NCT #NCT05305547

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

Study Acronym: SCORPIO-HR

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by: Shionogi*
Funded by: National Institute of Allergy and Infectious Diseases (NIH), Division of AIDS (DAIDS)

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23 Jun 2022

ACTG
AIDS CLINICAL TRIALS GROUP

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SIGNATURE PAGE

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonisation Guideline for Good Clinical Practice (E6); Institutional Review Board/Independent Ethics Committee determinations; all applicable in country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator:_____
Print/Type

Signed: _____ Date: _____
Name/Title

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GLOSSARY OF PROTOCOL-SPECIFIC TERMS

ACTG	AIDS Clinical Trials Group
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}48hr}$	area under the mean concentration curve until 48 hours after first administration
$AUC_{0\text{-}inf}$	area under the curve from time 0 to infinity
$AUC_{0\text{-}last}$	area under the curve from time 0 to last measured concentration
$AUC_{0\text{-}tau}$	area under the curve to the end of the dosing period
BCRP	breast cancer resistance protein
BMI	body mass index
C_{24hr}	concentration 24 hours after last dose
C_{48hr}	concentration at 48 hours after first administration
CC_{50}	concentration achieving 50% of cytotoxicity
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019; caused by SARS-CoV-2
CoVs	coronaviruses
CPE	cytopathic effect
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
C_{trough}	minimum concentration
CV%	coefficient of variation
CYP	cytochrome P450
DAIDS	Division of AIDS
DDI	drug-drug interaction
DSMB	data safety monitoring board
eCRF	electronic case report form
EC_{50}	half maximal (50%) effective concentration
EC_{90}	90% maximal effective concentration E/CIA enzyme or chemiluminescence immunoassay
EQ-5D-5L	EuroQol–5 Dimensions–5 Levels
EU	European Union
EUA	Emergency Use Authorization
EUL	Emergency Use Listing
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
hAEC	human airway epithelial cells
HBsAg	hepatitis B surface antigen

HCV	hepatitis C virus
HDL	high-density lipoprotein
HEK	human embryonic kidney
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgM	immunoglobulin M
IL-6	interleukin-6
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
KL-6	Krebs von den Lungen-6
LDH	lactate dehydrogenase
LLoQ	lower limit of quantification
mAb	monoclonal antibody
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
NOAEL	no observed adverse effect limit
NP	nasopharyngeal
OAT	organic anion transporter
OATP	organic anion transporter polypeptide
OCT	organic cation transporter
OHRP	Office for Human Research Protections
PA-EC_{50}	protein-adjusted half (50%) maximal effective concentration
PA-EC_{90}	protein-adjusted 90% maximal effective concentration
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PD	pharmacodynamic/s
PK	pharmacokinetic/s
PT	Preferred Term
RSC	(DAIDS) Regulatory Support Center
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV	severe acute respiratory syndrome coronavirus
SD	standard deviation
SF-36v2	Short Form 36 Health Survey Questionnaire, version 2
SOC	System Organ Class
SOE	Schedule of Evaluations
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
TARC	thymus and activation regulated chemokine (chemokine ligand 17)
TEAE	treatment-emergent adverse event
TimeHigh	total time above the target plasma concentration

TMPRSS2	VeroE6/transmembrane protease, serine 2
ULN	upper limit of normal (range)
UK	United Kingdom
US	United States
vs.	versus
VOC	variant of concern
WHO	World Health Organization

SCHEMA

ACTIV-2d/A5407

DESIGN	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 non-hospitalized adults with high and low risk of progression to severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection.
REGIMEN	S-217622 or placebo orally once daily for 5 days (375 mg on Day 1 followed by 125 mg on Days 2 to 5).
DURATION	Days 1 through 29 intensive study, followed by limited study through 24 weeks.
STRATIFICATION	Randomization will be stratified by geographic region and high risk versus (vs.) low risk of severe coronavirus disease 2019 (COVID-19)
POPULATION	Outpatient adults (≥18 years) with: a) documented positive SARS-CoV-2 nucleic acid or antigen test from a sample collected ≤120 hours (5 days) prior to randomization, b) onset of symptoms of COVID-19 ≤5 days prior to randomization, c) presence of 1 or more select COVID-19 symptoms within 24 hours prior to randomization. Participants will be eligible regardless of vaccination status and will be classified as either high risk or low risk. High-risk participants: defined as aged ≥65 years or those with presence of high-risk conditions. Low-risk participants: defined as those not meeting the high-risk definition.
SAMPLE SIZE	Approximately 1490 participants (745 on S-217622 and 745 on placebo) will be randomized into the study. Approximately 50% of enrollment will be high-risk participants and 50% will be low-risk participants. All locally provided standard-of-care, including COVID-19 monoclonal antibody (mAb) treatment, outpatient intravenous (IV) remdesivir, and oral antivirals compatible with S-217622 will be permitted after enrollment, in addition to the randomized treatment.
OUTCOME MEASURES	The primary outcome measure is: Time in days from the start of S-217622 to sustained symptom resolution; the definition of sustained symptom resolution is the first of 4 consecutive days without symptoms (all targeted symptoms recorded as absent) and being alive and without hospitalization for any reason by Day 29.

1. STUDY OBJECTIVES

The main intent of the study is to evaluate the efficacy of S-217622 vs. placebo. The study will be conducted in the setting of locally available standard of care COVID-19 treatment. High-risk and low-risk participants will be analyzed together for the primary analysis and separately for secondary analyses. The following primary, secondary, and exploratory objectives will be addressed in the modified intent-to-treat (mITT) population, except for the safety analyses, which will be analyzed in the Safety population, and pharmacokinetic (PK) analyses, which will be analyzed in the PK population.

1.1. Primary Objective

To determine if S-217622 will reduce the time to sustained symptom resolution through Day 29. Time to sustained symptom resolution is defined as the time from start of study intervention to the first day of 4 consecutive days with complete resolution of 13 COVID-19 symptoms on participant self-assessment AND alive and without hospitalization for any reason by 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.

1.2. Secondary Objectives

1.2.1. Key secondary objective: 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.

1.2.2. Key secondary objective: 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.

1.2.3. To determine if S-217622 will decrease the proportion of participants with detectable SARS-CoV-2 viral culture on NP swab at Day 4.

1.2.4. To explore differences between S-217622 and placebo in time to sustained symptom resolution through Day 29 among subgroups, including by high risk vs. low risk at enrollment, by COVID-19 vaccination status, by receipt of COVID-19 treatments, and by time from symptom onset at enrollment.

1.2.5. 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. low risk at enrollment, by COVID-19 vaccination status, by receipt of COVID-19 treatments, and by time from symptom onset at enrollment.

1.2.6. To determine whether S-217622 reduces all-cause hospitalization and all deaths regardless of occurring prior to hospitalization (not adjudicated) through Day 29.

1.2.7. 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.

1.2.8. To determine the efficacy of S-217622 to increase the proportion of participants with NP SARS-CoV-2 RNA levels by quantitative polymerase chain reaction (PCR) below the lower limit of quantification (LLoQ) on Days 4 and 8.

1.2.9. 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.

1.2.10. To determine whether S-217622 results in a shorter time to return to pre-COVID-19 health compared with placebo through Day 29.

1.2.11. 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) (see Section 6.3.16).

1.2.12. To determine the efficacy of S-217622 to maintain pulse oximetry measurement of ≥96% through Day 29.

1.2.13. To evaluate the safety of S-217622.

1.2.14. To explore measures of psychological health, functional health, and health-related quality of life in participants through end of study follow-up (Week 24).

1.2.15. To determine whether S-217622 reduces death due to any cause through end of study follow-up (Week 24).

1.2.16. To determine the PK of S-217622.

1.3. Exploratory Objectives

1.3.1. 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.

1.3.2. To explore the impact of S-217622 on participant-reported rates of new SARS-CoV-2 positivity of household contacts through Day 29.

1.3.3. To explore whether baseline and follow-up laboratory markers are associated with clinical and virologic outcomes in relation to S-217622 use.

1.3.4. To explore baseline and emergent viral resistance to S-217622 through Day 16.

1.3.5. To explore differences between S-217622 and placebo in NP SARS-CoV-2 RNA levels among subgroups, including by high risk vs. low risk at enrollment, by COVID-19 vaccination status, by receipt of COVID-19 treatments, and by time from symptom onset at enrollment.

1.3.6. To explore possible predictors of outcomes, including death and hospitalization, across the study population, including by time from symptom onset, symptoms at baseline, sex assigned at birth, demographic characteristics, geographic region, and vaccination status.

1.3.7. To explore and develop a model for the interrelationships between virologic outcomes and clinical outcomes in each study group.

1.3.8. To explore the association between viral genotypes and phenotypic susceptibility to S-217622 and clinical outcomes and virologic response to S-217622.

1.3.9. To explore the prevalence, severity, and types of persistent symptoms and clinical sequelae in participants through end-of-study follow-up (Week 24).

1.3.10. To explore relationships between exposure of S-217622 with laboratory markers and clinical outcomes.

1.3.11. To evaluate the safety of S-217622 in the high-risk and low-risk subpopulations.

1.3.12. 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 low-risk subpopulations.

1.3.13. To explore 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 in the setting of new or worsening clinical symptoms, in both study groups.

1.3.14. To explore the frequency of viral rebound in both treatment arms, 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.

1.3.15. 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.

2. INTRODUCTION

2.1. Background

Virology

Coronaviruses (CoVs) are positive-sense, single-stranded, enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. Over the past 2 decades, emerging pathogenic CoVs capable of causing life-threatening disease in humans and animals have been identified, namely, SARS-CoV-1 in 2002 to 2003 and Middle East Respiratory Syndrome coronavirus (MERS-CoV) in 2012 [1].

New Threat

A novel pneumonia caused by a previously unknown betacoronavirus emerged in Wuhan, China, in December 2019 [2]. The virus is closely related to SARS-CoV-1, which caused an outbreak in 2003, and has been named SARS-CoV-2. The human disease caused by SARS-CoV-2 is called COVID-19.

During the current SARS-CoV-2 outbreak, the incidence of known cases has rapidly increased. On January 30, 2020, the International Health Regulations Emergency Committee of the WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern. On January 31, 2020, the United States (US) Department of Health and Human Services declared a public health emergency in the US. Despite quarantine measures, SARS-CoV-2 has spread widely. As of April 2022, there have been >508 million confirmed cases of COVID-19 and >6 million deaths attributed to COVID-19 globally [3]. Global efforts to evaluate novel antivirals and therapeutic interventions to treat COVID-19 have intensified. Therefore, there is an urgent public health need for rapid development of novel interventions.

Disease Course

Once infection occurs, the clinical course is variable. Previous data suggest that fewer than 2.5% of infected persons will show symptoms within 2.2 days (confidence interval [CI], 1.8 to 2.9 days) of exposure, and symptom onset will occur within 11.5 days (CI, 8.2 to 15.6 days) for 97.5% of infected persons that do develop symptoms [4]. In most (~80%) cases, COVID-19 presents as a mild-to-moderately severe, self-limited, acute respiratory illness with fever, cough, and shortness of breath. It remains unclear exactly what the rate of progression of COVID-19 is and what the predictors are for complications, including pneumonia, thromboembolic disease, acute respiratory distress syndrome (ARDS), kidney failure, and death. It is clear that older age, male sex, and comorbidities, including obesity, diabetes, and hypertension, increase the risk for worse outcomes [5, 6]. In an early meta-analysis, the main clinical symptoms were fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (28.2%), and dyspnea (21.9%). Minor symptoms included headache or dizziness (12.1%), diarrhea (4.8%), and nausea and vomiting (3.9%) [7]. Laboratory examinations showed that lymphocytopenia (64.5%), increase of C-reactive protein (CRP) (44.3%), leukocytopenia (29.4%), and increase of lactate dehydrogenase (LDH) (28.3%) were more common in those hospitalized with COVID-19 [5, 8].

Figure 2.1-1 shows the time course of symptoms as COVID-19 progresses.

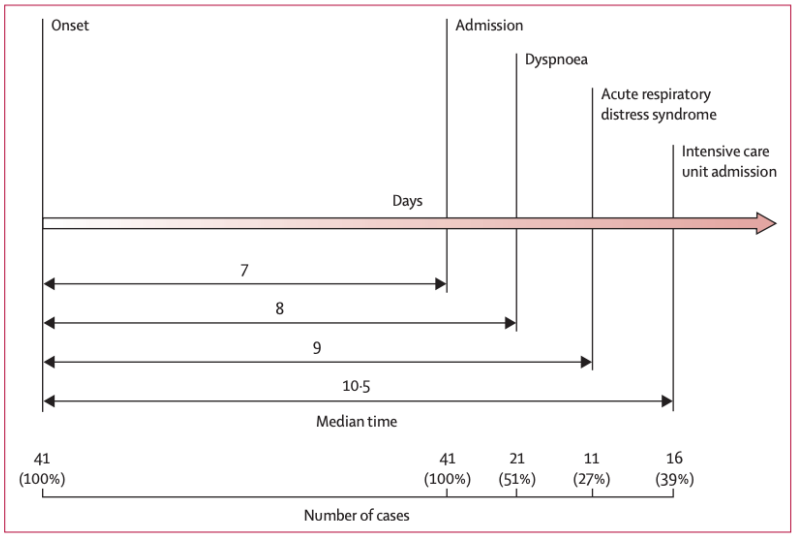


Figure 2.1-1 Timeline of COVID-19 Disease Progression. Onset refers to onset of symptoms.

Shedding

Coronaviruses spread through respiratory droplets and aerosols. Understanding the dynamics of viral shedding is important to understanding epidemic spread and how shedding relates to disease progression. The best evidence available now suggests that viral shedding, especially in upper respiratory secretions, is detectable around 2 days before symptoms develop and continues throughout the symptomatic phase. This shedding can be quite high during active disease and can continue at low levels for a prolonged period, with a quarter of persons still with RNA detectable at 3 weeks in NP swabs [7].

Biomedical Interventions

Multiple therapies have received Food and Drug Administration (FDA) Emergency Use Authorization (EUA) for treatment of COVID-19 in the outpatient setting for persons at higher risk for progression to hospitalization or death, including mAbs, IV remdesivir, and nirmatrelvir plus ritonavir, which demonstrated ~98% relative reduction in COVID-19-related hospitalizations and all-cause deaths in the pre-delta, pre-omicron variant period of the pandemic [9, 10, 11, 12, 13], as well as molnupiravir, which demonstrated lower efficacy. The emergence of variants of concern (VOCs), and the omicron variant in particular, has rendered multiple mAbs significantly less inhibitory in *in vitro* assays, so they are thus not expected to be clinically effective, leading to withdrawal of authorization or limited authorization for use [14]. Emerging variants will continue to threaten COVID-19 therapeutics that target a single or limited number of spike epitopes and may also threaten non-spike-targeting therapeutics. The available therapeutics are also hindered by requirement of IV administration, with remdesivir given once daily for 3 days, necessitating resources that make it often difficult to deliver to a large population and limits uptake by health systems; lower efficacy (molnupiravir); or twice daily dosing with multiple pills (nirmatrelvir plus ritonavir).

The susceptibility of emergency-use-authorized mAbs to emerging VOCs and the challenges to delivery of currently available therapeutics highlight the continued need for investigation of novel therapeutics that are highly effective, easy to administer, and likely to retain activity in the face of current and future SARS-CoV-2 variants.

