Protocol C4671005

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 INCREASED RISK OF PROGRESSING TO SEVERE ILLNESS

Statistical Analysis Plan (SAP)

Version: **1.5 (Amendment)**

Date: **28APR2022**

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1.0	1.0		SAP original version
1.1	2.0	Due to uncertainty on the effect of time from symptom onset relative to initiation of treatment on the effectiveness of an antiviral, a change has been made to the primary analysis set. The primary analysis set (mITT) has been refined to include just those participants who were treated ≤3 days after COVID-19 symptom onset (mITT).	As of protocol amendment 2, dated 02 August 2021 the following changes have been incorporated: • On Section 2.1.1 the primary estimand changed to specify inclusion of participants who did not receive COVID-19 therapeutic mAbs and who were treated ≤3 days after COVID-19 symptom onset. • On Section 2.1.2 the key secondary efficacy endpoint was added as a consequence of the change in primary efficacy analysis and the analysis will include participants regardless of their symptom onset mITT2). • Updated sample size in Section 2.3 from 2260 to approximately 3000 participants. Enrollment of participants that had COVID-19 symptom onset >3 days prior to randomization is expected to be approximately 25% and will be limited to approximately 1000 participants. Sample size has been adjusted, and the analysis of all participants is now a secondary analysis. • Updated definition of baseline visit and baseline derived variables (Section 3.4).

			• Added definition of stratification variable geographical region (Section 3.5). • Added list of stratification variables by analyses population (Section 3.5). • Throughout the document, replaced "subject" by "participant". • Analyses populations mITT, mITT1 and mITT2 populations were updated (Section 4). mITT analysis set added now includes participants who did not receive nor were expected to receive COVID-19 therapeutic mAb, and who were treated ≤3 days after COVID-19 symptom onset. • Changed analysis set for the primary efficacy analysis from mITT1 to mITT (Section 4). • Added sequential testing for efficacy secondary endpoints (Section 5.1). • Updated Section 5.2.2 to include the ANCOVA model or change from baseline to Day 5 of viral load data (POC analysis). • Added details on methods of handling missing data (Section 5.3). • Updated Section 6.1.1.1 due to the change in primary analysis. Two new sensitivity analyses were added as well. • Updated Section 6.1.1.2 on logistic regression analysis model. • Updated analyses populations for all secondary efficacy

			endpoints/analyses (Sections 6.2.3 up to 6.2.12). • Updated statistical methodology for three secondary efficacy endpoints (Section 6.2.5 and 6.2.8), logistic regression is used instead the previous KM methodology. • Added two subgroup analyses (by baseline serology status & baseline viral load) for two secondary endpoints (Section 6.2.4 and 6.2.5). • Updated Table of summary of efficacy analysis in Appendix 1 to reflect the protocol amendment changes in analyses populations, a new key secondary analysis of primary endpoint, POC analysis and logistic regression model as statistical analyses for three secondary efficacy endpoints previously analysed by KM method. • Table of summary of efficacy analyses in Appendix 1. • Appendix 1 changed analyses populations, as well as methodologies for secondary endpoints (ie. logistic regression for secondary endpoints). • Updated visit window for efficacy endpoints to Appendix 2. • Added Appendix 4 with list of adverse events of special interest. • Added Appendix 5 with list of Targeted signs/symptoms. As of DMC Blinded Data Review, dated 01Oct 2021 the following changes have been incorporated:

			• Clarified text for sustained alleviation analysis (Section 6.2.4). • Updated Section 6.2.5 categories labels for vomiting, diarrhea, sense of smell and sense of taste signs/symptoms. • Updated sections 6.2.5, 6.2.7,-6.2.8, 6.2.9 on statistical methodology for the logistic regression model. • Updated Section 6.2.11 to include a sensitivity analyses for change from baseline and Day 5 in viral load. These are the samples that will be used on the proof-of-concept (POC) analysis. • Updated Section 6.5.2 to reflect changes to disposition tables based on DMC blinded data reviews. • Clarified language regarding safety analyses (Section 6.6). • Updated Section 6.6.2 to include laboratory shift tables/analyses. • Section 7.1 has been updated and references the interim analysis plan SAP.
V1.2	3.0	To include an additional planned interim analysis for efficacy and futility to be done after approximately 70% of participants in the mITT analysis set complete the Day 28 assessments (ie, 28 days after randomization).	• Updated Section 2.3 with sample size increased from approximately 3000 to approximately 3100 due to addition of second interim analysis. • Updated Section 2.3 text to allow for a 5% dropout rate, enrollment will be stopped after approximately 1870 participants have been enrolled to ensure at least 1779 participants are available for the primary analysis. Current language matches language in protocol.

			• Changed sequential testing order for efficacy secondary endpoints (Section 5.1) to match protocol. • Updated Section 6.1.1.1 due to the addition of second interim analysis. • Updated Section 6.1.1.1 a new sensitivity analyses were added as well. • Clarification regarding the stratification variables specified on Section 3.5 was added to Sections 6.1.1.2, 6.2.4, 6.2.7 and 6.2.11. • Updated Section 7.1 text to include a second interim analysis. Interim analysis methodology was updated throughout the section. • Updated visit window for Day 34 for efficacy endpoints to Appendix 2. • To remove the second interim (70% interim that was added under amendment # 3) from the protocol because the objective of the planned 45% IA met. • To include the sensitivity analysis requested by FDA. • Updated to include additional analysis for severe targeted signs and symptoms of COVID-19. • Updated to included subgroup analysis for mITT & mITT1. • Due to limited number of participants enrolled in Brazil, Brazil region will combine with rest of the World region.

