hypothesis (H_1) is that there is a difference in median time to sustained alleviation of targeted symptoms of COVID-19 between PF-07321332/ritonavir and placebo.*

Because the prespecified 45% interim analysis of the primary endpoint was not met, the following secondary endpoints will be analyzed to provide a point estimate and 95% CI to measure associated variability. The analysis will be performed with a nominal alpha:

1) Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28.

2) Number of COVID-19-related medical visits through Day 28.

In support of the COVID-19 related medical visits endpoint, the number of days in hospital and ICU stay in patients with COVID-19-related hospitalization through Day 28 will be summarized.

Other secondary endpoints listed below will be subsequently tested following the Hochberg procedure.

- Time (days) to sustained resolution of all targeted signs/symptoms through Day 28 mITT1 population.

- Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5 mITT1 population.

- Proportion of participants with severe signs/symptoms attributed to COVID 19 through Day 28.

5.2. General Methods

All data will be presented by treatment groups. Descriptive statistics will be provided for efficacy endpoints. The following listing of individual participants data will also be produced: (Disposition Events, Potentially Important Protocol Deviations, Subject Evaluation Groups, Demographic Information, Primary Diagnosis, Concomitant Medications, Compliance with Study Intervention, primary efficacy endpoint [time to sustained alleviation of all targeted signs and symptoms through Day 28], and the two key secondary endpoints [proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28; number of COVID-19-related medical visits through Day 28], Adverse Events, Laboratory Data – Standardized (all the variables that are listed in the SAP Section 6.4 plus visit ID, participant ID, treatment).

The number of participants screened will be reported. The number of participants randomized to the double-blind treatment phase, completing the study drug administration, completing the study, completing the follow-up phase (through Day 34 visit) and discontinued the study will be summarized from the FAS analysis set for each treatment group.

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

For mITT1 population, strata will be region, vaccination subgroup/strata, onset of signs and symptoms of COVID-19 (≤3 days, >3-5 days), nasopharyngeal (Y/N), and baseline viral load.

5.2.1. Analyses for Binary Endpoints

Binary endpoints other than COVID-19 related hospitalization and death due to any cause (ie, proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28, worsening status in 1 or more self-reported COVID-19 associated symptoms through Day 28 and proportion of participants with death [all cause] through Week 24) will be summarized with the number and percent of participants satisfying the endpoint. Treatment comparisons between groups will be presented as odds ratios with 95% confidence intervals and P-value based on logistic regression model (if data permits).

5.2.2. Analyses for Continuous Endpoints

For continuous endpoints (ie, viral titers measured via RT-PCR in nasal swabs over time), an MMRM analysis of covariance model will be used to analyze change from baseline over time. Estimated mean differences between treatments and their respective 95% CI and P-values will be calculated. In addition, an ANCOVA model will be used to analyze change from baseline (Day 1) to Day 5 in viral titers.

For mITT1 population, the strata will be region, vaccination subgroup/strata, baseline serology (positive or negative), and baseline viral load ($<10^4$ copies/mL, $\geq 10^4$ copies/mL).

5.2.3. Analyses for Categorical Endpoints

For categorical endpoints, (ie, proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5), proportion of participants for each category will be summarized for each group and a test for homogeneity of odds ratio using Breslow-Day test will be summarized.

5.2.4. Analyses for Count Endpoints

For count endpoints (ie, number of COVID-19 related medical visits through Day 28 and number of days of hospitalizations/ICU stay in participant with COVID-19-related hospitalization through Day 28), a negative binomial regression model analysis, using the

log total number of days of data collection as the participant offset variable, will be conducted and the difference in estimated rate will be provided.

5.2.5. Analyses for Time-to-Event Endpoints

Time-to-event endpoints (ie, Time (days) to sustained resolution of all targeted signs/symptoms through Day 28) will be summarized with Kaplan-Meier curves. Log-rank test will be used to compare the time-to-event between the treatment group.

5.3. Methods to Manage Missing Data

For missing efficacy data other than time to event endpoints, last observation carried forward (LOCF) approach will be used. For efficacy endpoints related to COVID-19 sign/symptoms, missing data at baseline will be treated as mild.

