STATISTICAL ANALYSIS PLAN

ACTIV-2d/A5407

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, 24-WEEK STUDY OF THE CLINICAL AND ANTIVIRAL EFFECT OF S-217622 COMPARED WITH PLACEBO IN NON-HOSPITALIZED PARTICIPANTS WITH COVID-19

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V3.0 (Dated 13Mar2024) for Protocol ACTIV-2d/A5407. Shionogi updated V3.0 after IQVIA finalized V1.0 and V2.0.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1	25Jan2022	[redacted]	Not Applicable – No Authorized Version Yet
0.2	21Feb2022	[redacted]	No Authorized Version Yet. Updates made based on Sponsor review comments on v0.1 and to reflect changes between draft protocol dated 12Jan2022 and draft protocol dated 10Feb2022.
0.3	19Aug2022	[redacted]	No Authorized Version Yet. Updates made based on Sponsor review comments on v0.2, discussion at the IQVIA and Sponsor SAP Comments Review Meeting held on 25Mar2022, and changes in the protocol between draft protocol dated 10Feb2022 and final protocol dated 23Jun2022. Detailed descriptions of changes are not provided since there were significant changes to the study design and primary and key endpoints, and no statistical analysis or programming work has been started.
0.4	08Sep2022	[redacted]	No Authorized Version Yet. Updates made following Sponsor comments on v0.3 for the purpose of presenting the SAP to the DSMB for discussion. The key updates made were to Sections 4.3, 16.1.2 and Appendix 1.
0.5	19Oct2022	[redacted]	No Authorized Version Yet. Updates made at the request of the Sponsor following their discussions with the DSMB.

			Important updates are: a paragraph relating to sample size re-estimation in Section 4.2; information regarding efforts to reduce missing data in the *intermittent missing data* part of Section 16.1.2; addition of a corresponding sensitivity analysis in Section 16.1.4; and updates to Appendix 1 regarding rules for study termination due to efficacy being established at an interim analysis.
1.0	03Feb2023	[redacted]	No changes except the version number and date. Updated the version number from v0.5 to v1.0 to finalize for signatures.
1.1	31Mar2023	[redacted]	Updates made to reflect changes in Protocol version 5.0 compared to version 3.0. Significant changes are: Revised description of "low-risk" participants to "standard-risk" to reflect the current epidemiology; Revision of the definition and the analysis of sustained symptom resolution (primary efficacy endpoint outcome measure) as the first of 2 consecutive days (instead of 4 days) without symptoms using restricted mean symptom duration up to Day 28; Adjustment of the primary analysis set to only include those participants enrolled within 3 days of symptom onset (mITT set), and revised primary, secondary, and exploratory objectives/outcomes/estimands accordingly and in line with the protocol revisions; Addition of the mITT1 set (which includes participants regardless of time of enrollment

			relative to symptom onset) and Viral Culture set; Addition of 3 key secondary objectives, corresponding to the previous primary and key secondary objectives, to be analyzed using the mITT1 set; Movement of 3 exploratory objectives related to persistent symptoms and viral rebound to secondary objectives and added corresponding secondary endpoints and their analyses; Changes to the sample size to target 90% statistical power and adjust for a) participants enrolled before the protocol amendment with a symptom duration of 4 or 5 days prior to randomization, and b) non-GCP-compliant sites; Changes to interim analyses in that efficacy data will be reviewed but no formal analyses will be undertaken, and as such there are no stopping rules for efficacy and no alpha-spending prior to final analysis.
1.2	01Jun2023	[redacted]	Section 5 has been updated to note that "Analysis sets for this study will only include enrolled participants with GCP compliance." This statement will be clarified in a future version of this SAP; Updates to Section 7.5 to change the order of analyses for hierarchical testing; Section 9.1: replaced Time to discontinuation with a categorical analysis for the Day 1 to Day 29 period; Where applicable, for the Primary Analysis. data will summarized separately for both data

			through Study Day 29, and also on all available data (including data beyond Day 29); Updated definitions for persistent symptoms, clinical sequelae and viral rebound.
1.3	18Aug2023	[redacted]	Section 5 updated to add the provision that participants at sites with GCP non-compliance may (but not definitely) be excluded from analysis sets; In Section 10.1, a derivation has been added for age, and additional information on how to determine vaccination status; Section 16.1.3 updated to reflect that Study Day is being used in analyses, i.e., there is no Day 0 (Day 1 is the day of 1st dose of study intervention); Section 16.1.5 updated to mention study Day to be used for censoring and the tau to be used in the restricted mean regression analyses; Section 16.1.6, tests for subgroup by intervention interactions added; Section 16.2.13 and 16.2.3.13– return to pre-COVID health question added into these sections; Section 16.2.1.4 – rules for defining viral rebound updated to reflect latest Sponsor and FDA definitions; Sections 17.1.1.3 and 17.1.3.3 removed; Sections 16.2.1.16 and 16.2.3.16, updated to include relevant information from deleted Sections 17.1.1.3 and 17.1.3.3 that were not already included in Sections 16.2.1.13 and 16.2.3.13; Sections 16.2.1.14, 16.2.1.15, 16.2.3.14,

			16.2.3.15 updated to reflect that the endpoints is now defined as “from Day 6 to Day 29”, rather than “after Day 4 to Day 29”.
2.0	27Oct2023	[redacted]	Section 10.1 updated to note that the date of last dose can include booster dose when determining completion of primary series > or ≤ 3 months prior to enrolment; Section 16.1.3 updated to clarify the restricted mean duration analysis, including updating the tau to be used to 27, and reference to SAS PROC LIFETEST with bias correction option; Section 16.1.5 taus to be used updated to 28 and 25 respectively; Section 16.2.1.14 updated to clarify that this is two separate endpoints and the definition of worsening clinical symptoms was updated and supplementary analyses added to this section and Section 16.2.3.14; Section 16.2.1.15 – updated to clarify that this is two separate endpoints; and the definition of PCR based viral rebound was amended to use LLoQ+1 and LoD+1 rather than specific values; definitions of both PCR and culture based viral rebound were moved to this section from Section 16.2.1.14.
3.0	13Mar2024	[redacted]	Updates made to reflect changes in Protocol version 6.0. Significant changes include the key secondary objectives for the key secondary endpoint of the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 12;

			After programming preparation under blinded data, the analysis method of the key secondary analysis for change from baseline in log_{10} SARS-CoV-2 RNA at Day 4 was changed from the median regression to the ANCOVA because the former method was considered to work improperly with parameter estimates unsuccessfully converged. The median regression will be performed as a sensitivity analysis. Additional secondary objectives not specified in the protocol were added; One exploratory endpoint was added; Section 2.4.3 updated to include additional key secondary endpoint of the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 12; Two analysis sets of mITT2 and mITT3 are added; Section 6.1 updated to add the calculation of Study day of time in days from the start of study intervention until sustained resolution Section 7.5 updated to change the statistical hierarchy order by adding additional key secondary endpoint; Section 7.7 added to describe how to treat multiple records issue per day in patient diary;

			Section 7.8 added to describe how to treat multiple records issue within the analysis visit window at Week 12 or Week 24; Sections 16.1.3 and 16.1.6 added to describe how to address participant with resolution at Day 1. Section 16.1.4 added to describe the additional secondary Analysis of primary efficacy endpoint under mITT2 and mITT3; Sections 16.2.1.4 and 16.2.1.5 added to describe additional key secondary endpoint of the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 12; Sections 16.2.1.11 was added to describe the secondary endpoint of quantitative log_{10} SARS-CoV-2 viral culture in NP swab at Day 4 and Day 8; Section 16.2.1.16 added to describe secondary endpoint of the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 24; Section 16.2.1.16 added to describe additional endpoint of the proportion of participants who had at least one symptom and whose usual health (pre-COVID) had not returned at Week 12 and Week 24; Appendix 4a ii) is changed Section 16.2.2.1 updated to reflect how to impute value when LLoQ and/or ULoQ are

			measured and how to treat NPH and NAS results in the analysis. Section 16.2.3.4 added to describe the analysis method of the secondary endpoint of quantitative log_{10} SARS-CoV-2 viral culture in NP swab; Sections 16.2.3.5 and 16.2.3.6 updated to add supportive and supplemental analysis including Peto-Prentice's generalized Wilcoxon test and how to address participants with symptom resolution at Day 1; Section 16.2.3.10 added to describe the analysis method of quantitative log_{10} SARS-CoV-2 viral culture in NP swab; Section 16.2.3.18 added to describe the analysis method of the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 24; Section 16.2.3.19 added to describe the analysis method of the proportion of participants who had at least one symptom and whose usual health (pre-COVID) had not returned at Week 12 and Week 24; Appendix 4 a.ii is changed to exclude participants in which there is no data regarding targeted symptoms to be evaluated and death or hospitalization.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Class
BDRM	blinded data review meeting
BMI	body mass index
BP	bodily pain
BUN	blood urea nitrogen
C_{24hr}	concentration 24 hours after last dose
CI	confidence interval
COVID-19	coronavirus disease 2019; caused by SARS-CoV-2
CRP	C-Reactive protein
CSR	clinical study report
CV	coefficient of variation
DAIDS	Division of AIDS
DBP	diastolic blood pressure
DSMB	data and safety monitoring board
eCRF	electronic case report form
EQ-5D-5L	EuroQol–5 Dimensions–5 Levels
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GH	general health
HDL	high density lipoprotein
ITT	intent-to-treat
IV	intravenous
LLN	lower limit of normal (range)
LLoQ	lower limit of quantification
LoD	limit of detection
mAb	monoclonal antibody
MCAR	missing completely at random

Abbreviation	Term
MCH	mean corpuscular hemoglobin
MCS	mental component summary
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MH	mental health
mITT	modified intent-to-treat (set)
mITT1	modified intent-to-treat 1 (set)
NIAID	National Institute of Allergy and Infectious Diseases
NP	nasopharyngeal
PCR	Polymerase chain reaction
PCS	physical component summary
PD	pharmacodynamic
PF	physical functioning
PK	pharmacokinetics
PT	Preferred Term
RBC	red blood cells
RE	role emotional
RMST	restricted mean survival time
RND	all randomized participants (set)
RP	role physical
RSC	(DAIDS) Regulatory Support Center
SAE	serious adverse event
SAF	Safety Analysis set
SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
SBP	systolic blood pressure
SCR	all screened participants (set)
SD	standard deviation
SE	standard error
SF	social functioning
SF-36v2	Short Form 36 Health Survey Questionnaire, version 2
SOC	System Organ Class
SOE	Schedule of Evaluations
TEAE	treatment-emergent adverse event

Abbreviation	Term
TTE	time-to-event
ULN	upper limit of normal (range)
ULoQ	upper limit of quantification
VAS	visual analog scale
VC	Viral Culture (set)
VT	vitality
WBC	white blood cells
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy, safety and pharmacokinetic (PK) concentration data for Protocol ACTIV-2d/A5407. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on the final protocol Version 6.0 dated 25Oct2023.

Additional SAPs will be developed for Data Safety Monitoring Board (DSMB) analyses, and population PK analyses.

The analyses for endpoints associated with exploratory objectives will be described in an updated version of this SAP or in a separate SAP.

2. STUDY OBJECTIVES AND ESTIMANDS

The main intent of the study is to evaluate the efficacy of S-217622 vs. placebo among outpatient adults with mild and moderate coronavirus disease 2019 (COVID-19) starting intervention within 3 days of symptom onset. The study will be conducted in the setting of locally available standard-of-care COVID-19 treatment. High-risk and standard-risk participants will be analyzed together for the primary analysis and separately for subgroup analyses. The primary efficacy objectives will be addressed in the modified intent-to-treat (mITT) set (see Section 5.3), which includes those participants starting intervention within 3 days of symptom onset. Key secondary objectives will be analyzed using the mITT set, and the mITT1 set which includes participants regardless of the time to enrollment relative to symptom onset. Other secondary and exploratory objectives will mainly be addressed using the mITT set, and some will be analyzed using mITT1. Selected analyses will also be undertaken on the mITT2 set, which includes those participants starting intervention within 3 days of symptom onset and who are baseline PCR positive, or the mITT2 set, which includes those participants starting intervention and baseline PCR positive regardless of the time to enrollment relative to symptom onset. The safety analyses will be analyzed in the Safety Analysis set, viral culture endpoints will be analyzed in the Viral Culture set and PK endpoints will be analyzed in the PK set.

2.1. Primary Objective

The primary objective is to determine if S-217622 will reduce the time to sustained symptom resolution through

Day 29 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.

Time to sustained symptom resolution is defined as the time from start of study intervention to the first day of 2 consecutive days with complete resolution of COVID-19 symptoms on participant self-assessment AND alive and without hospitalization for any reason by Day 29 and will be compared using restricted mean symptom duration up to Day 28, which is the last timepoint at which the outcome can be achieved. Hospitalization is defined as ≥24 hours of acute care, in a hospital or similar acute care facility, including emergency rooms, urgent care clinics, or facilities instituted to address medical needs of those with COVID-19.

2.2. Secondary Objectives

The key secondary objectives are:

- To determine the effect of S-217622 compared with placebo on the change from baseline in quantitative $\log_{10}$ severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) RNA levels by polymerase chain reaction (PCR) on nasopharyngeal (NP) swab at Day 4 among outpatient adults with SARS-CoV-2 starting intervention within 3 days of symptom onset.
- To determine whether S-217622 reduces COVID-19-related hospitalization (adjudicated) and all deaths regardless of occurrence outside of hospital or during hospitalization (not adjudicated) through Day 29 among outpatient adults with SARS-CoV-2 starting intervention within 3 days of symptom onset.
- To determine if S-217622 will reduce the time to sustained symptom resolution through Day 29 among all outpatient adults with SARS-CoV-2.
- To determine the effect of S-217622 compared with placebo on the change from baseline in quantitative $\log_{10}$ SARS-CoV-2 RNA levels by PCR on NP swab at Day 4 among all outpatient adults with SARS-CoV-2.
- To determine whether S-217622 reduces COVID-19-related hospitalization (adjudicated) and all deaths regardless of occurrence outside of hospital or during hospitalization (not adjudicated) through Day 29 among all outpatient adults with SARS-CoV-2
- To determine the effect of S-217622 compared with placebo on the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 12 among outpatient adults with SARS-CoV-2 starting intervention within 3 days of symptom onset.

- To determine the effect of S-217622 compared with placebo on the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 12 among all outpatient adults with SARS-CoV-2.

Other secondary objectives are:

- To determine if S-217622 will reduce the time to sustained symptom resolution through Day 29 based on assessments for 2 consecutive days of 6 targeted symptoms (nasal obstruction or congestion, nasal discharge, sore throat, cough, feeling feverish, and fatigue), among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine if S-217622 will reduce the time to sustained symptom resolution through Day 29 based on assessments for 2 consecutive days of all targeted symptoms excluding loss of taste and smell, among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine if S-217622 will decrease the proportion of participants with detectable SARS-CoV-2 by viral culture (unless viral culture is specified not to be performed at the investigative site) on NP swab at Day 4 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore differences between S-217622 and placebo in time to sustained symptom resolution through Day 29 among subgroups, including by high-risk vs. standard-risk at enrollment, by COVID-19 vaccination status, by receipt of COVID-19 treatments, and by time from symptom onset at enrollment among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore differences between S-217622 and placebo in the proportion of participants with detectable SARS-CoV-2 by viral culture from NP swab at Day 4 among subgroups, including by high-risk vs. standard-risk at enrollment, by COVID-19 vaccination status, by receipt of COVID-19 treatments, and by time from symptom onset at enrollment among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine whether S-217622 reduces all-cause hospitalization and all deaths through Day 29 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine if S-217622 will decrease the proportion of participants with detectable SARS-CoV-2 by viral culture from NP swab at Day 8 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine the efficacy of S-217622 to increase the proportion of participants with NP SARS-CoV-2 RNA

levels by quantitative PCR below the lower limit of quantification (LLoQ) on Days 4 and 8 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.

- To determine whether S-217622 reduces levels of SARS-CoV-2 RNA by quantitative PCR in NP swabs from participants on Days 4 and 8 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine whether S-217622 results in a shorter time to return to pre-COVID-19 health compared with placebo through Day 29 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To evaluate the efficacy of S-217622 compared with placebo based on the assessment of symptoms using the World Health Organization (WHO) ordinal scale (1-8) among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine the efficacy of S-217622 to maintain pulse oximetry measurement of ≥96% through Day 29 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine the prevalence, severity, and types of persistent symptoms and clinical sequelae in participants through end-of-study follow-up (Week 24) among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine the prevalence, severity, and types of persistent symptoms and clinical sequelae in participants through end-of-study follow-up (Week 24) among outpatient adults with mild and moderate COVID-19 in all participants.
- To determine the frequency of symptomatic viral rebound, defined as an increase in quantitative NP SARS-CoV-2 viral culture or NP SARS-CoV-2 RNA levels by quantitative PCR after Day 4 up to Day 29 in the setting of new or worsening clinical symptoms, in both study groups among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine the frequency of symptomatic viral rebound, defined as an increase in quantitative NP SARS-CoV-2 viral culture or NP SARS-CoV-2 RNA levels by quantitative PCR after Day 4 up to Day 29 in the setting of new or worsening clinical symptoms, in both study groups among all outpatient adults with mild and moderate COVID-19.
- To determine the frequency of viral rebound in both treatment groups, defined as an increase in quantitative NP

SARS-CoV-2 viral culture or NP SARS-CoV-2 RNA levels by quantitative PCR after Day 4 up to Day 29 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.

- To determine the frequency of viral rebound in both treatment groups, defined as an increase in quantitative NP SARS-CoV-2 viral culture or NP SARS-CoV-2 RNA levels by quantitative PCR after Day 4 up to Day 29 among all outpatient adults with mild and moderate COVID-19.
- To evaluate the safety of S-217622.
- To explore measures of psychological health, functional health and health related quality of life in participants through end of study follow-up (Week 24) among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine whether S-217622 reduces death due to any cause through end of study follow-up (Week 24).
- To determine the PK of S-217622.

Additional secondary objectives (Not specified in the protocol)

- To determine if S-217622 will reduce the time to sustained symptom resolution through Day 29 based on assessments for 2 consecutive days of 15 targeted symptoms, among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset and baseline PCR positive.
- To determine if S-217622 will reduce the time to sustained symptom resolution through Day 29 based on assessments for 2 consecutive days of 15 targeted symptoms, among outpatient adults with mild and moderate COVID-19 and baseline PCR positive.
- To determine if S-217622 will reduce the time to sustained symptom resolution through Day 29 based on assessments for 2 consecutive days of 15 targeted symptoms, among outpatient adults with mild and moderate COVID-19 starting intervention within 2 days of symptom onset.
- To determine if S-217622 will reduce the time to sustained symptom resolution through Day 29 based on assessments for 1 consecutive days of 6 targeted symptoms, among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine if S-217622 will reduce the time to sustained symptom resolution through Day 29 based on assessments for 1 consecutive day of 6 targeted symptoms, among outpatient adults with mild and moderate

COVID-19 starting intervention within 2 days of symptom onset.

- To determine if S-217622 will reduce the time to sustained symptom resolution through Day 29 based on assessments for 2 consecutive days of all targeted symptoms excluding loss of taste and smell, among outpatient adults with mild and moderate COVID-19 starting intervention within 2 days of symptom onset.

2.3. Exploratory Objectives

The exploratory objectives are:

- To evaluate whether S-217622 reduces a COVID-19 Severity Ranking Scale score based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death through Day 29 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore the impact of S-217622 on participant-reported rates of new SARS-CoV-2 positivity of household contacts through Day 29 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore whether baseline and follow-up laboratory markers are associated with clinical and virologic outcomes in relation to S-217622 use among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore baseline and emergent viral resistance to S-217622 through Day 16 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore differences between S-217622 and placebo in NP SARS-CoV-2 RNA levels among subgroups, including by high-risk vs. standard-risk at enrollment, by COVID-19 vaccination status, by receipt of COVID-19 treatments, and by time from symptom onset at enrollment among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore possible predictors of outcomes including death and hospitalization across the study population, including by time from symptom onset, symptoms at baseline, sex at birth, demographic characteristics, geographic region and vaccination status among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore and develop a model for the interrelationships between virologic outcomes and clinical outcomes in each study group among outpatient adults with mild and moderate COVID-19 starting intervention within 3

days of symptom onset.