			• To include the sensitivity analysis excluding all participants from Site1470. • Updated to include the sensitivity analysis excluding all data from India Sites. • Updated the section of the sample size due to removal of second interim analysis.
V1.3	4.0		• Updated visit window for Day 34 for efficacy endpoints to Appendix 2. • To remove the second interim (70% interim that was added under amendment #3) from the protocol because the objective of the planned 45% IA met. • To include the sensitivity analysis requested by FDA. • Updated to include additional analysis for severe targeted signs and symptoms of COVID-19. • Updated to included subgroup analysis for mITT & mITT1. • Due to limited number of participants enrolled in Brazil, Brazil region will combine with rest of the World region. • To include the sensitivity analysis excluding all participants from Site1470. • Updated to include the sensitivity analysis excluding all data from India Sites.

			• Updated the section of the sample size due to removal of second interim analysis.
V1.4	4	To update the mITT, mITT1 and mITT2 population definition based on FDA request.	• Section 4 is updated to modify mITT, mITT1 and mITT2 populations as requested by FDA.
V1.5	4	To add additional efficacy analyses at Week 12 and Week 24 and additional analyses clarifications.	• Updated Section 6.2.5 by adding an additional analyses: Summary of Proportion of Participants with Any Signs/Symptoms Attributed to COVID-19 at Week 12 and Week 24. • Updated Section 6.2.9 to allow the possibility of cells with zero counts. • Updated/added more information for analysis sets in Section 4 handling duplicate enrollment for IA and PCD primary efficacy analyses. • Updated Appendix 1 with sensitivity analysis for IA and PCD primary efficacy analyses.

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 increased risk of progressing to severe illness.

2.1. Study Objectives, Endpoints, and Estimands

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

Secondary Efficacy Objective*: 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 increased 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 increased risk of progression to severe disease.*

2.1.1. Primary Estimand

The difference in proportions of patients experiencing COVID19 related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease (as defined in Section 5.1 in Protocol) who did not receive COVID-19 therapeutic mAb treatment, and were treated ≤3 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.

2.1.2. Secondary Estimands

The estimand associated with the key secondary efficacy objective is the difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease and who did not receive COVID-19 therapeutic mAb treatment. This will be estimated without regard to adherence to randomized treatment.

The estimand associated with the secondary efficacy objective regarding the duration and severity of signs and symptoms is the absolute difference in median time to sustained alleviation or resolution of symptoms for all nonhospitalized adult patients with COVID 19 who are at increased risk of progression to severe disease. This will be estimated irrespective of adherence to randomized treatment.

The hospitalization/death rate through Day 28 is considered the main clinical outcome measure and signs/symptom duration is considered key secondary for this study and so estimands for these measures are presented. Estimands for the other outcome measures that are considered supportive of the primary outcome measures and of the sign/symptoms duration and severity outcome measure are not presented.

2.2. Study Design

This Phase 2/3, randomized, double-blind, placebo-controlled study in approximately 2260 symptomatic participants with COVID-19 who are nonhospitalized 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 and ritonavir or placebo orally q12h for 5 days (10 doses total). Randomization will be stratified by geographic region and by whether participants have received/are expected to receive treatment with COVID-19 therapeutic mAbs based on the

site investigator's assessment at time of randomization. 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.

The total study duration is up to 24 weeks and includes a screening period of no more than 48 hours, 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 to ensure the safety of participants on an ongoing basis throughout the duration of the study, as specified in the E-DMC Charter. In addition to up to weekly reviews of safety, the E-DMC will review the following:

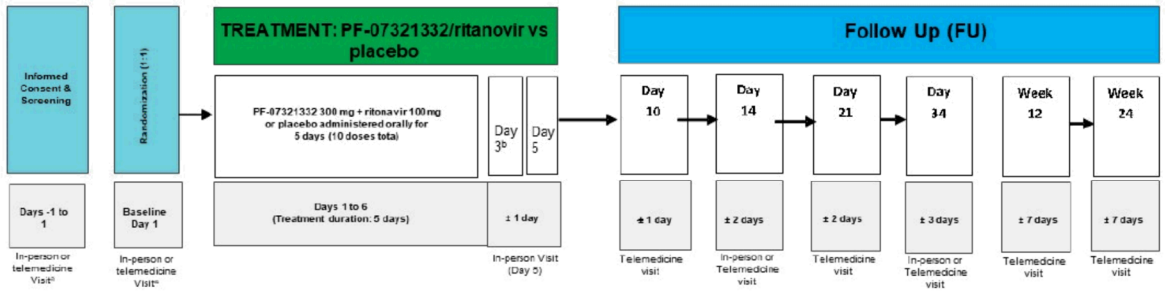
- *Sentinel cohort safety review: The E-DMC will review unblinded safety data after approximately the first 60 participants have completed Day 10 of the study, at which point enrollment will be paused pending E-DMC review of the safety data. After review of the sentinel cohort, the frequency of safety reviews may be reduced subsequently based on E-DMC recommendations.*

- *Proof-of-concept assessment: The E-DMC will review viral load data when approximately 200 participants in the primary analysis set with evaluable data 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.*

- *Formal interim analysis: A planned formal interim analysis for efficacy and futility with a sample size re-estimation will be done after approximately 45% of participants in the mITT analysis set complete the Day 28 assessments.*

Subsequent to the planned interim analyses, there will be 2 analyses for reporting the results of this study. The primary analysis will be performed after all participants have completed the Day 34 visit. The follow-up analysis will be performed after all participants have completed the Week 24 visit. The study schematic is provided in Figure 1.