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 time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28 in the mITT1 population.

Sustained alleviation of all targeted COVID-19 signs/symptoms is defined as the event occurring on the first of 4 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 4 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/resolved (missing severity at baseline will be treated as mild).

Day 25 is the last possible day the symptom alleviation and resolution endpoints can be achieved (definition includes data from the subsequent three days) and Day 28 is the last day participants report their daily signs and symptoms.

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

- For a participant with sustained symptom alleviation/resolution (event), 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/resolution (censored), censoring date will be at the last date on which symptom alleviation/resolution is assessed, and time will be calculated as (Censoring Date) – (First Dose Date) +1 or Day 25 whichever occurs first.

The decision to require 4 consecutive days of all targeted symptoms alleviation/resolution was based on exploratory analyses of data from the ACTIV-2/A5401 study, which suggested that this choice (rather than requiring fewer consecutive days) better captured sustained symptom resolution with low probability of subsequent relapse.

Participants who are hospitalized for the treatment of COVID-19 or death from any cause during the 28-day period will be classified as not achieving sustained symptom alleviation and will be censored at Day 25.

Time to sustained alleviation of all targeted COVID-19 signs/symptoms will be summarized with Kaplan-Meier curves. Log-rank test will be used to compare the difference in time (days) to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 between treatment groups.

6.1.1.2. Sensitivity and Supplemental Analyses

Sensitivity analyses will be performed to the primary efficacy endpoint:

The primary efficacy analyses will also be conducted using the PP population as supplemental analyses.

The primary endpoint will also be analyzed in which participants who discontinued the study before Day 28 without event will be censored at Day 25.

For sensitivity analysis of primary endpoint, Cox proportion hazard models with terms including treatment and treatment strata (ie, region, vaccination, baseline serology, baseline viral load $<10^4$ copies/mL vs $\geq 10^4$ copies/mL). These factors will be used to estimate the hazard ratio (the ratio of alleviation of all targeted signs and symptoms) and its 95% CI. Additional analyses may be performed adjusting for baseline covariates (such as age, gender, etc) as additive terms to the primary model, if necessary.

Based on FDA request, a sensitivity analysis excluding participants only from Site 1488 will be conducted as well.

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 COVID-19 Related Hospitalization or Death From Any Cause Through Day 28

The estimand for proportion of participants experiencing COVID-19 related hospitalization or death from any cause through Day 28 is the difference in proportions of participants experiencing COVID-19 related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with COVID-19 who are at low risk of progression to severe disease and were treated ≤5 days after COVID-19 symptom onset. This will be estimated irrespective of adherence to randomized treatment.

The statistical methodology for proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 will be as follows:

The cumulative proportion of participants hospitalized for the treatment of COVID-19 or death during the first 28 days of the study will be estimated for each treatment group using the Kaplan-Meier method to take account of lost to follow-up and summarized graphically for each treatment group. The estimand is the difference of the proportions in the 2 groups and its 95% CI will be presented, as well as, the associated two sample proportion test (Wald test results). For the 95% CI, the corresponding estimate of the standard error is computed using Greenwood's formula[4]. The Greenwood's formula to estimate the variance of the difference of proportions at Day 28 is [$Var(S_{PF}(28)) + Var(S_{Placebo}(28))$]. Instead of dealing with $S(t_i)$ the log-log approach to CI will be used. The 95% CI will be computed for the estimate of $L(t)= \log(\log(S(t))$, the log hazard function.

The CI will be in the right range when transformed back to $S(t) = \exp (-\exp (L(t))$. Antilogging this CI will give a 95% confidence interval for the difference itself.

A sensitivity analysis for proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 will be provided using mITT1 as follows:

For participants with missing data due to lost to follow up for COVID-19 related hospitalization or death from any cause, the sensitivity analysis will implement the following event imputation methodology for those with missing data:

- If the participant's last observed data is prior to Day 21, then impute as an event with event day as day of last observed data +1.
- If the participant's last observed data is on or after Day 21, then no imputation for event will be done and participant remains censored at day of last observed data.