Vaccination

Vaccination has been an important tool to reduce infection and complications of infections, and vaccination campaigns are underway globally with variable reach, course completion, and uptake. Unfortunately, variants of SARS-CoV-2 have emerged that are more transmissible and may reduce vaccine efficacy, especially over time [15]. During the omicron surge, vaccine efficacy has been shown to wane after the initial 3 to 4 months for protection against both symptomatic disease [16] and, in some series, hospitalization [17]. Thus, it has become clear that fully vaccinated and/or boosted individuals can still develop COVID-19 and may develop severe disease, due to waning vaccine efficacy or risk factors for infection, such as being immunocompromised or of older age. Thus, vaccination status will be recorded but will not be part of eligibility assessment for enrollment.

2.2. Rationale

Despite the EUA of anti-SARS-CoV-2 mAbs for emergency use in the US and some other countries, as well as off-label use of repurposed agents under evaluation for SARS-CoV-2 treatment in some regions of the world, effective therapeutics for non-hospitalized adults with COVID-19 are not widely available or accessible, and deaths due to COVID-19 continue to accumulate [18].

Rationale for Placebo-controlled Trial

A randomized, placebo-controlled Phase 3 design, as offered by ACTIV-2d/A5407, provides a rigorous evaluation of treatment efficacy of the oral protease inhibitor S-217622 and seeks to accelerate the availability of a potentially effective oral therapy, which is a pressing need. Oral COVID-19 treatment will be much more scalable than injectables, and given the global burden of COVID-19, there is a need for multiple safe, effective oral options to ensure widespread access. Effective oral therapy is needed to reduce the risk of hospitalization and death in those at higher risk of COVID-19 progression. All COVID-19 patients, both high and low risk, may benefit from therapy that reduces COVID-19 related morbidity by reducing symptom duration and active viral replication, which may impact transmissibility to others.

In addition to potential COVID-19 treatment, the study offers close clinical monitoring that may not be available outside of the trial, increasing the likelihood of more timely referral for escalated level of care, if needed. As a global trial, health needs outside of the US are recognized by the study, and the design informed by local investigators and community advisors.

The inclusion of a placebo group, rather than an untreated open-label control group, is considered important for the integrity of the study to reduce the possibility of differential retention of participants randomized to S-217622 vs. the control group, as well as to minimize subjective bias in completion of symptom diaries by participants.

Participants may receive any locally available standard-of-care COVID-19 therapies after enrollment, as long as compatible with study intervention. Compatible therapies include but are not limited to anti-SARS-CoV-2 mAbs, outpatient IV remdesivir, molnupiravir, convalescent plasma, inhaled budesonide, favipiravir, and fluvoxamine after study enrollment. Treatment of COVID-19 with Paxlovid™ will not be permitted due to potential for drug-drug interaction (DDI) and lack of data to inform safety of coadministration with S-217622.

Participants will be fully informed of the proven efficacy of alternative standard-of-care or other available therapy and of the 50% chance of receiving placebo in this study.

All participants will be able to access any locally available COVID-19 treatment compatible with the study intervention after enrollment and will be informed of authorized treatments available in their region. However, participants who are not considered high risk generally are not expected to receive locally available COVID-19 treatment, given that it is not currently approved or authorized for low-risk participants.

This study will only enroll those that, despite being fully informed of other options, choose to participate in this trial. The reason for participation in this study will be recorded at enrollment to understand why individuals are choosing to participate.

Rationale for the Enrollment of Participants at High Risk for Severe COVID-19

Individuals with symptomatic COVID-19 and risk factors for progression to severe COVID-19 will be recruited to this trial, as they will benefit most from therapeutics that are effective at preventing severe or critical COVID-19, well-tolerated, and easily accessed.

Rationale for Enrollment of Participants at Low Risk for Severe COVID-19

Individuals at low risk for severe COVID-19 may benefit from an oral treatment that reduces the duration of symptoms, thus reducing the morbidity that symptomatic COVID-19 infection can incur. Low-risk patients may experience symptoms for weeks, which can have a substantial impact on quality of life. In the Phase 2b study of S-217622 (Study 2108T1221), a lower-risk patient population with symptomatic COVID-19 had a median of 18 days until sustained resolution of all symptoms, demonstrating the substantial impact COVID-19 infection can have, even in lower-risk populations [19]. In addition, COVID-19 treatment can reduce viral replication, which may reduce transmissibility. Initial data from the Phase 2 study, which enrolled low-risk participants, indicates that S-217622 was generally safe and well tolerated.

Outcome Measures

The ACTIV-2d/A5407 study primarily evaluates the potential effect of S-217622 on the primary endpoint of time to sustained symptom resolution and the key secondary endpoints of change from baseline in quantitative SARS-CoV-2 RNA levels by PCR on NP swab at Day 4 and reduction in COVID-19-related hospitalization (adjudicated) and all deaths (not adjudicated) through Day 29. Time to sustained symptom resolution is defined as the time from start of study intervention to the first day of 4 consecutive days with complete resolution of 13 assessed COVID-19 symptoms AND alive and without hospitalization for any reason by Day 29. The symptom endpoint relies on 13 targeted symptoms that have been associated with COVID-19 and that are expected to be dynamic and improve with effective anti-SARS-CoV-2 therapy. In a Phase 2b study

(Study 2108T1221), S-217622 treatment was associated with a reduction in the time to sustained symptom resolution from 14 to 11.4 days.

In addition to evaluating safety, as secondary measures, this study will also evaluate the intervention's treatment efficacy on viral shedding by quantitative PCR and COVID-19 associated symptoms, as well as all-cause hospitalization and death. COVID-19-related hospitalization, as determined by an independent blinded adjudication committee, and death due to any cause also will be evaluated. An adjudication committee charter provides details of this activity.

The study includes a 29-day period of intensive monitoring to collect information on the virologic and clinical symptom outcomes. Additionally, the study includes a less intensive follow-up period to collect information on reinfections and long-term sequalae of COVID-19.

Multi-site Design

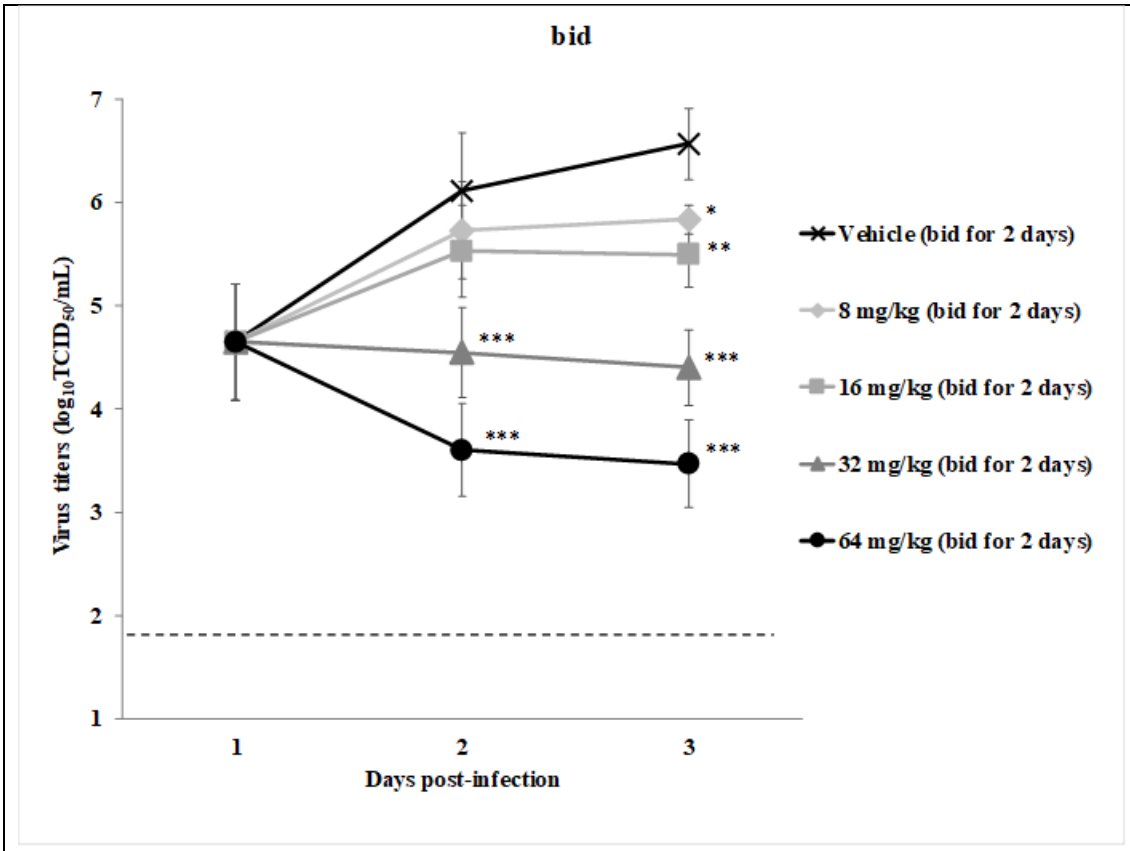
In any multi-site study, outcomes can potentially differ due to variation in site populations, stage of epidemic spread, diagnostic capability, and clinical management. Although it is expected that any differences between sites will be balanced between groups through randomization, the trial will also be stratified by geographic region and by high risk or low risk for severe COVID-19, as assessed at enrollment.

Investigational Agent: S-217622

The SARS-CoV-2 3CL protease is a virally encoded enzyme, which is essential for viral replication [20]. 3CL protease cleaves the virus P1a and P1ab polyproteins at multiple junctions to generate a series of proteins critical for virus replication and transcription, including RNA-dependent RNA polymerase (RdRp), the helicase, and the 3CL protease itself. No close human analogs of the coronavirus 3CL proteases are known. The essential functional importance in virus replication cycle, together with the absence of closely related homologs in humans, make the 3CL protease an attractive antiviral drug target. S-217622 is a SARS-CoV-2 3CL protease inhibitor demonstrating antiviral activity at nanomolar concentrations.

Available non-clinical and clinical studies are summarized below. S-217622 may confer advantages as a 1 pill once-a-day regimen, after the initial loading dose. Additionally, the long half-life (between 42 and 48 hours) will prolong exposure of the antiviral beyond the 5-day treatment period, ensuring optimal antiviral efficacy and potentially reducing the risk of viral rebounds, which may be a feature of drugs with a shorter half-life.

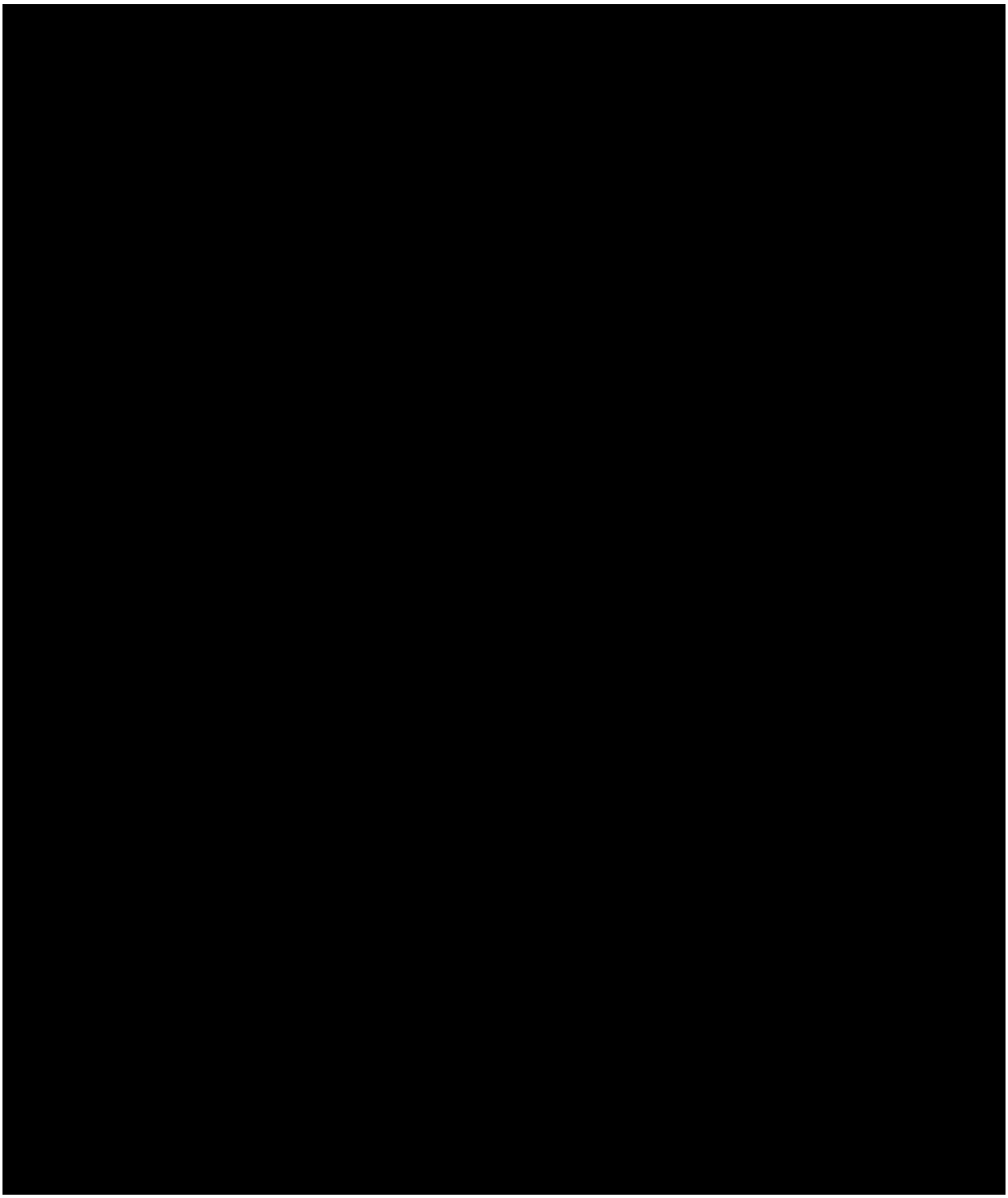
More detailed information about the known and expected benefits, risks, and reasonably expected adverse events (AEs) of S-217622 may be found in the Investigator's Brochure (IB).



bid = twice daily, SD = standard deviation, $TCID_{50}$ = tissue culture infectious dose which will infect 50%, vs. = versus
Mice were orally administered (10 mL/kg) with S-217622 or vehicle (0.5 w/v% methylcellulose). The first administration was performed 24 hours after virus infection.
The administration doses are indicated as free form.
Each point represents the mean ± SD of 5 mice.
Broken line represents the lower limit of quantification (1.80 log_{10} $TCID_{50}$/mL).
The following *P*-values were calculated by Dunnett's method. * *P*-value < 0.05, ** *P*-value < 0.01, *** *P*-value <0.0001 vs. vehicle

Figure 2.2-1 The Time-course of the Effect of S-217622 Treatment (bid) on the Virus Titers in Lungs in SARS-CoV-2 (hCoV-19/Japan/TY7-501/2021)-infected Mice

[redacted]



Metabolism

In an *in vitro* metabolism study of [^{14}C]-S-217622 using cryopreserved human hepatocytes, a glucuronide of oxidized S-217622 and 2 types of demethylated S-217622 were detected as major metabolites. These metabolites observed in human hepatocytes were also detected in monkey hepatocytes or the hepatocytes from rats and monkeys; therefore, human-specific metabolites are considered unlikely to be produced.