Figure 1. C4671005 Study Design



a. The baseline and screening visits may be a combination of in-person and telemedicine visits.
b. The Day 3 visit should be conducted in-person for the first 60 participants (sentinel cohort) and thereafter only if a PK sample (not using Tasso) is collected by an HCP or if ECG is required.

2.3. Sample Size Determination

This study is designed to have 90% statistical power to show a difference of 3.5% in the proportion of participants hospitalized/dying that did not receive COVID-19 therapeutic mAb between the treatment arms (PF07321332/ritonavir versus placebo) and were treated ≤ 3 days after COVID-19 symptom onset, using a 2-sided Type I error rate of 5%. Based on the BLAZE study[2], the proportion of hospitalization/death in the placebo arm is assumed to be 7%.

Using EAST (Version 6.5) for a 2 sample proportion test[1], the sample size needed to detect a 3.5% difference with 90% power at a 2-sided significance level of 5% was determined to be 1717 randomized participants. Enrollment of participants who at baseline had received or were expected to receive COVID-19 therapeutic mAb treatment is estimated to be approximately 20% of participants and limited/capped to 25% enrollment.

Enrollment of participants-that had COVID-19 symptom onset >3 days prior to randomization is expected to be approximately 25% and will be limited to approximately 1000 participants. Assuming a 5% dropout rate, the total sample size for this study will be approximately 3000 participants.

To allow for a 5% dropout rate, enrollment will be stopped after approximately 1717 participants are available for the primary analysis.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

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

3.2. Secondary Endpoint(s)

- *The first key secondary efficacy endpoint is the proportion of participants with COVID-19 related hospitalization or death due to any cause through Day 28 in the mITT1 analysis set.*
- *Incidence of treatment emergent adverse events (TEAEs).*
- *Incidence of SAEs and AEs leading to discontinuations.*
- *Time (days) to sustained alleviation of all targeted signs/symptoms 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 signs/symptoms through Day 28.*

- *Duration of each targeted COVID-19 sign/symptom.*
- *Progression to a worsening status in 1 or more self reported COVID19 associated symptoms through Day 28.*
- *Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.*
- *Proportion of participants with death (all-cause) through Week 24.*
- *PF-07321332 PK in plasma and whole blood (if feasible).*
- *Viral titers measured via RT-PCR in nasal swabs over time.*
- Number of COVID-19 related medical visits.
- *Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization.*

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3.4. Baseline Variables

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. Laboratory assessments Signs and Symptoms, Vital Signs and ECG: Baseline window will be Day -2 to Day 1, without any consideration to the time factor.

The following baseline variables will be used in efficacy analyses. See below a list of derived baseline variables based on baseline viral load data:

- Baseline viral load defined as: $<10^4$ copies/mL vs $\geq 10^4$ copies/mL.
- Baseline viral load defines as: $<10^7$ copies/mL vs $\geq 10^7$ copies/mL.
- Baseline serology status defined as positive or negative.

3.5. Stratification Variables

Randomization will be stratified by geographic region and whether participants had received or were expected to receive COVID-19 therapeutic mAb treatment (yes/no) based on the site investigator's assessment at the time of randomization. Randomization for the strata where participants had received or were expected to receive COVID-19 therapeutic mAb treatment will be capped at a maximum of 25% enrollment. Unless otherwise indicated analyses will include calculated values for quantitative stratification variables. Geographical region is defined as follows:

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

If a region enrolled <10 participants, the region will be combined with the "rest f the word" region.

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

- mITT analyses will include the following stratification variables: Baseline viral load, baseline serology status, geographic region.
- mITT1 analysis will include: Baseline viral load, baseline serology status, geographic region and symptom onset days to first dose date (≤3 days, >3 days).
- mITT2 analyses will include: Baseline viral load, baseline serology status, geographic region, received or were expected to receive mAb treatment (yes/no) and symptom onset days to first dose date (≤3 days, >3 days).

3.6. Safety Endpoints

The safety endpoints of this study are:

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

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

3.6.1. 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 will be collected. Medication history of prescription or nonprescription drugs (including vaccinations), and dietary and herbal supplements taken within 30 days prior to the planned first dose will be collected.

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.
Modified Intent-To-Treat (mITT)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 onset. Participants will be analyzed according to the study intervention to which they were randomized.
Modified Intent-To-Treat 1 (mITT1)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, and who at baseline

Population	Description
	did not receive nor were expected to receive COVID-19 therapeutic mAb treatment. Participants will be analyzed according to the study intervention to which they were randomized.
Modified Intent-To-Treat 2 (mITT2)	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 to which 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.