6.2.4. Proportion of Participants with Death (all cause) through Week 24

Descriptive statistics will be used to summarize proportion of death through Week 24 by treatment group using mITT1 populations. Treatment comparisons between groups will be presented as odds ratios with 95% confidence intervals and P-value based on logistic regression model (if data permit).

If zero counts are observed in either treatment group, the Fishers Exact test will be performed (instead of logistic regression) and p-value provided.

The participants enrolled under or after protocol amendment 6 will not include this summary.

6.2.5. Number of COVID-19 Related Medical Visits through Day 28

The number of COVID-19 related medical visits will 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). The resulting analysis will evaluate the difference in estimated rate of number of medical visits between treatment groups and the associated 95% CI. The analyses will be done using mITT1 populations.

6.2.6. Number of Days of Hospital and ICU Stay in Participants with COVID-19 Related Hospitalization

Health resource utilization data will be summarized by treatment group for each treatment. The analyses will be done using mITT1 populations. Descriptive statistics (ie, mean, median, range) will be used to summarize this endpoint.

The resulting analysis will provide the estimated difference in the average of number of days stayed in the hospital between treatment groups, with p-value and 95% confidence interval. The analyses will be done using the mITT1 population.

6.2.7. Proportion of Participants with Severe Signs/symptoms Attributed to COVID19 through Day 28

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. A participant with severe score for any targeted symptoms post-baseline will be counted as severe.

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

The proportion of participants with any severe targeted signs/symptoms attributed to COVID-19 through Day 28 will be summarized by treatment group. Observed proportions for each targeted signs and symptom with severe category only will be plotted over time through Day 28. Additionally, observed proportion of participants reporting the presence of each targeted sign and symptom that is mild, moderate or severe categories will also be presented.

Treatment comparisons between groups will be presented as odds ratios with 95% CI and p-value based on logistic regression model and using the mITT1 population.

To evaluate the severity of signs/symptoms attributed to COVID-19, the following analysis will be performed and treatment comparison between groups will be done using the same statistical method as mentioned above:

- Proportion of participants with any severe (ie, any targeted symptoms with severe baseline score) targeted signs/symptoms attributed to COVID-19 at Day 1 (baseline).
- Proportion of participants with any severe targeted signs/symptoms attributed to COVID-19 Day 2 to Day 6 (during treatment).
- Proportion of participants with any severe targeted signs/symptoms attributed to COVID-19 Day 7 to Day 28 (post treatment).

The above severity endpoint is based on participant daily diary data only. To align the severity of signs and symptoms with the primary and key secondary endpoints, an expanded evaluation of severity of will be assessed to include hospitalization due to COVID-19 and death of any cause in the severity assessment based on CRF data.

An expanded definition severity of signs and symptoms that will include CRF data (hospitalization due to COVID-19 and death of any cause) is defined as follows: Participant with hospitalization due COVID-19 or death of any cause will be considered as having severe signs and symptoms, this definition overrides the observed severity of signs and symptoms from participant diary. To incorporate hospitalization and death in the severity of signs and symptoms, the date of hospitalization and date of discharged will be used. Treatment comparisons between groups for expanded severity will be presented as odds ratios with 95% CI and p-value based on logistic regression model and using the mITT1 population

This analysis will be performed for overall, baseline (Day 1), Day 2 to Day 6 (during treatment) and Day 7 to Day 28 (post treatment).

6.2.8. Time (days) to Sustained Resolution of All Targeted COVID-19 Signs/symptoms through Day 28

The secondary endpoint of time (days) from start of study intervention or placebo (Day 1) until sustained resolution of all targeted COVID-19 associated signs/symptoms will be based on self-assessment.

Sustained resolution is defined as when all targeted symptoms are scored as absent for 4 consecutive days. The first day of the 4 consecutive-day period will be considered the First Event Date.

The censoring method and analysis of time (days) to sustained resolution of all targeted COVID-19 signs/symptoms will be similar to the censoring method and analysis of the primary endpoint. The analysis will be done using mITT1 population.