Pharmacokinetic Drug-drug Interactions

The following PK DDIs have been observed

- CYP inhibition: In a cytochrome P450 (CYP) inhibition study, S-217622 directly inhibited CYP2C8 (IC_{50} 35 µmol/L) and the IC_{50} for the other CYP enzymes (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A) was >100 µmol/L. S-217622 has a time-dependent inhibition on CYP3A.
- CYP induction: S-217622 is a weak CYP inducer; however, CYP3A inhibition dominated induction in a midazolam DDI study (see below).
- Transporter substrate: S-217622 is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but not a substrate of organic anion transporter polypeptide (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 1, OCT2, multidrug and toxin extrusion (MATE) 1, or MATE2-K.
- Transporter inhibition: S-217622 inhibited P-gp (IC_{50}: 11.5 µmol/L), BCRP (IC_{50}: 8.71 µmol/L), OATP1B1 (IC_{50}: 13.2 µmol/L), OATP1B3 (IC_{50}: 3.51 µmol/L), OAT1 (IC_{50}: 47.7 µmol/L), OAT3 (IC_{50}: 8.37 µmol/L), OCT1 (IC_{50}: 7.24 µmol/L), OCT2 (IC_{50}: 202 µmol/L), MATE1 (IC_{50}: 82.3 µmol/L), and MATE2-K (IC_{50}: >250 µmol/L).

Furthermore, drugs that also inhibit CYP enzymes described above may also have DDI.

Overview of Clinical Trials

S-217622 has undergone extensive preclinical testing (Good Laboratory Practice) and has been assessed for safety, PK, and tolerability in healthy volunteer studies. A 2-part Phase 2a and 2b/3 study in participants with mild or asymptomatic SARS-CoV-2-infection is underway in Japan and several other countries.

Preliminary Results From Clinical Studies

Pharmacokinetics in Healthy Volunteers

Single-dose S-217622 (20 to 1000 mg, suspension) was orally administrated to 32 healthy volunteers (6 participants in each dose group except 8 participants in the 250-mg cohort) in the fasted and fed (250 mg only) states (Study 2102T1211). The geometric means of C_{max}, area under the curve from time 0 to infinity ($AUC_{0\text{-}inf}$), and terminal elimination half-life ($t_{1/2,z}$) when single doses of S-217622 20 to 1000 mg were administered in the fasted state were 1.70 to 63.8 µg/mL, 91.44 to 3370 µg·hr/mL, and 42.2 to 48.1 hours, respectively. The C_{max} and AUC increased in an almost dose-proportional manner across the dose range from 20 to 1000 mg. Overall, drug levels were similar in the fasting and fed states (Figure 2.2-2 for 250-mg dosed group with high-calorie, high-fat meal), although the time to reach C_{max} (i.e., T_{max}) in the fed state was delayed compared with that in the fasted state).

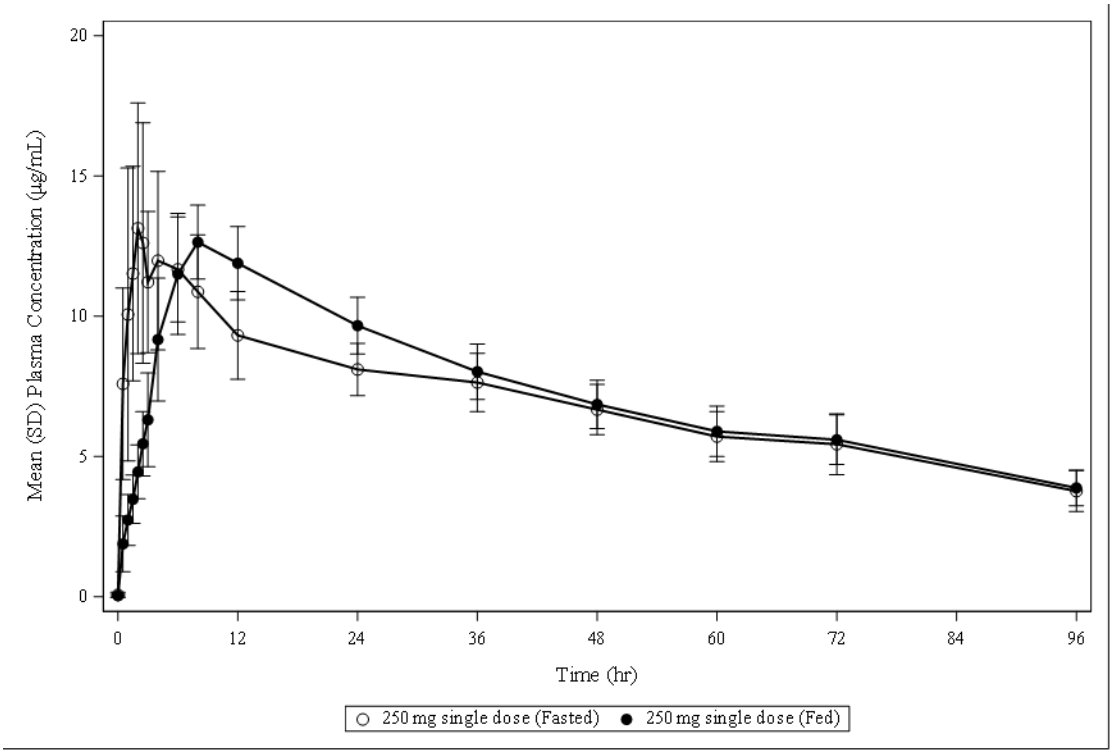
Multidose PK studies with 5 days of S-217622 (suspension) were performed in 24 healthy participants (Study 2102T1211): 8 Japanese volunteers received 750 mg loading dose/250 mg daily thereafter, 8 Japanese volunteers received 375 mg loading dose/125 mg daily thereafter, and 8 White volunteers received 375 mg loading dose/125 mg daily thereafter in the fasted state. Loading doses are used to rapidly

increase the minimum concentration (C_{trough}) above the target plasma concentration. In the Japanese cohort, the plasma C_{max} and area under the curve to the end of the dosing period ($AUC_{0\text{-}tau}$) increased in a dose dependent manner on Days 1 and 5 (Day 5 C_{max} 30.4 µg/mL and $AUC_{0\text{-}tau}$ 598.3 µg·hr/mL for 375-mg loading dose/125 mg daily thereafter group, and Day 5 C_{max} 63.7 µg/mL and $AUC_{0\text{-}tau}$ 1353 µg·hr/mL for the 750 mg loading dose/250 mg daily thereafter group). In the White cohort, the plasma C_{max} and $AUC_{0\text{-}tau}$ were lower than the Japanese cohort at the same dose: C_{max} 22.7 and 26.3 µg/mL and $AUC_{0\text{-}tau}$ were 351.2 and 517 µg·hr/mL on Days 1 and 5, respectively, for the 375-mg loading dose/125 mg daily thereafter group. The geometric least squares mean ratios (90% CIs) of C_{max} and $AUC_{0\text{-}tau}$ S-217622 (White/Japanese) on Day 1 were 0.7699 (0.6738 to 0.8796) and 0.7238 (0.6515 to 0.8040), respectively. Those on Day 5 were 0.8651 (0.7774 to 0.9627) and 0.8641 (0.7738 to 0.9649), respectively. The trough concentrations (concentration 24 hours after last dose [C_{24hr}]) were also lower in the White cohort vs. Japanese cohort on Day 1: 12.7 vs. 17.1 µg/mL, respectively, and Day 5: 19.0 vs. 21.3 µg/mL, respectively.

Results of the preliminary PK analysis for multidose PK studies suggest that exposures with the tablet formulation were lower than those with the suspension formulation. After 5 days of S-217622 tablet formulation, 750-mg (three 250-mg tablets) loading dose and 250 mg (one 250-mg tablet) daily thereafter in Japanese participants (Study 2102T1211), the C_{max} and $AUC_{0\text{-}tau}$ on Days 1 and 5, were 32.4 and 43.9 µg/mL, 550.6 and 855.5 µg·hr/mL, respectively. The C_{24hr} on Days 1 and 5 were 20.3 and 30.8 µg/mL, respectively.

Pharmacokinetics in Participants With SARS-CoV-2 Infection

In the Phase 2b part of Study 2108T1221, the plasma concentrations of S-217622 on Days 2 and 6 were evaluated in the 375/125- and 750/250-mg groups in participants with SARS-CoV-2 infection (110 and 109 points on Day 2, respectively; 98 and 95 points on Day 6, respectively). Although blood sampling points varied among the participants, the plasma concentrations of S-217622 were similar between Days 2 and 6 in both S-217622 375/125- and 750/250-mg groups.

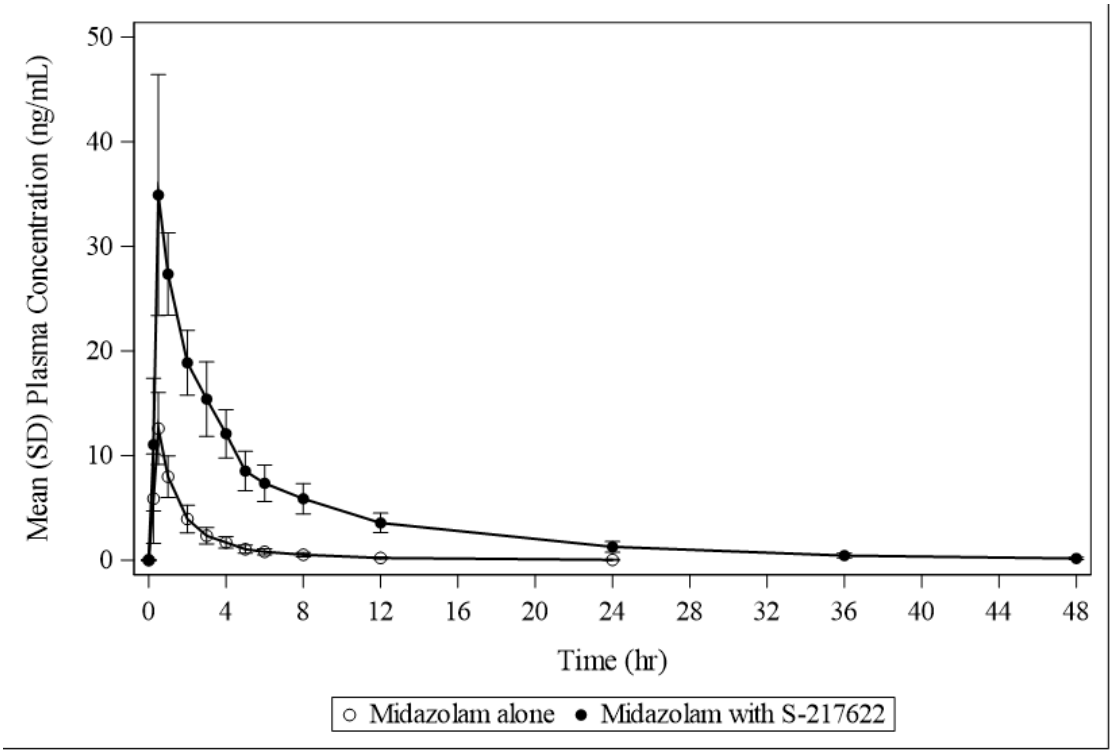


hr = hours; SD = standard deviation

Figure 2.2-2 Mean (± SD) Plasma S-217622 Concentration After Single-dose Administration of S-217622 (Suspension) 250 mg in the Fasted and Fed States

Drug-drug Interactions

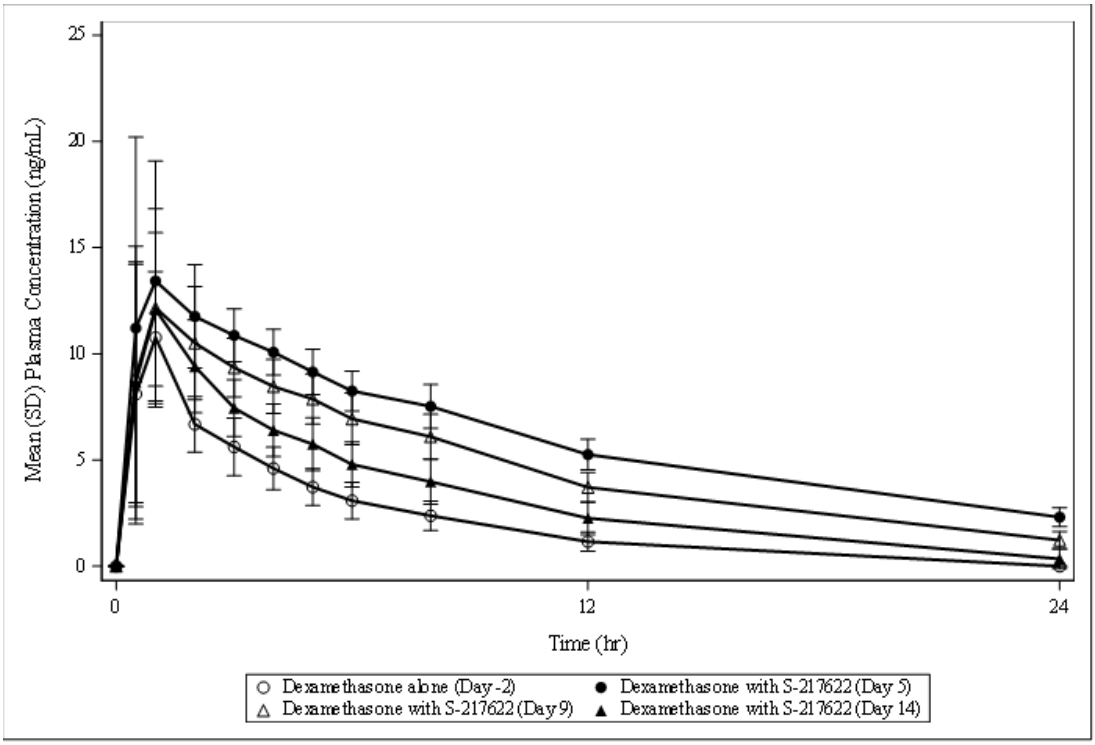
Given that S-217622 is an inhibitor of CYP3A, the effect of S-217622 on the PK of midazolam, a CYP3A substrate, following multiple-dose administration in Japanese healthy adult male participants was assessed. Plasma concentration profiles of midazolam following single-dose administration of midazolam alone and co-administration with S-217622 are presented in Figure 2.2-3. The C_{max}, area under the curve from time 0 to last measured concentration ($AUC_{0\text{-last}}$), and $AUC_{0\text{-inf}}$ of midazolam following single-dose administration of midazolam co-administered with S-217622 once daily for 6 days (375 mg on Day 1 and 125 mg on Days 2 to 6) were 2.80-, 6.90-, and 6.77-fold, respectively, compared with those following single-dose administration of midazolam alone. The results indicated that S-217622 is considered to be a strong CYP3A inhibitor at a dose of 375 mg on Day 1 and 125 mg on Days 2 to 6.



hr = hours, SD = standard deviation

Figure 2.2-3 Mean (± SD) Plasma Midazolam Levels Following Single-dose Administration of Midazolam Alone and Co-administration with S-217622

The effect of S-217622 on the PK of dexamethasone, following multiple-dose administration of S-217622 in Japanese healthy adult male participants, was confirmed. S-217622 was administered at 750 mg (three 250-mg tablets) as the loading dose on Day 1 and 250 mg (one 250-mg tablet) as the maintenance dose on Days 2 to 5. Dexamethasone was administered at 1 mg on Days -2, 5 (coadministration with S-217622), 9 (5th day after the last S-217622 dose) and 14 (10th day after the last S-217622 dose). Plasma concentration profiles of dexamethasone are presented in Figure 2.2-4. The C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of dexamethasone on Day 5 (coadministration with S-217622) were 1.47-, 3.19-, and 3.47-fold, respectively, those on Day 9 (5th day after the last S-217622 dose) were 1.24-, 2.45-, and 2.38-fold, respectively, and those on Day 14 (10th day after the last S-217622 dose) were 1.17-, 1.56-, and 1.58-fold, respectively, compared with those following single-dose administration of dexamethasone alone. The effect of S-217622 on the PK of dexamethasone was decreased over subsequent days after administration of S-217622.



hr = hours, SD = standard deviation

Figure 2.2-4 Mean (± SD) Plasma Dexamethasone Levels Following Single-dose Administration of Dexamethasone Alone and Co-administration with S-217622

A DDI study exploring the effect of S-217622 on the PK of prednisolone did not show a significant interaction.