For the primary efficacy analysis, the mITT set will be used and will be the primary analysis. A secondary analysis of the primary efficacy endpoint will be performed and will use mITT1 and mITT2 analysis set. For all other efficacy analyses mITT, mITT1, and mITT2 sets will be used (3 sets of analyses). The PP analysis set will be used in the analyses of primary efficacy endpoint. The Safety Analysis Set will be used in the analyses of the safety data.

For efficacy related analysis (mITT, mITT1 and mITT2), if a participant enters/is randomized into the study multiple times, a sensitivity analysis based on IA and PCD efficacy data will be conducted on the primary endpoint and all sensitivity analysis regarding primary endpoint. The data associated with first randomization will be included in the above sensitivity analyses conducted.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The primary hypothesis to be tested is whether or not there is a difference in proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 between PF-7321332/ ritonavir and placebo. The statistical hypothesis is as follows:

$$\left.\begin{array}{l} \text{Ho: } \pi_{\text{PF-7321332}} - \pi_{\text{placebo}} = 0 \\ \qquad \textit{versus} \\ \text{Ha: } \pi_{\text{PF-7321332}} - \pi_{\text{placebo}} \neq 0 \end{array}\right\} \qquad (1)$$

Where $p_{\text{PF-7321332}}$ and p_{placebo} are the proportion of participants with hospitalization or death through Day 28. The hypotheses will be tested at an overall significant level of 5% (2-sided).

Following the positive test of the primary endpoint, sequential testing will be performed for the following 2 secondary endpoints:

- Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 who did not receive COVID-19 therapeutic mAb treatment, regardless of their onset of COVID-19 related signs and symptoms.

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

The time to sustained alleviation of all targeted signs/symptoms through Day 28 will be tested first. If this test is positive, then will continue with second endpoint. The hypotheses will be tested at an overall level of 5% (2-sided).

Other secondary endpoints listed below will be subsequently tested following the Hochberg procedure[1]:

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

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

3. Number of COVID-19 related medical visits.

5.2. General Methods

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

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

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

5.2.1. Analyses for Binary Endpoints

For binary endpoints (ie, proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28, proportion of participants with severe targeted signs/symptoms attributed to COVID-19 through Day 28, worsening status in 1 or more self reported COVID19 associated targeted signs/symptoms through Day 28 and proportion of participants with death (all-cause) through Week 24), proportion of participant with the event will be summarized for each group. Treatment comparison between the group will be

presented as the difference of proportions with its 95% confidence intervals using a similar analysis method as the primary endpoints.

5.2.2. Analyses for Continuous Endpoints

For continuous endpoint, (ie, viral titers measured via RT-PCR in nasal swabs over time), an ANCOVA model will be used to analyze change from baseline (Day 1) to Day 5. 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.

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. Analyes for Count Endpoints

For count endpoints (ie. number of COVID-19 related medical visits and number of hospitalizations/ICU visits), 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

For time-to-event endpoints (ie, time (days) to sustained alleviation/resolution of all targeted signs/symptoms through Day 28 and duration of each targeted COVID-19 sign/symptom), 2 analyses may be provided: (1) a Cox proportional hazard regression model where the estimate of the hazard ratio for treatment (PF-07321332 vs Placebo), its confidence interval and p-value will be provided; and (2) Kaplan-Meier analysis where tabular summaries of the Kaplan-Meier curves providing the median and quartiles, will be provided for each treatment group. In addition, the KM curves will be presented graphically.

5.3. Methods to Manage Missing Data

For missing efficacy data other than time to event endpoints, a mixed baseline observation carried forward (BOCF)/ last observation carried forward (LOCF) approach will be used. See below:

- For efficacy endpoints related to COVID-19 targeted sign/symptoms, missing data at baseline will be treated as mild. If participant discontinues study due to AE or discontinues study at same time of treatment discontinuation due to lack of efficacy, missing data will use BOCF. Otherwise, missing data will use LOCF.

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

The estimand is then the difference of the proportions in the 2 treatment groups and its 95% confidence interval will be presented, as well as, the associated two-sample proportion test. For the 95% CI, the corresponding estimate of the standard error is computed using Greenwood's formula (Kalbfleisch and Prentice; 1980). 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 $S(t_i)$ we will use the log-log approach to CI. The 95% CI will be computed for the estimate of L(t)= log(-log(S(t))), the log hazard function.

$$Var\left(\hat{L}(t)\right) = Var\left[log\left(-log\left(\hat{S}(t)\right)\right)\right]$$

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

The above primary analysis will be conducted for the planned interim analyses as well. Two-sided 95% CI (adjusted for the planned interim analyses) and associated p-value (two-sample proportion test) for the null hypothesis of no difference between treatment groups will be presented. Significance level will be determined using the O'Brien-Fleming approach at the interim analysis and the final analysis. The overall significance level is set at 5% (2 sided).

For participants who complete Day 28 efficacy assessment (Day 34 visit), they will be censored at their last visits. For participants who discontinue before Day 28 assessment or are lost to follow-up, they will be censored at the last known date in the study.