6.2.9. Duration of Each Targeted COVID-19 Sign/symptom

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

For duration of each targeted COVID-19 sign/symptom, a Kaplan-Meier analysis providing the median and quartiles will be provided for each treatment group for mITT1 population set. Two additional figures (Number of Participants and Median Time to Sustained Alleviation of Each Targeted Sign/Symptom by Treatment Group [mITT1]) will be included for the endpoint of Duration of Each Targeted COVID-19 Sign/Symptom.

6.2.10. Progression to a Worsening Status in 1 or More Self-reported COVID-19 Associated Symptoms through Day 28

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 (mild) for 1 to 2 times, 2 (moderate) for 3 to 4 times, and 3 (severe) for 5 or greater.

Progression to a worsening status for any targeted symptom will be derived programmatically based upon increasing severity (ie, the first time any targeted symptom worsens after treatment relative to baseline):

Progression to worsening (Yes/No)	
Increasing severity	Yes
Not increasing severity	No

The proportion of participants with progression (increasing severity for any targeted symptom) will be summarized by treatment group. Treatment comparison between groups will be presented as odds ratios with 95% CIs and p-value based on logistic regression model. The analyses will be done using mITT1 population. Missing severity at baseline will be treated as mild.

The above definition of worsening was derived only from participant diary data, to align the worsening with the primary and keys secondary endpoint, an expanded evaluation of

worsening will be assessed to include hospitalization due to COVID-19 and death of any cause. An expanded definition of worsening of signs and symptoms that will include CRF data (hospitalization due to COVID-19 and death of any cause) is defined as follows: Participant with hospitalization due COVID-19 or death of any cause will be considered as having worse signs and symptoms, this definition overrides the observed worsening of signs and symptoms from participant diary data. To incorporate hospitalization and death in the expanded worsening of signs and symptoms, date of hospitalization and date of discharge will be used.

To evaluate the progression to worsening of symptoms attributed to COVID-19, the following analysis will be performed for both worsening and expanded worsening and treatment comparison between groups will be done using the same statistical method as mentioned above:

- Proportion of participants with any progression to worsening of targeted symptoms attributed to COVID-19 Day 2 to Day 6 (during treatment).

- Proportion of participants with any progression to worsening of targeted symptoms attributed to COVID-19 Day 7 to Day 28 (post treatment).

6.2.11. Proportion of Participants with a Resting Peripheral Oxygen Saturation ≥ 95% at Days 1 and 5

The oxygen saturation level will be measured for each participant. A resting peripheral oxygen saturation will be derived programmatically based on following table:

Oxygen saturation (Yes/No)	
≥95%	Yes
<95%	No

The count and proportion of participants with a resting peripheral oxygen saturation ≥95% will be summarized by treatment group and by visits (Days 1 and 5). A cross tabulation will be presented for both Day 1 and Day 5, ie, for each proportion presented at Day 1, both proportions at Day 5 will be summarized. Treatment comparison between group for the odds ratio (baseline (Day 1) ≥95% vs <95%) of comparing oxygen saturation ≥95% at Day 5 will be analyzed with a Breslow-Day test for homogeneity of the odds ratios. The analyses will be done using mITT1 populations. Missing data at Day 1 or Day 5 will be excluded from the analysis.

6.2.12. 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.

6.2.13. Viral Titers (quantitative RT-PCR) Measured in Nasal Swabs Over Time

The viral load data measured at Day 1 and Day 5 are nasopharyngeal samples. These are the samples that were used on the POC analysis. POC analysis of viral load data occurred when 25% (approximately 200 participants in the primary analysis set with evaluable data) in the mITT1 population with evaluable data complete the Day 5 assessments.

Descriptive statistics by treatment group for the change from baseline will be provided. An analysis of covariance (ANCOVA) model will be used to analyze the change from baseline in log base10 transformed viral load (copies/mL) data. The ANCOVA model will include treatment group, baseline viral load, baseline serology, geographical region and vaccination status. Symptom onset to first dose date (≤3 days, >3 days) will be used in the model dependent of population. Participants are excluded from the analysis for reasons of Not Detected, Zero or Missing baseline viral load result. Results from samples collected at non-nasopharyngeal site (like nostril, other or missing) are also excluded, as well as exclusions due to non-validated swab use (only viral load data based on samples collected through validated swab will be used for analyses).