- To explore the association between viral genotypes and phenotypic susceptibility to S-217622 and clinical outcomes and virologic response to S-217622 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore relationships between exposure of S-217622 with laboratory markers and clinical outcomes among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To evaluate the safety of S-217622 in the high-risk and standard-risk subpopulations.
- To explore differences between S-217622 and placebo in death due to any cause through end of study follow-up (Week 24) in the high-risk and standard-risk subpopulations.
- To explore differences between S-217622 and placebo to reduce levels of SARS-CoV-2 RNA by quantitative PCR in NP swabs from participants on Days 4 and 8 among participants who have a positive culture at baseline among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore differences between S-217622 and placebo for Week 12 and 24 endpoints evaluated by a positive response to "return to normal health."

2.4. Estimands

2.4.1. Primary Estimand Description

The difference in restricted mean symptom duration up to Day 28 among outpatient adults with SARS-CoV-2 starting treatment within 3 days of symptom onset. Restricted mean symptom duration up to Day 28 will be used to compare time (days) from start of intervention (S-217622 vs. placebo) until sustained resolution based on assessments for 2 consecutive days of targeted symptoms meeting the requirements for the endpoint (see Section 16.1.1) and being alive and not hospitalized for any reason by Day 29 among high-risk and standard-risk outpatient adults with SARS-CoV-2 starting intervention within 3 days of symptom onset.

2.4.2. Key Secondary Virologic Estimands Description

- Difference in medians will be used to compare change from baseline in $\log_{10}$ SARS-CoV-2 RNA at Day 4 for

S-217622 vs. placebo among high-risk and standard-risk outpatient adults with SARS-CoV-2 starting intervention within 3 days of symptom onset.

- Difference in medians will be used to compare change from baseline in $\log_{10}$ SARS-CoV-2 RNA at Day 4 for S-217622 vs. placebo among outpatient adults with SARS-CoV-2 in all high-risk and standard-risk outpatient adults with SARS-CoV-2.

2.4.3. Key Secondary Clinical Estimands Description

- A risk ratio will be used to compare the cumulative probability of hospitalization (adjudicated) or death from Days 1 to 29 for S-217622 vs. placebo among high-risk and standard-risk outpatient adults with SARS-CoV-2 starting intervention within 3 days of symptom onset.
- The difference in restricted mean symptom duration up to Day 28 in all high-risk and standard-risk outpatient adults with SARS-CoV-2. Restricted mean symptom duration up to Day 28 will be used to compare time (days) from start of intervention (S-217622 vs. placebo) until sustained resolution based on assessments for 2 consecutive days of targeted symptoms meeting the requirements for the endpoint (see Section 16.1.1) and being alive and not hospitalized for any reason by Day 29 in all high-risk and standard-risk outpatient adults with SARS-CoV-2.
- A risk ratio will be used to compare the cumulative probability of hospitalization (adjudicated) or death from Days 1 to 29 for S-217622 vs. placebo in all high-risk and standard-risk outpatient adults with SARS-CoV-2.
- A risk ratio will be used to compare the proportion of participants with the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 12 among outpatient adults with SARS-CoV-2 starting intervention within 3 days of symptom onset.
- A risk ratio will be used to compare the proportion of participants with the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 12 among all outpatient adults with SARS-CoV-2

The primary, and key secondary objectives and the components of the estimands to support regulatory decisions are described in Table A:

Table A: Objectives and Estimand Components

Objective	Estimand
Primary	
To determine if S-217622 will reduce the time to sustained symptom resolution through Day 29 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset. Time to sustained symptom resolution is defined as the time from start of study intervention to the first day of 2 consecutive days with complete resolution of COVID-19 symptoms on participant self-assessment AND alive and without hospitalization for any reason by Day 29.	**Treatment condition:** The randomized intervention (S-217622 or placebo) plus any locally provided standard-of-care, including COVID-19 monoclonal antibody (mAb) treatment, outpatient intravenous (IV) remdesivir, and oral antivirals
	Population: High-risk and standard-risk outpatient adults with SARS-CoV-2 starting study intervention within 3 days of symptom onset
	Variable (endpoint): Time (days) from start of S-217622 or placebo (Day 1) until sustained symptom resolution for participants alive and never hospitalized by Day 29 based on assessments for 2 consecutive days of targeted symptoms meeting the requirements for the endpoint (see Section 16.1.1)
	Intercurrent event handling: Participants who are hospitalized for any cause or die from any cause during the 29-day period will be classified as not achieving sustained symptom resolution and will be censored at Day 28. Treatment policy strategy (see Section 7.4) will be used to evaluate intervention effects irrespective of all other intercurrent events (e.g., irrespective of whether a participant received all doses of S-217622/placebo, mAbs, molnupiravir, outpatient IV remdesivir, favipiravir, fluvoxamine, convalescent plasma, or any other antiviral medications)
	Summary measure: Difference in restricted mean symptom duration (S-217622 group minus placebo group) up to Day 28

Key Virologic Secondary (The below describes two estimands, which only differ in terms of population)	
To determine the effect of S-217622 compared with placebo on the change from baseline in quantitative log_{10} SARS-CoV-2 RNA levels by PCR on NP swab at Day 4.	**Treatment condition:** The randomized intervention (S-217622 or placebo) plus any locally provided standard-of-care, including COVID-19 mAb treatment, outpatient IV remdesivir, and oral antivirals
	Population: a) High-risk and standard-risk outpatient adults with SARS-CoV-2 starting study intervention within 3 days of symptom onset b) All high-risk and standard-risk outpatient adults with SARS-CoV-2
	Variable (endpoint): Change from baseline in quantitative log_{10} SARS-CoV-2 RNA level by PCR on NP swab at Day 4
	Intercurrent event handling: Participants who are hospitalized for any cause or die from any cause prior to providing a Day 4 sample, but for whom a baseline sample is available, will have their change from baseline to Day 4 imputed as the worst change in RNA observed in those participants for whom a change can be calculated. Treatment policy strategy (see Section 7.4) will be used to evaluate intervention effects irrespective of all other intercurrent events (e.g., irrespective of whether a participant received all doses of S-217622/placebo, mAbs, molnupiravir, outpatient IV remdesivir, favipiravir, fluvoxamine, convalescent plasma, or any other antiviral medications)
	Summary measure: Difference (S-217622 minus Placebo group) in mean change from baseline in quantitative log10 SARS-CoV-2 RNA level by PCR on NP swab at Day 4

Key Clinical Secondary (The below describes two estimands, which only differ in terms of population)	
To determine whether S-217622 reduces COVID-19-related hospitalization (adjudicated) and all deaths regardless of occurrence outside of hospital or during hospitalization (not adjudicated) through Day 29 Hospitalization is defined as ≥24 hours of acute care, in a hospital or similar acute care facility, including emergency rooms, urgent care clinics, or facilities instituted to address medical needs of those with COVID-19.	**Treatment condition:** The randomized intervention (S-217622 or placebo) plus any locally provided standard-of-care, including COVID-19 mAb treatment, outpatient IV remdesivir, and oral antivirals
	Population: a) High-risk and standard-risk outpatient adults with SARS-CoV-2 starting study intervention within 3 days of symptom onset b) All high-risk and standard-risk outpatient adults with SARS-CoV-2
	Variable (endpoint): The proportion of COVID-19 participants with related hospitalization (adjudicated) or death due to any cause regardless of occurrence outside of hospital or during hospitalization (not adjudicated) during the 29-day period from and including the day of the first dose of S-217622 or placebo. Hospitalization is defined as ≥24 hours of acute care, in a hospital or similar acute care facility, including emergency rooms, urgent care clinics or facilities instituted to address medical needs of those with COVID-19
	Intercurrent event handling: Treatment policy strategy (see Section 7.4) will be used to evaluate intervention effects irrespective of intercurrent events (e.g., irrespective of whether a participant received all doses of S-217622/placebo, mAbs, molnupiravir, outpatient IV remdesivir, favipiravir, fluvoxamine, convalescent plasma, or any other antiviral medications)
	Summary measure: Risk ratio (S-217622 divided by placebo group) of cumulative probability of death or COVID-19-related hospitalization over 29 days

Key Clinical Secondary (This estimand is the same as the primary estimand except for the population)	
To determine if S-217622 will reduce the time to sustained symptom resolution through Day 29 among all outpatient adults with SARS-CoV-2 Time to sustained symptom resolution is defined as the time from start of study intervention to the first day of 2 consecutive days with complete resolution of COVID-19 symptoms on participant self-assessment AND alive and without hospitalization for any reason by Day 29.	**Treatment condition:** The randomized intervention (S-217622 or placebo) plus any locally provided standard-of-care, including COVID-19 monoclonal antibody (mAb) treatment, outpatient intravenous (IV) remdesivir, and oral antivirals
	Population: All high-risk and standard-risk outpatient adults with SARS-CoV-2
	Variable (endpoint): Time (days) from start of S-217622 or placebo (Day 1) until sustained symptom resolution for participants alive and never hospitalized by Day 29 based on assessments for 2 consecutive days of targeted symptoms meeting the requirements for the endpoint (see Section 16.1.1)
	Intercurrent event handling: Participants who are hospitalized for any cause or die from any cause during the 29-day period will be classified as not achieving sustained symptom resolution and will be censored at Day 28. Treatment policy strategy (see Section 7.4) will be used to evaluate intervention effects irrespective of all other intercurrent events (e.g., irrespective of whether a participant received all doses of S-217622/placebo, mAbs, molnupiravir, outpatient IV remdesivir, favipiravir, fluvoxamine, convalescent plasma, or any other antiviral medications)
	Summary measure: Difference in restricted mean symptom duration (S-217622 group minus placebo group) up to Day 28

Additional information on the handling of missing data for the endpoints of these estimands is described in Sections 16.1.2 and 16.2.2.

Key Clinical Secondary (The below describes two estimands, which only differ in terms of population)	
To determine the effect of S-217622 compared with placebo on the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 12 based on participants' assessments of the 5 symptoms specified by the WHO plus taste disturbance and smell disturbance The occurrence of persistent and/or late-onset symptoms of COVID-19 is defined if either 1 of the following criteria is met: · Occurrence of at least 1 of the following symptoms at Week 12: difficulty with concentration/thinking, difficulty reasoning/solving problems, or memory loss, or · Occurrence of at least 1 of the following symptoms at both the final evaluation time point in the Study Diary (e.g., Day 29) and Week 12: fatigue, shortness of breath/difficulty breathing, taste disturbance, or smell disturbance (i.e., persistent symptoms)	**Treatment condition:** The randomized intervention (S-217622 or placebo) plus any locally provided standard-of-care, including COVID-19 mAb treatment, outpatient IV remdesivir, and oral antivirals **Population:** a) High-risk and standard-risk outpatient adults with SARS-CoV-2 starting study intervention within 3 days of symptom onset b) All high-risk and standard-risk outpatient adults with SARS-CoV-2 **Variable (endpoint):** The proportion of participants with the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 12 **Intercurrent event handling:** Treatment policy strategy (see Section 7.4) will be used to evaluate intervention effects irrespective of intercurrent events (e.g., irrespective of whether a participant received all doses of S-217622/placebo, mAbs, molnupiravir, outpatient IV remdesivir, favipiravir, fluvoxamine, convalescent plasma, or any other antiviral medications) **Summary measure:** Risk ratio (S-217622 divided by placebo group) of proportion of participants with the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 12

3. Study Design

3.1. General Description

ACTIV-2d/A5407 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of S-217622 for the treatment of symptomatic high-risk and standard-risk non-hospitalized adults with SARS-CoV-2 infection.

A total of approximately 2000 participants who meet the enrollment criteria will be randomized 1:1 to S-217622 or placebo using permuted block randomization.

Randomization will be stratified by geographic region (North America, South America, Europe, Africa, Asia) and by participant risk status (high-risk or standard-risk) for severe COVID-19.
Only standard-risk participants will be enrolled at sites in the United States.

Participants will be randomized to receive 1 of the following 2 regimens:

- S-217622 at a dose of 375 mg (3 tablets) for Day 1 and 125 mg (1 tablet) for Days 2 to 5 once daily

OR

- Placebo for S-217622 administered once daily for 5 days (Days 1 to 5 [3 tablets on Day 1 and 1 tablet on Days 2 to 5]).

S-217622 will be evaluated for safety, as well as for activity in reducing all cause hospitalization and death, SARS-CoV-2 viral titer by culture and RNA levels, and time to symptom improvement and resolution through study Day 29, as compared to placebo control.

The entire study duration for participants is up to 24 weeks after randomization.

3.2. Schedule of Evaluations

The schedule of evaluations (SOE) can be found in Table 6.1-1 of the protocol.

3.3. Sample Size

This Phase 3 study is designed to evaluate the efficacy of S-217622 to reduce the time to sustained symptom resolution through Day 29 in outpatient adults diagnosed with COVID-19 compared with those receiving placebo. The primary analysis will focus on the primary outcome measure of the time (days) from the start of intervention until sustained symptom resolution based on assessments of 2 consecutive days of targeted symptoms and being alive and not hospitalized for any reason by Day 29 in high-risk and standard-risk outpatient adults with SARS-CoV-2 starting treatment within 3 days of symptom onset.

A total of 791 evaluable participants per treatment group (1582 total) is required to provide 90% power at the 5% two-sided significance level to detect a difference in restricted symptom duration of 1.5 days in participants who are enrolled within 3 days of symptom onset, based on a restricted mean symptom duration of 13.4 days on placebo, a generalized gamma distribution, and tau=27 (Day 28 is the last point at which sustained symptom resolution can commence and Day 1 is the first day symptoms are recorded). A restricted mean symptom duration of 13.4 days on placebo and a generalized gamma distribution is consistent with data observed in the Phase 3 part of Study 2108T1221.

Allowing for a 5% loss to follow-up, a total of 833 evaluable participants per treatment group (1666 total) who are enrolled within 3 days of symptom onset is required. Additionally, previous versions of the protocol allowed participants to be enrolled >3 days from symptom onset. To allow for these participants, who will not be part of the primary analysis population, a total of approximately 2000 participants will be enrolled into the trial. This assumes that approximately 334 (17%) of participants will be enrolled >3 days from symptom onset.

Participants who are not evaluable as part of the primary analysis population due to Good Clinical Practice violations may be replaced.

3.4. Changes to Analysis from Protocol

- The protocol-defined secondary endpoints of *Symptomatic Viral Rebound after Day 4 up to Day 29 With New or Worsening Clinical Symptoms* (protocol Section 10.3.3.11) and *Viral Rebound after Day 4 up to Day 29 With New or Worsening Clinical Symptoms* (protocol Section 10.3.3.12) have been updated in this SAP to be *Symptomatic Viral Rebound from Day 6 up to Day 29 With New or Worsening Clinical Symptoms* and *Viral Rebound from Day 6 up to Day 29*. The change from "after Day 4" to "from Day 6" reflects footnote a of Table 6.1-1 of the protocol, where the emphasis is on post-treatment viral rebound (with study intervention not

planned to end until Day 5): "*incidence of post-treatment viral rebounds from Days 6 through 29*". For the second endpoint, the removal of "*With New or Worsening Clinical Symptoms"* has been done to distinguish the endpoint from the *"symptomatic"* version of the endpoint, and to align with protocol Sections 1.3.17 and 1.3.18).

- In the protocol (Section 10.8.2.1), the key secondary endpoint of the change from baseline in quantitative $\log_{10}$ SARS-CoV-2 RNA levels by PCR on NP swab at Day 4 was planned to be analysed using median regression, with $\log_{10}$ SARS-CoV-2 RNA values below the LLoQ at baseline to be set as equal to the LLoQ, and those at post-baseline timepoints to be censored. However, an assessment of the blinded data set using SAS QUANTLIFE suggested that the model may not converge or provide estimable parameter values that are required to interpret the results. Therefore, the alternative approach of using ANCOVA will be applied to the key secondary endpoint. Median regression will be performed as a sensitivity analysis if the model converges.
- Some new secondary objectives not specified in the protocol and associated analyses have been added.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Interim Analyses/DSMB meetings.
- Primary Analysis.
- Final Analysis.
- Exploratory Analysis.

4.1. Data and Safety Monitoring Board

A National Institute of Allergy and Infectious Diseases (NIAID)-appointed DSMB will conduct reviews of safety data at 25%, 50% and 75% enrolment (followed through Day 29 of the study) and otherwise at a frequency recommended by the DSMB. An interim review may also be convened if a concern is identified by the Division of AIDS (DAIDS) clinical representative or IQVIA™ Clinical Representative, the study chairs, or study statistician in consultation with the team.

The DSMB will review any death deemed related to study product or Grade 4 serious adverse events (SAEs) in 2

study participants that occur on study deemed related to study product, as determined by the investigator. Detailed plans for study monitoring are outlined in the Monitoring Plan developed prior to enrollment of the first participant.

Refer to the DSMB Charter for more details about the DSMB composition, responsibilities, meeting frequency, etc.

A DSMB SAP, describing the methodology and the presentation of and access to results will be provided by IQVIA as a separate document.

The IQVIA study team, including those responsible for creating the programs to produce the outputs for the DSMB data review meetings, will remain blinded. Once the programs have been produced by the IQVIA study team, these programs will be sent to an independent group, who will apply the randomization schedule and provide the DSMB members with a set of unblinded outputs.

All available appropriate follow-up data will be reviewed at each of these DSMB data review meetings. Where appropriate, derivations and definitions for the DSMB reviews of safety will be based on those required for the safety endpoints contained in this SAP. Any additions or deviations from this SAP, required for the interim analyses, will be covered in the DSMB SAP. The list of the unblinded personnel will be documented in an Unblinding Plan, which will be finalized before the data cut-off for the first DSMB data review meeting.

Further details of distribution of unblinded information for the DMSB will be included in an unblinding plan, separate to this SAP.

4.2. Interim Analyses

Three interim analyses of safety data will coincide with the DSMB reviews of safety data when 25%, 50% and 75% of the planned enrollment has been completed and followed through Day 29 or discontinued the study (or on a frequency as otherwise recommended by the DSMB), the results of which will be based on unblinded intervention groups. Summaries of symptom outcomes will also be provided to the DSMB at 50% and 75% of the planned enrolment, with no formal statistical comparisons undertaken and no intent of stopping the study early for efficacy or for futility based on interim symptom outcomes. See the DSMB SAP for more details.

4.3. Primary Analysis

All planned analyses of primary and secondary endpoints through Week 12, safety endpoints using all available data

at the time of the primary analysis, and also those using only data through Week 12, and PK analyses as identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this SAP, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of Treatment.

Further details of distribution of unblinded information to the Sponsor, and who will be unblinded at the time of this analysis, will be included in an unblinding plan, separate to this SAP.

4.4. Final Analysis

All planned analyses of secondary endpoints and safety endpoints through to Week 24 as identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this SAP, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of Treatment.

4.5. Exploratory Analysis

All planned analyses required to assess the exploratory objectives of the study will be performed, when required by the Sponsor, after completion of the Primary Analysis.

5. ANALYSIS SETS

Analysis sets for this study may exclude enrolled participants from sites with non-compliance to Good Clinical Practice (GCP).

5.1. All Screened Participants [SCR] Set

The all screened participants (SCR) set will contain all participants who provide informed consent for screening for this study.

5.2. All Randomized Participants [RND] Set

The all randomized participants (RND) set will contain all participants in the SCR set who were randomized to study intervention. For analyses and displays based on the RND set, participants will be classified according to randomized intervention.