Data from a cocktail DDI study with digoxin (a P-pg substrate), rosuvastatin (a BCRP and OATP1B1/1B3 substrate) and metformin (a MATE1 and OCT1 substrate) are available (Study 2130T1215). Coadministration of S-217622 500 mg increased C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of digoxin by 2.17-, 1.30-, and 1.31-fold, respectively. Coadministration of S-217622 500 mg also increased C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of rosuvastatin by 1.97-, 1.64-, and 1.65-fold, respectively. The geometric least squares mean ratios of C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ (metformin + S-217622/metformin alone) were close to 1 and their 90% CIs were all contained within the range of 0.8000 to 1.2500, suggesting no MATE1 and OCT1 inhibition by S-217622 500 mg. These results suggest S-217622 is a weak inhibitor of P-gp, BCRP, and OAT1B1/1B3, but not of MATE1 and OCT1 (including MATE2-K and OCT2, of which metformin is also a substrate).

Safety

Safety in Phase 1

A Phase 1 single-ascending-dose and multiple-ascending-dose study was performed in healthy volunteers across different doses of S-217622 or placebo. No serious treatment-emergent AEs (TEAEs) have occurred. The most common TEAEs were nausea, diarrhoea, headache, and abdominal pain, all of which were reported as mild. One participant received study intervention on Day 1 and was withdrawn from the study on Day 2 due to rash that was reported on Day 1 and was moderate in severity. The rash was urticarial in nature and caused redness on the chest and neck without constitutional symptoms and was not associated with changes in vital signs. There was no mucous membrane involvement and the rash was treated with an antihistamine and IV hydrocortisone and resolved 10 days after study intervention administration. Decreased high-density lipoprotein (HDL) was the most frequent of the TEAEs that occurred, and all returned to pretreatment levels within 7 days after cessation of treatment. Triglyceride elevations occurred in 2 volunteers receiving S-217622, in 1 volunteer following a single dose of 1000 mg, and in 1 volunteer dosed at the 750-mg loading dose, 250 mg during coadministration with midazolam. Both were graded as mild and resolved with cessation of S-217622.

Safety in Phase 2a

Of the 69 randomized participants, 1 participant did not receive the study intervention and was excluded from the Safety Analysis population. A total of 68 participants with mild/moderate or asymptomatic SARS-CoV-2 infection (21 in the 375/125-mg group, 23 in the 750/250-mg group, and 24 in the placebo group) were included in the Safety Analysis population in the Phase 2a part.

The overall incidence of TEAEs in the Phase 2a part was 52.4% (11/21 participants) in the 375/125-mg group, 69.6% (16/23 participants) in the 750/250-mg group, and 37.5% (9/24 participants) in the placebo group. The overall incidence of treatment-related TEAEs was 23.8% (5/21 participants) in the 375/125-mg group, 43.5% (10/23 participants) in the 750/250-mg group, and 0% (0/24 participants) in the placebo group.

TEAEs reported in at least 3 participants in any of the treatment groups in the Phase 2a part were HDL decreased (14.3% [3/21] and 52.2% [12/23] in the 375/125- and 750/250-mg groups, respectively), and headache and blood triglycerides increased (13.0% [3/23] each in the S-217622 750/250-mg group). No TEAEs were reported in 3 or more participants in the placebo group. The only treatment-related TEAE reported in at least 3 participants in any of the treatment groups was HDL decreased (14.3% [3/21] and 34.8% [8/23] in the 375/125- and 750/250-mg groups, respectively).

No severe TEAEs were reported, and most of the TEAEs were categorized as mild. Three moderate TEAEs were reported, but all these moderate events were considered unrelated to study intervention.

No deaths, serious TEAEs, or TEAEs leading to discontinuation of study intervention were reported in the Phase 2a part.

Safety in Phase 2b

Of the 428 randomized participants, 7 participants did not receive study intervention and were excluded from the safety analysis population. A total of 421 participants with mild/moderate SARS-CoV-2 infection (140 in the 375/125-mg group, 140 in the 750/250-mg group, and 141 in the placebo group) were included in the safety analysis population.

Based on the results up to Day 28, the overall incidence of TEAEs in the Phase 2b part was 34.3% (48/140 participants) in the 375/125-mg group, 42.9% (60/140 participants) in the 750/250-mg group, and 31.2% (44/141 participants) in the placebo group. The overall incidence of treatment-related TEAEs was 13.6% (19/140 participants) in the 375/125-mg group, 22.1% (31/140 participants) in the 750/250-mg group, and 5.0% (7/141 participants) in the placebo group.

TEAEs that were reported in ≥2% of the participants in any of the treatment groups of Phase 2b part were HDL decreased (20.7% [29/140], 23.6% [33/140], and 2.1% [3/141] in the 375/125-mg group, in the 750/250-mg group, and in the placebo group, respectively), hypertriglyceridaemia (2.9% [4/140] in the 750/250-mg group), headache, diarrhoea, back pain, and dyslipidaemia (2.1% [3/140] each in the 750/250-mg group), blood creatine phosphokinase increased (2.8% [4/141] in the placebo group), and abdominal pain upper and rash (2.1% [3/141] each in the placebo group).

Treatment-related TEAEs that were reported in ≥2% of the participants in any of the treatment groups were HDL decreased (9.3% [13/140] in the 375/125-mg group and 15.7% [22/140] in the 750/250-mg group) and dyslipidaemia (2.1% [3/140] in the 750/250-mg group). No treatment-related TEAEs were reported in ≥2% in the placebo group.

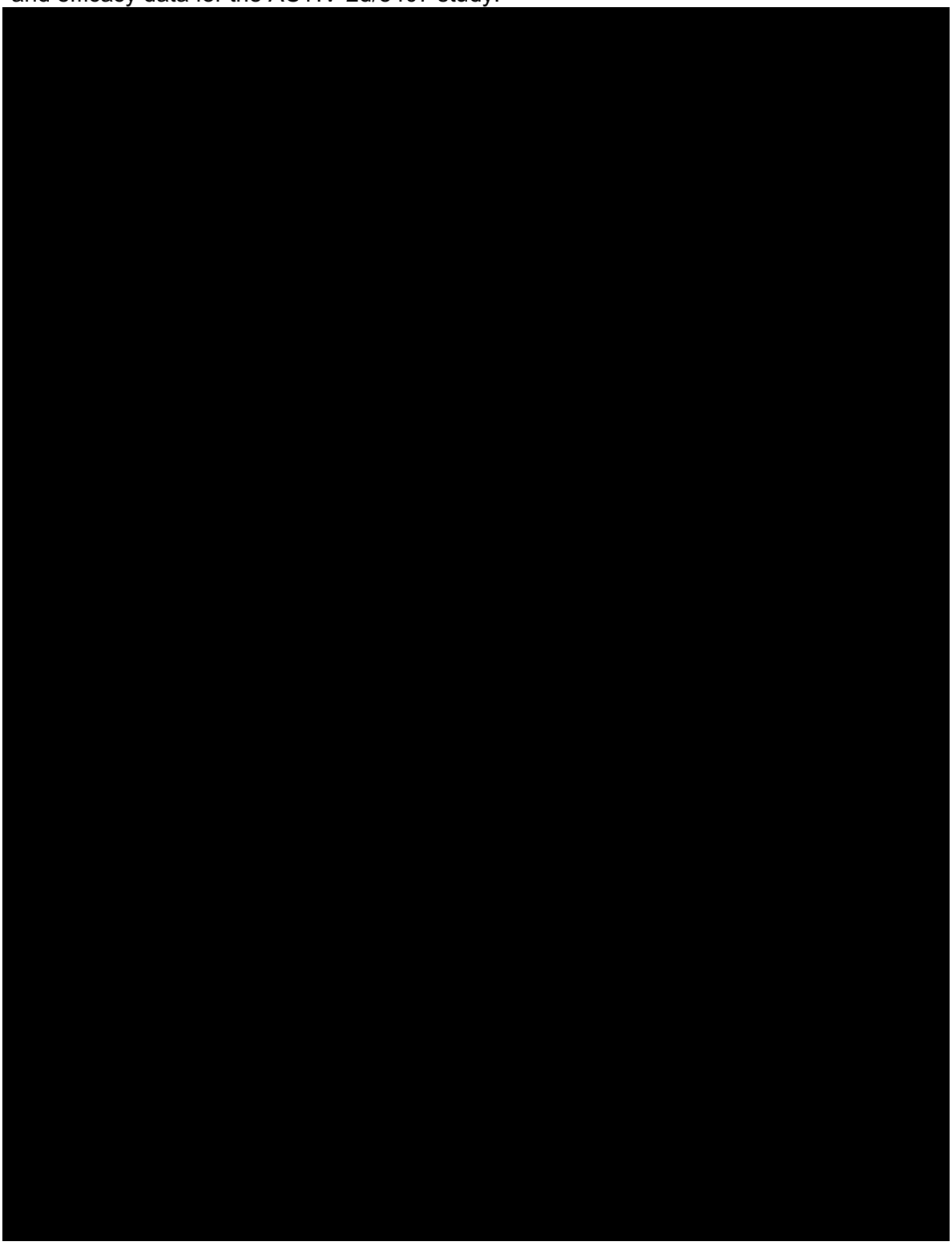
No severe TEAEs were reported in the 375/125- or 750/250-mg groups. Seven moderate TEAEs were reported, but most of TEAEs were categorized as mild.

No deaths or serious TEAEs were reported. TEAEs leading to discontinuation of study intervention were reported in 2 participants in the 375/125-mg group, and both were considered related.

Efficacy

An ongoing 2-part Phase 2a and 2b/3 study in participants with SARS-CoV-2 infection who either have mild or moderate disease or are asymptomatic was initiated in September 2021 in Japan and is expanding to several other countries including Singapore, Vietnam, and South Korea. This study is a multicenter, randomized, double-blind, placebo-controlled study in participants with mild and moderate disease and without risk factors for severe disease. The study consists of 3 intervention groups: S-217622 lower dose group (initial dose of 375 mg followed by 125 mg daily), S-217622 higher dose group (initial dose of 750 mg followed by 250 mg daily), and placebo group, each with 5 days of total treatment. The main purpose of the Phase 2a part is to confirm the antiviral effect of multiple doses of S-217622. The Phase 2a part provided antiviral proof of concept and determined the dose to be implemented in Phase 3 studies. The Phase 2b/3 part is to verify the efficacy in mild, moderate, and asymptomatic participants with SARS-CoV-2-infection without risk factors for severe disease. The study is examining time to cessation of virus shedding and time to improvement/resolution of

symptoms in the participants with symptomatic disease. In asymptomatic participants, the study is assessing the occurrence of symptomatic disease. It is planned to include approximately 2600 participants in these studies, which will provide supportive safety and efficacy data for the ACTIV-2d/5407 study.



[redacted]

Clinical Data

Phase 2a

The primary efficacy endpoint in the Phase 2a part was the change from baseline in SARS-CoV-2 viral titer at each timepoint.

In the overall participants with mild/moderate and asymptomatic SARS-CoV-2 infection, the mean (standard deviation [SD]) changes from baseline in virus titer (tissue culture infectious dose that will infect 50% [$TCID_{50}$]) (log_{10} [$TCID_{50}$/mL]) in the 375/125-mg, 750/250-mg, and placebo groups were −1.05 (1.17), −2.03 (1.21), and −0.86 (0.93), respectively, on Day 2; −2.42 (1.42), −2.81 (1.21), and −1.54 (0.74), respectively, on Day 4; and −2.56 (1.35), −2.76 (1.19), and −2.08 (0.91), respectively, on Day 6. When compared with the placebo group, the changes from baseline in virus titer were greater decreased by 1 log_{10} ($TCID_{50}$/mL) in the 750/250-mg group on Day 2 and by approximately 1 log_{10} ($TCID_{50}$/mL) in both the 375/125- and 750/250-mg groups on Day 4. In the 375/125-mg group, the virus titers decreased to the lower detection limit in all the participants on Day 6.

Phase 2b

The primary efficacy endpoints in the Phase 2b part were the time-weighted average change in total score of 12 COVID-19 symptoms from initiation of administration (Day 1) up to 120 hours (Day 6) and the change from baseline on Day 4 in SARS-CoV-2 viral titer.

For the time-weighted average change in total score of 12 COVID-19 symptoms from initiation of administration (Day 1) up to 120 hours (Day 6), the mean (SD) changes in the 375/125-mg, 750/250-mg, and placebo groups were −5.95 (4.02), −5.42 (3.70), and −4.92 (3.25), respectively. No significant difference was observed in either the 375/125- or 750/250-mg group compared with the placebo group. The estimated value of the least squares means was larger in both the 375/125- and 750/250-mg groups than in the placebo group.

For time to sustained resolution of 12 COVID-19 symptoms, defined as when all targeted symptoms are scored as absent for 4 consecutive days, both the 375/125- and 750/250-mg groups showed more rapid sustained resolution compared with placebo. In the randomized population receiving 375/125 mg of S-217622 (regardless of a positive SARS-CoV-2 viral culture at baseline), the time to sustained resolution of 12 symptoms was achieved at 11.4 days compared with 14 days for placebo recipients.

For the change from baseline on Day 4 in SARS-CoV-2 viral titer (log_{10} [$TCID_{50}$/mL]), mean changes (SD) in the 375/125-mg, 750/250-mg, and placebo groups were −1.69

(0.84), −1.43 (0.83), and −1.06 (0.99), respectively. The estimated value of the least squares means was decreased by 0.41 $\log_{10}$ ($TCID_{50}$/mL) in the 375/125- and 750/250-mg groups, and significant differences were observed in both the 375/125- and 750/250-mg groups compared with the placebo group ($p<0.0001$).