Participants will be analysed under the mAb stratum assigned at randomization/baseline.

The proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 will be summarized graphically using Kaplan-Meier plots for each of the treatment groups, the analyses will be done using mITT, mITT1, and mITT2 populations.

The sensitivity analysis associated with primary endpoint will be conducted using the mITT2 population set. Four addditional sensitivity analysis for the primary endpoint will be performed:

- a sensitivity analysis excluding all data from India sites for the mITT population;
- a sensitivity analysis excluding all participants from Site 1470 for the mITT, mITT1 and mITT2 populations;
- a sensitivity analysis excluding participants from the sentinel cohort of the study treated with active treatment (3 doses of 100 mg) for the mITT population;
- An additional sensitivity analysis for participants with missing data (i.e., participant who was without any COVID-19 related hospitalization or death of any cause but discontinued from study due to lost to follow up and their last observations are <28 days) will be performed for the mITT population. The sensitivity analysis will implement the following event imputation methodology for those with missing data for primary endpoint:
    - 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 participant remains censored at day of last observed data.

6.1.1.2. Supplementary Analyses

Supplemental analyses will be performed to the primary efficacy endpoint. See below:

1. An analysis in the mITT analysis set of the primary endpoint where participants who received a therapeutic COVID-19 mAb treatment postbaseline will be considered as an event for the endpoint (in addition to COVID-19 related hospitalization and death due to any cause) with mAb treatment date as the time of event.
2. A logistic regression model will be fitted to the primary endpoint of hospitalization/death and will include treatment and region effect as independent variables. In addition the stratification variables specified in Section 3.5 will be added to the model analyses depending on the analysis population. Odds ratios, 95% CI and p-values will be summarized (p-values will be reported from main model likelihood ratio test). Additional analyses may be performed adjusting for baseline covariates (such as age, gender, etc.) as additive terms to the primary model, if necessary. For the primary endpoint, a model including main terms and interaction term for treatment and region will be fitted and p-value from the interaction term will be summarized.
3. A completers only analysis similar to the primary efficacy analysis will be conducted. Completers are mITT participants who have been in the study for at least 28 days, or any participant with COVID-19 related hospitalization or Death from any cause through Day 28.

4. An analysis associated with primary endpoint will be conducted using the per-protocol (PP) population set.

6.2. Secondary Endpoint(s)

6.2.1. Proportion of Participants with COVID-19 Related Hospitalization or Death due to All Cause through Day 28 in mITT1 Analysis Set

The proportion of participants with COVID-19 related hospitalization or death due to any cause through Day 28 in the mITT1 analysis set will be similar to the primary endpoint analysis.

6.2.2. 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.

6.2.3. 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.

6.2.4. Time (days) to Sustained Alleviation and Time to Resolution of Targeted COVID-19 Sign/Symptoms through Day 28

The time (days) to sustained alleviation and time to resolution will be defined for all targeted COVID-19 associated symptoms based on self-assessment.

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.

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.

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 with all targeted symptoms absent 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/resolution and will be censored at day 25.

Cox proportional hazard model analyses will be used for time to sustained symptom alleviation/resolution. Cox proportional hazard model will include treatment and region effect as independent variables. In addition, the stratification variables specified in Section 3.5 will be added to the model analyses depending of the analysis population.

Time to sustained symptom alleviation/resolution will be summarized graphically using Kaplan-Meier plots for each of the treatment groups, the analyses will be done using the mITT population only.

In the mITT populations, the analysis will be repeated in subgroups based on baseline serology status (positive, negative), by baseline viral load ($<10^4$ copies/mL, $\geq 10^4$ copies/mL), and ($<10^7$ copies/mL, $\geq 10^7$ copies/mL).

6.2.5. Proportion of Participants with Severe Signs/Symptoms Attributed to COVID-19 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 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. A participant with severe score for any targeted symptoms post-baseline will be counted as severe. Proportions for each targeted signs and symptom with severe category only will be plotted over time through Day 28. Additionally, the proportion of participants reporting the presence of each targeted sign and symptom that is mild, moderate or severe categories will also be presented. In addition, to understand the severity of signs/symptoms attributed to COVId-19, the following analysis will be performed:

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

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

3. Proportion of participants with any severe targeted signs/symptoms attributed to COVID-19 Day 7 to Day 28 (post treatment).

Treatment comparison between the group will be presented as odds ratio and 95% CI using logistic regression with a similar analysis model as specified in Section 6.1.1.2. The analyses will be done using mITT, mITT1, and mITT2 populations.

In the mITT population, the analysis will be repeated in subgroups based on baseline serology status (positive, negative), by baseline viral load ($<10^4$ copies/mL, $\geq 10^4$ copies/mL) and ($<10^7$ copies/mL, $\geq 10^7$ copies/mL).

An additional follow-up analysis for signs/symptoms data will be conducted at Week 12 and Week 24 for all signs/symptoms (not just targeted signs/symptoms, See Appendix 5). The Week 12 and Week 24 signs/symptoms data is collected from a long-term FU telemedicine interview performed by the site to participant and collected in CRF (diary data is not colected after Day 34).