5.3. Modified Intent-to-treat [mITT] Set

The modified intent-to-treat (mITT) set is defined as all randomized participants who took ≥1 dose of S-217622 or placebo and who started intervention within 3 days of symptom onset. For efficacy outcomes, this population will be analyzed according to the study intervention the participants were randomized to, regardless of study intervention the participants actually received. This will be the primary analysis population.

5.4. Modified Intent-to-treat 1 (mITT1) Set

The modified intent-to-treat 1 (mITT1) set is defined as all randomized participants who took ≥1 dose of S-217622 or placebo. For efficacy outcomes, this population will be analyzed according to the study intervention the participants were randomized to, regardless of study intervention the participants actually received.

5.5. Modified Intent-to-treat 2 [mITT2] Set (Not specified in the protocol)

The modified intent-to-treat 2 (mITT2) set is defined as all randomized participants who took ≥1 dose of S-217622 or placebo and who started intervention within 3 days of symptom onset with baseline PCR positive. For efficacy outcomes, this population will be analyzed according to the study intervention the participants were randomized to, regardless of study intervention the participants actually received. This will be applied to analyses for the primary and key secondary endpoints.

5.6. Modified Intent-to-treat 3 [mITT3] Set (Not specified in the protocol)

The modified intent-to-treat 3 (mITT3) set is defined as all randomized participants who took ≥1 dose of S-217622 or placebo with baseline PCR positive. For efficacy outcomes, this population will be analyzed according to the study intervention the participants were randomized to, regardless of study intervention the participants actually received. This will be applied to analyses for the primary and key secondary endpoints.

5.7. Viral Culture (VC) Set

The Viral Culture (VC) set will include all participants in the mITT population who have documented viral culture at baseline, i.e., detectable (>LLoQ) viral culture result at baseline.

5.8. Safety Analysis Set [SAF]

The Safety Analysis set (SAF) is defined as all randomized participants who took ≥1 dose of S-217622 or the placebo. This population will be analyzed according to the study intervention that the participants actually received, rather than the study intervention to which the participants were randomized.

If participants receive both S-217622 and placebo they will be analyzed under the S-217622 group, regardless of the number of doses of each study intervention they received.

5.9. Pharmacokinetic [PK] Set

The PK set is defined as all randomized participants who received at least 1 dose of S-217622 with at least 1 evaluable plasma concentration of S-217622 value. This population will be used for the drug concentration listing and graphical presentations.

After plasma concentration measurement, the data for which inappropriateness for analysis can be clearly explained by the person in charge of PK analysis at the sponsor will be excluded. The reason for any exclusion will be described in the clinical study report (CSR). This person will provide IQVIA with a list of such exclusions.

Note that only specific sites with facilities for PK sample processing will be selected to provide PK data for approximately 400 participants, see Section 19 for further details.

5.10. Process for Analysis Set Assignment

A blinded data review meeting (BDRM) will take place prior to database lock and prior to unblinding, for each of the primary and final analyses.

At or following the BDRM, the sponsor will determine which participants or sites are to be excluded from the analysis sets, along with the reasons for exclusion.

6. GENERAL CONSIDERATIONS

6.1. Reference Start Date and Study Day

Study day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. It will appear in every listing where an assessment date or event date appears.

Reference start date is defined as the day of the first dose of study intervention (Day 1 is the day of the first dose of study intervention).

Study day will be computed as follows:

- Study Day = (Date of event – Date of first dose of study intervention) + 1 if the date of the event is on or after the date of the first dose of study intervention;
- Study Day = (Date of event – Date of first dose of study intervention) if the date of the event is prior to the date of the first dose of study intervention.

For the primary and secondary endpoints of time in days from the start of study intervention until sustained resolution, Study day will be computed as follows:

- Study Day = (Date of event – Date of first dose of study intervention) if the date of the event is on or after the date of the first dose of study intervention;

In the situation where the event date is partial or missing, study day and any corresponding durations will appear partial or missing in the listings.

For participants who are randomized but do not receive study intervention, study day will be calculated using the date of randomization as the reference start date.

6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date or on the reference start date but prior to the first dose of study intervention (including unscheduled

assessments). In the case where the last non-missing measurement and the reference start date coincide, and the time of that measurement is not available and/or the time of the measurements coincide, the measurement will be considered as baseline if the assessment is planned per protocol to take place prior to first study intervention administration. AEs and medications commencing on the reference start date will be considered post-baseline unless otherwise indicated based on available start date/time combination.

6.3. Retests, Unscheduled Visits and Early Termination Data

For by-visit summaries, data will be summarized based on analysis visits, as described in Section 6.4. Unscheduled, retest and early termination measurements may be included in by-visit summaries, and will contribute to the baseline timepoint and/or maximum value, where required (e.g., shift table).

Listings will include all scheduled, unscheduled, retest, discharge, and premature study discontinuation visit data.

6.4. Windowing Conventions

Study visit windows for reporting are based on the SOE in Table 6.1-1 of the protocol and will be derived based on the event/sample date and study intervention initiation date as per Section 6.1. In the event that multiple results fall within the same analysis window, the one closest to the target time point will be prioritized, or if equidistant from the target time point, the earlier result will be prioritized. For interim analyses, if a result does not fall in an analysis window, the visit label will be used to identify the target time point. The analysis visit windows are provided in Table B:

Table B: Analysis Visit Windows

Visit	Protocol Range (Days)	Analysis Window (Days)	Analysis Window Difference to Scheduled (Days)
Screening	-3, 1	-10, 1	-10, 0
Day 1*	1	-1, 1	-1, 0
Day 4	3, 5	2, 5	-2, +1
Day 8	7, 9	6, 11	-2, +3

Day 16	12,16	12, 22	-4, +6
Day 29	29, 33	23, 39	-6, +10
Week 12 (Day 85)	71, 99	57, 113	+/- 28
Week 24 (Day 169)	155, 183	141, 197	+/- 28

*The Day 1 analysis window is designed to capture data in scenarios where data are captured at the "Study Entry (Randomization)/Day 1" visit, per the SOE, including when randomization occurs on the day prior to intervention initiation.

Note that analysis visits are allocated to each evaluation, but the analysis visit will not be used in visit-based analyses if the visit is not a scheduled visit for that evaluation. For example if an observation is recorded on Day 150, for an evaluation that is not scheduled to be done at the Week 24 visit, then the evaluation would be mapped to the Week 24 visit window but will not appear in visit-based analyses, since only analysis visits with a corresponding scheduled visit in the SOE are included in visit based analyses. It would however appear as the Week 24 visit in the relevant data listing.

6.5. Statistical Tests

The default significance level will be (5%); confidence intervals (CIs) will be 2-sided 95% and all tests will be 2-sided, unless otherwise specified in the description of the analyses.

6.6. Common Calculations

For quantitative measurements, change from baseline will be calculated as:

- Test value at Visit X – baseline value.

6.7. Descriptive Statistics

Unless otherwise stated, continuous variables will be summarized using the number of non-missing observations, mean, standard deviation (SD), median, interquartile range (Q1 and Q3), and min and max; categorical variables will be summarized using frequency and percentage.

6.8. Software Version

All analyses will be conducted using SAS version 9.4 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. Adjustments for Covariates and Factors to be Included in Analyses

The following covariates and factors are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Baseline log-10 transformed SARS-CoV-2 RNA level.
- Baseline resting peripheral oxygen saturation

7.2. Multicenter Studies

This study will be conducted by multiple investigators at multiple centers internationally. One of the stratification factors for randomization to intervention group is geographic region.

Geographic region will be categorized as follows:

- North America
- South America
- Europe
- Africa
- Asia

For analysis purposes countries which enroll participants will be assigned to geographic region based on the mappings provided in APPENDIX 1.

Terms for geographic region and intervention by geographic region interaction will not be included in any efficacy analysis models, however, geographic region will be included as a subgroup in subgroup analyses of the primary

efficacy endpoint and the key secondary efficacy endpoints.

7.3. Missing Data

Missing safety data will not be imputed.

Missing efficacy data will be handled as described in Sections 16.1.2, 16.2.2 and subsections of Section 16.2.3 of this SAP.

7.4. Intercurrent Events

In general, a treatment policy approach will be used in analyses and summaries. That is, the occurrence of intercurrent events is considered irrelevant in defining the treatment effect of interest; the values for the variable of interest are used regardless of whether the intercurrent event occurs. However, where appropriate the following intercurrent events will be considered:

- Death from any cause;
- Hospitalization;
- Loss to follow-up;
- Molnupiravir, mAb treatment, outpatient IV remdesivir, favipiravir, fluvoxamine, convalescent plasma or any other antiviral medications.

7.5. Multiple Comparisons/ Multiplicity

The primary hypothesis is based on the primary outcome measure. The difference in restricted mean symptom duration up to Day 28 will be used to compare time (days) from start of intervention (S-217622 vs. placebo) until sustained resolution based on assessments for 2 consecutive days of targeted symptoms and being alive and not hospitalized for any reason by Day 29 in the mITT set. If the comparison is statistically significant at the 2-sided 5% level, it will be concluded that S-217622 is superior to placebo in reducing the time to sustained resolution of targeted symptoms.

Following testing of the primary outcome measure, key secondary outcome measures will be tested sequentially at

the 2-sided 5% alpha level, as part of the statistical hierarchy in the following order:

1. The change from baseline in quantitative $\log_{10}$ SARS-CoV-2 RNA levels by PCR in NP swab at Day 4, in the mITT set.
2. The proportion of participants with the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 12, in the mITT set.
3. The change from baseline in quantitative $\log_{10}$ SARS-CoV-2 RNA levels by PCR in NP swab at Day 4, in the mITT1 set.
4. The proportion of participants with the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 12, in the mITT1 set.
5. The difference in restricted mean symptom duration up to Day 28, in the mITT1 set.
6. Adjudicated hospitalization due to COVID-19 or death due to any cause through Day 29, in the mITT set.
7. Adjudicated hospitalization due to COVID-19 or death due to any cause through Day 29, in the mITT1 set.

All tests performed higher in the hierarchy must be statistically significant at the 2-sided 5% level to allow alpha to be passed down the chain to the next test. If at any point the chain is broken with a non-statistically significant result, the remaining tests will not be considered to be statistically significant and will be considered to provide supportive information[1].

There will be no adjustments made for multiplicity for analyses of all other secondary endpoints. For analyses of non-key secondary endpoints, statistical inference will be exploratory in nature and will be based on 95% CIs for effects comparing S-217622 to placebo, and associated 2-sided tests of no difference between arms using a 5% Type I error rate. No formal adjustment will be made for multiple comparisons across these endpoints.

7.6. Examination of Subgroups

Subgroup analyses will be conducted as stated in the relevant analysis sections. It should be noted that the study was not designed to detect intervention differences with high statistical power within subgroups.

The following subgroups will be assessed and described within the relevant analysis sections:

- Risk (of severe COVID-19) status at enrollment, as captured in the *Stratification* item on the *Randomization* electronic case report form (eCRF) page
    - High-risk

- Standard-risk

- COVID-19 vaccination status*
  - Not vaccinated
  - Completed primary series with last vaccine >3 months prior to enrollment
  - Completed primary series with last vaccine ≤3 months prior to enrollment

- Time from onset of COVID-19 -related symptoms at baseline
  - ≤1 day
  - ≤2 days
  - ≤3 days
  - >3 days.

- Sex at birth
  - Female
  - Male.

- Geographic region
  - North America
  - South America
  - Europe
  - Africa
  - Asia.

- Concurrent standard of care+
  - mAbs or outpatient IV remdesivir after randomization
  - No COVID-19 standard-of-care treatment after randomization
  - COVID-19 standard-of-care with any treatment that is not mAbs or outpatient IV remdesivir after randomization

Information related to concurrent standard of care treatment will be derived from the *COVID Standard of Care Therapy* page of the eCRF.

Additional subgroup analyses may be considered based on demographic and baseline characteristics. If appropriate, subgroups may be combined or revised to ensure sufficient numbers of participants in each subgroup.

* See Section 10.1 for information on how these categories will be determined.
+ This subgroup involves post-randomization data, and as such any analyses performed on it are to be considered as exploratory only.

7.7. Multiple records issue per day in Patient Diary

The patient diary is to be entered electronically through eCOA on each evaluation day of the observation period, but if there is a problem with the eCOA system or if the eCOA system is unavailable, the patient diary may be entered on paper or by the facility staff through a proxy. Therefore, patient diary data may be entered through three different input routes throughout the observation period: eCOA, paper, and proxy. In the analysis, input data at each day is used regardless of the input route. If multiple input data per day via multiple input routes exist and those input data is not identical, data from the input route with the most severe symptom on each evaluation date will be used. If multiple input data per day exist via a single input route, the most severe symptom on each evaluation date will be used.

7.8. Multiple records issue at Week 12 or Week 24

If there are multiple records collected on the different date within the analysis visit window (Table B) for each of Week 12 or Week 24, the closest value to the scheduled day will be used in the analysis, or if equidistant from the target time point, the earlier result will be prioritized. In case that there are multiple records collected on the same date within the analysis visit window for each of Week 12 or Week 24, the worst value will be used in the analysis.

8. Output Presentations

APPENDIX 2 shows conventions for presentation of data in outputs.

The templates provided as a separate document to this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics. Separate templates will also be provided in a separate document to supplement the DSMB SAP.

Some analyses or summaries are planned to be repeated on more than one analysis set. If the analysis sets are identical in terms of both the participants in the analysis set and the study intervention to which each participant is assigned for those analysis sets, then the summary will only be performed in one of the analysis sets.

9. Disposition and Withdrawals

All participants who provide informed consent will be accounted for in this study.

9.1. Disposition

The number of participants screened and randomized will be presented, and for screen failures the reasons for screen failure will be summarized. Participant disposition and reasons for withdrawal from study intervention and from the study will be presented for each of the RND, the mITT set and the mITT1 set. For the Primary Analysis, disposition including reasons for discontinuation, will be provided overall and for up to and including Day 29, and the number and percentage of participants reaching Day 29 and ongoing in the study at the time of the Primary Analysis will also be presented. Analysis set disposition and reasons for exclusion from each analysis set will be presented for the RND set.

For participants who discontinue from the study prior to Day 29 the study day of discontinuation will be summarized as a categorical variable for each of the mITT and the mITT1 sets.

9.1.1. Derivations

For participants who do not complete the study, the time to discontinuation (in days) will be used in analyses and will be derived as follows:

- (The earliest of the date of death or study discontinuation) – (date of first dose of study intervention) + 1.

For censored observations the time used in analyses will be derived as follows:

- (Date of study completion) – (date of first dose of study intervention) + 1.

9.2. Protocol Deviations

All protocol deviations (critical, major, and minor) will be recorded in the clinical trial management system (CTMS) protocol deviations log for the duration of the study (refer to the Protocol Deviations Management Plan for the definition of critical, major, and minor protocol deviations). Site-level identified protocol deviations will be replicated for all participants ongoing in the study at the site at the time of the protocol deviation and presented in the summary outputs as participant-level protocol deviations.
The number and percentage of participants with critical and major protocol deviations will be provided overall and by intervention group based on the mITT set, for each category of protocol deviations specified in the Protocol Deviations Management Plan. For the Primary Analysis, protocol deviations occurring up to and including Day 29, and protocol deviations at any time will be summarized separately.

A listing of all protocol deviations (critical, major, and minor) will be provided.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the mITT set and for the mITT1 set, by treatment group for all participants and by risk status category at baseline (high risk and standard risk) .

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of first dose of study intervention, as a continuous variable
- Age group (years) – calculated relative to date of first dose of study intervention
  - ≤ 30
  - 31-50

- 51-64
- 65-79
- ≥ 80

and also

- < 65
- ≥ 65

- Sex at Birth
  - Male
  - Female
  - Ambiguous genitalia/Intersex
  - Unknown
- Childbearing potential for non-male participants only
  - Yes
  - No
- Race
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islanders
  - White
  - Other
  - Not Reported (includes the eCRF options *Not Reported* and *Prefer not to answer*)
  - Unknown.

- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not Reported
  - Unknown.
- Weight (kg), as a continuous variable
- Height (cm), as a continuous variable
- Body mass index (BMI) (kg/m^2), as a continuous variable
- BMI group (kg/m^2)
  - <30
  - ≥30
- Smoking Status
  - Never
  - Former
  - Current.
- Geographic region (see Section 7.6).
- COVID-19 Vaccination status as per eCRF (see Section 10.1)
  - Not vaccinated
  - Completed primary series with last vaccine >3 months prior to enrollment
  - Completed primary series with last vaccine ≤3 months prior to enrollment
- Risk (of severe COVID-19) status at enrollment, as captured in the *Stratification* item on the *Randomization* eCRF page
  - High-risk
  - Standard-risk (which is captured on the eCRF as "Low-risk")

10.1. Derivations

- Only the year of birth of participants is being captured on the eCRF. Date of birth will be imputed as 1st of July of the year of birth and Age will be derived as the integer part of (Date of first dose of study intervention – imputed date of birth + 1)/365.25.
- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$.

Vaccination status as per eCRF will be derived using information on the *COVID 19 Vaccine History* page of the eCRF.

Participants will be classified as not vaccinated if they answer No to *Has the subject taken COVID-19 Vaccines?* or if they been vaccinated but have not completed a primary series of vaccinations.

Two doses of any vaccine is considered to be completion of a primary series of vaccinations, except for the *Janssen/ Johnson & Johnson (Ad26.COV2.S)* vaccine for which one dose is considered completion of the primary course. The determination of whether the primary series was completed > or ≤ 3 month prior to enrolment (based on informed consent date) will be performed programmatically by IQVIA Biostatistics based on the date of the last dose received, where the date of the last dose received will include the date of booster dose, if a booster was received.

11. DISEASE HISTORY

The following disease history characteristics will be summarized overall and by intervention group based on the mITT set:

- Time since first symptoms onset (days) – calculated relative to date of first dose of study intervention.
- Time since COVID-19 diagnosis (days) – calculated relative to date of first dose of study intervention.
- Time since positive COVID-19 test (days) – calculated relative to date of first dose of study intervention.
- Presence and severity (No, mild, moderate, severe) of each of the following COVID-19 symptoms within 24 hours prior to study entry, as captured on the *COVID-19 symptom screen_24 hours* page of the eCRF:
    - Cough;
    - Shortness of breath or difficulty breathing;

- Feeling feverish;
- Chills;
- Fatigue;
- Body pain or muscle pain or aches;
- Diarrhea;
- Nausea;
- Vomiting;
- Headache;
- Sore throat;
- Nasal obstruction or congestion;
- Nasal discharge.

Presence (Yes/No) of each of the following COVID-19 symptoms within 5 days prior to study entry, as captured on the *COVID-19 symptom screen_5 days* page of the eCRF:

- Loss of taste;
- Loss of smell

Note: Loss of taste/smell was initially a single question in this study, but was subsequently separated out into separate symptoms. Whenever loss of taste/smell was assessed as a single question, a yes or no answer will be considered as a yes or no answer to each of loss of taste and loss of smell.

All disease history characteristics will be listed.

11.1. Derivations

- Time since symptoms onset (days) = (Date of first dose of study intervention – Date of first symptom onset)
- Time since COVID-19 diagnosis (days) = (Date of first dose of study intervention – Date of COVID-19 diagnosis)

Date of first symptom onset is the *Onset date of first symptom related to current SARS-Cov-2 infection* as captured on the *COVID-19 symptom screen 5 days* page of the eCRF.

Date of COVID-19 diagnosis is the date of positive COVID-19 test is the *SARS-CoV-2 Collection Date* with *Result* = Positive, captured on the *Documentation of SARS-COV-2 infection* page of the eCRF.

12. MEDICAL HISTORY

Medical History information will be summarized for the mITT set.
Medical History captured via the *Medical History Diagnosis* field of the *Medical History* page of eCRF will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary Version 23.0 or higher and summarized via System Organ Class (SOC) and Preferred Term (PT).