In an intent-to-treat infected analysis (defined as those with a positive SARS-CoV-2 viral culture at baseline, the proportion of participants with a negative virus titer (<0.8 $\log_{10}$ $TCID_{50}$/mL) at Day 4 (after 3 doses of study intervention), 89% were negative in the 750/250-mg group, 96% were negative in the 375/125-mg group, and 50% were negative in the placebo group ($p<0.0001$). An analysis in the randomized population (regardless of a positive baseline SARS-CoV-2 culture) showed that at Day 4, 85% in the 375/125-mg group, 94.2% in the 750/250-mg group, and 55.1% (61/136) in the placebo group had a negative viral culture ($p\leq0.0001$). The 375/125-mg dose was chosen given the equivalent antiviral potency compared with the higher 750/250-mg dose and the signal toward improved time to sustained symptom resolution. The lower dose is anticipated to have less DDI and TEAEs while maintaining potent antiviral activity.

In-vitro susceptibility to SARS-CoV-2 omicron variant

VeroE6/TMPRSS2 cells and HEK293T/angiotensin-converting enzyme 2 (ACE2)-TMPRSS2 cells, which are susceptible to infection with SARS-CoV-2, were infected with the following clinical isolates to determine the concentration achieving 50% inhibition of the cytopathic effect (CPE) induced by SARS-CoV-2 (EC_{50}) values of S-217622 for these strains on Day 3 after infection: alpha strains (hCoV-19/Japan/QHN001/2020, hCoV-19/Japan/QHN002/2020, and hCoV-19/Japan/QK002/2020); beta strain (hCoV-19/Japan/TY8-612/2021); gamma strains (hCoV-19/Japan/TY7 501/2021 and hCoV-19/Japan/TY7 503/2021); and delta strains (hCoV-19/Japan/TY11-927-P1/2021). Additionally, the EC_{50} value of omicron strain (hCoV-19/Japan/TY38-873/2021) was determined on Day 4 after infection.

S-217622 inhibited CPE regardless of the virus lineages or strains, with EC_{50} values ranging from 0.31 to 0.50 µmol/L using VeroE6/TMPRSS2 cells and 0.026 to 0.083 µmol/L using HEK293T/ACE2-TMPRSS2 cells (see Table 2.2-1). The CC_{50} of S-217622 for VeroE6/TMPRSS2 cells and HEK293T/ACE2-TMPRSS2 cells was >100 and 55 µmol/L, respectively. These *in vitro* susceptibility results for circulating SARS-CoV-2 variants demonstrated that S-217622 retained activity against alpha, beta, gamma, and delta strains. Additionally, activity was retained for a clinical isolate of the omicron SARS-CoV-2 variant.

Table 2.2-1 *In Vitro* Susceptibility to SARS-CoV-2 Variants

Half maximal (50%) effective concentration (EC_{50})	S-217622	
	VeroE6/TMPRSS2	HEK293T/ACE2-TMPRSS2
WK-521 strain	0.37 μM	0.027 μM
α strain (QHN001/QHN002/QK002)	0.31/0.46/0.33 μM	NT/NT/0.044 μM
β strain (TY8-612)	0.40 μM	0.038 μM
γ strain (TY7-501/TY7-503)	0.50/0.43 μM	0.026/NT μM
δ strain (TY11-927-P1)	0.41 μM	0.058 μM
ο strain (TY38-873)	0.36 μM	0.083 μM
Concentration achieving 50% of cytotoxicity (CC_{50})	>100 μM	55 μM

3. STUDY DESIGN

3.1. Overview of Study Design

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 low-risk non-hospitalized adults with SARS-CoV-2 infection.

Evaluations

S-217622 will be evaluated for safety, as well as for activity in reducing the time to sustained symptom resolution and the proportion of participants with viral culture positivity at Day 4, in addition to hospitalization, all-cause mortality, SARS-CoV-2 viral RNA levels, and clinical status on an ordinal scale as compared with placebo control.

Early Termination

The DAIDS data safety monitoring board (DSMB) will review interim safety results on a regular basis as recommended by the DSMB. The DSMB may recommend early termination of randomization to S-217622 if there are safety or efficacy concerns (see Section 7.3).

3.2. Isolation Procedures

Given that SARS-CoV-2 is spread through respiratory secretions, each site must develop procedures to protect study staff and participants in other trials from infectious exposure. Each site will have a plan for appropriate protection by providing personal protective equipment (PPE), setting up isolation rooms, and providing special access points or contact with study participants, including the possibility for home or other non-clinic, in-person visits. Each site will develop their own set of procedures for such participant contact.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1. Eligibility Criteria

4.1.1. Inclusion Criteria

For all participants

4.1.1.1. Ability and willingness of participant to provide informed consent prior to initiation of any study procedures.

4.1.1.2. Age ≥18 years.

4.1.1.3. Documentation of laboratory-confirmed active SARS-CoV-2 infection, as determined by a nucleic acid (e.g., reverse-transcriptase PCR) or antigen test from any respiratory tract specimen (e.g., oropharyngeal, NP or nasal swab, or saliva) collected ≤120 hours (5 days) prior to randomization.

4.1.1.4. Participants are expected to begin study intervention ≤5 days from self-reported date of onset of any of the COVID-19-related symptoms from the following list:

- 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 or smell

4.1.1.5. One or more of the following signs/symptoms present within 24 hours prior to randomization (all criteria in Section 4.1.1.4 except loss of taste or 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
- Nasal discharge

4.1.1.6. Oxygenation saturation of ≥92% on room air adjusted for altitude and obtained at rest by study staff within 24 hours prior to randomization. (See Manual of Procedures [MOP] for details of adjustments for altitude.)

NOTE: For a potential participant who regularly receives chronic supplementary oxygen for an underlying lung condition, oxygen saturation measured while on their standard home oxygen supplementation level must be ≥92%.

4.1.1.7. Agrees to not participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 during the study period unless meeting hospitalization criteria or reaching Day 29, whichever is earliest.

4.1.1.8. For participants who are of reproductive potential, negative serum or urine pregnancy test within 48 hours prior to randomization. Reproductive potential is defined as:

- Participants who have reached menarche
- Participants who have not been postmenopausal for at least 12 consecutive months with follicle-stimulating hormone (FSH) ≥40 IU/mL or 24 consecutive months if an FSH level is not available
- Participants who have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or bilateral salpingectomy)

Note: For individuals with permanent infertility due to an alternate medical cause (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry and need for pregnancy testing.

4.1.1.9. Participants who are of reproductive potential who engage in sexual activity that may lead to pregnancy must agree to use effective contraception from study entry through 14 days after the last dose of study intervention. Effective methods of contraception include:

- Sexual abstinence
- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (e.g., oral, intravaginal, transdermal, injectable) PLUS an additional barrier method
- Progestogen-only hormone contraceptive associated with inhibition of ovulation: oral, injectable PLUS an additional barrier method
- Implanted progestogen-only contraceptives associated with inhibition of ovulation PLUS an additional barrier method
- Intrauterine devices (with or without release of hormones)
- Bilateral tubal occlusion (e.g., bilateral tubal ligation)
- Vasectomized partner
- Barrier methods that include male or female condom (cervical cap, diaphragm or sponge with spermicide)

The investigator, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a participant with an early undetected pregnancy.

NOTE: Participants not of reproductive potential are eligible without requiring the use of a contraceptive method. Participant-reported history is acceptable documentation of surgical sterilization and menopause, including vasectomy in a sole partner.

4.1.1.10. Participants assigned female sex at birth who are of reproductive potential must agree not to donate eggs (ova, oocytes) for the purpose of reproduction from study entry through 14 days after the last dose of S-217622 or placebo.

4.1.1.11. Participants with pregnant partners must agree to use condoms during vaginal intercourse from study entry through 14 days after the last dose of S-217622 or placebo administration.

NOTE: Participants are also strongly advised to inform their non-pregnant sexual partners of reproductive potential to use effective contraceptives (as described in Section 4.1.1.9) from study entry through 14 days after the last dose of study intervention is administered.

4.1.1.12. Participants assigned male sex at birth must agree to refrain from sperm donation from study entry through 14 days after the last dose of S-217622/placebo administration.

4.1.1.13. Participant is willing and able to comply with the study requirements and procedures as judged by the investigator.

For high-risk participants (limited to 50% of enrollment)

4.1.1.14. Participants at high risk are defined as having 1 or more factors that lead to a higher risk of progression to severe COVID-19:

- Age ≥65 years
- Age ≥18 with 1 of the following:
  - Obesity (body mass index [BMI] ≥30 kg/m^2). Note: BMI is rounded to the nearest whole number, for example 29.5 kg/m^2 is rounded to 30 kg/m^2.
  - Diabetes mellitus
  - Hypertension
  - Cardiovascular disease (including congenital heart disease)
  - Chronic lung disease (e.g., chronic obstructive pulmonary disease [COPD], moderate to severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension)
  - Chronic kidney disease, as long as the participant does not have known creatinine clearance (CrCl) <30 mL/min by Cockcroft-Gault or require dialysis (see Exclusion Criterion 4.1.2.9)
  - Down syndrome
  - Sickle cell disease
  - One of the following immunocompromising conditions or immunosuppressive treatments:
    - Receiving chemotherapy or other therapies for cancer
    - Hematologic malignancy (active or in remission)
    - History of a hematopoietic stem cell or a solid organ transplant
    - HIV infection: not on antiretroviral therapy or with CD4+ cell count <200 cells/mm^3
    - Combined primary immunodeficiency disorder
    - Taking immunosuppressive medications (e.g., drugs to suppress rejection of transplanted organs or to treat rheumatologic and gastrointestinal conditions, such as anti-TNF agents, mycophenolate, and rituximab)

  Note: Current use of some corticosteroids is exclusionary, due to concern for possible DDI with S-217622. See Section 5.4.2 for prohibited medications.

For low-risk participants (limited to 50% of enrollment)

Participants at low risk for progression to severe COVID-19 are defined as <65 years of age and with none of the risk factors in Inclusion Criterion4.1.1.14.

4.1.2. Exclusion Criteria

4.1.2.1. History of hospitalization for the current SARS-CoV-2 infection (i.e., prior hospitalization for a prior episode of SARS-CoV-2 infection is allowable).

4.1.2.2. For the current SARS-CoV-2 infection, any positive SARS-CoV-2 molecular (nucleic acid) or antigen test from any respiratory tract specimen (e.g., oropharyngeal, NP or nasal swab, or saliva) collected >120 hours (5 days) prior to randomization. Participants with reinfection, defined as prior SARS-CoV-2 infection that began >90 days prior to the current onset of symptoms with interval resolution of symptoms are eligible as long as the current infection has not been present for more than 5 days prior to randomization.

4.1.2.3. Current need for hospitalization or immediate medical attention in the opinion of the investigator.

4.1.2.4. Current use of any medications prohibited with the study intervention, as described in Section 5.4.2. Use of Paxlovid at any time and the use of any oral, inhaled, or injectable medication intended to treat symptomatic SARS-CoV-2 infection before enrollment are excluded. After enrollment, locally available SARS-CoV-2 treatment (including but not limited to molnupiravir, mAbs, outpatient IV remdesivir, convalescent plasma, inhaled budesonide, favipiravir, and fluvoxamine) will be permitted, as long as there are no concerns for DDIs as outlined in Section 5.4.2.

4.1.2.5. Receipt of any investigational treatments for the current episode of SARS-CoV-2 at any time prior to randomization is exclusionary.

NOTE: This does not include drugs approved for other uses and taken for those indications or COVID-19 vaccines.

NOTE: Use of locally authorized or approved therapies to prevent COVID-19, such as mAbs given solely to prevent COVID-19, are not exclusionary.

4.1.2.6. Any comorbidity requiring surgery within 7 days prior to randomization or that is considered life threatening in the opinion of the investigator within 28 days prior to randomization.

4.1.2.7. Currently pregnant or breastfeeding.

4.1.2.8. Known allergy/sensitivity or any hypersensitivity to components of S-217622 or placebo for S-217622.

4.1.2.9. Known current renal impairment defined as CrCl <30 mL/min by Cockcroft-Gault or requiring dialysis.

4.1.2.10. Known history of cirrhosis or liver decompensation (including ascites, variceal bleeding, or hepatic encephalopathy).

4.1.2.11. Participants who have used any of the following drugs within 14 days prior to enrollment:

– Strong CYP3A inducer

– Products containing St. John's Wort

See Section 5.4.2 for a listing of CYP3A inducers.

4.2. Study Enrollment Procedures

All sites will be registered by the contract research organization (CRO). Sites will be notified if the high-risk or low-risk cohort has been fully enrolled and will not be able to randomize into a fully enrolled cohort.

Participants from whom a signed informed consent has been obtained may be screened and enrolled, if they otherwise qualify. A screening checklist must be entered through the web-based interactive response technology (IRT) system.

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, a Screening Failure Results form must be completed and keyed into the database.

Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened once. Rescreened participants should be assigned a new participant number for rescreening and need to be identifiable from the original screening number. Retesting of a participant for a specific laboratory test during the Screening period will be allowed at the investigator's discretion and will not be considered rescreening. A participant who is rescreened is not required to sign another informed consent form (ICF) if the rescreening occurs within 2 days from the previous ICF signature date. Entry evaluations must occur ≤72 hours after consent (see Section 6.2.3).

4.2.1. Randomization

Participants who meet the enrollment criteria will be randomized to a study group.

All participants will be centrally assigned to randomized study intervention using the IRT system. Randomization will be stratified by geographic region and by determination as high risk or low risk for severe COVID-19. Before the study is initiated, directions for use of the IRT system will be provided to each site.

Study intervention will be administered as summarized in the Schedule of Evaluations (SOE) in Table 6.1-1.

Returned study product should not be re-dispensed to the participants.

4.2.2. Unblinding

This is a double-blind study in which participants and investigators are blinded to study intervention.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. Given possible decrease in HDL cholesterol with S-217622 dosing, HDL values will not be reported to the sites. Temporary decrease in HDL does not represent a safety concern.

The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment, unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. The date and reason for unblinding must be recorded in the source documentation.

Sponsor safety staff may unblind the intervention assignment for any participant with a serious AE (SAE). If the SAE requires that an expedited regulatory report be sent to at least 1 regulatory agency, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

4.2.3. Coenrollment Guidelines

Coenrollment in an interventional study for the treatment of COVID-19 or its complications is allowed during or following hospitalization for COVID-19 and after 28 days post-entry (i.e., after Day 29).

For specific questions and approval for coenrollment in other studies, sites should follow the directions described in the protocol MOP.

5. INVESTIGATIONAL AGENT

Study intervention is either S-217622 or placebo.

5.1. Regimen, Administration, and Duration

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.

  Doses of S-217622 or matching placebo can be taken without food restriction. The tablets should be swallowed whole and should not be chewed, broken, or crushed.

  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 5 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 treatment period. Missed doses and remaining tablets at the end of 5 days should be returned to the site.

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

5.2. Formulation, Storage, and Preparation

5.2.1. Formulation and Storage

S-217622 tablet: Supplied as a white, 9-mm round tablet. Store at 15 to 30°C (59 to 86°F).

Placebo for S-217622: Supplied as a white, 9-mm round tablet to visually match the active drug. Store at 15 to 30°C (59 to 86°F).

5.2.2. Preparation

One blister pack of S-217622 or placebo containing 7 tablets will be dispensed to each participant.

5.2.3. Labeling of S-217622 and Matching Placebo

A participant-specific label must be affixed on the blister pack prior to dispensing to the participant.