The viral load measured in nasal or nasopharyngeal samples over time will be evaluated. The change from baseline to each visit (Day 3, Day 5, Day 10, Day 14) in viral load will be analyzed using an MMRM method. Viral load, including change from baseline, will be summarized by treatment group. Change from baseline to Day 3/Day 5/Day 10/Day 14 in viral load in the log base 10 scale will be statistically analyzed using a linear mixed-effect model. The model will contain log base 10 transformed baseline as a covariate, baseline serology status, treatment, day, treatment-by-day as fixed effects. Symptom onset to first dose date (≤3 days, >3 days), nasopharyngeal (Y/N) will be used in the model as described in Section 3.4 and 3.5, dependent of population. The LS means and treatment difference will be calculated and presented with their corresponding 95% CIs. The analyses will be done using mITT1populations.

CCI

[redacted]

CCI

[redacted]

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CCI [redacted]

[redacted]

6.4. Subset Analyses

Subgroup analyses of the primary endpoint and key secondary endpoint (hospitalization due to COVID-19 and death of any cause) will only be performed for vaccination status and others will be analyzed if necessary for post hoc. The subgroup variables include:

- Age group (<65, ≥ 65);
- Sex;
- Race;
- Vaccination status. The vaccination subgroup is defined as follows:

  a) Participant who enrolled prior to PA #5 and were completely vaccinated are considered high risk group.

  b) Participants who enrolled prior to PA#5 and were not vaccinated, plus all participants enrolled after implementation of PA#5 are considered as standard risk group.

- Baseline serology (PCR positive, PCR negative);
- Baseline viral load defined as: $<10^4$ copies/mL vs $\geq 10^4$ copies/mL;
- Maximum severity of targeted baseline signs and symptoms (mild, moderate, severe)
- Vaccination status and by maximum severity of targeted baseline signs and symptoms (mild, moderate, severe)
- Baseline viral load defined as: $<10^7$ copies/mLvs $\geq 10^7$ copies/mL;
- BMI category (<30, ≥30);
- Type of COVID-19 variant (i.e., Omicron, BA2);
- Baseline Comorbidities:
  - Smoking;

[redacted]

- Chronic lung disease requiring medication;
- Hypertension (taking medications for hypertension);
- Cardiovascular disorders;
- Diabetes (taking medications for diabetes) for safety reporting;
- Chronic kidney disease;
- Sickle cell disease;
- Neurodevelopmental disorders;
- Cancer other than localized skin cancer;
- Medical-related technological dependence.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

The demographic characteristics will be summarized by treatment group within the FAS. This will include age, gender, race, ethnicity baseline height, and baseline weight. All baseline disease characteristics will be summarized by treatment group within the FAS.

6.5.2. Study Conduct and Participant Disposition

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

In addition, the number of participants who were excluded from the PP analysis set will be summarized by reasons for the exclusion.

6.5.3. Study Treatment Exposure

Duration of treatment 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 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 Clinical Data Interchange Standards Consortium (CDISC) and Pfizer Standards (CaPS) for safety reporting for the following parameters: adverse events, lab parameters, vital signs, discontinuations from study, discontinuations from treatment, and treatment duration.

6.6.1. Adverse Events

All adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by treatment group within SAS population. Only TEAE summaries to AEs that started on or prior to Day 34 will be summarized. A list of pre-specified AESIs is provided in Appendix 5.

6.6.2. Subgroup Analysis of Adverse Events and Serious Adverse Events

A subgroup analysis of treatment emergent AEs and SAEs will be provided by vaccination status.

6.6.3. Laboratory Data

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

Laboratory shift tables from baseline will be presented for the following laboratory abnormalities at baseline: D-dimer levels, Liver function tests (ALT/AST), Creatinine Clearance (derived using Cockcroft-Gault Equation), TSH, T4 (free), fibrinogen, platelets, PT, aPTT, albumin, and total proteins.