The observed proportion of participants with any mild, moderate, and severe of all signs/symptoms attributed to COVID-19 at Week 12 and Week 24 will be summarized by treatment group and overall. Observed proportion of participants reporting the presence of each sign and symptom that is mild, moderate, or severe categories will also be summarized by treatment group and overall.

The analyses will be done using mITT, mITT1, and mITT2 populations.

6.2.6. Duration of Each Targeted COVID-19 Sign/Symptom through Day 28

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.

Duration of each targeted COVID-19 sign/symptom with a mild or worse severity will be summarized for each group within mITT, mITT1, and mITT2 populations.

For duration of each targeted COVID19 sign/symptom, a Kaplan-Meier analysis providing the median and quartiles will be provided for each treatment group for mITT population set. Two additional figures (Number of Participants and Median Time to Sustained Alleviation of Each Targeted Sign/Symptom by Treatment Group [mITT) will be included for the endpoint of Duration of Each Targeted COVID-19 Sign/Symptom.

6.2.7. 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 symptoms worsen 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% confidence intervals and P-value based on logistic regression model as specified in Section 6.1.1.2. The analyses will be done using mITT, mITT1, and mITT2 population. Missing severity at baseline will be treated as mild.

6.2.8. 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 the 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 table will be presented for both Day1 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 mITT, mITT1, and mITT2 populations. Missing data at Day 1 or Day 5 will be excluded from the analysis.

6.2.9. Proportion of Participants with Death (all-cause) Through Week 24

The proportion of participants with death (all-cause) through Week 24 will be summarized by treatment group. Treatment comparison between the group will be presented as odds ratio and its 95% CI using logistic regression with a similar analysis model as specified in Section 6.1.1.2. The analyses will be done using mITT, mITT1, and mITT2 populations.

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

As mortality is the most important of the efficacy at Week 24, this pertains specifically to that endpoint. If the impact s minimal (defined below), then no sensitivity analysis is required.

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

The PK analyses will be performed and summarized by the PK/PD group.

6.2.11. Viral Titers Measured via RT-PCR in Nasal Swabs Over Time

The viral load data measured in Day 1 and Day 5 are nasopharyngeal samples. These are the samples that will be used on the POC analysis. POC analysis of viral load data will occur when approximately 200 participants in the mITT 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 Log10 transformed viral load (copies/mL) data. The ANCOVA model will include treatment group, baseline viral load and baseline serology status. The mAb treatment (yes/no) as well as 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, and local (nonvalidated) swabs use. 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). In addition, a sensitivity analysis summaries will be performed excluding all data from India sites.

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. Sampling site (Nasopharyngeal or not) will be included as covariate in the model if applicable. The mAb treatment (yes/no) as well as symptom onset to first dose date (≤3 days, >3 days) will be used in the model 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 mITT, mITT1 and mITT2 populations.

In the mITT and mITT1 populations, the analysis will be repeated in subgroups based on baseline serology status (positive, negative), by baseline viral load ($<10^4$ copies/mL, $\geq 10^4$ copies/mL) and ($<10^7$ copies/mL, $\geq 10^7$ copies/mL).

To assess the association between baseline viral strain and primary endpoint, the proportion of participants with primary endpoint events will be summarized according to COVID-19 variants of concern and variants of interests.

6.2.12. Number of COVID-19 Related Medical Visits

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. The resulting analysis will show the difference in estimated rate of medical visits between treatment groups. The analyses will be done using mITT, mITT1, and mITT2 populations.

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

Health resource utilization data will be summarized by treatment group. This will include number (days) of hospital stay and number (days) of ICU stay. The analyses will be done using mITT, mITT1 ,and mITT2 populations. Descriptive statistics (ie, mean, median, range) will be used to summarize this endpoint.

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[redacted]

6.4. Subset Analyses

For the primary endpoint, forest plots for the following subgroups on mITT, mITT1 and mITT2) will be presented.

Subgroup analyses of the primary endpoint will include:

- age group (<65, >=65);
- Gender;
- Race;
- BMI category (<25, 25-29, ≥30);
- Baseline viral load (<10^4 copies/mL, ≥10^4 copies/mL) and (<10^7 copies/mL, ≥10^7 copies/mL);
- Baseline serology status (positive, negative);
- Number of baseline comorbidities present (0-1, 2-3, >=4);
- Viral strain/linage at Day 1 if appropriate;
- Present of any of these baseline comorbidities/risk factors:
  - Smoking (yes, no);
  - Diabetes mellitus;
  - Immunosuppression disorders (including use of corticosteroids, biologics or those undergoing chemotherapy);
  - Chronic lung disease requiring medication;
  - Hypertension (taking medications for hypertension);
  - Cardiovacular disorders;
  - Chronic kidney disease;
  - HIV Infection;
  - Sickle Cell Disease;
  - Neurodevelopmental Disorder;
  - Cancer;
  - Device Dependence.

For a particular risk factor to be summarized, a minimum of 100 subjects in risk group is required. The sub-group analysis will be performed for mITT and mITT1 populations.

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, 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 PPanalysis 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 4.

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.

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.

6.6.3. Vital Signs

The measurement taken immediately prior to start of study drug will be used as the baseline for calculating changes in vital signs.

All vital sign data will be descriptively summarized by treatment group within SAS population and reported in accordance with the Pfizer Data Standards for safety reporting.