Label each blister pack with the following information:

a. Participant identifier(s)
b. Protocol number: ACTIV-2d/A5407
c. Study intervention name: S-217622 or placebo
d. Route: oral administration and dosing instructions (3 tablets Day 1, followed by 1 tablet daily Days 2 to 5)
e. Any additional information required by jurisdiction

5.3. Supply, Distribution, and Accountability

5.3.1. Supply/Acquisition/Distribution

S-217622 125 mg and matching placebo for S-217622 will be provided and supplied by Shionogi.

5.3.2. Accountability

The site pharmacist or authorized designee is required to maintain complete records of all study interventions received from Shionogi and subsequently dispensed. All unused study interventions must be returned after the study is completed or terminated. The site pharmacist must follow the instructions provided in the Study Reference Manual or Site Instructions Document for the destruction of unused study interventions.

5.4. Concomitant Medications

Whenever a concomitant medication or study intervention is initiated or a dose changed, investigators must review the concomitant medications and the relevant protocol sections as well as the most recent package insert, IB, or updated information from Shionogi to obtain the most current information on DDIs, contraindications, and precautions.

Any medications given for the treatment of adverse reactions will be documented as a concomitant medication.

Additional drug information may be found on the AIDS Clinical Trials Group (ACTG) Precautionary and Prohibited Medications Database located at https://www.ppmdb.org/PPMD.

Locally available standard-of-care COVID-19 treatment, including but not limited to mAbs, outpatient IV remdesivir, molnupiravir, convalescent plasma, inhaled budesonide, favipiravir, and fluvoxamine, is permitted after enrollment as long as not prohibited on the basis of DDI (see Section 5.4.2). Any COVID-19 treatment must be recorded on a case report form (CRF) for COVID-19 standard-of-care treatment, including timing of initiation.

5.4.1. Allowable Symptomatic Relief

The study site will not supply symptomatic-relief medication. The use of these symptomatic relief medications for COVID-19 symptom control will be allowable at any time during the study. The date and time of administration, as well as the name and dosage regimen, must be recorded.

5.4.2. Prohibited and Precautionary Medications

Use of the following therapies is prohibited from the time of informed consent to the completion of examinations on Day 29 or upon hospitalization, at which point the study medication should be stopped. However, even if a prohibited concomitant therapy is used, the participant should continue the study procedures according to the specified SOE (Table 6.1-1) to the extent possible.

- Paxlovid (nirmatrelvir plus ritonavir), hydroxychloroquine, and ivermectin are prohibited due to DDIs with S-217622. Paxlovid is a CYP3A inhibitor and substrate and thus has potential for significant DDI with S-217622. Hydroxychloroquine and ivermectin are both CYP3A substrates and thus may also be substantially impacted by S-217622 with an increase in drug levels.

- Corticosteroids administered via any route (including intranasal, inhaled, oral, intra-articular but excluding topical). However, prednisolone is permitted (unless specifically used to treat COVID-19) based on a lack of significant interaction in a clinical DDI study. Furthermore, intranasal or inhaled beclomethasone is allowed based on demonstration of the lack of a significant interaction with darunavir/ritonavir [24], and dexamethasone can be administered the day after the last dose of study intervention administration based on the results of clinical DDI study with dexamethasone (refer to Section 2.2). If dexamethasone is required earlier and during treatment with S-217622 for urgent treatment of deteriorating disease, investigators should be aware of the continuing interaction and increased exposure to dexamethasone.
- CYP3A substrates. S-217622 is considered to be a strong inhibitor of CYP3A4. (Note: remdesivir and combined oral contraceptives are permitted). Examples of CYP3A substrates include the following medications: Paxlovid (nirmatrelvir plus ritonavir), alfentanil, avanafil, buspirone, chloroquine, conivaptan, darifenacin, darunavir, ebastine, everolimus, hydroxychloroquine, ibrutinib, ivermectin, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, and tolvaptan. For additional CYP3a substrates, see: https://go.drugbank.com/categories/DBCAT002646.

Use of the following therapies is prohibited from the time of informed consent to the day after the last study intervention administration or 24 hours following the time of early discontinuation.

- Strong CYP3A inducers. Examples include phenytoin, rifampin. For additional strong CYP3A inducers, see https://go.drugbank.com/categories/DBCAT003816.
- OAT-3 substrates with a narrow therapeutic index, such as methotrexate. For additional information on OAT 3 substrates, see https://go.drugbank.com/categories/DBCAT002661.
- P-gp substrates with a narrow therapeutic index, such as digoxin, and sensitive substrates, such as aliskiren. For additional information on P-gp substrates, see https://go.drugbank.com/categories/DBCAT004027.
- High-dose of rosuvastatin (20 to 40 mg), as it is considered a high-dose BCRP substrate.

The above are examples of prohibited medications. Sites should confirm the route of metabolism of all medications to ensure not prohibited; this can be done using https://go.drugbank.com.

6. CLINICAL AND LABORATORY EVALUATIONS

6.1. Schedule of Evaluations

Table 6.1-1 Schedule of Evaluations

Evaluations	Screening	Study Entry (Randomization)/ Day 1	Day 4	Day 8	Day 16[a]	Day 29	Week 12	Week 24	Event Driven Evaluation: Worsening Symptoms Days 6 to 29[b]	Premature Study D/C (Before Day 29 Visit)	Premature Study D/C (After Day 29 Visit)	Event Driven Evaluation: SARS-CoV-2 Reinfection
Visit Window	-72 hours		+/-1 day	+/-1 day	-4 days	0/+4 days	+/-14 days		+3 days after initial contact			
Informed Consent	X											
Documentation of SARS-CoV-2 Infection	X											X
COVID-19 Symptom Screen	X											
Pre-COVID-19 Symptom Screen	X											
Demographic Data Including Reported Race & Ethnicity	X											
Medical/ Medication History	X											
Assessment of Expectation to Receive mAbs or Outpatient IV Remdesivir	X	X										
Smoking Status	X											
Height	X											
Weight	X	X	X	X		X				X		
Oxygen Saturation	X	X										

Evaluations	Screening	Study Entry (Randomization)/ Day 1	Day 4	Day 8	Day 16[a]	Day 29	Week 12	Week 24	Event Driven Evaluation: Worsening Symptoms Days 6 to 29[b]	Premature Study D/C (Before Day 29 Visit)	Premature Study D/C (After Day 29 Visit)	Event Driven Evaluation: SARS-CoV-2 Reinfection
Visit Window	-72 hours		+/-1 day	+/-1 day	-4 days	0/+4 days	+/-14 days		+3 days after initial contact			
Physical Examination		X										
Targeted Physical Examination			X	X	X	X				X	X	X
Concomitant Medications	X	X	X	X	X	X				X	X	X
Any COVID-19 Standard-of-care Therapy Recorded in eCRF		X	X	X	X	X						
Assessment for Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Collect/Update Secondary Contacts		X	X	X	X	X	X	X				
Vital Status Check			If participant cannot be reached per Section 6.3.12									
Study Intervention Initiated (for 5 days treatment)		X										
Unused/Empty Study Intervention Returned				X								
Study Kit Dispensed		X										
Review Study Medication Log			X	X								

Evaluations	Screening	Study Entry (Randomization)/ Day 1	Day 4	Day 8	Day 16[a]	Day 29	Week 12	Week 24	Event Driven Evaluation: Worsening Symptoms Days 6 to 29[b]	Premature Study D/C (Before Day 29 Visit)	Premature Study D/C (After Day 29 Visit)	Event Driven Evaluation: SARS-CoV-2 Reinfection
Visit Window	-72 hours		+/-1 day	+/-1 day	-4 days	0/+4 days	+/-14 days		+3 days after initial contact			
Participant-completed Study Diary		Every day through Day 29										
Study Diary Reminder		Days 1 to 29										
Staff Review of Study Diary			X	X	X	X				X		
Retrieval of Study Diary						X				X		
Complete Ordinal Scale of COVID-19 Severity		X	X	X	X	X				X		
Post-acute COVID-19 Questionnaire							X	X			X	
EQ-5D-5L		X				X	X	X			X	
SF-36v2		X				X	X	X			X	
Household Infection and Linkage Report		X		X		X				X		
Staff-collected NP Swab for Viral Load Testing and Sequencing		X	X	X	X				X	X		X[c]

Evaluations	Screening	Study Entry (Randomization)/ Day 1	Day 4	Day 8	Day 16[a]	Day 29	Week 12	Week 24	Event Driven Evaluation: Worsening Symptoms Days 6 to 29[b]	Premature Study D/C (Before Day 29 Visit)	Premature Study D/C (After Day 29 Visit)	Event Driven Evaluation: SARS-CoV-2 Reinfection
Visit Window	-72 hours		+/-1 day	+/-1 day	-4 days	0/+4 days	+/-14 days		+3 days after initial contact			
Staff-collected NP Swab for Viral Culture		X	X	X	X				X			
Staff-collected Anterior Nasal Swab		X										
Biomarkers: TARC (CCL17), IL-6, Procalcitonin and KL-6		X										
HepB, HCV test[d]		X										
SARS-CoV-2 Serology (including quantitative IgG)		X				X				X		X
Hematology		X	X	X	X	X	X		X	X	X	
Chemistry		X	X	X	X	X	X		X	X	X	
Creatinine clearance		X	X	X		X				X		
Pregnancy Testing		X				X	X			X	X	
Pharmacokinetics (see Section 6.3.22)		X	X	X								
Documentation of Reason for Discontinuation										X	X	

Ab = antibody; COVID-19 = coronavirus disease 2019; D/C = discontinuation; EQ-5D-5L = EuroQol–5 Dimensions–5 Levels; HbSAg = hepatitis B surface antigen; HCV = hepatitis C virus; HepB = hepatitis B virus; IgG = immunoglobulin G; IL6 = interleukin-6; IV = intravenous; KL-6 = Krebs von den Lungen-6; mAb = monoclonal antibody; NP = nasopharyngeal; PASC = post-acute sequalae of COVID-19; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SF-36v2 = Short Form 36 Health Survey Questionnaire, version 2; TARC (CCL17) = thymus and activation regulated chemokine (chemokine ligand 17)

[a] Participants will be asked if any household members have been newly diagnosed with COVID-19.

[b] Any participant reporting worsening symptoms should be recalled for an unscheduled visit where both viral culture and quantitative SARS-CoV-2 PCR, as well as hematology and chemistry, are performed to assess the incidence of post-treatment viral rebounds from Days 6 through 29, within 3 days of initial contact.

[c] NP swab is only collected if the diagnosis of reinfection is within 7 days of symptom onset suggesting reinfection. See Section 6.2.5 for instructions.

[d] HbSAg and HCV Ab; İf HCV Ab is positive, will reflex to HCV RNA; if HbSAg is positive, will reflex to HepB DNA.

6.2. Timing of Evaluations

6.2.1. Screening Evaluations

Screening evaluations must occur prior to the participant starting any study medications, treatments, or interventions.

Screening and Study Entry visit evaluations will be combined.

Study Entry visit evaluations must be done prior to administration of study intervention.

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the database.

6.2.2. Smoking Status

A smoking status questionnaire will be completed as part of medical history and recorded on the electronic case report form (eCRF).

6.2.3. Entry Evaluations

Entry evaluations must occur ≤72 hours after consent unless otherwise specified.

Participants must begin study intervention no more than 5 days from self-reported onset of COVID-19 related symptoms or measured fever as noted in Section4.1.1.4.

6.2.4. Post-entry Evaluations

On-treatment/Post-treatment Evaluations

Evaluations should occur in the visit windows described in the SOE (Table 6.1-1).

Study Completion Evaluations

Participants will be evaluated at Week 24.

6.2.5. Event-driven Evaluations

Table 6.1-1 From Days 6 through 29, any participant reporting worsening symptoms should be recalled for an unscheduled visit where both viral culture and SARS-CoV-2 quantitative PCR (as well as hematology and chemistry) are performed as outlined in the SOE (Table 6.1-1) to assess the incidence of post-treatment viral rebounds.

SARS-CoV-2 Reinfection

If a participant reports a SARS-CoV-2 reinfection to the site ≥30 days after study entry (confirmed by a positive SARS-CoV-2 antigen or nucleic acid test), they should be evaluated within 7 calendar days of the report, with evaluations as per the SOE (Table 6.1-1). Sites must collect documentation of the reinfection prior to the additional specimen collection (i.e., participant

verbal report alone is not sufficient documentation to trigger this reinfection evaluation visit). If the reinfection evaluation visit occurs within 7 days of the date of confirmed reinfection (defined as the date of specimen collection for the positive test), an NP swab and blood will be collected. If this visit occurs >7 days after the date of confirmed reinfection, only blood will be collected. Date of symptom onset (if a symptomatic reinfection) and date of sample collection for the positive test should both be recorded on the eCRF.

If a participant reports a reinfection that cannot be confirmed by documentation (positive test), a reinfection evaluation visit should not be performed, but the event should still be documented as an AE as per Section 7.2.

A SARS-CoV-2 Reinfection visit may be combined with other study visits if the windows for both visits are met.

Discontinuation Evaluations

Evaluations for Randomized Participants Who Do Not Start Study Intervention (S-217622 or Placebo)

All eCRFs must be keyed for the period up to and including the Study Entry visit. Participants who were randomized but do not start study intervention will be prematurely discontinued from the study and will not be followed.

Premature Treatment Discontinuation Evaluations

Participants who discontinue study intervention early should remain on study and all evaluations should be performed as outlined in the SOE in Table 6.1-1.

Premature Study Discontinuation Evaluations

Participants who discontinue study participation should have premature study discontinuation evaluations, as outlined in the SOE in Table 6.1-1, prior to being taken off the study, unless the reason for premature study discontinuation was that they did not start the study intervention (S-217622 or placebo).

6.3. Instructions for Evaluations

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to Section 7 for information on reporting of AEs.

In the event of hospitalization, targeted physical examination, study diary entry and review, and specimen collection do not need to be completed during hospitalization, but should be restarted after discharge. Other evaluations should be performed as feasible, including ascertainment of interventions, including medications received, AEs, and outcomes of interest/study endpoints.

Location of Study Visits

Sites should, in discussion with participants, determine the most appropriate place to conduct study visits, whether at the trial site or remote.

In person visits will take place at the clinic, at the participant's home, or at another non-clinic location if the site is able to accomplish all of the scheduled study visit evaluations.

Some visits that do not require blood or swab collection can occur over the phone or via telemedicine systems approved for use at the site.

6.3.1. Documentation of SARS-CoV-2 Infection

Section 4.1.1.3 specifies assay requirements for SARS-CoV-2 infection documentation. SARS-CoV-2 infection documentation is recorded on the eCRF.

See the MOP for further guidance.

6.3.2. COVID-19 Symptoms

COVID-19 Symptom Screen

Participants will be asked about their first symptoms related to their current SARS-CoV-2 infection and their current symptoms. Date of symptom onset must be recorded.

See the MOP for guidance on calculating symptom duration.

6.3.3. Pre-COVID-19 Symptom Screen

At entry, participants will be asked at Screening if preexisting symptoms of cough, myalgia, or fatigue were present within the last 30 days and if they were worsened by COVID-19 (since these symptoms may pre-exist with high-risk conditions such as COPD, asthma, cardiovascular disease, etc.). Participants will be asked to rate the severity at baseline and this will be the severity that needs to improve. This will be collected in the eCRF.

6.3.4. Documentation of Reason for Study Participation

The reason participant elects to participate in ACTIV-2d/A5407 instead of receiving treatment outside of the trial prior to enrollment will be recorded on an eCRF.