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

6.6.4. Vital Signs

The measurement taken immediately prior to start of study drug will be used as the baseline for calculating change from baseline.

All vital signs data will be descriptively summarized by treatment group within SAS population and reported in accordance with Pfizer data standard for safety reporting.

7. INTERIM ANALYSES

7.1. Interim Analyses and Summaries

There were 3 interim analyses as follows:

First interim analysis (45% planned enrollment through Protocol Amendment 4): An interim analysis was conducted for efficacy, futility and sample size re-estimation, and reviewed by an independent E-DMC after a prespecified accrual of participants (ie, approximately 45% overall participants have completed Day 28 efficacy assessment in the mITT population), according to the SAP and E-DMC charter. The sample size could be increased one time and the increase is limited to 30 to 35%. A well-established method described by Cui, Hung, and Wang (1999)[2] (implemented in EAST 6.5) would be used to control the Type I error probability.[3]

The nominal significance level for the interim and final time to sustained alleviation of all targeted COVID-19 signs/symptoms analyses was determined by means of the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary, with an overall 2-sided type I error rate of 5%.

O'Brien-Fleming approach was used for decision making, ie, reject H_0 with 2-sided p-value ≤ 0.002, or reject H_1 with 2-sided p-value >0.924 at the formal interim analysis. At the final analysis, the p-value for rejecting H_0 will be ≤ 0.049 (2-sided) or reject H_1 with 2-sided p-value >0.049 will be considered.

Before any interim analysis was performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs was documented and approved in an E-DMC charter.

The first interim analysis (45% planned enrollment through Protocol Amendment 4) summarized above was performed as described.

Second interim analysis (80% planned enrollment through Protocol Amendment 4): Upon review of the 45% analysis, the E-DMC requested the Sponsor to consider appropriate course of action for the ongoing trial to assess the clinical benefit. In order to respond properly to fulfill the E-DMC recommendation, the RRP decided that a second interim analysis should be conducted to address the E-DMC's request. This resulted in the analysis of 80% of enrolled participants through Protocol Amendment 4, without any adjustment to the alpha.

Third interim analysis (100% planned enrollment through Protocol Amendment 4): A third interim analysis was completed on enrolled participants who had risk factors for severe COVID-19 illness (ie, vaccinated against the SARS-CoV-2 virus) as well as participants who did not have risk factors for severe COVID-19 illness (ie, not vaccinated). Data from the study are required to support regulatory submissions thereby necessitating an interim analysis utilizing the 19 December 2021 dataset. This dataset had not been analyzed previously because the protocol was amended to increase the sample size and extend enrollment to assess the potential benefit of participants at low risk of progression to severe

COVID-19 in the clinically relevant endpoint of hospitalization or death (Protocol Amendment 5, 21 January 2022). The participants who were vaccinated are considered the high risk population and the unvaccinated participants are considered standard risk in the statistical analysis.

7.2. Data Monitoring Committee

This study will use an E-DMC. The E-DMC is independent of the study team and includes only external members. The E-DMC charter describes the role of the DMC in more detail.

The E-DMC will be responsible for ongoing monitoring of the 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.

7.3. Blinding of the Sponsor

The majority of sponsor staff will be blinded to study intervention allocation. There will be an unblinded team supporting the interactions with, and the analyses for, the E-DMC while the study is ongoing. The team will consist of medical monitor/clinicians, reporting statistician and reporting programmer(s) and will be separate from the direct members of the study team. The reporting team may include designated ad hoc member(s).

After all participants complete the Day 34 visit (or Early Termination (ET) prior to Day 34 visit), the study will be unblinded and analyses through Day 34, including the primary efficacy endpoint analyses, will be conducted. A blinded team will remain in place to monitor and manage the study until primary completion date is attained (all participants have reached Day 34 visit or discontinued prior to Day 34 visit).

Details of the unblinded sponsor staff supporting the E-DMC and the timing of unblinding will be outlined in the Unblinding Plan.