In addition, the number and percentage of participants with a history of the following risk factors, as recorded in the *Risk Factors* section of the *Medical History* page of the eCRF will be summarized:

- Autoimmune disease;
- Pulmonary embolism;
- Deep venous thrombosis;
- HIV infection;
- Cancer (exclusive of basal/squamous cell skin cancer);
- Acute viral respiratory infection;
- Chronic lung disease;
- Asthma requiring daily inhaled medication;

- Obesity (BMI ≥ 30 kg/m^2);
- Hypertension;
- Cardiovascular disease;
- Diabetes mellitus;
- Chronic Kidney Disease;
- Cirrhosis;
- Exogenous or endogenous immunosuppression?
- Down syndrome
- Sickle cell disease
- Previous COVID-19 infection

All medical history data will be listed.

13. MEDICATIONS

All medications collected on the *Concomitant Medications* page of the eCRF will be classified as either:

- Prior medications, defined as any medication that started and stopped prior to the date of study Day 1 (refer to Section 6.1)

OR

- Concomitant medications, defined as:
    - Any medication that started before the date of study Day 1 AND ended on or after the date of study Day 1, or were ongoing at that time;
    - Any medication that started on or after the date of study Day 1.

Partially or completely missing medication start and stop dates will be handled as described in APPENDIX 3.

All medications will be coded using the WHO Drug Global dictionary, version March 2020 B3 or later.

Prior and concomitant medications will be summarized separately, by Anatomical Therapeutic Class (ATC) level 2 and preferred drug name overall and by randomized intervention group based on the mITT set. A participant having more than one medication within the same ATC level 2 or preferred drug name will be counted only once for that ATC level 2 or preferred drug name. For the Primary Analysis, separate summaries will be provided for concomitant medications starting up to and including Day 29, and those starting at any time (including beyond Day 29).

Rescue medications are defined as any additional COVID-19 treatment initiated >72 hours after randomization. These will be identified via a blinded medical review of concomitant medications and summarized separately, via ATC Level 2 and preferred drug name. For the Primary Analysis, separate summaries will be provided for rescue medications starting up to and including Day 29, and those starting at any time (including beyond Day 29).

All medications (prior and concomitant) will be listed.

14. STUDY INTERVENTION EXPOSURE

Exposure to study intervention data will be presented for each of the SAF and the mITT set.

Participants are to receive either S-217622 tablets or matching placebo tablets, as applicable, in a double-blind manner for 5 days or until death, or discontinuation of study intervention, whichever occurs first.

Participants will be randomized to receive 1 of the following 2 regimens:

- S-217622 at a dose of 375 mg (3 tablets) for Day 1 and 125 mg (1 tablet) for Days 2 to 5 once daily

OR

- Placebo for S-217622 administered once daily for 5 days (Days 1 to 5 [3 tablets on Day 1 and 1 tablet on Days 2 to 5]).

S-217622 will be administered as 125 mg tablets or matching placebo.

The first dose should be taken on site the same day as Study Entry/Day 1. All subsequent doses (i.e., Days 2 to 5) will be self-administered outside the study site (e.g., at home). The second dose must be taken 24 ± 8 hours after the

first dose, allowing the participant to select a convenient 24-hour dosing schedule thereafter to complete a total of five doses.

Subsequent doses of S-217622 or matching placebo should be separated by 24 ± 2 hours, ideally. If a dose is delayed, it should be taken as soon as possible, but no more than 12 hours later than expected. If the delay is greater than 12 hours, the dose must be skipped and the next dose taken as scheduled. Dosing will be stopped at the end of the 5-day intervention period.

If a participant vomits after dosing, the dose should not be repeated.

Reason for dose modification of study intervention (i.e., dose increased, dose reduced, drug interrupted, drug withdrawal, and unknown) will be captured on the *Exposure* page of the eCRF.

The exposure to study intervention will be summarized by intervention group, as follows:

- Duration of exposure
    - Duration of exposure (days) as a continuous variable;
    - Duration of exposure (days) as a categorical variable: 1, 2, 3, 4, 5 or >5 days
    - Total number of tablets received per participant, summarized as a continuous variable.
- Average dose (mg/day) per participant, summarized as a continuous variable, broken down by Day 1 and Days 2-5.
- Dose adjustments
    - Number and percentage of participants with at least one dose interruption.
    - Number and percentage of participants with a dose interruption by reason for dose interruption
        - AEs
        - Other.

All dosing and exposure data will also be listed.

The date of first study intervention administration will be the first *Date of study medication* recorded on the *Study Intervention* page of the eCRF. The date of last study intervention will be taken from the *Date of treatment completion/discontinuation* on the *End of Study Treatment* page of the eCRF.

Interruptions are not taken into account for duration of exposure.

14.1. Derivations

Duration of exposure to study intervention, in days, will be computed as follows:

- Duration of exposure (days) = (Date of last dose of study intervention – Date of first dose of study intervention) + 1.

The average dose per day will be computed as follows:

- Average dose (mg/day) = Total cumulative dose (mg) / duration of exposure (days)

where the total cumulative dose is the computed total cumulative dose (mg) taken by a participant during the course of the study. The dose for each administration of S-217622 will be derived as 125 mg x the *Number of tablets taken*, captured on the *Exposure* eCRF page, or 0 mg for matching placebo.

15. Study Intervention Compliance

Compliance to study intervention will be summarized for both the SAF and the mITT set.

Compliance with study intervention will be summarized by intervention group. In addition to the summary of compliance as a continuous variable, the number and percentage of participants in the following compliance categories will be presented:

- < 80%;
- ≥ 80% to < 100%;
- 100%;
- > 100%.

Compliance data will also be listed.

Note that compliance of >100% would occur if a participant takes more than 3 tablets on Day 1 or more than 1 tablet on any of Days 2 to 5 particular day and at the time of discontinuation or death before Day 5 have taken more tablets

than the number of days they should have taken them.

15.1. Derivations

For each participant, the compliance will be computed as follows:

- Compliance (%) = (Actual total number of tablets / Expected total number of tablets) x 100

where:

- Actual total number of tablets is defined as the number of tablets taken throughout the course of the study.
- Expected total number of tablets is defined as the sum of protocol-defined tablets to be taken through the course of the study and is computed as follows:
    - For participants who are alive and have not discontinued study intervention by Day 5:
        - Expected total number of tablets = 7 (3 for Day 1 +1 for each of Days 2 to 5)
    - For participants who have died or discontinued study intervention prior to Day 5
        - Expected total number of tablets = 3 (for Day 1) +1 for each day up to and including the day of death or discontinuation of study intervention.

16. EFFICACY ENDPOINTS

16.1. Primary Efficacy

16.1.1. Primary Efficacy Endpoint & Derivation

The primary efficacy endpoint is the time in days from the start of study intervention until sustained resolution of all targeted symptoms (including those occurring prior to COVID-19 infection), and being alive and without hospitalization for any reason by Day 29.

The targeted symptoms are:

- Cough;

- Shortness of breath or difficulty breathing;
- Feeling feverish;
- Chills;
- Fatigue;
- Body pain or muscle pain or aches;
- Diarrhea.
- Nausea;
- Vomiting;
- Headache;
- Sore throat;
- Nasal obstruction or congestion;
- Nasal discharge;
- Loss of taste;
- Loss of smell.

Note: Loss of taste/smell was initially a single question in this study, but was subsequently separated out into separate symptoms Whenever loss of taste/smell was assessed as a single question, a yes or no answer will be considered as a yes or no answer to each of loss of taste and loss of smell.

Each symptom is scored daily by the participant as absent, mild, moderate, or severe.

Resolution of all targeted symptoms is defined as the first of 2 consecutive days when all targeted symptoms are evaluated as resolved, assessed according to the following rules:

For the pre-existing symptoms that were present prior to COVID-19 onset and considered by the participant to have worsened at baseline (Day 1 diary (Participant Study Diary_Paper page of the eCRF**)**, completed prior to study intervention initiation), the severity should be improved to be considered resolved.

- Severe at baseline: improved to Moderate, Mild, or Absent post-baseline;
- Moderate at baseline: improved to Mild, or Absent post-baseline.

(In the event that a participant declares a symptom as Mild at baseline and worsened from prior to COVID-19, the severity should remain as Mild or be improved to Absent.)

For the pre-existing symptoms that were present prior to COVID-19 onset and considered by the participant not to have worsened at baseline (preintervention examination), the severity should remain the same or be resolved.

- Severe at baseline: Severe, Moderate, Mild, or Absent post-baseline;
- Moderate at baseline: Moderate, Mild, or Absent post-baseline;
- Mild at baseline: Mild or Absent post-baseline.

Symptoms other than the above (symptoms not present prior to COVID-19 onset), the severity should become or remain Absent.

- Severe or Moderate at baseline: Absent post-baseline;
- Mild at baseline: Absent post-baseline;
- Absent at baseline: Absent post-baseline.

Further details regarding the derivation of this variable are provided in Section 16.1.2.

16.1.2. Intercurrent Event Handling and Data Imputation for Primary Efficacy Endpoint

This endpoint is a time-to-event (TTE) variable, potentially involving censoring due to loss-to-follow-up up or premature termination of diary completion or if a participant did not meet the outcome criteria for symptoms resolved during the 28 days of completing the diary.

Censoring of follow-up for this endpoint will occur on the last day that the outcome could have been achieved. Specifically, as two consecutive days of symptoms meeting the endpoint criteria are required, censoring would be one day before the last day of completion of the diary card (e.g., this would be Day 28 for participants with complete diaries through Day 29, as meeting the criteria requires completion of the diary on each of Days 28 and 29).

Participants who die from any cause or are hospitalized for any cause prior to Day 29 will remain in the risk-set to Day 28 and will be considered to have not had the symptom resolution event with time to event censored at Day 28.

For each participant, the symptom data that contribute to the calculation of the TTE endpoint and the censoring time (and associated censoring indicator variable) can be described as a panel of evaluations (absent/mild/ moderate/ severe) for each of 15 targeted symptoms on each of 29 days (Day 1 through Day 29). The following general principles will be applied for the handling of particular intercurrent events and missing data:

- **Deaths or Hospitalizations**. Participants who die or are hospitalized, on or before Day 29 will remain in the risk-set to Day 28 and will be considered to have not had the symptom resolution event with time to event censored at Day 28. A participant who dies from any cause or is hospitalized up to and including Day 29 after achieving sustained symptom improvement is considered not to have achieved symptom resolution, with time to event censored at Day 28.

- **Losses to Follow-up and Early Termination of Evaluation of Targeted Symptoms**. Participants who have not died and have not been hospitalized up to and including Day 29, and are lost to follow-up or terminate providing evaluations of the targeted symptoms in their study diaries before Day 29 for any reason have monotonic missing data (i.e., a sequence of missing values during follow-up through to and including Day 29). For these participants, the TTE endpoint will be censored at the last day that the relevant criterion for symptom improvement could have been met (this would be the latest of Day1 or one day before the last diary entry for one or more targeted symptoms). These criteria for censoring assume that the censoring is non-informative about when the TTE outcome would have been met if diaries had been fully completed after the last diary entry for one or more targeted symptoms.

  Intermittent Missingness. Participants who have not died or been hospitalized up to and including Day 29 and have intermittent missing evaluations for a specific symptom (i.e., one or more successive evaluations with preceding and succeeding evaluations for the same symptom) will have the missing evaluation(s) imputed as the worst of the preceding and succeeding evaluations for the same symptom. There may be no impact of this on the TTE endpoint if evaluations of other symptoms are completed and do not meet the TTE outcome during the period of missingness for the specific symptom. If there is an impact, it may be to move the TTE outcome earlier (than if the evaluations had been done) if both the preceding and succeeding evaluations for the specific symptom meet the criteria for improvement/ resolution; and, conversely, to move the TTE outcome later (than if the evaluations had been done), if both the preceding and succeeding evaluations for the specific symptom don't meet the criteria for improvement/resolution. In an effort to reduce intermittent missingness, should participants fail to enter diary data on the day of the symptoms, site personnel will be permitted to enter diary data on behalf

of the participant for a period of 24 hours immediately following the day of expected data entry. Symptom data will be relayed to site personnel for entry into the database and will be used in the analysis alongside data entered on the day of symptom assessment.

APPENDIX 4 includes a detailed description of an algorithm for handling missing targeted symptom data following these general principles that can be implemented programmatically.

16.1.3. Primary Analysis of Primary Efficacy Endpoint

The time (days) from the start of intervention (S-217622 or placebo) until sustained resolution will be compared using restricted mean symptom duration up to Day 28, which is the last timepoint at which the outcome can be achieved, from 1 to 27 days as time limit, to provide an estimate of the difference in restricted mean symptom durations for intervention (S--217622 vs. placebo), along with a 95% CI and 2-sided p-value. The SAS LIFETEST procedure with RMST option, using a tau of 27 and bias correction to the standard error, will be used for this analysis. Days used in the analysis are study day, as defined in Section 6.1. Diary entries prior to the date of study treatment intervention will not be included in analyses.

If a participant has resolution regarding the 15 targeted symptoms on Day 1 and the resolution sustains on Day 2, the participant will be treated as though sustained resolution were achieved at Day 1 with the time until sustained resolution of "zero" as long as the participants did not die or did not experience hospitalization for any reason on or before Day 29.

If a participant has resolution regarding the 15 targeted symptoms on Day 1, but none of the targeted symptoms were evaluated from Day 2 onwards, the participant will be treated as censored at Day 1 (see Appendix 4) with the censored time until sustained resolution of "zero" as long as the participants did not die or did not experience hospitalization for any reason on or before Day 29.

Kaplan-Meier estimates of the median and quartiles (with associated 95% CIs) and range will be provided for each intervention group. In addition, the Kaplan-Meier curves will be presented graphically.
These analyses will be performed on the mITT set.

16.1.4. Additional Secondary Analysis of Primary Efficacy Endpoint

As the additional secondary analysis of the primary efficacy endpoint, the same analyses as that of the primary

endpoint in Section 16.1.3 will be conducted on the mITT2 and mITT3 sets.
In addition, a subgroup of participants starting study intervention within 2 days of symptom onset out of the mITT set will be conducted.

16.1.5. Sensitivity Analysis of Primary Efficacy Endpoint

A sensitivity analysis evaluating the impact of the late entry of diary data, defined as that collected during the 24-hour period that occurs immediately- after the day of the assessment, (see *Intermittent Missingness* sub-section of Section 16.1.2) may be undertaken if sufficiently high amounts of data are collected in this manner. This analysis will use the same methodology and analysis set as the primary analysis (see Section 16.1.3). The primary analysis would include late entered data and the sensitivity analysis would exclude it.

16.1.6. Supplementary and Supportive Analyses of Primary Efficacy Endpoint

Other supplementary analyses will include comparing the treatment groups using Peto-Prentice's generalized Wilcoxon test. This test is available in the SAS PROC LIFETEST procedure using TEST=PETO in the STRATA statement.

Supportive analyses will be carried out in a similar manner to the primary analysis of this endpoint but for symptom resolution based on 1 and 4 consecutive days with Days 29 and 26, respectively, being the last day that the outcome can be achieved.

For the endpoint of symptom resolution based on 1 day of resolution, censoring will occur on Day 29, and the tau use in the restricted mean duration analysis will be 28. In case of participants with symptoms resolution based on 1 consecutive day of regarding the 15 targeted symptoms on Day 1, these participants will be excluded from the analyses.

For the endpoint of symptom resolution based on 4 days of resolution, censoring will occur on Day 26, and the tau use in the restricted mean duration analysis will be 25. If a participant has resolution regarding the 15 targeted symptoms on Day 1 and consecutive sustained resolution observed until Day 4, the participant will be treated as sustained resolution achieved at Day 1 with the time until sustained resolution of "zero" as long as the participants did not die or did not experience hospitalization for any reason on or before Day 29. If a participant has resolution regarding the 15 targeted symptoms on Day 1, but none of the targeted symptoms was evaluated from Day 2

onwards, the participant will be treated as censored at Day 1 with the censored time until sustained resolution of "zero" as long as the participants did not die or did not experience hospitalization for any reason on or before Day 29.

Additionally, as supportive information, the number and percentage of subjects completing the study diary on each study day from Day 1 to 29, will be provided.

These analyses will be performed on the mITT set.

16.1.7. Subgroup Analyses of Primary Efficacy Endpoint

In addition, the primary analysis of the primary efficacy endpoint will be repeated within each of the subgroups specified in Section 7.6.

It should be noted therefore that the sample size for these subgroup analyses will be smaller than for the primary analysis, with a subsequent reduction of power to detect a statistically significant difference between intervention groups.

A forest plot of the difference in restricted mean symptom durations and corresponding 95% CI for each subgroup, and the primary efficacy analysis result, will be produced.

16.2. Secondary Efficacy

16.2.1. Secondary Efficacy Endpoints & Derivations

16.2.1.1. Key Secondary Virologic Efficacy Endpoint of Change from Baseline in Quantitative Log_{10} SARS-CoV-2 RNA Levels by PCR in NP Swab at Day 4

The key secondary virologic efficacy endpoint is the change from baseline in quantitative Log_{10} SARS-CoV-2 RNA levels by PCR in NP swab at Day 4.

The change from baseline will be derived as per Section 6.6.

Imputation rules for SARS-CoV-2 RNA below the assay LLoQ or above the upper limit of quantification (ULoQ),

and the handling of intercurrent events are provided in Section 16.2.2.

16.2.1.2. KEY SECONDARY CLINICAL EFFICACY ENDPOINT OF THE CUMULATIVE PROPORTION OF PARTICIPANTS HOSPITALIZED DUE TO COVID-19 OR DIED (DUE TO ANY CAUSE), FROM DAY 1 THROUGH DAY 29

This key secondary clinical efficacy endpoint is the proportion of participants with the composite endpoint of COVID-19-related hospitalization (adjudicated) and all deaths regardless of occurrence outside of hospital or during hospitalization (not adjudicated) through Study Day 29 (i.e., up to 28 days post first dose of study intervention per Section 6.1).

Hospitalization is defined as ≥24 hours of acute care, in a hospital or similar acute care facility, including emergency rooms, urgent care clinics, or facilities instituted to address medical needs of those with COVID-19.
Note that for the Primary Analysis (Day 29 analyses) of this study, hospitalization for any reason will be taken into consideration.

The time to death or COVID-19-related hospitalization (in days) will be used in analyses and will be derived as follows:

- (The earliest of the date of death or first COVID-19-related hospitalization) – (date of first dose of study intervention) + 1.

Similarly for censored observations (see Section 16.2.2) the time used in analyses will be derived as follows:

- (Date of censoring) – (date of first dose of study intervention) + 1.

Date of death will be that recorded on the *Death Details* page of the eCRF.

From among those hospitalizations that are adjudicated to be COVID-19-related, date of first COVID-19-related hospitalization for a participant will be the earliest *Start Date* captured on the *Hospitalization and Acute care* page of the eCRF where any of the following conditions are met:

- *Hospitalization outcome* is *Expired*
- *Start date, Time of Hospitalization, Stop date and Time of Discharge* are all non-missing and complete and based on these, the duration of hospitalization was ≥24 hours

- *Start Date* is before *Stop Date* if both dates are not missing but time is missing for either start or stop
- *Stop Date* is missing or *Ongoing* is ticked.

Note: For each hospitalization within a participant (sorted by hospitalization start date), these criteria will be considered in the sequential order as above to determine if the hospitalization should be considered in the time to death or hospitalization endpoint: if a condition is met, the conditions that follow will not be checked; if a condition is not met, the next condition in the sequence will be checked.

The handling of intercurrent events for this endpoint is described in Section 16.2.2.

16.2.1.3. Key Secondary Clinical Efficacy Endpoint of Time to Sustained Resolution of All Targeted Symptoms and Being Alive and Without Hospitalization for Any Reason by Day 29

Another key secondary clinical efficacy endpoint is time in days from the start of study intervention until sustained resolution of all targeted symptoms (including those occurring prior to COVID-19 infection), and being alive and without hospitalization for any reason by Day 29. The analysis for this key secondary endpoint will be performed on the mITT1 set. This is the same endpoint as the primary efficacy endpoint (see Section 16.1.1), but with a different target population, to evaluate a key secondary clinical estimand rather than the primary estimand (see Table A:).