6.3.5. Demographic Characteristics Including Race and Ethnicity

Demographic Characteristics will be recorded. Self-reported race and ethnicity will be recorded and participants will have the option to decline to state.

Documentation of high risk vs. low risk must be recorded at the time of enrollment. Enrollment may be closed to a specific risk group if the 50% enrollment has been met.

6.3.6. Medical History

At Screening, a complete medical history, including all diagnoses regardless of grade within the past 120 days and signs and symptoms regardless of grade within the past 30 days, must be recorded. Additionally, the following

diagnoses must be recorded, regardless of when the diagnosis was made, except where noted:

- Autoimmune disease
- Pulmonary embolism
- Deep venous thrombosis
- HIV infection
- Cancer (exclusive of basal/squamous cell skin cancer)
- Acute viral respiratory infection (influenza, parainfluenza, respiratory syncytial virus [RSV], rhinovirus) within the previous 14 days (if known by participant)
- Chronic lung disease
- Asthma requiring daily inhaled medication
- Obesity (BMI ≥30 kg/m^2)
- Hypertension
- Cardiovascular disease
- Diabetes mellitus
- Chronic kidney disease
- History of cirrhosis
- Exogenous or endogenous immunosuppression

All COVID-19 vaccines will be recorded.

Any allergies to any medications and their formulations must also be documented.

6.3.7. Medication History

A medication history must be present, including start and stop dates. Table 6.3.7-1 below lists the medications that must be included in the history at Screening.

Table 6.3.7-1 Medication History

Medication/Category	Timeframe
All prescription drugs	Last 7 days
Corticosteroids, anabolic steroids	Last 30 days
Prescription drugs for high blood pressure	Last 30 days
Prescription drugs for diabetes and pre-diabetes	Last 30 days
Prescription drugs for lung disease	Last 30 days
Prescription drugs for heart disease	Last 30 days
Prescription drugs for autoimmune disease	Last 30 days
Cancer chemotherapy	Last 30 days
Antiviral (including antiretroviral) therapy	Last 30 days
Immune-based therapy	Last 90 days
Blinded investigational product	Last 365 days
SARS-CoV-2-related vaccines or treatments	Complete history
Antibiotics	Last 30 days
Anti-parasitics	Last 30 days
Alternative therapies (e.g., herbal medicines)	Last 30 days
All vaccinations	Last 30 days

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

6.3.8. Assessment for Expectation of Treatment With mAb or Outpatient IV Remdesivir

At Entry/Day 1 assess whether participant expects to receive treatment with locally provided mAb therapy or outpatient IV remdesivir after enrollment.

6.3.9. Clinical Assessments

Height/Weight/Oxygen Saturation

At Screening, measure weight and resting peripheral oxygen saturation and record height (height may be by participant self-report). Weight will be collected at all visits for which CrCl will be calculated.

Physical Examination

At Entry/Day 1, perform a physical examination, including, at minimum, a cardiac examination, pulmonary examination, and vital sign measurements (temperature, pulse, blood pressure, and resting peripheral oxygen saturation), prior to S-217622/placebo administration.

At study entry, if peripheral oxygen saturation is <92% (on room air if the participant does not use oxygen chronically or on usual supplemental oxygen level for those on chronic supplemental oxygen) and if indicated based on the investigator's clinical assessment, the participant should be referred for emergency department evaluation, should not initiate study intervention and should not be enrolled. If the participant is already enrolled, they should not initiate study intervention and should be prematurely discontinued.

Targeted Physical Examination

Post-entry, perform a targeted physical examination as per the SOE in Table 6.1-1. The targeted physical examination includes vital sign measurements (temperature, pulse, blood pressure, and resting peripheral oxygen saturation) and examinations driven by any previously identified or new AE/targeted condition that the participant has experienced. Peripheral oxygenation saturation measures <96% should be reviewed by an investigator and referral for medical attention made at the discretion of the investigator.

Post-entry, see Section 8.2 for collection requirements for pregnancy.

Concomitant Medications

Post-entry, the following new and discontinued concomitant medications must be recorded through Day 29 and at the time of an AE occurring after Day 29:

- Medications for high blood pressure and other cardiovascular conditions
- Corticosteroids (oral, injected, inhaled, intranasal) or other immunosuppressive or immunomodulatory medication
- Cancer therapies
- Antibiotics, antifungals, antiparasitics, and antivirals (including antiretrovirals)
- Anticoagulants
- Antiplatelets
- Any approved or investigational product felt to have potential COVID-19 activity (including but not limited to outpatient IV remdesivir, molnupiravir, favipiravir, fluvoxamine, inhaled budesonide, anti-SARS-CoV-2 mAbs, convalescent plasma)
- All vaccines including COVID-19 vaccines (approved/authorized or investigational)
- Medications for symptoms of COVID-19, including aspirin, ibuprofen, acetaminophen, other non-steroidal anti-inflammatory drugs (NSAIDs), zinc, dietary supplements, herbal remedies, decongestants, cough suppressants, and antihistamines
- Supplemental oxygen

Assessment for Adverse Events

At every visit, beginning from informed consent, participants will be assessed (remote or in person) for any AEs and, if present, the relationship of these to study intervention or procedure.

Hospitalizations and deaths occurring at any time during study follow-up will be recorded on an eCRF.

6.3.10. COVID-19 Standard-of-Care Treatment

Post-entry, any new treatment provided specifically to treat SARS-CoV-2 will recorded through Day 29.

6.3.11. Collect/Update Secondary Contacts

Sites will capture contact information for at least 2 individuals that the site can contact if the participant cannot be reached (e.g., spouse, friend, or neighbor). Sites will also request health care provider contact information and hospital(s) that the participant is likely to go to if they get sick.

Contact information for secondary contacts or health care provider will not be recorded on an eCRF.

At study entry only, sites will record the participant's home address in site records (it will not be reported on an eCRF).

6.3.12. Vital Status Check

If a participant cannot be reached after 2 attempts 24 hours apart, then their listed secondary contact person(s) or health care provider will be contacted for a check of the participant's vital status and study endpoints. In addition, for participants who prematurely discontinue for reasons other than withdrawal of consent or non-initiation of study intervention, or at any time the site becomes aware of a potential hospitalization or death after the participant discontinued study, site personnel should attempt to obtain information on the vital status of the participant and study endpoints as outlined in the MOP.

Vital status and other reported information should be recorded on the eCRFs.

6.3.13. Study Intervention (S-217622 or Placebo) Administered

The full course of S-217622 or placebo tablets (blister as described in Section 5.1) will be dispensed to the participant at the Study Entry/Day 1 visit.

Site staff should provide counseling to participants on the dosing requirements/schedule and participant-completed medication log during the Study Entry/Day 1 visit. The first dose of S-217622 or placebo will be taken by the participant on Study Entry/Day 1, observed by site staff. Date and time of first dose will be recorded in site records and in the participant medication log. All doses of S-217622 or placebo after the initial dose at Study Entry/Day 1 visit will be self-administered by the participant at home per instructions in Section 5 of this protocol.

The participant should be informed to contact site staff/doctor as soon as possible if they experience any concerning signs or symptoms and seek immediate medical help, if warranted.

At entry and post-entry (if applicable), record any initial dose of treatment, modification to treatment, treatment interruption, and permanent discontinuation of treatment, and the reason for the modification, interruption, or discontinuation.

6.3.14. Study Kit Dispensed

The kit will include:

- Copy of informed consent
- Information about the study
- Pocket/wallet card with site staff contact information
- Instructions on what to do if participants have worsening symptoms/become hospitalized
- Study diary (see below)

Dispensation of study kit is not recorded on an eCRF.

6.3.15. Study Diary

Participant-completed Study Diary

Participants will be asked to keep a log of symptoms and major events, such as an urgent visit to an emergency room or clinic and hospitalization, in their study diary. This log will be completed on paper or electronically, if appropriate electronic systems are available. Refer to the MOP for further details.

At Study Entry, participants will complete the study diary with site staff prior to initiating S-217622 or placebo. Participants will be asked to complete subsequent entries daily on their own through Day 29. The diary should be completed at approximately the same time every day.

If the Day 29 visit occurs on Day 29, then the Day 29 study diary may be completed with the site staff during the Day 29 visit; otherwise, it should be completed by the participant on Day 29.

Study Diary Reminder and Staff Review of Study Diary

Participants will be contacted every day on Days 1 through 29 and reminded to complete their study diary. This reminder is through the electronic diary or may be by telephone, text message, email, or other method for which the participant provides permission. A direct response from the participant is not required. Contact attempts to remind participants to complete their diary are not recorded on an eCRF.

The study diary will be reviewed by study staff in person or remotely with each participant according to the SOE in Table 6.1-1. If an appropriate electronic system is available, the participant's diary entries will automatically be captured in the eCRF. If such a system is not available, the study staff will record the participant's answers on the study diary eCRF. If the participant uses a paper diary and it is feasible, prior to or during the remote study visits, sites will ask the participant to send images of each of their study diary entries to be reviewed at the next study contact. The diary, not the images, are considered the source document. See the MOP for requirements for timely eCRF entry of diary data.

Participants who report worsening symptoms from any cause during the trial may be referred to their health care provider or closest emergency room. Such instances will be recorded at the time of the notification, and during follow-up to assess study endpoints, including time to symptom resolution, hospitalization, or death.

Retrieval of Study Diary

If the participant uses a paper diary, the study diary should be collected following diary completion. See the MOP for additional instructions on retrieval of study diary.

Documentation of retrieval of the paper diary is not recorded on an eCRF.

6.3.16. Assessment of COVID-19 Severity on WHO Ordinal Scale

The severity of COVID-19 disease will be assessed and recorded in the participant as detailed in the SOE (Table 6.1-1) according to the scale shown in Table 6.3.16-1. The highest score on the day of score assessment will be recorded.

Table 6.3.16-1 Ordinal Scale For COVID-19 Severity

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

Source: https://www.who.int/docs/default-source/documents/emergencies/minimalcoreoutcomemeasure.pdf

6.3.17. Post-acute COVID-19 Assessment Diary, EQ-5D-5L Questionnaire, and SF-36v2 Questionnaire

Participants will be asked about potential COVID-19-related symptoms and diagnoses, including psychological health, functional health, and health-related quality of life, using standardized questionnaires (a study Post-acute COVID-19 Questionnaire/diary and the EuroQol–5 Dimensions–5 Levels [EQ-5D-5L] and Short Form 36 Health Survey Questionnaire, version 2 [SF-36v2] instruments) according to the SOE in Table 6.1-1.

6.3.18. Household Infection and Linkage Report

At Study Entry/Day 1, participants will be asked how many rooms they have in their house, how many people reside in their household, defined as sharing

indoor living space or housekeeping space (i.e., kitchen, dining area, or bathroom), whether they have been diagnosed with SARS-CoV-2 infection ever and in the last 14 days, and if any household members are also enrolled in the study, and the responses will be recorded on the eCRF. If a household member is enrolled in the study, the participant ID for the first household member enrolled into the study will be recorded. Participants will be asked what kind of COVID-19 isolation or preventative procedures are followed at home, such as using a separate room, wearing a mask, hand washing, ventilation of the room, or others.

At Days 8, 15, and 29, participants will be asked if any household members have been newly diagnosed with SARS-CoV-2 infection, and the response will be recorded on the eCRF.

6.3.19. Staff-collected Nasopharyngeal Swab

Two NP swabs will be collected by staff during in-person visits, for measurement of SARS-CoV-2 RNA levels by quantitative PCR, viral genotype (viral sequence analysis that will include spike gene sequence analysis and listing of the location of amino acid substitution in participants with amino acid substitution in the 3CL protease domain compared with reference strains) and phenotype (EC_{50}) and viral titer by culture. At Study Entry/Day 1, the sample should be collected prior to the first dose of S-217622 or placebo.

Additional information can be found in the central Laboratory Manual and Flowchart.

6.3.20. Staff-collected Anterior Nasal Swab

Influenza, RSV, and other respiratory viral testing will be performed on anterior nasal swabs.

6.3.21. Laboratory Evaluations

Refer to the Laboratory Manual and Flowchart for details of collection, processing, and shipping.

At Screening/Study Entry/Day 1, and post-entry, all laboratory values must be recorded.

At Study Entry/Day 1, blood samples should be collected prior to initiation of the study intervention.

Blood can be collected outside of a clinic setting (e.g., home).

<u>Serology</u>

Participants will have blood drawn for quantitative serology to SARS-CoV-2 proteins.

<u>Hematology</u>

Participants will have blood drawn for d-dimer, complete blood cell count with automated differential and platelet count (platelet count, red blood cell count, hemoglobin, hematocrit, red blood cell index [mean corpuscular volume,

mean corpuscular hemoglobin, reticulocyte count] white blood cell count, differential white blood count [neutrophils, lymphocytes, monocytes, eosinophils, basophils]).

Chemistry

Participants will have blood drawn for CRP, ferritin, glucose, non-fasting lipid profile (HDL cholesterol, low density lipoprotein cholesterol, triglycerides), liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin, direct bilirubin, albumin, and total protein), renal function tests (blood urea nitrogen [BUN], creatinine, potassium, and sodium), and CrCl will be calculated.

Viral Hepatitis

Participants will have blood drawn for HCV antibody and hepatitis B surface antigen (HbSAg). Positive tests will lead to reflex testing for confirmation: HCV RNA for HCV-antibody-positive and HepB DNA for HbSAg-positive results.

Pregnancy Testing

For participants of reproductive potential: serum or urine β-human chorionic gonadotropin (urine test must have a sensitivity of ≤25 mIU/mL).

Postscreening pregnancy testing should be done any time pregnancy is suspected and per the SOE (Table 6.1-1).

In the event of pregnancy occurring during the study, record pregnancy and pregnancy outcome.

Refer to the Laboratory Manual and Flowchart for details of collection, processing, and shipping.

Exploratory Biomarkers

The following exploratory biomarkers will be collected at study entry: thymus and activation regulated chemokine (chemokine ligand 17) (TARC [CCL17]), IL-6, procalcitonin, and Krebs von den Lungen-6 (KL-6). These biomarkers may be associated with the risk of severe COVID-19 and will be evaluated in post-hoc exploratory analyses.

6.3.22. Pharmacokinetics

Plasma samples will be collected and used to measure S-217622 levels. Date and time of all PK sample collections and date and time of each dose will be recorded in the eCRF.

Plasma PK sampling:

PK plasma samples will be collected on Day 1, at 60 minutes (±5 minutes) and 90 minutes (±5 minutes) post-dose, Day 4 (predose and 60 to 90 minutes postdose), and Day 8 (anytime) in a subgroup of 150 participants. This will be offered to study participants until all 150 spots are filled. The day and 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 participants (to reach a total of 400 for the PK substudy). The day and 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).

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of S-217622 will be assayed using a validated bioanalytical method. Samples from placebo participants will be collected and stored but may only be analyzed if needed for investigational purposes. Remaining PK samples may be used for measurement of any metabolites or free drug concentrations (if needed), or as deemed appropriate by the sponsor. Samples will be retained for up to 2 years after last participant visit.

6.3.23. Participant-completed Medication Log, Staff Review of Medication Log, and Retrieval of Medication Log

Treatment adherence will be assessed by a study medication log completed by the participant from first dose of study intervention to last dose of study intervention.