6.6.4. Electrocardiograms

Central reader will provide the reading of all ECG parameters. Descriptive statistics will be provided for change from baseline to each measurement time for heart rate, PR interval, QRS width, QT interval and QTcF (Fridericia correction) values. Baseline will be defined as the mean of the pre-dose triplicates at the Baseline Visit. Additionally, the incidence of categorical increases in QTc intervals will be provided. Categories for QTcF are ≥450 msec, ≥480 msec, and ≥500 msec. Categories for QTcF as change from baseline are ≥30 msec increase and ≥60 msec increase. QTcF is considered the primary QTc value for measurements of change and for clinical decision making as this correction is more accurate with changes in heart rate.

7. INTERIM ANALYSES

7.1. Interim Analyses and Summaries

A planned interim analysis for efficacy and futility with a sample size-re-estimation will be conducted and reviewed by an independent E-DMC after approximately 45% overall participants have completed the Day 28 assessments in the mITT analysis set(ie, 28 days after randomization).

At the time of planning the Phase 2/3 study, there was uncertainty about the rate of COVID-19-related hospitalization or death in the primary analysis population, and about the treatment effect of PF-07321332. Hence, a sample size re-estimation will be conducted during the first interim analysis based on conditional power. The sample size can be adjusted one time and the increase will be capped at 30%. A well-established method described by

Cui, Hung, and Wang (1999)[1] (implemented in EAST 6.5) will be used to control the Type I error probability.[2]

The nominal significance level for theplanned interim and final proportion of hospitalization/death analyses is 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 will be used for decision making, ie, reject H0 with 2-sided p-value ≤0.002, or reject H1 with 2-sided p-value >0.924. The final p-value for rejecting H0 will be ≤0.049 (2-sided) or reject H1 with 2-sided p-value >0.049. The actual stopping boundaries will depend on the exact timing of the interim analysis. If the efficacy boundary is crossed at the interim analysis, a final analysis will be conducted as a supportive analysis.

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 the interim analysis SAP.

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.

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. However, a blinded study team will manage the completion of the study until all participants have completed the Week 24 visit (or ET prior to the Week 24 visit). The blinded team will be separate from the unblinded team.

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

8. REFERENCES

1. Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinicaltrials. Biometrics. 1999;55(3):853-7.

2. FDA. Food and Drug Administration Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics November 2019. Available from: https://www.fda.gov/media/78495/download. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance documents/ assessing-covid-19-related-symptoms- outpatient-adult-and-adolescent subjects-clinical-trials-drugs. Accessed on: 16 June 2021.

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 with COVID-19 related hospitalization or death from any cause through Day 28.	Primary Efficacy analysis	mITT	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 primary endpoint	mITT2	All data collected will be included regardless of intercurrent events. Kaplan-Meier method to take account of losses to follow-up.	Kaplan-Meier
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Sensitivity analysis for primary analysis	mITT	Analysis excluding all data from India sites and participants from Site 1470.	Kaplan-Meier method
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Sensitivity analysis for primary analysis	mITT	Analysis excluding all participants from Site 1470.	Kaplan-Meier method
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Sensitivity analysis for primary analysis	mITT	Analysis excluding participants from the sentinel cohort of the study treated with active treatment (3 doses of 100 mg).	Kaplan-Meier method
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Sensitivity analysis for primary analysis	mITT	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 participant remains censored at day of last observed data	Kaplan-Meier method
Proportion of participants with COVID-19 related	Supplemental analysis for primary analysis	mITT	All data collected will be included regardless of intercurrent events.	logistic regression model

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
hospitalization or death from any cause through Day 28.			Use stratification variables as in Section 3.5.	
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Supplemental analysis for primary analysis	Completers Analysis	Only data collected are 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.	Supplemental analysis for primary analysis	mITT	In the mITT population, participants that received a therapeutic COVID-19 mAb treatment post-baseline will be considered as an event for the endpoint (in addition to hospitalization and death due to any with mAb treatment date as the time of event). 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.	Primary Efficacy analysis	mITT including only data with first randomization	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 primary endpoint	mITT2 including only data with first randomization	All data collected will be included regardless of intercurrent events. Kaplan-Meier method to take account of losses to follow-up.	Kaplan-Meier
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Sensitivity analysis for primary analysis	mITT including only data with first randomization	Analysis excluding all data from India sites and participants from Site 1470.	Kaplan-Meier method
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Sensitivity analysis for primary analysis	mITT including only data with first randomization	Analysis excluding all participants from Site 1470.	Kaplan-Meier method

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Sensitivity analysis for primary analysis	mITT including only data with first randomization	Analysis excluding participants from the sentinel cohort of the study treated with active treatment (3 doses of 100 mg).	Kaplan-Meier method
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Sensitivity analysis for primary analysis	mITT including only data with first randomization	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 participant remains censored at day of last observed data.	Kaplan-Meier method
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Supplemental analysis for primary analysis	mITT including only data with first randomization	All data collected will be included regardless of intercurrent events. Use stratification variables as in Section 3.5.	logistic regression model
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Supplemental analysis for primary analysis	Completers Analysis including only data with first randomization	Only data collected are 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.	Supplemental analysis for primary analysis	mITT including only data with first randomization	In the mITT population, participants that received a therapeutic COVID-19 mAb treatment post-baseline will be considered as an event for the endpoint (in addition to hospitalization and death due to any with mAb treatment date as the time of event). 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.	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