16.2.1.4. Key Secondary Clinical Efficacy Endpoint Of The proportion of participants with persistent and/or late-onset symptoms of COVID-19 at Week 12

This key secondary clinical efficacy endpoint is the proportion of participants with persistent and/or late-onset symptoms of COVID-19 at Week 12 based on participants' assessments of the 5 symptoms specified by the WHO (fatigue, shortness of breath/difficulty breathing, difficulty with concentration/ thinking, difficulty reasoning/solving problems, and memory loss) plus taste disturbance and smell disturbance among outpatient adults with SARS-CoV-2 starting intervention within 3 days of symptom onset.
A participant will be considered to have persistent and/or late-onset symptoms if either 1 of the following criteria is met:

- Occurrence of at least 1 of the following symptoms at Week 12: difficulty with concentration/thinking, difficulty reasoning/solving problems, or memory loss,

  or

- Occurrence of at least 1 of the following symptoms at both the final evaluation time point in the Study Diary (e.g., Day 29) and Week 12: fatigue, shortness of breath/difficulty breathing, taste disturbance, or smell disturbance (i.e., persistent symptoms)

At the final evaluation time point in the Study Diary (e.g., Day 29), occurrence for persistent symptoms of COVID-19 is attained for any individual symptom that has not resolved. The definition of the resolution is shown in Section 16.1.1. At Week 12, the occurrence for persistent and/or late-onset symptoms of COVID-19 in the Post-acute COVID-19 Questionnaire is defined as mild or more in severity for each symptom. The analysis for this key secondary endpoint will be performed on the mITT set.

16.2.1.5. Key Secondary Clinical Efficacy Endpoint Of The Proportion Of Participants With Persistent And/Or Late-Onset Symptoms Of COVID-19 At Week 12

This key secondary clinical efficacy endpoint is the proportion of participants with persistent and/or late-onset symptoms of COVID-19 at Week 12 based on participants' assessments of the 5 symptoms specified by the WHO (fatigue, shortness of breath/difficulty breathing, difficulty with concentration/ thinking, difficulty reasoning/solving problems, and memory loss) plus taste disturbance and smell disturbance among outpatient adults. The analysis for this key secondary endpoint will be performed on the mITT1 set. This is the same endpoint as the key secondary efficacy endpoint (see Section 16.1.1.4), but with a different target population (see Table A:).

16.2.1.6. Time to Sustained Resolution of 6 Targeted Symptoms and Being Alive and Not Hospitalized for Any Reason by Day 29

The endpoint of time (days) from start of S-217622 or placebo (Day 1) until sustained resolution based on assessments for 2 consecutive days of 6 targeted symptoms (nasal obstruction or congestion, nasal discharge, sore throat, cough, feeling feverish, and fatigue) and being alive and not hospitalized for any reason by Day 29, will be derived similarly to the primary efficacy endpoint (see Section 16.1.1), but based only on the 6 target symptoms.

16.2.1.7. Time to Sustained Resolution of Targeted Symptoms (Excluding Loss of Taste and Loss of Smell) and Being Alive And Not Hospitalized For Any Reason by Day 29

The endpoint of time (days) from start of S-217622 or placebo (Day 1) until sustained resolution (where cough and fatigue can be considered resolved if they remain mild) based on assessments for 2 consecutive days of all targeted symptoms excluding loss of taste and loss of smell (cough, shortness of breath or difficulty breathing, feeling feverish, chills, fatigue, body pain or muscle pain or aches, diarrhea, nausea, vomiting, headache, sore throat, nasal obstruction or congestion, and nasal discharge) and being alive and not hospitalized for any reason by Day 29 will

be derived similarly to the primary efficacy endpoint (see Section 16.1.1).

16.2.1.8. Time To Hospitalization Due to Any Cause and All Deaths Through Day 29

This endpoint will be derived in a similar manner to the key secondary clinical efficacy endpoint (see Section 16.2.1.2) but with any hospitalization considered rather than just adjudicated COVID-19-related hospitalizations.

16.2.1.9. Detectable SARS-CoV-2 by Viral Culture from NP Swab at Each of Days 4 and 8

At each of Days 4 and 8 (and Day 1) non-missing viral culture will be classified as either undetectable or detectable.

16.2.1.10. Change From Baseline in Quantitative Log_{10} SARS-CoV-2 RNA in NP Swabs at Day 8

The change from baseline in quantitative Log_{10} SARS-CoV-2 RNA levels by PCR in NP swab at Day 8 will be derived as per Section 6.6.

Imputation rules for SARS-CoV-2 RNA below the assay LLoQ or above the ULoQ are provided in Section 16.2.2.

16.2.1.11. Change From Baseline in Quantitative Log_{10} Viral Culture in NP Swabs at Each of Days 4 and 8

The change from baseline in quantitative log_{10} SARS-CoV-2 viral culture in NP swab at Day 4 and Day 8 will be derived as per Section 6.6.

Imputation rules for SARS-CoV-2 RNA below the assay LLoQ or above the ULoQ are provided in Section 16.2.2.10.

16.2.1.12. SARS-CoV-2 RNA levels by PCR in NP Swabs Below the LLoQ at Each of Days 4 and 8

At each of Days 4 and 8 (and Day 1) SARS-CoV-2 RNA results from NP swabs will be classified as either <LLoQ or ≥ LLoQ.

16.2.1.13. TIME TO RETURN TO USUAL (PRE-COVID-19) HEALTH THROUGH DAY 29

Time (days) from start of S-217622 or placebo (Day 1) until the first of 2 consecutive days that a participant reported return to usual (pre-COVID-19) health as recorded in a participant's study diary through Day 29.

This endpoint is supportive for the primary efficacy endpoint in Section 16.2.1.1.

This endpoint will be derived in a similar manner to the primary efficacy endpoint but based on two consecutive days with an answer of Yes to the question *Have you returned to your usual (pre-COVID) health?* in ***Participant Study Diary_Paper*** page of the eCRF.

16.2.1.14. PARTICIPANTS HAVING A SCORE OF ≥2, ≥3, ≥4, ≥5, ≥6, ≥7, OR ≥8 ON THE ORDINAL SCALE

The severity of COVID-19 disease for each participant will be assessed and recorded on the *Ordinal Scale for Clinical Severity* page of the eCRF, at Days 1, 4, 8, 16 and 29, as detailed in the SOE in Table 6.1-1 of the protocol, according to the scale shown below. The highest score on the day of score assessment will be recorded for that day.

Participant State	**Descriptor**	**Score**
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized mild disease	Hospitalized no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized severe disease	Non-invasive ventilation or high flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation and additional organ support, pressors, renal replacement therapy, extra corporeal membrane oxygenation	7
Dead	Death	8

For the intercurrent event of Death, participants will have an ordinal scale score of 8 imputed for each scheduled time point after death. For participants who are hospitalized at the timepoint of interest (using dates of hospitalization from the *Hospitalization and Acute care* page of the eCRF) (Day 1, 4, 8, 16 or 29), missing scores will be imputed as a score of 3. For all other missing scores, imputation will not be performed. A sensitivity analysis of this imputation will be performed as described in Section 16.2.3.13.

16.2.1.15. Resting Peripheral Oxygen Saturation Through Day 29

This will be both a quantitative measure (change from baseline, derived as per Section 6.6) and actual values categorized as follows: <96% and ≥96%.

16.2.1.16. The Prevalence, Severity, and Types of Persistent Symptoms and Clinical Sequelae In Participants Through End-of-Study Follow-up (Week 24).

Persistent symptoms are defined as any of the targeted symptoms used in the primary efficacy endpoint (see Section 16.1.1) remaining (not absent) at Week 24 follow-up.

Persistent symptoms and clinical sequelae will be defined as those symptoms still present at Weeks 12 or 24 based on the information provided in the *Post-Acute COVID-19 Questionnaire* page of the eCRF, i.e.,:

- Cough;
- Shortness of breath or difficulty breathing;
- Feeling feverish;
- Chills;
- Fatigue (low energy);
- Body pain or muscle pain or aches;
- Diarrhea;
- Nausea;
- Vomiting;
- Headache;
- Sore throat;
- Nasal obstruction or congestion
- Nasal discharge;
- Muscle weakness;

- Insomnia;
- Hair loss;
- Smell disorder;
- Palpitations or fast heart beat;
- Joint pain;
- Decreased appetite;
- Taste Disorder;
- Dizziness/balance issues;
- Chest pain;
- Skin rash;
- Difficulty with concentration and thinking;
- Difficulty reasoning and solving problems;
- Memory loss (short or long term).

The presence or not of any (rather than individual symptoms) will be assessed using the question "Please choose the response below that best describes the worst severity of your COVID-19 symptoms over the past 4 weeks". In addition, general health will be assessed using the question "Please choose the response below that best describes your general physical health over the past 4 weeks".

The return to pre-COVID-19 health at each of Weeks 12 and 24 will also be assessed, using the question "Have you returned to your usual (pre-COVID) health?" on the *Post-Acute COVID-19 Questionnaire* page of the eCRF.

16.2.1.17. Secondary Clinical Efficacy Endpoint Of The proportion of participants with persistent and/or late-onset symptoms of COVID-19 at Week 24

This secondary clinical efficacy endpoint is the proportion of participants with persistent and/or late-onset symptoms of COVID-19 at Week 24 based on participants' assessments of the 5 symptoms specified by the WHO (fatigue, shortness of breath/difficulty breathing, difficulty with concentration/ thinking, difficulty reasoning/solving problems, and memory loss) plus taste disturbance and smell disturbance among outpatient adults with SARS-CoV-2 starting intervention within 3 days of symptom onset.

A participant will be considered to have persistent and/or late-onset symptoms if either 1 of the following criteria is met:

- Occurrence of at least 1 of the following symptoms at Week 24: difficulty with concentration/thinking, difficulty reasoning/solving problems, or memory loss,

  or
- Occurrence of at least 1 of the following symptoms at both Week 12 and Week 24: fatigue, shortness of breath/difficulty breathing, taste disturbance, or smell disturbance (i.e., persistent symptoms)

At Week 12 and Week 24, the occurrence for persistent and/or late-onset symptoms of COVID-19 in the Post-acute COVID-19 Questionnaire is defined as mild or more in severity for each symptom.

16.2.1.18. Clinical Efficacy Endpoint Of The proportion of participants who had at least one symptom and whose usual health had not returned at each of Week 12 and At Week 24

This endpoint is related to persistent and/or late-onset symptoms of COVID-19, and is the proportion of participants who had at least one symptom and whose usual health (pre-COVID) had not returned at Week 12 and Week 24, when the participants meet the following:

- The answer to the comprehensive question "Have you returned to your usual (pre-COVID) health?" will be "No" in the PASC questionnaire.
- The severity of Mild, Moderate, or Severe will be observed in at least one symptom out of the 5 symptoms specified by WHO (fatigue, shortness of breath/difficulty breathing, difficulty with concentration/ thinking, difficulty reasoning/solving problems, and memory loss) plus taste disturbance and smell disturbance.

The similar analysis will be performed for the endpoint with the below targeted symptoms as well as the 5 symptoms specified by WHO plus taste disturbance and smell disturbance.

- At least one symptom out of the 15 symptoms for the primary endpoint
- At least one symptom out of the 4 neurological symptoms (concentration/ thinking, difficulty reasoning/solving problems, insomnia, and memory loss)

- At least one symptom out of all 27 symptoms (Section 16.2.1.16)
- Each of the 27 symptoms (Section 16.2.1.16)

16.2.1.19. Symptomatic Viral Rebound from Day 6 up to Day 29 With New or Worsening Clinical Symptoms

Symptomatic viral rebound (PCR) is defined as an increase in quantitative NP SARS-CoV-2 RNA levels by quantitative PCR from Day 6 up to Day 29 in the setting of new or worsening clinical symptoms, where viral rebound is defined in Section 16.2.1.20.

Symptomatic viral rebound (culture) is defined as an increase in NP SARS-CoV-2 viral culture from Day 6 up to Day 29 in the setting of new or worsening clinical symptoms, where viral rebound is defined in Section 16.2.1.20.

New or worsening clinical symptoms is defined as:

- At least one moderate or severe symptom recorded for at least 2 consecutive days in any of the targeted symptoms (from Day 6 up to and including Day 29) used in deriving the primary endpoint of the study (see Section 16.1.1).
- Occurring after a participant is deemed to have achieved symptom resolution as described in Section 16.1.1 (primary endpoint definition).
- Where, for each of the targeted symptoms, the most recent Day with non-missing symptom data up to and including the Day that viral rebound is detected, and the next day with non-missing data, will be compared with most recent (single) Day with non-missing symptoms data up to and including the previous visit that was used in determining viral rebound to determine whether new or worsening symptoms have been observed.
- For pre-existing symptoms that were present prior to COVID-19 onset, the following rule will be applied :
    - In the case of the pre-existing moderate symptoms considered by the participant not to have worsened at baseline, the targeted symptoms should become severe
    - In the case that pre-existing symptoms considered by the participant to have worsened to severe at baseline, the targeted symptoms should remain severe
    - In all other cases (i.e. pre-existing mild or moderate symptoms regardless of whether or not considered by the participant to have worsened at baseline due to COVID-19 or any other condition), targeted symptoms should worsen to severe or moderate.

For use in supplementary analyses, for participants who achieved the primary endpoint, symptomatic viral rebound will be defined as:

- New or worsening symptom clinical symptoms defined per the above and viral rebound are both observed from Day 6 up to and including Day 29 (regardless of when each event occurs) after the later of Day 6 or the day on which the primary endpoint was achieved.
- For pre-existing symptoms that were present prior to COVID-19 onset, the same the above rule is applied.

16.2.1.20. VIRAL REBOUND FROM DAY 6 UP TO DAY 29

Viral rebound (PCR) is defined as:

- an increase of at least 1.0 $\log_{10}$ from the previous non-missing visit when previous visit was detected;
- an increase to at least LLoQ + 1.0 $\log_{10}$ when the previous non-missing visit was below LLoQ;
- an increase to at least LoD + 1.0 $\log_{10}$ when the previous non-missing visit was undetected.

Viral rebound (culture) is defined as:

- an increase of at least 1.0 $\log_{10}$ from the previous non-missing visit when the previous non-missing visit was detected; and
- an increase to above or equal to LLoQ when the previous non-missing visit was undetected.

For each of viral rebound (PCR) and viral rebound (culture), for a sensitivity analysis, rebound will be defined as:

- an increase of at least 1.0 $\log_{10}$ from the previous non-missing visit when previous non-missing visit was detected and ≥ LLoQ;
- greater than or equal LLoQ when the previous non-missing visit was detected but below LLoQ;
- detected when the previous non-missing visit was undetected.

Unlike the endpoints in Section 16.2.1.19, for these endpoints, clinical symptoms are not considered.

16.2.1.21. MEASURES OF PSYCHOLOGICAL HEALTH, FUNCTIONAL HEALTH, AND HEALTH-RELATED QUALITY OF LIFE

Measures of psychological health, functional health, and health-related quality of life in participants through end of study follow--up (Week 24) (based on survey instruments – Post-acute COVID-19 questionnaire, Short Form 36 Health Survey Questionnaire, version 2 [SF-36v2] and EuroQol–5 Dimensions–5 Levels [EQ-5D-5L]). Refer to Section 17.1.1 for the definition of endpoints relating to SF-36v2 and EQ-5D-5L.

At Weeks 12, 24 and at premature study discontinuation, participants will complete a post-acute COVID-19 questionnaire. Items from this questionnaire relating to severity of COVID-19 symptoms, general health and return to pre-COVID-19 health are already included in Section 16.2.1.16.

The questionnaire also captures the following information relating to medical care:

- Sought urgent medical care at an emergency room or clinic for any of the above symptoms?
    - Yes; No.
- Been diagnosed by a doctor with any of the following problems?
    - Pulmonary embolism (a blood clot in the lungs) [Yes; No].
    - Deep vein thrombosis (a blood clot in the veins) [Yes; No].
    - Myocardial infarction (heart attack) [Yes; No].
    - Cerebrovascular accident (stroke) [Yes; No].
- Been newly prescribed any anticoagulant (blood thinning) medication?
    - Yes; No.
- Been newly prescribed any corticosteroid medication?
    - Yes; No.

16.2.1.22. DEATH DUE TO ANY CAUSE THROUGH WEEK 24 VISIT

The time to death due to any cause during the 24 weeks of follow-up from and including the day of the first dose of S-217622 or placebo will be derived as follows:

- (Date of death date) – (date of first dose of study intervention) + 1.

For participants alive at the time of analysis the time used in analyses will be derived as follows:

- (Date last known to be alive) – (date of first dose of study intervention) + 1.

16.2.2. Intercurrent Event Handling and Data Imputation for Key Secondary Efficacy Endpoints

16.2.2.1. KEY SECONDARY VIROLOGIC ENDPOINT

For the key secondary virologic endpoint SARS-CoV-2 RNA results may be below the assay LLoQ or above the ULoQ. For analyses of quantitative $\log_{10}$ SARS-CoV-2 RNA, baseline and Day 4 values will be imputed as follows for both formal and descriptive analyses:

- Baseline values below the LLoQ (= 2.0) will be imputed as equal to $\log_{10}$(10^LLoQ / 2) (= 1.7). In the case that values below a figure different from LLoQ of 2.0 such as "<2.11", those will be imputed in the same way as that for LLoQ. For example, <2.11 will be imputed as equal to $\log_{10}$(10^2.11 / 2).
- Values below the LLoQ, but detected, will be imputed as equal to $\log_{10}$(10^LLoQ / 2) (= 1.7). In the case that values below a figure different from LLoQ of 2.0 such as "<2.11", those will be imputed in the same way as that for the LLoQ. For example, <2.11 will be imputed as equal to $\log_{10}$(10^2.11 / 2);
- Values below the LLoQ and Not detected will be imputed as zero;
- Values above the ULoQ (= 8.0) will be imputed as equal to the $\log_{10}$ transformed $\log_{10}$(2 x 10^ULoQ); actual values obtained from assay reruns with dilution will be used instead, if available.
- Generally, NPH result will be used. If NPH result is missing and NAS result is only observed, NAS result will be used. Where duplicate values of NPH result are present for the same scheduled visit, the worst case (highest) value will be used in the analysis. The same is true in the case that NAS result is only observed at the same scheduled visit.

Intercurrent Event Handling

- For summaries and analyses, participants who are hospitalized for any cause or die from any cause prior to providing a Day 4 sample, but for whom a baseline sample is available, will have their change from baseline to Day 4 imputed as the worst change in RNA observed in those participants for whom a change can be calculated.
- For other intercurrent events (e.g., irrespective of whether a participant received all doses of S-217622/placebo, mAbs, molnupiravir, outpatient IV remdesivir, favipiravir, fluvoxamine, convalescent plasma, or any other antiviral medications), a treatment policy strategy will be used to evaluate intervention effects irrespective of the intercurrent event.

16.2.2.2. KEY SECONDARY CLINICAL ENDPOINTS

It is possible, that the number of hospitalizations/deaths in a randomized intervention group (S-217622 or placebo) will be very small and hence the asymptotic (large sample size) statistical theory underpinning the statistical analyses of this endpoint may be questionable. Further details about specific analysis rules are provided in Section 16.2.3.2. If there are zero events in both intervention groups, this will be stated and no formal statistical inferential analyses will be undertaken.

Participants will have follow-up censored at the date they were last known to be alive and not having met the definition of hospitalized (see Section 16.1.1) through Study (Day 29, i.e., up to 28 days post first dose of study intervention per Section 6.1). The primary analysis of the endpoint assumes non-informative censoring.

For the key secondary clinical endpoint of time in days from the start of study intervention until sustained resolution of all targeted symptoms (including those occurring prior to COVID-19 infection), and being alive and without hospitalization for any reason by Day 29, in the mITT1 set, the handling of intercurrent events and data imputation are the same as the primary efficacy endpoint (see Section 16.1.2).