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
Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28.	Primary efficacy Analysis	mITT1	All data collected will be included. Missing severity at baseline will be treated as mild. Other missing data will be estimated with KM (lifetest) procedure	Kaplan-Meier & Log rank test
Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28.	Sensitivity analysis for primary endpoint	mITT1	All data collected will be included. Missing severity at baseline will be treated as mild.	Cox proportional hazard model
Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28.	Sensitivity analysis for primary endpoint	mITT1 exclude site 1488	All data collected will be included. Missing severity at baseline will be treated as mild.	Cox proportional hazard model
Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28.	Supplemental analysis for primary endpoint	PP	Participants who discontinued the study before Day 28 without event will be censored at Day 25.	Kaplan-Meier & Log rank test
Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28.	Sensitivity analysis for Primary Efficacy analysis for multiple enrollers	mITT1 including only data with first randomizatio n within the study	All data collected will be included regardless of intercurrent events. Kaplan-Meier method to take account of losses to follow-up.	Kaplan-Meier method
Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28 by vaccination status	Subgroup analysis for primary endpoint	mITT1	Use baseline variables as described in Section 6.4.	Cox proportional hazard model
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28	Key secondary analysis	mITT1	All data collected will be included regardless of intercurrent events. Kaplan-Meier method to take account of losses to follow-up.	Kaplan-Meier method
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28	Sensitivity analysis for key secondary endpoint	mITT1	If the participant's last observed data is prior to Day 21, then impute as an event with event day as day of last observed data +1. If the participant's last observed data is on or after Day 21, do not impute an event and	Kaplan-Meier method

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
			participant remains censored at day of last observed data.	
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28	Sensitivity analysis for key secondary efficacy analysis for multiple enrollers	mITT1 including only data with first randomizatio n within the study	All data collected will be included regardless of intercurrent events. Kaplan-Meier method to take account of losses to follow-up.	Kaplan-Meier method
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 by vaccination status	Subgroup analysis for key secondary endpoint	mITT1	Subset analysis identified in Section 6.4.	Kaplan-Meier method
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28	Supplemental analysis for key secondary efficacy endpoint	PP	Participants who discontinued the study before Day 28 without event will be censored at Day 25.	Kaplan-Meier & Log rank test
Proportion of participants with death (all cause) through Week 24.	Secondary analysis	mITT1	All data collected will be included regardless of intercurrent events exclude participants enrolled under PA6	Logistic Regression
Number of COVID-19 related medical visits through Day 28.	Secondary analysis	mITT1	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Descriptive statistics (based on negative Binomial Model)
Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization through Day 28.	Secondary analysis	mITT1	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Descriptive statistics
Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28.	Secondary Efficacy Analysis	mITT1	All data collected will be included regardless of intercurrent events, LOCF for missing data.	Logistic regression model
Proportion of participants with any severe targeted signs/symptoms attributed to COVID 19 at Day 1(baseline).	Supplemental analysis for secondary endpoint	mITT1	Any severe (ie, any targeted symptoms with severe baseline score) LOCF for missing data.	Logistic regression model
Proportion of participants with any severe targeted signs/symptoms	Supplemental analysis for secondary endpoint	mITT1	Any severe (ie, any targeted symptoms with severe baseline score) LOCF for missing data.	Logistic regression model