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Subgroup Analysis for primary endpoint	mITT	Subset analysis identified in Section 6.4.	Kaplan-Meier method
Time to sustained alleviation and time to sustained resolution of all targeted signs/symptoms through Day 28.	Secondary analysis	mITT & mITT1 & mITT2	All data collected will be included regardless of intercurrent events. Missing severity at baseline will be treated as mild. Use stratification variables as in Section 3.5.	Cox proportional hazard model
Time to sustained alleviation of all targeted signs/symptoms through Day 28.	Subgroup Analysis of secondary endpoint	mITT	All data collected will be included regardless of intercurrent events. Missing severity at baseline will be treated as mild. Use stratification variables as in Section 3.5. Subset analysis by baseline serology status and baseline viral load.	Cox proportional hazard model
Time to sustained resolution of all targeted signs/symptoms through Day 28.	Subgroup Analysis of secondary endpoint	mITT	All data collected will be included regardless of intercurrent events. Missing severity at baseline will be treated as mild. Use stratification variables as in Section 3.5. Subset analysis by baseline serology status and baseline viral load.	Cox proportional hazard model
Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28.	Secondary analysis	mITT, mITT1 & mTT2	All data collected will be included regardless of intercurrent events. Use BOCF/LOCF for missing data. Use stratification variables as in Section 3.5.	~~Kaplan Meier method~~ Logistic regression

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28.	Subgroup Analysis of secondary endpoint	mITT	All data collected will be included regardless of intercurrent events. Use BOCF/LOCF for missing data. Use stratification variables as in Section 3.5. Subset analysis by baseline serology status and baseline viral load.	Logistic regression
Duration of each targeted COVID-19 sign/symptom.	Secondary analysis	mITT, mITT1 & mTT2	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Descriptive statistics
Progression to a worsening status in 1 or more self-reported COVID-19-associated symptoms through Day 28.	Secondary analysis	mITT, mITT1 & mTT2	All data collected will be included regardless of intercurrent events. Use BOCF/LOCF for missing data. Use stratification variables as in Section 3.5.	Logistic regression
Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.	Secondary analysis	mITT, mITT1 & mTT2	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
Proportion of participants with any signs/symptoms attributed to COVID-19 through Week 12 & Week 24.	Additional follow-up analysis	mITT, mITT1 & mITT2	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Descriptive Statistics
Proportion of participants with death (all cause) through Week 24.	Secondary analysis	mITT, mITT1 & mTT2	All data collected will be included regardless of intercurrent events. Missing data will not be imputed. Use stratification variables as in Section 3.5.	Logistic regression or Fisher Exact test (if appropriate)
Viral titers measured via RTPCR in nasopharyngeal samples at Day 1 and Day 5.	Sensitivity analysis (POC)	mITT, mITT1 & mTT2	All data collected will be included regardless of intercurrent events. Use baseline viral load (continuous).	ANCOVA analysis

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Viral titers measured via RT-PCR in nasal swabs over time.	Secondary analysis	mITT, mITT1 & mTT2	All data collected will be included regardless of intercurrent events. Use baseline viral load (continuous).	MMRM analysis
Number of COVID-19 related medical visits.	Secondary analysis	mITT, mITT1 & mTT2	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Descriptive statistics (based on negative Binomial Distribution)
Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization.	Secondary analysis	mITT, mITT1 & mTT2	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	Descriptive statistics

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 days, (ie, days 2 to 4)
4	Day 5	= Day 5, with a window of ±1 days, (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 and ECG: 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.

- Sign and symptom data at Week 12 & Week 24: No visit windowing will be applied. The nominal visits will be used.

Appendix 3. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse events of special interest
ANCOVA	analysis of covariance
BOCF	baseline observation carried forward
CDARS	Clinical Data Analysis and Reporting System
CI	confidence interval
ECG	electrocardiogram
E-DMC	external data monitoring committee
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration (United States)
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
ITT	intent-to-treat
MMRM	mixed-effects model with repeated measures
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per-protocol
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. 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

Appendix 5. COVID-19 Signs/Symptoms

Daily Sign and Symptom Collection	Entry Criterion #3 Targeted (used for study entry)	Daily Signs and Symptoms Collection	Targeted Symptom Analysis	Long Term Follow-Up
Cough	X	X	X	X
Shortness of Breath or difficulty breathing	X	X	X	X
Fever	X			X
Feeling Feverish		X	X	
Chills or shivering	X	X	X	X
Fatigue (low energy or tiredness)	X	X		X
Malaise				X
Muscle or Body Aches	X	X	X	X
Diarrhea (loose or watery stools)	X	X	X	X
Nausea (feeling like you wanted to throw up)	X	X	X	X
Vomiting (throw up)	X	X	X	X
Headache	X	X	X	X
Sore Throat	X	X	X	X
Stuffy or runny nose (Rhinorrhea)	X	X	X	X
Loss of smell		X		X
Loss of taste		X		X
Difficulty with concentration				X
Sleep disturbances				X
Heart palpitations				X
Other Symptoms				X