For the key secondary clinical endpoint of proportion of participants with the persistent and/or late-onset symptoms of COVID-19 at Week 12, participants in whom this endpoint was not able to be evaluated due to intercurrent event such as death, hospitalization, losses to Follow-up or participants without intercurrent event but with missing in the Study Diary and/or in the Post-acute COVID-19 Questionnaire will be conservatively treated as those with the persistent and/or late-onset symptoms of COVID-19 at Week 12.

16.2.3. Analysis of Secondary Efficacy Endpoints

The analyses of key secondary efficacy endpoints will be performed on the mITT set as the primary analysis of the key secondary endpoint, and on the mITT1 set as a secondary analysis of the key secondary endpoint. Other secondary analysis of the key secondary endpoints will be also performed on the mITT2 set, but testing results from these analyses will not be included in the statistical hierarchy in Section 7.5. The exception is the endpoint in Section 16.2.1.3, which will only be analyzed on the mITT1 set (as the endpoint analyzed on the mITT set is the primary efficacy endpoint).

For the analyses of non-key secondary endpoints, the analysis sets to be used for these endpoints is provided in the relevant subsections (16.2.3.5 through 16.2.3.21).

16.2.3.1. Analysis of The Key Secondary Virologic Efficacy Endpoint

The number of participants with missing SARS-CoV-2 RNA results at each of Days 1 and 4 will be summarized along with the reasons for the missing data (e.g. hospitalization, death, sample obtained but no result, loss to follow-up, other).

For participants with baseline value < LLoQ the number and percentage of participants with results <LLoQ or ≥LLoQ at Day 4 will be provided.

Descriptive statistics will be used to describe the levels of $\log_{10}$ SARS-CoV-2 RNA at each of Days 1 and 4 for changes from baseline in $\log_{10}$ SARS-CoV-2 RNA at Day 4.

The population summary measure is the difference in mean change from baseline in $\log_{10}$ SARS-CoV-2 RNA at Day 4. To adjust for any (chance) imbalance between S-217622 and placebo groups at baseline (Day 1) and to increase precision, ANCOVA with baseline $\log_{10}$ SARS-CoV-2 RNA as a covariate will be used to obtain an estimate of the intervention group difference in mean and associated 95% CI adjusted for $\log_{10}$ SARS-CoV-2 at Day 1 (baseline).

Participants who are alive and not hospitalized on Day 4 but who have missing RNA values (including due to loss to follow-up, samples not obtained, lost samples, laboratory issues, etc.) will be excluded from the analysis: the missingness is assumed to be missingness completely at random. Based on experience in the similar ACTIV-2/A5401 study, such missingness is expected to be no more than about 10%.

Sensitivity Analyses

There will be three sensitivity analyses performed:

- The main analysis will be repeated without baseline $\log_{10}$ SARS-CoV-2 RNA in the model and an unadjusted estimate and associated 95% CI will also be obtained;
- The main analysis of this endpoint will be repeated with missing data on Day 4 having change from baseline treated as zero (i.e., baseline observation carried forward approach).
- The main analysis will be repeated, restricting only to participants with baseline SARS-CoV-2 RNA ≥ LLoQ.
- The median regression analysis will be conducted to obtain an estimate of the intervention group median difference with associated 95% CI in terms of the change from baseline in $\log_{10}$ SARS-CoV-2 RNA at Day 4,

with baseline $\log_{10}$ SARS-CoV-2 RNA as a covariate. The median regression analysis will consider post-baseline $\log_{10}$ SARS-CoV-2 RNA values below the LLoQ as having left censored change from baseline measurements with the censored value = LLoQ minus baseline value.

Based on data previously obtained in the ACTIV-2/A5401 study, it is possible that the mean change in $\log_{10}$ SARS-CoV-2 RNA in a group may not be observed (if many Day 4 RNA values are below the LLoQ) making the estimation of the difference in medians difficult (though a bound on the difference may still be possible if the median in one group is observed). In this case, the analysis of the secondary endpoint of percentage of participants with SARS-CoV-2 RNA less than the LLoQ will become more important in interpreting possible intervention effects at that time.

Subgroup Analyses

In addition, the primary analysis of the key secondary virologic efficacy endpoint will be repeated within each of the subgroups specified in Section 7.6.

Within each subgroup, the difference in means between intervention groups along with its 95% CI will be estimated.

It should be noted that the sample size for these subgroup analyses will be smaller than for the primary analysis, with a subsequent reduction of power to detect a statistically significant difference between intervention groups.

A forest plot of the intervention group difference in means and corresponding 95% CI for each subgroup, and the primary analysis result for this endpoint, will be produced.

16.2.3.2. Analysis of The Key Secondary Clinical Efficacy Endpoint of The Cumulative Proportion of Participants Hospitalized Due to COVID-19 or Died (Due to Any Cause), From Day 1 Through Day 29

The analysis will compare the cumulative proportion of participants hospitalized due to COVID-19 or died (due to any cause), from Day 1 through Day 29, between randomized intervention groups using a ratio of proportions. Hospitalizations that begin on Day 29 and deaths that occur on Day 29 will be included. The cumulative proportion will be estimated for each intervention group using Kaplan-Meier methods to account for losses to follow up (and differences in follow-up between the two intervention groups). Participants will have follow-up censored at the date they were last known to be alive and not hospitalized through Day 29. The primary analysis assumes non-informative censoring.

The absolute difference in the estimated log-cumulative proportion will be calculated between randomized arms; a 95% CI will be obtained for this difference in log-cumulative proportion calculated using a variance for this difference being the sum of the variances for each randomized intervention group obtained using Greenwood's formula. Results will be anti-logged to give the estimated ratio of cumulative proportions through Day 29 (S-217622 vs placebo). A 2-sided 95% CI for this risk ratio, and p-value (for the test of no difference between intervention groups) will be obtained.

Derivations: The estimated intervention effect on the log scale is determined by calculating the difference between arms in log-transformed cumulative proportion estimated using Kaplan-Meier methods:

$$\hat{\delta} = \ln(\hat{p}_{active}) - \ln(\hat{p}_{placebo}).$$

The standard error (SE) of the intervention effect on the log scale is determined by taking the square root of the sum of the variances of log-transformed cumulative proportion in each arm:

$$SE(\hat{\delta}) = \sqrt{var[ln(\hat{p}_{active})] + var[ln(\hat{p}_{placebo})]},$$

with the variances obtained using Greenwood's formula. The estimated risk ratio comparing active agent to placebo is then estimated by $\exp(\hat{\delta})$, with CI calculated by taking the exponential of the confidence bounds for δ calculated on the log scale. A Wald test of the null hypothesis of no intervention effect can be constructed using the z-statistic equal to $\hat{\delta}/SE(\hat{\delta})$.

A cumulative incidence plot of the time to death due to any cause or hospitalization due to COVID-19 will be provided.

Note: using a standard rule of thumb, if there are fewer than 5 events (hospitalizations/deaths) in either intervention group, inference based on Fisher's exact test to compare arms will be adopted instead of using Greenwood's formula to calculate CIs for the difference between intervention groups and associated p-values. If there are zero events in both intervention groups, this will be stated and no formal statistical inferential analyses will be undertaken.

Subgroup Analyses

In addition, the primary analysis of the key secondary clinical efficacy endpoint will be repeated within each of the subgroups specified in Section 7.6. Within each subgroup the 2-sided 95% CI for this risk ratio (S-217622 vs placebo) will be obtained.

It should be noted therefore that the sample size for the analysis will be smaller than for the analysis of this

endpoint, with a subsequent reduction of power to detect a statistically significant difference between intervention groups.

Within each subgroup, the difference between randomized arms in the log-proportion will be estimated.

In the event that the number of events in a subgroup in either intervention group is low (less than 5), descriptive summaries (i.e., no confidence intervals) of the number of COVID-19 related hospitalizations and deaths by subgroup and intervention group will be provided.

A forest plot of the risk ratio and corresponding 95% CI for each subgroup, and the main analysis result for the key secondary clinical efficacy endpoint, will be produced.

16.2.3.3. Analysis of The Key Secondary Clinical Efficacy Endpoint of Time to Sustained Resolution of All Targeted symptoms and Being Alive and Without Hospitalization for any Reason by Day 29

The analysis of this endpoint will be identical to the primary analysis of the primary endpoint (see Section 16.1.3) but in the mITT1 set.

16.2.3.4. Analysis of The Key Secondary Clinical Efficacy Endpoint of The proportion of participants with persistent and/or late-onset symptoms of COVID-19 at Week 12

The number and proportion of participants with the persistent and/or late-onset symptoms of COVID-19 at Week 12 defined in Section 16.2.1.4 will be summarized, and the proportion of participants with the persistent and/or late-onset symptoms of COVID-19 at Week 12 will be compared using a risk ratio (S-217622 vs placebo), along with a 95% CI of the risk ratio and associated p-value. This analysis will be performed on the mITT and the mITT1 sets.

Participants in whom this endpoint was not able to be evaluated due to missing in the Study Diary and/or in the Post-acute COVID-19 Questionnaire will be treated as those with the persistent and/or late-onset symptoms of COVID-19 at Week 12.

For supplementary analyses, the same analyses will be performed with participants who have evaluated measurements in the Study Diary and/or in the Post-acute COVID-19 Questionnaire. This supplementary analysis will be performed on the mITT and the mITT1 sets.

16.2.3.5. Analysis of Time to Sustained Resolution of 6 Targeted Symptoms and Being Alive and Not Hospitalized for any Reason by Day 29

The analysis of this endpoint will be identical to the primary analysis of the primary endpoint (see Section 16.1.3). As supplementary analyses, the treatment groups will be compared using Peto-Prentice's generalized Wilcoxon test (Section 16.1.5). These analyses will be performed on the mITT set.
For handling of participants with symptoms resolution regarding the 6 targeted symptoms on Day 1, the same rule in Section 16.1.3 will be applied to 6 targeted symptoms.

Supportive analyses will be carried out in a similar manner to the above analysis of this endpoint but for symptom resolution based on 1 consecutive day with Day 29, being the last day that the outcome can be achieved. For the endpoint of symptom resolution based on 1 consecutive day of resolution, censoring will occur on Day 29, and the tau use in the restricted mean duration analysis will be 28. For this endpoint, Peto-Prentice's generalized Wilcoxon test will be applied to compare the treatment groups. These analyses will be performed on the mITT set. Peto-Prentice's generalized Wilcoxon test will also be applied on a subgroup of participants starting study intervention within 2 days of symptom onset out of the mITT set. In the supportive analyses, in case of participants with symptoms resolution based on 1 consecutive day regarding the 6 targeted symptoms on Day 1, these participants will be excluded from the analyses.

16.2.3.6. Analysis of Time to Sustained Resolution of Targeted Symptoms (Excluding Loss of Taste and Loss of Smell) and Being Alive and Not Hospitalized for any Reason by Day 29

The analysis of this endpoint will be identical to the primary analysis of the primary endpoint (see Section 16.1.3). As supplementary analyses, the treatment groups will be compared using Peto-Prentice's generalized Wilcoxon test (Section 16.1.5). These analyses will be performed on the mITT set.

Supportive analysis includes the same analysis as the primary analysis of the primary endpoint on a subgroup of participants starting study intervention within 2 days of symptom onset out of the mITT set.

For handling participants with symptoms resolution regarding the 13 targeted symptoms (excluding loss of taste and loss of smell) on Day 1, the same rule in Section 16.1.3 will be applied to 13 targeted symptoms.

16.2.3.7. Analysis of Hospitalization Due to Any Cause and All Deaths Through Day 29

The analysis of this endpoint will be identical to the analysis of the key secondary efficacy endpoint (see Section 16.2.3.2), but excluding subgroup analyses. The analysis will be performed on the mITT set.

16.2.3.8. Analysis of SARS-CoV-2 RNA in NP Swabs <LLoQ at Each of Days 4 and 8

Descriptive statistics (number and percentage) will be used to describe the proportion of participants with SARS-CoV-2 RNA < LLoQ and those with SARS-CoV-2 RNA ≥ LLoQ from staff-collected NP swabs at each of Days 1, 4 and 8.

The proportion of participants with SARS-CoV-2 RNA < LLoQ at each of Days 4 and 8, separately, will be compared between intervention groups using the absolute difference in proportion, with a 95% CI of the difference in proportions and p-value (for the test of no difference between intervention groups) calculated using the normal approximation to the binomial distribution.

Missing data are assumed to be missing completely at random (MCAR) and will be ignored in these analyses.

As a sensitivity analysis, at each of Day 4 or 8, if results are missing due to the intercurrent events of death (on or prior to each of Day 4 or Day 8) or hospitalization (at Day 4 and/or Day 8 respectively) then the result will be imputed as ≥ LLOQ.

The analysis will be performed on the mITT set.

16.2.3.9. Analysis of Change from Baseline in Quantitative Log_{10} SARS-CoV-2 RNA Levels by PCR in NP Swabs at Day 8

The main analyses of this secondary endpoint will be the same as the Day 4 version of this endpoint (the key secondary virologic endpoint), see Section 16.2.3.1.

Sensitivity analyses for this endpoint will be as follows:

- The main analysis will be repeated without baseline log_{10} SARS-CoV-2 RNA in the model and an unadjusted estimate and associated 95% CI will also be obtained;
- The main analysis of this endpoint will be repeated with non-missing Day 4 result used if Day 8 result is

missing, (i.e., last observation carried forward). If Day 4 is also missing, change from baseline will be treated as zero.

- The main analysis will be repeated, restricting only to participants with baseline SARS-CoV-2 RNA ≥ LLoQ.

Based on data previously obtained in the ACTIV-2/A5401 study, it is possible that the median SARS-CoV-2 RNA in a group will be below the LLoQ making the estimation of the difference in medians difficult (though a bound on the difference may still be possible if the median in one group is observed). In this case, the analysis of the secondary endpoint of percentage of participants with SARS-CoV-2 RNA less than the LLoQ will become more important in interpreting possible intervention effects at Day 8.

16.2.3.10. Analysis of Change from Baseline in Quantitative Viral Culture Levels in NP Swabs at Days 4 and 8

The main analyses of this secondary endpoint will be the same as the Day 4 version of this endpoint (the key secondary virologic endpoint), see Section 16.2.3.1.
For quantitative viral culture, baseline and Day 4 or Day 8 values will be imputed as follows for both formal and descriptive analyses:

- Values below the LLoQ (=1.0), but detected, will be imputed as 0.75;
- Values below the LoD (=0.75) will be imputed as 0.5;
- Values above the ULoQ (=5.40) will be imputed as 5.5.

The analysis will be performed on the VC set and the additional set which consists all participants in the mITT1 population who have documented viral culture at baseline, i.e., detectable (>LLoQ) viral culture result at baseline.

16.2.3.11. Analysis of Detectable SARS-CoV-2 by Viral Culture at Days 4 and 8

Analysis of undetectable viral culture at Days 4 and 8 will be undertaken in the same way as the SARS-CoV-2 RNA <LLoQ endpoint, i.e., descriptive statistics (number and percentage) will be used to describe the proportion of participants with undetectable and detectable viral culture, at Days 4 and 8.

The proportion of participants with undetectable viral culture at each of Days 4 and 8, separately, will be compared between intervention groups using the absolute difference in proportion, with a 95% CI of the difference in

proportions p-value (for the test of no difference between intervention groups) calculated using the normal approximation to the binomial distribution.

The analysis will be performed on the VC set.

16.2.3.12. Analysis of Time to Self-reported Return to Usual (pre-COVID-19) Health Through Day 29

Time to self-reported return to usual (pre-COVID-19) health will be summarized and analyzed undertaken in the same way as the primary analysis of the symptom duration endpoint (the primary efficacy endpoint).

The analysis will be performed on the mITT set.

16.2.3.13. Analysis of Proportion of Participants Having a Score of ≥2, ≥3, ≥4, ≥5, ≥6, ≥7, or ≥8 On The Ordinal Scale

Proportion of participants reaching a score ≥2, ≥3, ≥4, ≥5, ≥6, ≥7, or ≥8 on the ordinal scale at each scheduled timepoint will be summarized, and analyzed using Fishers exact test and an exact 95% CI for the absolute difference in proportions (S-217622 versus placebo) will be calculated using the Chan and Zhang method[2].

A sensitivity analysis will be performed with missing scores for participants who are hospitalized at the timepoint of interest (using dates of hospitalization from the *Hospitalization and Acute care* page of the eCRF) (Day 1, 4, 8, 16 or 29), missing scores will be imputed as a score of 7. This is a worst-case imputation for such missing data, compared to the best-case imputation of a score of 3, used in the main analysis for these endpoints.

These analyses will be performed on the mITT set.

16.2.3.14. Analysis of Resting Peripheral Oxygen Saturation Through Day 29

Analysis of change from baseline resting peripheral oxygen saturation as a quantitative measure will be undertaken for each scheduled measurement time in the same way as the analysis of the key secondary virology efficacy endpoint of quantitative $\log_{10}$ SARS-CoV-2 RNA (see Section 16.2.3.1, i.e., via median regression adjusted for baseline resting peripheral oxygen). A sensitivity analysis (i.e., median regression without adjusting for baseline resting peripheral oxygen) will be performed.

Descriptive statistics (number and percentage) will be used to describe the proportion of participants with either

resting peripheral oxygen <96% or ≥96% at each scheduled timepoint.

The proportion of participants with resting peripheral oxygen ≥96%, at each post-baseline scheduled visit separately, will be compared between intervention groups using the absolute difference in proportion, with a 95% CI of the difference in proportions and a p-value (for the test of no difference between intervention groups) calculated using the normal approximation to the binomial distribution.

The analysis will be performed on the mITT set.

16.2.3.15. Analysis of The Prevalence, Severity, And Types of Persistent Symptoms And Clinical Sequelae In Participants Through End-of-Study Follow-up (Week 24).

The number and proportion of participants with the worst-severity of any COVID-19 symptoms over the past 4 weeks (No symptoms, Mild, Moderate and Severe) at Week 12 and Week 24 will be summarized, and the proportion of participants with any severity other than No symptoms, i.e., Mild, Moderate or Severe will be compared using a risk ratio (S-217622 vs placebo), along with a 95% CI of the risk ratio and associated p-value. The general physical health over the past 4 weeks (Excellent, Very good, Good, Fair and Poor) will be summarized and the proportion of participants with Poor general physical health will be analyzed in the same way as the worst-severity of any COVID-19 symptoms over the past 4 weeks.

For each of the symptoms described in Section 16.2.1.16, the number and proportion of participants with the worst-severity of the symptom over the past 4 weeks (Absent, Mild, Moderate and Severe) at Week 12 and Week 24 will be summarized, and the proportion of participants with each of the Post-Acute COVID-19 symptoms remaining (not Absent) at Week 12 and Week 24 follow-up will be summarized. Intervention groups will be compared using a risk ratio (S-217622 vs placebo), along with a 95% CI of the risk ratio and associated p-value.

The return to usual (pre-COVID) health (Yes, No) at Week 12 and 24 will be summarized and the proportion of participants who answered Yes will be analyzed in the same way as the worst-severity of any COVID-19 symptoms over the past 4 weeks.

Only participants with symptoms data at each of Weeks 12 and 24 respectively will be included in the analysis.

The analysis will be performed on both the mITT and mITT1 sets.

16.2.3.16. Analysis of Symptomatic Viral Rebound from Day 6 up to Day 29 With New or Worsening Clinical Symptoms

The proportion of participants with symptomatic viral rebound at any time during Day 6 to Day 29 will be summarized, and analyzed using Fishers exact test and an exact 95% CI for the absolute difference in proportions (S-217622 versus placebo) will be calculated using the Chan and Zhang method[2].

Only participants with measurements from Day 6 to Day 29 of quantitative NP SARS-CoV-2 viral culture or NP SARS-CoV-2 RNA levels by quantitative PCR, and with post-Day 4 symptom assessment, will be included in the analysis.

This analysis will be performed on both the mITT and mITT1 sets.

A sensitivity analysis will be performed in an identical manner using an alternative definition of viral rebound as described in Section 16.2.1.20.