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
attributed to COVID 19 from Day 2 to Day 6 (during treatment)				
Proportion of participants with any severe targeted signs/symptoms attributed to COVID 19 from Day 7 to Day 28 (post treatment)	Supplemental analysis for secondary endpoint	mITT1	Any severe (ie, any targeted symptoms with severe baseline score) LOCF for missing data.	Logistic regression model
Proportion of participants with severe signs/symptoms attributed to COVID 19 through Day 28.	Supplemental analysis for secondary endpoint	mITT1	Observed proportions for each targeted signs and symptom with severe category only will be plotted over time through Day 28. Additionally, observed proportion of participants reporting the presence of each targeted sign and symptom that is mild, moderate or severe categories will also be presented	Plot/Figure
Time (days) to sustained resolution of all targeted COVID-19 signs/symptom through Day 28.	Secondary analysis	mITT1	All data collected will be included. Missing severity at baseline will be treated as mild. Other missing data will be estimated with KM (lifetest) procedure	Kaplan-Meier & Log rank test
Duration of each targeted COVID-19 sign/symptom.	Secondary analysis	mITT1	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Kaplan-Meier estimate, Descriptive statistics (median, quartiles)
Progression to a worsening status in 1 or more self-reported COVID19 associated symptoms through Day 28.	Secondary analysis	mITT1	All data collected will be included regardless of intercurrent events. Missing severity at baseline will be treated as mild.	Logistic regression model
Progression to a expanded worsening status in 1 or more self-reported COVID19 associated symptoms through Day 28.	Secondary analysis	mITT1	All data collected will be included regardless of intercurrent events. Missing severity at baseline will be treated as mild.	Logistic regression model
Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.	Secondary analysis	mITT1	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Breslow-Day test for Homogeneity of the Odds Ratios
Viral titers measured via RT-PCR in nasal swabs over time.	Secondary analysis	mITT1	All data collected will be included regardless of intercurrent events. If visit data in viral load is missing, the earliest measurement	MMRM analysis

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
			closest to the visit will be used for the visit.	
Viral titers measured via RTPCR in nasopharyngeal samples at Day 1 and Day 5.	Sensitivity analysis (POC)	mITT1	All data collected will be included regardless of intercurrent events. Use baseline viral load (continuous).	ANCOVA analysis
CCI [redacted]	CCI [redacted]	CCI [redacted]	CCI [redacted]	CCI [redacted]

* All: Combining mITT1 population from before and after Protocol Amendment #6, dated 09 Jun 2022.

Pre-PA5: mITT1 population from before Protocol Amendment #5, dated 21 Jan 2022,

Post-PA5: mITT1 population from after Protocol Amendment #5, dated 21 Jan 2022

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Visit Windows in Reporting

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

Visit Number	Visit Label	Definition [Day window]
2	Baseline	= Day -2 to Day 1
3	Day 3	= Day 3, with a window of ±1 Day, (ie, Days 2 to 4)
4	Day 5	= Day 5, with a window of ±1 Day, (ie, Days 4 to 6)
5	Day 10	= Day 10, with a window from Days 7 to 11
6	Day 14	= Day 14, with a window from Days 12 to 17
7	Day 21	= Day 21, with a window from 18 to 24
8	Day 34	= Day 34, with a window from days 25 to 37
9	Week 12	= Day 84, with a window of ±7 Days, (ie, Days 77 to 91)
10	Week 24	= day 168 with a window of ±7 days, (ie, Days 161 to 175)

- Viral Load: Baseline visit is set up according to study days of Day -2 to Day 1. The only viral load results collected after the start of dosing during the Baseline visit that are treated as Baseline data are those that were collected within 1 hour post start of dosing.

- Labs, COVID-19 Signs and Symptoms, Vital Signs: Baseline window will be Day -2 to Day 1, without any consideration to the time factor.

- When data from study Day 4 has an overlap between Day 3 and Day 5 windows, decision made is to assign the window according to the nominal visit. The rule will not be applicable to other study days 2 and 3 for Day 3 window, and days 5 and 6 for Day 5 window.

- If multiple readings fall into the same window, choose the one closer to the target day. If equidistant, then select the later one after the target day. If multiple observations fall on the same day after the windowing logic has been applied, average observations.

Appendix 3. List of Abbreviations

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
BOCF	baseline observation carried forward
CDARS	Clinical Data Analysis and Reporting System
CI	confidence interval
E-DMC	external data monitoring committee
FAS	full analysis set
FDA	Food and Drug Administration (United States)
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model with repeated measures
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per-protocol
POC	Proof-of-concept
RRP	Recommendation Review Panel
PT	preferred term
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety Analysis Set
SD	standard deviation
SOC	Schedule of Activities
SOP	standard operating procedure
WHO	World Health Organization

Appendix 4. Signs and Symptoms Attributable to COVID-19

Daily Sign and Symptom Collection[28]	Entry Criterion#3 Targeted (used for study entry)	Daily 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	
Loss of taste		X	

Appendix 5. 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