Supplementary analyses will be performed, using the alternative definition of symptomatic viral rebound as described in the final paragraph of Section 16.2.1.19. These supplementary analyses will be performed using each of the definition of viral rebound (PCR and Culture) and the corresponding sensitivity analysis definitions of viral rebound (PCR and Culture) found in Section 16.2.1.20.

16.2.3.17. Analysis of Viral Rebound from Day 6 up to Day 29

The proportion of participants with viral rebound at any time during Day 6 to Day 29 will be summarized, and analyzed using Fishers exact test and an exact 95% CI for the absolute difference in proportions (S-217622 versus placebo) will be calculated using the Chan and Zhang method[2].

Only participants with measurements from Day 6 to Day 29 of quantitative NP SARS-CoV-2 viral culture or NP SARS-CoV-2 RNA levels by quantitative PCR, will be included in the analysis.

This analysis will be performed on both the mITT and mITT1 sets.

A sensitivity analysis will be performed in an identical manner using an alternative definition of viral rebound as described in Section 16.2.1.20.

16.2.3.18. Analysis of Proportion of Participants with Persistent and/or Late-Onset Symptoms of COVID-19 at Week 24

The number and proportion of participants with the persistent and/or late-onset symptoms of COVID-19 at Week 24 defined in Section 16.2.1.17 will be summarized, and the proportion of participants with the persistent and/or late-onset symptoms of COVID-19 at Week 24 will be compared using a risk ratio (S-217622 vs placebo), along with a 95% CI of the risk ratio and associated p-value. This analysis will be performed on the mITT and the mITT1 sets.

Participants in whom this endpoint was not able to be evaluated due to missing in the Study Diary and/or in the Post-acute COVID-19 Questionnaire will be treated as those with the persistent and/or late-onset symptoms of COVID-19 at Week 24.

For supplementary analyses, the same analyses will be performed with participants who have evaluated measurements in the Study Diary and/or in the Post-acute COVID-19 Questionnaire. This supplementary analysis will be performed on the mITT and the mITT1 sets.

16.2.3.19. Analysis of of Proportion of Participants Who Had at Least One Symptom and Whose General Health Had Not Returned at Week 12 and At Week 24

The number and proportion of participants who had at least one symptom and whose general health had not returned at Week 12 and Week 24 defined in Section 16.2.1.18 will be summarized, and the proportion of participants who had at least one symptom and whose general health had not returned at Week 12 and Week 24 will be compared using a risk ratio (S-217622 vs placebo), along with a 95% CI of the risk ratio and associated p-value. This analysis will be performed on the mITT and the mITT1 sets.

Participants in whom this endpoint was not able to be evaluated due to missing in the Study Diary and/or in the Post-acute COVID-19 Questionnaire will be treated as those who had at least one symptom and whose general health had not returned at Week 12 and at Week 24.

For supplementary analyses, the same analyses will be performed with participants who have evaluated measurements ~~in the Study Diary and/or~~ in the Post-acute COVID-19 Questionnaire. This supplementary analysis will be performed on the mITT and the mITT1 sets.

16.2.3.20. ANALYSIS OF MEASURES OF PSYCHOLOGICAL HEALTH, FUNCTIONAL HEALTH, AND HEALTH-RELATED QUALITY OF LIFE

At each scheduled visit, responses to each individual question in Section 16.2.1.21 from the Post-acute COVID-19 questionnaire, will be descriptively summarized for participants at each scheduled visit. The analysis will be performed on both the mITT and mITT1 sets.

For analyses relating to SF-36v2 and EQ-5D-5L, refer to Section 17.1.3.

16.2.3.21. ANALYSIS OF DEATH DUE TO ANY CAUSE THROUGH WEEK 24

Proportion of participants with death due to any cause during the 24 weeks of follow-up including the day of the first dose of S-217622 or placebo will be analyzed using the same approach as for the analysis of the secondary efficacy endpoint of hospitalization or death through Day 29 (see Section 16.2.1.8).

This analysis will be performed on the mITT set.

16.3. Exploratory Efficacy

Exploratory efficacy analyses to be added in future versions of this SAP, while some of them will be conducted dependent on the outcomes of the pre-specified efficacy analyses.

17. QUALITY OF LIFE ANALYSIS

Psychological Health, Functional Health, and Health-related Quality of Life will be assessed using the following survey instruments – Post-acute COVID-19 questionnaire, SF-36v2 and EQ-5D-5L.

17.1.1. Endpoints & Derivations

17.1.1.1. SF-36v2

SF-36 is a 36-item, participant-reported survey of participant health.
SF-36 measures eight scales: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH).

Two sets of scores will be derived from the SF-36: eight scale scores, and two summary scores: physical component summary (PCS) score and mental component summary (MCS) scores. Licensed software from the vendor QualityMetrics will be used to perform the derivation of SF-36 scores.

Change from baseline at each scheduled visit will be derived for each of scale score and the PCS and MCS scores as described in Section 6.6.

17.1.1.2. ED-5D-5L

The EQ-5D-5L is a health Status instrument for self-reported assessment of 5 domains of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain is rated by selecting 1 of 5 standardized categorizations ranging from no problem to extreme problem. The final question is a visual analogue scale (VAS) to rank health status from best health imaginable (100) to worst health imaginable (0).

EQ VAS is a 0-100 scale where the participants are asked to self-rate health. The VAS can be used as a quantitative measure of health outcome that reflects the participant's own judgement.

Change from baseline at each scheduled visit will be derived for each of the VAS as described in Section 6.6.

17.1.2. Intercurrent Event Handling and Data Imputation

Data will be summarized using a treatment policy approach.

If questionnaires are not completed for any reason, including hospitalization or death, no imputation will be performed for these data.

17.1.3. Analysis of QOL Endpoints

All analyses of QOL endpoints will be performed on the mITT set.

17.1.3.1. Analysis of SF-36v2

The actual scores and the change from baseline in for the eight scale scores and the two summary scores will be summarized descriptively at each scheduled visit.

At each scheduled visit, for each scale score and the two summary scores, an analysis of covariance (ANCOVA) will be performed to compare the change from baseline between the two groups, with randomize study intervention and baseline score in the ANCOVA model. For each intervention group, the least-squares mean and standard error will be provided for the change from baseline, and the least-squares mean and its 95%CI will be provided for the intervention group difference.

17.1.3.2. ANALYSIS OF EQ-5D-5L

The 5 domains of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression will be summarized via the number and percentage of participants in each of the 5 levels of the domain at baseline and each post-baseline scheduled visit, and also via shift tables of baseline level vs post-baseline level, for each domain, at each post-baseline scheduled visit.

The actual scores and the change from baseline in the VAS will be summarized at each scheduled visit.

For the VAS score, ANCOVAs will be performed, as described in Section 17.1.3.1.

18. SAFETY OUTCOMES

All safety analyses and summaries will be presented by intervention group based on the SAF. Unless otherwise specified there will be no statistical comparisons between the intervention groups for safety data.

For the Primary Analysis, safety analyses will be performed on all data through Study Day 29, with adverse event data also summarized on all available data (including data beyond Day 29).

18.1. Adverse Events

AEs will be coded using MedDRA central coding dictionary, Version 23.0 or higher.

Treatment emergent AEs (TEAEs) are defined as AEs that started on or after the date/time of first dose of study intervention.

See APPENDIX 3 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e., treatment emergent.

Summaries by SOC and PT will be sorted as follows: SOCs will be sorted by decreasing order of total number of participants with the event, and within each SOC, PTs will be sorted by decreasing order of total number of participants with the event.

Should a participant experience multiple events within a category, the participant will be counted only once for that category.

An overall summary of number and percentage of participants within each of the categories described in the sub-sections below, will be provided.

In addition, Kaplan-Meier methods will be used in each intervention group (S-217622 or placebo) to estimate the cumulative proportion of participants experiencing a TEAE along with its corresponding 95% CI and a cumulative incidence plot of the time to first occurrence of any TEAE will be provided. Participants will be included in the analysis based on the time in days to their first TEAE and participants with no TEAEs will be censored at their date of study completion or discontinuation.

Listings will include TEAEs and Non-TEAEs.

18.1.1. All TEAEs

Incidence of TEAEs will be presented overall and by SOC and PT and broken down further by maximum severity and relationship to study intervention.

18.1.1.1. Severity

Severity will be classed as mild (Grade 1)/ moderate (Grade 2)/ severe (Grade 3)/ potentially life threatening (Grade 4), death (Grade 5) based on the DAIDS AE Grading Table, corrected Version 2.1, July 2017 DAIDS Adverse Event Grading Tables | DAIDS Regulatory Support Center (RSC) (nih.gov)

TEAEs starting after the first dose of study intervention with a missing severity will be classified as severe. If a participant reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

18.1.1.2. Relationship to Study Intervention

Relationship to study intervention, as indicated by the Investigator, is classed as not related, or related. TEAEs with a missing relationship to study intervention will be regarded as related to study intervention in summaries of AEs.

If a participant reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study intervention will be used in the corresponding relationship summaries.

Relationship to non-study treatment and relationship to study procedure for TEAEs will not be summarized but will be provided in data listings.

18.1.1.3. Timing of Onset

Incidence of all TEAEs by SOC and PT will also be provided separately based on day of onset, for the periods up to and including Day 29, and Day > 29.

18.1.2. TEAEs Leading to Study Discontinuation

TEAEs leading to study discontinuation are those events recorded with Yes for *Did the AE cause the subject to*

discontinue from the study? on the *Adverse Events* page of the eCRF. A summary of TEAEs leading to study discontinuation overall and by SOC and PT will be prepared.

A listing of all AEs leading to study discontinuation will be provided.

18.1.3. TEAEs Leading to Discontinuation of Study Intervention

TEAEs leading to permanent discontinuation of study intervention are those events recorded with *Action Taken with study treatment* of *Drug withdrawal* on the *Adverse Events* page of the eCRF. A summary of TEAEs leading to permanent discontinuation of study intervention overall and by SOC and PT will be prepared.

In addition, a similar summary will be provided for TEAEs leading to permanent discontinuation of study intervention that are related to study intervention.

A listing of all AEs leading to permanent discontinuation of study intervention will be provided.

18.1.4. TEAEs Leading to Drug Interruption

TEAEs leading to drug interruption are those events recorded with *Action Taken with study treatment* on the *Adverse Events* pages of the eCRF of *Drug interrupted*. A summary of TEAEs leading to drug interruption by SOC and PT will be prepared.

18.1.5. Serious Adverse Events

SAEs are those events recorded as *Serious* on the *Adverse Events* page of the eCRF. A summary of serious TEAEs overall and by SOC and PT will be prepared.

In addition, a similar summary will be provided for serious TEAEs that are related to study intervention.

A listing of all SAEs will be provided

18.1.6. Commonly Occurring Non-Serious Adverse Events

Number and percentage of participants with at least one most common non-serious TEAE will be presented by PT,

where most common is defined as a PT with at least 5% of participants in at least one intervention group.

18.1.7. Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded with outcome of *Fatal* on the *Adverse Event*s page of the eCRF. A summary of TEAEs leading to death overall and by SOC and PT will be prepared.

18.1.8. Adverse Events Of Special Interest

An adverse event of special interest (AESI) (serious or nonserious) is defined as an AE or SAE of scientific and medical concern specific to the investigational agent, for which ongoing monitoring and rapid communication by the investigator to the sponsor **is** appropriate.

Rash is an AESI for this study; all new rashes occurring from the time of study enrollment to Day 29 should be reported with any treatment required, time to resolution and investigator evaluation of relationship to study intervention.

AESIs will be identified via the response to the question *Was the event an AE of Special Interest?* on the *Adverse Events* page of the eCRF.

A summary of treatment-emergent AESIs overall and by SOC and PT will be prepared. This will include AESIs recorded at any time, noting however that AESIs are only panned to be collected up to Day 29.

18.1.9. New Grade 3 or Higher AEs Through 29 Days and Through 24 Weeks

For these secondary endpoints a treatment policy approach will be taken in the analysis (i.e., there are no intercurrent events that affect the variable of interest-note that death is a Grade 5 AE and hence determines the value of the variable of interest).

To handle censoring due to loss to follow-up before Day 29 in statistical analysis, and for participants who reach Day 29 with no new Grade 3 or higher AE, a time variable for study day of first new Grade 3 or higher AE or censoring (earlier of Day 29 or day of last contact with participant) will be created as follows:

- (The start date of the AE, if on or before Day 29) – (date of first dose of study intervention) + 1.

Similarly for participants with no new Grade 3 of higher AE on or before Day 29 the censored time used in analyses will be derived as follows:

- (Earliest date from date of Day 29 and date of last contact) – (date of first dose of study intervention) + 1.

To handle censoring due to loss to follow-up before Week 24 in statistical analysis, and for participants who reach Week 24 with no new Grade 3 or higher AE a time variable for study day of first new Grade 3 or higher AE or censoring (earlier of Day 169 or day of last contact with participant) will be created as follows:

- (The start date of the AE, if on or before Day 169) – (date of first dose of study intervention) + 1.

Similarly for participants with no new Grade 3 of higher AE on or before Day 169 the censored time used in analyses will be derived as follows:

- (Earliest date from date of Day 169 and date of last contact) – (date of first dose of study intervention) + 1.

The date of last contact will be the date of discontinuation recorded on the *Disposition* page of the eCRF.

Kaplan-Meier methods will be used in each intervention group to estimate the cumulative proportion (and its 95% CI) of participants having a new Grade 3 or higher AE by each of Day 29 and Week 24 taking account of censoring due to loss to follow-up, which is assumed to be noninformative. This endpoint will be analyzed in a similar way to the one of the key secondary clinical efficacy endpoints (see Section 16.2.3.2), i.e., the absolute difference in the estimated log-cumulative proportion of new Grade 3 or higher AEs will be calculated between randomized arms; a 95% CI will be obtained for this difference in log-cumulative proportion calculated using a variance for this difference being the sum of the variances for each randomized intervention group obtained using Greenwood's formula. Results will be anti-logged to give the estimated ratio of cumulative proportions through each of Day 29 and Week 24 (S-217622 vs placebo) and associated 95% CI. A 2-sided 95% CI and p-value (for the test of no difference between groups) will be obtained.

Cumulative incidence plots of the time to first new Grade 3 or higher AE by each of Day 29 and Week 24 will be provided.

18.1.10. New Grade 2 or Higher AEs Through 29 Days and Through 24 Weeks.

For the secondary endpoints of new DAIDS Grade 2 or higher AEs through Day 29 and through Week 24, the derivation of the appropriate indicator variables and the time to event/censoring will be identical to that described for new Grade 3 or higher AEs in Section 18.1.9.

The analysis of this secondary endpoint and associated cumulative incidence plots will be the same as for new Grade 3 or Higher AEs (see Section 18.1.9).

18.2. Deaths

If any participants die during the study, as recorded on the *Death Details* page of the eCRF, the number of deaths will be summarized and death details, including primary cause of death, will be presented in a data listing.

All deaths, and deaths up to and including Day 29 will be summarized separately for both the Primary Analysis and the Final Analysis.

18.3. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for Hematology and Chemistry. A list of laboratory assessments to be included in the outputs is included in APPENDIX 5.

Local laboratory data, if captured, will be listed only.

The data from the central laboratory will be provided in SI units.

Quantitative laboratory measurements reported as "< X", i.e., below the lower limit of quantification or "> X", i.e., above the upper limit of quantification, will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e., as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by scheduled visit.
- Line plots (mean +/SE) of actual values over time, by scheduled visit.
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical

measurements) at each post-baseline visit.

- Shift from baseline to the minimum post-baseline value, according to normal range criteria (for quantitative measurements and categorical measurements).
- Shift from baseline to the maximum post-baseline value, according to normal range criteria (for quantitative measurements and categorical measurements).
- Shift from baseline according to worst post-baseline grade according to DAIDS toxicity grading system.
- Listing of participants with DAIDS Grade 3 or higher laboratory toxicities.
- Maximum post-baseline ALT/AST observed value categorized as < 3 x upper limit of normal (ULN), ≥ 3 to < 5 x ULN, ≥ 5 to < 10 x ULN or ≥ 10 ULN by concurrent post-baseline total bilirubin observed value categorized as < 2 x ULN or ≥ 2 x ULN.
- Scatter plot of all post-baseline observed ALT values by the concurrent post-baseline observed total bilirubin values, both expressed as multiple of ULN.
- Scatter plot of all post-baseline observed AST values by the concurrent post-baseline observed total bilirubin values, both expressed as multiple of ULN.
- A listing of participants with at least one observed value in ALT value > 3 x ULN, AST value > 3 x ULN or total bilirubin value ≥ 2 x ULN will be provided.

18.3.1. Laboratory Reference Ranges

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range;
- Normal: Within the laboratory reference range (upper and lower limit included);
- High: Above the upper limit of the laboratory reference range.

18.3.2. DAIDs Grading for Laboratory Data

Laboratory measurements will be graded using the DAIDs Toxicity grading system as defined in the following

document: DAIDS Adverse Event Grading Tables | DAIDS Regulatory Support Center (RSC) (nih.gov).

The criteria, specific to the hematology and chemistry parameters being collected in this study are provided in APPENDIX 6.

18.4. Vital Signs

The following vital sign parameters will be collected for this study as part of the targeted physical examination per the SOE (refer to protocol, Table 6.1-1):

- Systolic blood pressure (SBP) (mmHg);
- Diastolic blood pressure (DBP) (mmHg);
- Pulse rate (beats per minute [bpm]);
- Resting peripheral oxygen saturation (%);
- Body temperature (degrees celsius).

The following summaries will be provided by intervention group based on the SAF for each vital sign parameter:

- Observed and change from baseline by visit.
- Line plots of mean +/ SE over time for observed values.
- Number and percentages of participants with at least one markedly abnormal post-baseline observed value (refer to Section 18.4.1).
- Listing of participants with at least one markedly abnormal observed value/change from baseline (refer to Section 18.4.1).

All vital signs data will be listed.

18.4.1. Vital Signs Markedly Abnormal Criteria

Markedly abnormal vital sign observed values and/or change from baseline will be identified in accordance with the following predefined markedly abnormal criteria:

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
DBP	mmHg	≤ 50 mmHg AND change from ≤ -15 mmHg	≥ 105 mmHg AND change from baseline ≥ 15 mmHg
Pulse rate	bpm	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm
Body temperature	°C	Not applicable	≥ 38.3 °C AND change from baseline ≥ 1.1 °C

18.5. Targeted Physical Examination

A targeted physical examination including vital signs (temperature, pulse, blood pressure, and resting peripheral oxygen saturation) and examinations driven by any previously identified or new adverse event/targeted condition that the participant has experienced will be performed at scheduled visits as per Table 6.1-1 of the protocol.

Summaries of vital signs are described in Section 18.4.

The following body systems will be assessed as normal, abnormal or not done:

- General appearance;
- Head, eyes, ears and nose;
- Mouth, teeth and throat;
- Neck and thyroid;
- Chest;
- Cardiovascular;
- Abdominal;

- Dermatologic;
- Musculoskeletal;
- Circulatory;
- Neurological;
- Lymphatic;
- Other (data to be listed only);

The following summaries will be provided for each body system:

- Incidence of abnormalities at baseline
- Incidence of newly-occurring abnormalities at any time post-baseline

A newly occurring abnormality is defined as an abnormality in a body system for which the result at baseline was either not done or normal.

For the incidence of newly occurring abnormalities at any time post-baseline the denominator for each body system will be the number of participants for whom the result at baseline was not abnormal.

All physical examination data will be listed.

19. PHARMACOKINETIC ANALYSIS

Only specific sites with facilities for PK sample processing will be selected to provide PK data. PK plasma samples will be collected on Day 1, at 60 minutes (+/-5 minutes) and 90 minutes (+/- 5 minutes) post-dose, and Day 4 (predose and 60 to 90 minutes postdose) and Day 8 (anytime) in a subgroup of 150 evaluable participants. This will be offered to study participants until all 150 spots are filled. The day, time of each daily dose taken, and day and time of last meal before dose taken must be recorded for all S-217622 daily doses taken (on Days 1 to 5).

PK samples will be collected on Day 1 at 60 minutes (+/- 5 minutes) post-dose, and Day 4 (anytime) and Day 8 (anytime) for an additional subgroup of 250 evaluable participants. The day, time of each daily dose taken, and day and time of last meal before dose taken must be recorded for all S-217622 daily doses taken (on Days 1 to 5).

The PK concentrations will be summarized and presented for the PK set. The individual plasma S-217622 concentrations will be listed by study participant, along with the time elapsed from the previous dose before blood sampling. In addition, the time elapsed from the previous dose and the plasma S-217622 concentration will be graphically presented in a scatter plot. Plasma concentrations of S-217622 will be summarized for data at 60 and 90 minutes post dose on Day 1 and predose on Day 4 (C_{24hr}) by time and day with the number of non-missing observations, mean, standard deviation, and coefficient of variation (CV%, calculated by standard deviation/Mean × 100); geometric mean and CV% for geometric mean; and median, minimum and maximum values. The C_{24hr}, which is defined as the plasma concentration of S-217622 within 20 to 28 hours after the previous dose on Day 3 and prior to dose on Day 4 is also summarized.

For summary of plasma concentration, plasma concentration below limit of quantification will be treated as zero (0) for calculations of mean, standard deviation, CV%, median, minimum and maximum and treated as missing for calculation of geometric mean and CV% Geometric Mean.

The PK parameter (C_{24hr}) will be presented same precision as per the observed values.

Descriptive statistics will be presented as follows:

- N: no decimal place
- Mean, geometric mean, standard deviation, median, minimum and maximum: same precision as per each concentration or PK parameter in the listing.
- CV% and CV% Geometric Mean: one decimal place

After plasma concentration measurement, the data that the person in charge of PK analysis at the sponsor can clearly explain as inappropriate for analysis will be excluded. The reason for any exclusion should be described in the clinical study report (CSR).

If possible, population PK analysis will be performed using nonlinear mixed effect model (NONMEM version 7.4 or higher). When the population PK analysis is performed, the analysis plan and its report will be prepared separately. Exploration of relationships between exposures of S-217622 and laboratory markers and/or clinical outcomes may be approached using conventional and accepted methods for PK/pharmacodynamic (PD) data analyses. When these analyses are performed, the analysis plan and its report will also be prepared separately.

20. DATA NOT SUMMARIZED OR PRESENTED

Any variables (including comments) which are not to be summarized or presented per this SAP, will be available in the clinical study database, SDTM and/or ADaM datasets.

21. REFERENCES

1. FDA Guidance on Multiple Endpoints in Clinical Trials: Guidance for Industry. Draft Guidance. January 2017. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials-guidance-industry.

2. Chan, I. S. F., and Zhang, Z. (1999). Test-Based Exact Confidence Intervals for the Difference of Two Binomial Proportions. *Biometrics 55,*1202–1209.

APPENDIX 1. COUNTRIES AND GEOGRAPHIC REGION MAPPING

Region	Countries
North America	Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Belize, Bermuda, Bonaire, Canada, Caribbean Netherlands, Cayman Islands, Costa Rica, Cuba, Curaçao, Dominica, Dominican Republic, El-Salvador, Greenland, Grenada, Guadeloupe, Guatemala, Haiti, Honduras, Jamaica, Martinique, Mexico, Montserrat, Nicaragua, Panama, Puerto Rico, Saba, Saint Barthélemy, Saint Martin, Saint Kitts and Nevis, Saint Lucia, Saint Pierre and Miquelon, Saint Vincent and the Grenadines, Sint Eustatius, Trinidad and Tobago, Turks and Caicos, United States, Virgin Islands (British), Virgin Islands (U.S.)
South America	Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Falkland Islands, French Guiana, Guyana, Paraguay, Peru, Suriname, Uruguay, Venezuela
Europe	Albania, Andorra, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Gibraltar, Greece, Guernsey, Hungary, Iceland, Ireland, Isle of Man, Italy, Jersey, Kosovo, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Moldova, Monaco, Montenegro, Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, Russia, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, Ukraine, Vatican City
Africa	Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cabo Verde, Cameroon, Central African Republic (CAR), Chad, Comoros, Congo, Democratic Republic of the Congo, Republic of the Cote d'Ivoire, Djibouti, Egypt, Equatorial Guinea, Eritrea, Eswatini, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Libya, Madagascar, Malawi, Mali, Mauritania, Mauritius, Morocco, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, South Sudan, Sudan, Tanzania, Togo, Tunisia, Uganda, Zambia, Zimbabwe
Asia	Afghanistan, Armenia, Australia, Azerbaijan, Bahrain, Bangladesh, Bhutan, Brunei, Burma, Cambodia, China, Cook Islands, Cyprus, Fiji, Georgia, Hong Kong, India, Indonesia, Iran, Iraq, Israel, Japan, Jordan, Kazakhstan, Kiribati, Korea, North, Korea, South, Kuwait, Kyrgyzstan, Laos, Lebanon, Macau, Malaysia, Maldives, Marshall Islands, Micronesia Federated States, Mongolia, Nauru, Nepal, New Zealand, Niue, Oman, Pakistan, Palau, Palestine, Papua New Guinea, Philippines, Qatar, Russia, Samoa, Saudi Arabia, Singapore, Solomon Islands, Sri Lanka, Syria, Taiwan, Tajikistan, Thailand, Timor-Leste (East Timor), Tonga, Turkey, Turkmenistan, Tuvalu, United Arab Emirates, Uzbekistan, Vanuatu, Vietnam, Yemen

APPENDIX 2. PROGRAMMING CONVENTIONS FOR OUTPUTS

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Spelling Format

English US.

Paper Size, Orientation, and Margins

The size of paper will be letter and the page orientation will be landscape. Margins will provide at least 1 inch (2.54 centimeters) of white space all around the page.

Fonts

The font type 'Courier New' will be used, with a font size of 8. The font color will be black with no bolding, underlining, italics or subscripting.

Descriptive Statistics

If the original data has N decimal places, then the summary statistics will have the following number of decimal places:

- Minimum and maximum: N;
- Mean, Q1, median, Q3, geometric mean, lower and upper bounds of 2-sided 95% CI: N + 1;
- SD, SE: N + 2
- CV%: 2

Percentages

Percentages will be reported to one decimal place. Rounding will be applied, except for percentages < 0.1 but > 0.0 which will be presented as '< 0.1' and percentages < 100.0 but >99.9 which will be presented as '>99.9'.

Where counts are zero, no percentages will appear in the output.

p-values

p-values will be reported to four decimal places. Rounding will be applied, except for the p-values < 0.0001 which will be presented as '< 0.0001' and p-values < 1.0000 but > 0.9999 which will be presented as '> 0.9999'.

Presentation of Intervention Groups

For outputs, intervention groups will be represented as follows and in the given order:

Intervention Group	For Tables and Figures	For Listings (include if different to tables)
S-217622	S-217622	S-217622
Placebo	Placebo	Placebo
Not Randomized	N/A	Not Randomized
Not Treated	N/A	Not Treated

Presentation of Visits

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Scr
Day 1	D1
Day 4	D4
Day 8	D8
Day 14	D14

Long Name (default)	Short Name
Day 16	D16
Day 29	D29
Week 12	W12
Week 24	W24

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized intervention group (or intervention received if it's a safety output), first by S-217622 and then placebo;
- Center-participant ID;
- Date (where applicable) and time if captured;
- For listings where non-randomized participants are included, these will appear in a category after the randomized intervention groups labeled 'Not Randomized'.
- For listings where randomized but not treated participants are included, these will appear in a category after the intervention groups labeled 'Not Treated'.

APPENDIX 3. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study intervention start date/time, then not TEAE If start date >= study intervention start date/time, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study med start date OR Missing	Known	If stop date < study intervention start date, then not TEAE If stop date >= study intervention start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study intervention start date, then not TEAE If stop date >= study intervention start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known, Partial or Missing	Known	If medication stop date < study intervention start date, assign as prior; Otherwise, assign as concomitant
	Partial	If known components of medication stop date show that medication stopped before study intervention start date, assign as prior; Otherwise, assign as concomitant
	Missing, or ongoing	Can never be assigned as prior, therefore assign as concomitant.

APPENDIX 4. ALGORITHM FOR HANDLING MISSING SYMPTOM EVALUATIONS FOR THE PRIMARY EFFICACY ENDPOINT

The following algorithmic approach will be used to handle hospitalizations and deaths, as well as missing data, in constructing the TTE symptom-based primary efficacy endpoint. The steps of the algorithmic approach will be undertaken in the following order:

a. If a participant has none of the targeted symptoms evaluated at any time during follow-up (including if due to the diary never being returned):

i. If the participant died or was hospitalized on or before Day 29, then the participant will remain in the risk set to Day 28 and will be considered not to have had the symptom resolution event, with time to event censored at Day 28.

ii. If the participant was not known to have died or been hospitalized, the participant will be excluded from the analysis.

b. **If a participant has one or more (but not all) targeted symptoms with no evaluations for all days from Day 1 through Day 29**:

The TTE endpoint for this participant will be evaluated based on the remaining targeted symptoms with missing data handled for those targeted symptoms as described below in subsection c. [In essence, this is assuming that if the participant had evaluated the unscored symptoms that they would have shown improvement/resolution for two consecutive days at the same time, or earlier, as the symptoms that they did score. With this assumption, using the available symptom data is considered preferable to alternative strategies of censoring their TTE at Day 1 or assuming that the unscored symptoms never improved/resolved throughout follow-up with censoring at Day 28].

c. If participant has an evaluation on Day 1 and/or on days between Day 2 and Day 29 during follow-up on all targeted symptoms (or, per section b above, on a subset of targeted symptoms):

For each symptom having an evaluation on at least one day between Day 1 and Day 29 inclusive, programmatically values will be imputed for unobserved evaluations, and for missing values as follows:

i. Impute a missing score for a symptom on Day 1 as "mild". If also missing on Day 2 or for a sequence of consecutive days from Day 2 but with at least one score during follow-up, impute the missing values on Day 2 through to the first available score as "mild". This means that the TTE criteria cannot be met during follow-up while a participant has a sequence of one or more missing values starting on Day 1.

ii. For intermittent missingness during follow-up after Day 1, impute a missing score for a symptom as the worst of (a) the last available value before the missing value, and (b) the first available value after

the missing value, irrespective of the length of the sequence of missing values for the symptom. This gives potentially longer times until symptom improvement/resolution (compared with what might have occurred if the evaluations were available) if either of the preceding and succeeding values do not meet the criteria for improvement/ resolution, but potentially shorter times if both the preceding and succeeding values meet the criteria.

iii. For monotonic missingness through to Day 29 (i.e., a sequence of missing values during follow-up through to and including Day 29 due to loss to follow-up, participant choice not to fully complete their diary, or an early Day 29 clinic visit at which the diary is returned), censor the follow-up for this specific symptom at the last day that the relevant criterion for symptom improvement could have been met (this would be three days before the last diary entry for one or more targeted symptoms). This assumes that the censoring is non-informative about when the criterion would have been met if diaries had been fully completed.

The TTE endpoint is then calculated as the first of two successive days meeting the symptom improvement/ resolution criteria using the combined observed and imputed data for all symptoms with one or more evaluations observed during follow-up between Day 1 and Day 29, inclusive. In the event that the censoring due to monotonic missingness differs among targeted symptoms (e.g., because the participant stops completing the diary for one symptom earlier than for other symptoms), then the TTE endpoint will be calculated using the available observed and imputed data, and censoring of the TTE endpoint will be at the time of censoring of the symptom with the longest time to censoring.

To illustrate sub-points i), ii) and iii) of point c), examples of missing data imputation for individual targeted symptoms within a participant are provided below:

	Example 1				Example 2				Example 3		
Study Day	**Original Value**	**Imputed Value**	**Imputation Type**		**Original Value**	**Imputed Value**	**Imputation Type**		**Original Value**	**Imputed Value**	**Imputation Type**
Day 1	-	Mild	Day 1		Severe				-	Mild	Day 1
Day 2	Mild				-	Severe	Intermittent		-	Mild	Intermittent
Day 3	Moderate				Moderate				Absent		
Day 4	-	Moderate	Intermittent		Moderate				-	Absent	Intermittent
Day 5	-	Moderate	Intermittent		Moderate				Absent		
Day 6	-	Moderate	Intermittent		-	Moderate	Intermittent		Absent		
Day 7	Mild				-	Moderate	Intermittent		-	Absent	Intermittent
Day 8	Mild				Mild				Absent		
Day 9	Absent				Mild				Absent		
Day 10	Absent				Moderate				Absent		
Day 11	Absent				-	Moderate	Intermittent		Absent		
Day 12	Absent				Moderate				Absent		
Day 13	Absent				Mild				Absent		
Day 14	Absent				-		Monotone		Absent		
Day 15	Absent				-		Monotone		Absent		
Day 16	Absent				-		Monotone		Absent		

Day 17	Absent				-		Monotone		Absent		
Day 18	Absent				-		Monotone		Absent		
Day 19	Absent				-		Monotone		Absent		
Day 20	Absent				-		Monotone		Absent		
Day 21	Absent				-		Monotone		Absent		
Day 22	Absent				-		Monotone		Absent		
Day 23	Absent				-		Monotone		Absent		
Day 24	Absent				-		Monotone		Absent		
Day 25	Absent				-		Monotone		Absent		
Day 26	Absent				-		Monotone		Absent		
Day 27	Absent				-		Monotone		Absent		
Day 28	Absent				-		Monotone		Absent		
Day 29	Absent				-		Monotone		Absent		
Individual Targeted Symptom Resolution at Day 9 based on non-imputed data				Monotone missing data from Day 14 for this Targeted Symptom.				Individual Targeted Symptom Resolution at Day 3 based on original and imputed data			

Day 1 missing data imputation = imputation to "Mild"; Intermittent missing data imputation = worst score from the surrounding non-missing values, including the imputed Day 1 value.
For monotone missing data, there is no imputation and in the absence of achieving the endpoint before the monotone missingness, participants will have a censored time to event depending on the first targeted symptom with monotone missing data, (i.e., the earliest of Day1 or three days before the last diary entry for one or more targeted symptoms)

APPENDIX 5. LABORATORY ASSESSMENTS

Chemistry (SI unit)	
• C-Reactive protein (CRP) (mgl/L)	• Total bilirubin (µmol/L)
• Ferritin (µg/L)	• Direct bilirubin (µmol/L)
• Glucose (mmol/L)	• Albumin (g/L)
• HDL cholesterol (mmol/L)	• Total protein (g/L)
• LDL cholesterol (mmol/L)	• Blood urea nitrogen (BUN) (mmol/L)
• Triglycerides (mmol/L)	• Creatinine (µmol/L)
• Alanine aminotransaminase (ALT) (U/L)	• Sodium (mmol/L)
• Aspartate aminotransaminase (AST) (U/L)	• Potassium (mmol/L)
• Alkaline phosphatase (U/L)	• Creatinine clearance (mL/min)

Hematology (SI unit)	
• D-dimer (mg/L)	• Reticulocyte count (x10E9/L)
• Platelet count (x10E9/L)	• White blood cell (WBC) count (x10E9/L)
• Red blood cell count (RBC) (x10E12/L)	• Absolute neutrophils count (x10E9/L)
• Hemoglobin (g/L)	• Absolute lymphocyte count (x10E9/L)
• Hematocrit (ratio)	• Absolute monocytes count (x10E9/L)
• Mean corpuscular volume (MCV) (fL)	• Absolute eosinophils count (x10E9/L)
• Mean corpuscular hemoglobin (MCH) (g/dL)	• Absolute basophils count (x10E9/L)

APPENDIX 6. TOXICITY GRADES FOR LABORATORY DATA

From DAIDS Adverse Event Grading Tables | DAIDS Regulatory Support Center (RSC) (nih.gov) (accessed on 19Aug2022)

Chemistry:

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN; *30 to < LLN*	≥ 2.0 to < 3.0; *≥ 20 to < 30*	<2.0; *>=2*	NA
Alkaline phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
ALT, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
AST, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Direct bilirubin, *High*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
Total Bilirubin, High	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase to ≥ 2.0 x participant's baseline
Creatinine Clearance, Low	NA	90 to 60 ml/min OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min OR 30 to < 50% decrease from participant's baseline	< 30 ml/min OR ≥ 50% decrease from participant's baseline

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125; *6.11 to < 6.95*	> 125 to 250; *6.95 to < 13.89*	> 250 to 500; *13.89 to < 27.75*	≥ 500; *≥ 27.75*
Glucose, High (mg/dL; *mmol/L*)	116 to 160; *6.44 to < 8.89*	> 160 to 250; *8.89 to < 13.89*	> 250 to 500; *13.89 to < 27.75*	≥ 500 ≥ *27.75*
Glucose, Low (mg/dL; *mmol/L*)	55 to 64; *3.05 to <3.55*	40 to < 55; *2.22 to < 3.05*	30 to < 40; *1.67 to < 2.22*	< 30; *< 1.67*
Cholesterol, High (mg/dL; *mmol/L*)	200 to < 240; *5.18 to < 6.19*	240 to < 300; *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, High (mg/dL; *mmol/L*)	130 to < 160; *3.37 to < 4.12*	160 to < 190; *4.12 to < 4.90*	≥ 190; *≥ 4.90*	NA
Triglycerides, High (mg/dL; *mmol/L*)	150 to 300; *1.71 to 3.42*	>300 to 500; *>3.42 to 5.7*	>500 to < 1,000; *>5.7 to 11.4*	> 1,000; *> 11.4*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0; *5.6 to < 6.0*	6.0 to < 6.5; *6.0 to < 6.5*	6.5 to < 7.0; *6.5 to < 7.0*	≥ 7.0; *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4; *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5; *2.0 to < 2.5*	< 2.0; *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150; *146 to < 150*	150 to < 154; *150 to < 154*	154 to < 160; *154 to < 160*	≥ 160; *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135; *130 to < 135*	125 to < 130; *125 to < 130*	121 to < 125; *121 to < 125*	≤ 120; *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0; *0.45 to < 0.59*	10.0 to < 12.0; *0.59 to < 0.71*	12.0 to < 15.0; *0.71 to < 0.89*	≥ 15.0; *≥ 0.89*

LLN = Lower limit of normal; ULN = Upper limit of normal.

Hematology:

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Absolute Lymphocyte Count, Low (cell/mm3; *10^9/L*)	600 to < 650; *0.60 to < 0.65*	500 to < 600; *0.5 to < 0.6*	350 to < 500; *0.35 to < 0.5*	< 350; *< 0.35*
Absolute Neutrophil Count (ANC), Low (cells/mm3; *10^9/L*)	800 to 1,000; *0.8 to 1.0*	600 to 799; *0.6 to 0.799*	400 to 599; *0.4 to 0.599*	< 400; *< 0.4*
Hemoglobin, Low (g/dL; *mmol/L*) *(male)*	10.0 to 10.9; *6.19 to 6.76*	9.0 to < 10.0; *5.57 to < 6.19*	7.0 to < 9.0; *4.34 to < 5.57*	< 7.0; *< 4.34*
Hemoglobin, Low (g/dL; *mmol/L*) *(female)*	9.5 to 10.4; *5.88 to 6.48*	8.5 to < 9.5; *5.25 to < 5.88*	6.5 to < 8.5; *4.03 to < 5.25*	< 6.5; *< 4.03*
Platelets, Decreased (cells/mm3; *10^9/L*)	100,000 to <125,000; *100 to <125*	50,000 to < 100,000; *50 to <100*	25,000 to < 50,000; *25 to <50*	< 25,000; *< 25*
WBC, Decreased (cells/mm3; *cells/L*)	2,000 to 2,499; *2 to 2.499*	1,500 to 1,999; *1.5 to 1.999*	1,000 to 1,499; *1 to 1.499*	< 1,000; *< 1*