The study medication log will be reviewed by study staff with the participant as per the SOE (Table 6.1-1). The data will be recorded on an eCRF, and the log should be retrieved from the participant (see additional guidance in the MOP).

The participant should be instructed to return the blister pack (with any unused study intervention) to the site.

7. ADVERSE EVENTS AND STUDY MONITORING

7.1. Definitions of Adverse Events

Adverse Event

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/investigational agent/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

The scale used in the study diary for participant symptoms does NOT equate to the AE grading as found in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017.

Grading Severity of Events

The DAIDS AE Grading Table, corrected Version 2.1, July 2017, must be used and is available on the DAIDS Regulatory Support Center (RSC) website at:

DAIDS AE Grading Tables | DAIDS Regulatory Support Center (RSC) (https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables).

Lipids will be graded according to the DAIDS Grading Table, but will be conducted as non-fasting.

Renal function will be graded according to DAIDS Grading Table, but only using CrCl or estimated glomerular filtration rate. Absolute creatinine and percentage change from baseline will not be used to grade renal AEs in this protocol.

Serious Adverse Events

An SAE is defined as any untoward medical occurrence that results in any of the following outcomes:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes listed in the definition above

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.

Suspected Unexpected Serious Adverse Events

A suspected unexpected serious adverse reaction (SUSAR) is defined as a serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational agent).

7.2. Adverse Event Collection Requirements for This Protocol

AEs reported by the participant must be captured in source documents.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs or SAEs, considered related to the study intervention or study procedures or that caused the participant to discontinue the study intervention or withdraw from the study (see Section 9.1).

When an AE occurs, the investigator should take appropriate medical measures such as treatment, if necessary.

Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs will be collected from the signing of the ICF until Week 24 at the timepoints specified in the SOE (Table 6.1-1). Any AEs considered treatment-related that are ongoing at Week 24 will be followed until stabilization or resolution.

All SAEs will be recorded on an eCRF and reported to the CRO/sponsor or qualified designee immediately and under no circumstance should exceed 24 hours. The investigator will submit any updated SAE data to the CRO/sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study (out of period specified SOE [Table 6.1-1]), and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor by phone, email, or fax.

Investigator assessment of causality must be included with all SAEs reported to the sponsor. SAEs with missing investigator causality will be followed up by the CRO/sponsor urgently until response is provided to the sponsor.

Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

Reporting of SAEs

All SAEs must be reported to the CRO/sponsor in detail via the eCRF (or paper SAE CRF if eCRF is unavailable) within 24 hours from the timepoint when the investigator first becomes aware of the SAE.

SAE Reporting to CRO/sponsor via an eCRF

- The primary mechanism for reporting an SAE to the CRO/sponsor will be eCRF.
- If eCRF is unavailable, then the site will use the paper SAE form (see below) to report the event within 24 hours.
- The site will enter the SAE data into the eCRF as soon as it becomes available.
- After the study is completed at a given site, the eCRF will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after eCRF has been taken off-line, then the site can report this information on a paper SAE form (see below) or to the study medical monitor/sponsor safety group by telephone.

SAE Reporting via Paper SAE Form if eCRF is unavailable

- Facsimile transmission of the paper SAE form is the preferred method to transmit this information to the study medical monitor/sponsor safety group. Data collected using the paper SAE will be sent to the sponsor as follows:

Safety Fax Number:

[redacted] (for US and South America sites)

[redacted] (for Asia-Pacific sites)

[redacted] (for European Union [EU], United Kingdom [UK], Middle East, and Africa sites)

Email address:

[redacted] (for US and South America sites)

[redacted] (for Asia-Pacific sites)

[redacted](for EU, UK, Middle East, and Africa sites)

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the paper SAE form sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the investigator to complete and sign the paper SAE form within the designated reporting timeframes.

Safety telephone number:

[redacted] (for US and South America sites)

[redacted] (for Asia-Pacific sites)

[redacted] (for EU, UK, Middle East, and Africa sites)

Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor/CRO of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review it and file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

7.3. Study Monitoring

The protocol team will monitor the conduct and safety of the study via regular summaries of accrual, study discontinuation, and AEs leading to premature study intervention discontinuation, as appropriate.

The CRO (IQVIA) Clinical Representative will review reports for potential impact on the study participant safety and protocol conduct as per IQVIA policies, guidance documents, and standard operating procedures (SOPs), as applicable.

A National Institute of Allergy and Infectious Diseases (NIAID)-appointed DSMB will conduct reviews at 25%, 50%, and 75% enrolment (followed through Day 29 of the study) and otherwise at a frequency recommended by the DSMB. All available follow-up data concerning early treatment discontinuations, AEs, symptom resolution, all available virology data, and hospitalizations/deaths will be reviewed at each of these interim analyses. An interim review may also be convened if a concern is identified by the DAIDS clinical representative or IQVIA Clinical Representative, the study chairs, or study statistician in consultation with the team. See Section 10 for statistical and other considerations related to interim monitoring.

The DSMB will review any death deemed related to study product or Grade 4 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.

8. CLINICAL MANAGEMENT ISSUES

8.1. Toxicity

The grading system for drug toxicities is located in the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at:

DAIDS Adverse Event Grading Tables | DAIDS Regulatory Support Center (RSC) (https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables)

NOTE: The medical monitor must be notified within 72 hours regarding toxicities that result in a change in study regimen (see the MOP for instructions on how to contact the medical monitor).

If a participant develops a Grade ≥3 AE that is related to the study product as determined by the investigator, no further doses of the study intervention should be administered.

It is possible that some participants will experience transient or prolonged AEs during the study. As some of the visits will be conducted remotely, AEs will often be assessed remotely and at unplanned study visits scheduled if deemed necessary by the investigator. For any concerning AEs that are felt to require clinical intervention, participants should be instructed to contact their health care provider, seek urgent or emergent care, or call 911 (in the US), as appropriate.

Treatment may be discontinued without contacting the protocol team/medical monitor in advance, but the medical monitor should be notified within 72 hours of treatment discontinuation (see the MOP for instructions on how to contact the medical monitor).

Management of Side Effects

Participants should be instructed to contact their investigator if an AE is preventing them from taking study intervention (S-217622 or placebo) as directed.

Dose modification of study intervention is not allowed.

In the event of any treatment-related toxicity, the investigator has the option to discontinue study intervention (S-217622 or placebo) at their discretion, with reporting of premature study intervention discontinuation as described in Section 9.1.

If treatment is interrupted or permanently discontinued, the reason for the interruption or discontinuation must be recorded.

8.1.1. Overdose

An overdose is any dose of study intervention given to a participant or taken by a participant that exceeds the dose described in the protocol.

For this study, any dose of study intervention (S-217622 or placebo) greater than the designated dose (375 mg on Day 1 or 125 mg on Days 2 to 5) will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Treat participants with any AE/SAE resulting from overdose according to the standard-of-care.
2. Contact the CRO medical monitor immediately.
3. Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
4. Closely monitor the participant for any AE/SAE and laboratory abnormalities until S-217622 can no longer be detected systemically (at least 4 days).

5. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
6. Document the quantity of the excess dose as well as the duration of the overdose.

Any overdose must be reported to the CRO/sponsor medical monitor within 24 hours by the investigator via eCRF using a Special Situations Report Form. In the event that eCRF is not available, sites may submit paper reports to the medical monitor via email. If associated SAEs occur, the investigator must also complete and submit an SAE submission. The overdose itself is not to be reported as an AE. However, any AEs associated with the overdose are to be reported on relevant AE/SAE sections in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

There are no known cases of overdose with S-217622 in clinical studies to date. In nonclinical evaluations, no adverse toxicity was observed in animals dosed up to 1000 mg/kg/day (rats) or up to 10 mg/kg/day (monkeys).

8.2. Pregnancy

Since there are no data regarding the use of the S-217622 in participants who are pregnant, participants who are pregnant are not eligible for the study.

Participants of child-bearing potential and participants who may impregnate their partners are required to follow the instructions for prevention of pregnancy provided in the protocol.

If a participant is found to be pregnant during the study (post-entry), study intervention will be discontinued immediately, and study follow up will continue for the duration of the study.

The pregnancy event should be recorded on a Pregnancy Paper Form within 24 hours of site awareness. At the end of the pregnancy, the outcome of the pregnancy and any AEs for the participant and infant will be recorded on the Pregnancy Outcome Form.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 28 days after the last dose. The outcomes of those pregnancies will be followed until birth, miscarriage, or abortion.
- If a pregnancy is reported, the investigator should inform the CRO/sponsor within 24 hours of learning of the pregnancy and should follow the procedures, which require completion of the Pregnancy Form.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) will be considered SAEs.
- The outcome of the pregnancy (i.e., birth, miscarriage, abortion) should be followed by the investigator and must also be reported using the Pregnancy Outcome Form.

8.3. Breast-feeding

Since there are no data regarding the use of S-217622 in participants who are breast-feeding, participants who are breast-feeding are not eligible for the study.

8.4. Management of Liver Chemistry Abnormalities After Study Entry Visit

If any of the following liver chemistry results occur after Study Entry until Day 29:

- ALT or AST ≥5 × upper limit of normal (ULN)
- ALT or AST ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin)
- ALT or AST ≥3 × ULN **and** international normalized ratio (INR) >1.5, if INR measured

The following actions are required:

- Hold any further doses of study intervention (if applicable).
- Report the event to the CRO/sponsor within 24 hours.
- Complete the Liver Event Form and complete an SAE form on the eCRF if the event also met the criteria for an SAE*.
- Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see MONITORING).

* All events of ALT or AST ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT or AST ≥3 × ULN and INR >1.5 may indicate severe liver injury and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria met. The INR stated threshold value will not apply to participants receiving anticoagulants.

MONITORING

If ALT or AST ≥3 × ULN AND total bilirubin ≥2 × ULN or INR >1.5:

- Repeat liver chemistry tests (include ALT, AST, ALP, total bilirubin, and INR) and perform liver event follow-up assessments within 24 hours.
- Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline.
- A specialist or hepatology consultation is recommended.

Discuss with the sponsor or CRO medical monitor and consider the following, if clinically indicated:

- Antinuclear antibody, antismooth muscle antibody, type 1 antiliver kidney microsomal antibodies, and quantitative total immunoglobulin G or gamma globulins.
- Serum acetaminophen adduct assay to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week.
- Liver imaging (ultrasound, magnetic resonance imaging, or computed tomography) to evaluate liver disease; complete the Liver Event Form.

- Liver biopsy may be considered and discussed with local specialists if available in circumstances such as:
    - In participants when serology raises the possibility of autoimmune hepatitis.
    - In participants when suspected drug-induced liver injury progresses or fails to resolve on withdrawal of study intervention.
    - In participants with acute or chronic atypical presentation: hepatic vascular disorder, chronic hepatitis fibrosis, micro vesicular steatosis.

  If liver biopsy is conducted, then complete the Liver Event Form.

IF ALT or AST ≥5 × ULN:

Perform follow-up assessments, if clinically indicated, as described below:

- Repeat liver chemistry tests (include ALT, AST, ALP, total bilirubin, and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours**.
- Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.
- Obtain blood sample for PK analysis 1 day after the most recent dose.
- Obtain serum creatine phosphokinase and LDH.
- Obtain fractionated bilirubin, if total bilirubin ≥2 × ULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of liver injury or hypersensitivity on the eCRF as an AE.
- Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs, and other over-the-counter medications) on the eCRF.
- Record alcohol use on the Liver Event Form.

The following may be considered if clinically indicated for liver chemistry abnormalities described above (**ALT or AST ≥3 × ULN AND total bilirubin ≥2 × ULN or INR >1.5, or ALT or AST ≥5 × ULN)**; contact the sponsor or CRO medical monitor to discuss:

- Viral hepatitis serology for follow up if liver chemistry stopping criteria are met includes: hepatitis A immunoglobulin M (IgM) antibody; HBsAg and hepatitis B core antibody; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing]; and hepatitis E IgM antibody. In participants with underlying chronic hepatitis B at study entry (identified by positive HBsAg) quantitative hepatitis B DNA, and hepatitis delta antibody. If a hepatitis delta antibody assay cannot be performed, it can be replaced with a quantitative PCR measurement of hepatitis D RNA virus (where needed).

9. CRITERIA FOR DISCONTINUATION

Participants may discontinue from the study intervention or withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep participants in the study. The reasons for participants discontinuing the study intervention and/or withdrawing from the study will be recorded on an eCRF.

9.1. Permanent and Premature Treatment Discontinuation

- If the Day 1 chemistry shows an ALT or AST ≥5 × ULN range or ALT or AST ≥3 × ULN AND total bilirubin ≥2 × ULN (>35% direct bilirubin). Blood chemistry must be repeated urgently.
- If Day 1 CrCl is <30 mL/min (by Cockroft-Gault).
- At the time of hospitalization (≥24 hours of acute care in a hospital or similar acute care facility), should this occur.
- If a Grade ≥3 event occurs that is deemed related to the study intervention.
- An SAE that is considered related to study intervention.
- Requirement for prohibited concomitant medications (see Section 5.4.2), if the reason the medications are prohibited is due to DDIs or other concern for toxicity.
- Request by participant to terminate treatment. NOTE: The reason for treatment discontinuation should be documented (e.g., concern for AE, lack of efficacy, or other reason).
- Clinical reasons believed life threatening by site clinical staff, even if not addressed in Section 8.1 of the protocol.

9.2. Premature Study Discontinuation

- Failure to initiate study intervention.
- Request by the participant to withdraw consent.
- Request of the health care provider if they think the study is no longer in the best interest of the participant.
- At the discretion of the IRB/IEC, Shionogi, FDA, NIAID, ACTG, Office for Human Research Protections (OHRP),or other government agencies as part of their duties, investigator, or industry supporter.

In the event that a participant prematurely discontinues from the study, unless they have withdrawn consent or never initiated S-217622 or placebo, sites will attempt to obtain information regarding vital status (including date last seen alive, hospitalization, date of death, and primary cause of death) from other sources (e.g., family members, other designated secondary contacts, or clinic records). See the MOP for further guidance.

10. STATISTICAL CONSIDERATIONS

10.1. General Design Issues

This is a multicenter, Phase 3, double-blind, placebo-controlled trial of S-217622. Participants in both treatment arms may take any locally provided standard-of-care, including COVID-19 mAb treatment, outpatient IV remdesivir, and oral antivirals after randomization.

10.2. Analysis Populations

10.2.1. Modified Intent-to-treat (mITT) Population

The mITT population 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.

10.2.2. Safety Analysis Population

The Safety Population is defined as all randomized participants who took ≥1 dose of S-217622 or 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.

10.2.3. PK Population

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

10.3. Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the study's primary Statistical Analysis Plan (SAP), which will define the content of the Primary Analysis Report of outcomes through Day 29 of follow up and a Secondary Analysis Report of further outcomes through to Week 24. These reports will form the basis for the main study manuscript(s) and results reporting to ClinicalTrials.gov.

10.3.1. Primary Outcome Measure and Estimand

The following summarizes the primary efficacy outcome measure and the associated estimand under the placebo-controlled superiority design.

Symptom duration for all targeted symptoms (including those occurring prior to COVID-19 infection): Time (days) from start of S-217622 or placebo (Day 1) until sustained resolution and being alive and without hospitalization for any reason by Day 29. The targeted symptoms are feeling feverish, cough, shortness of breath or difficulty breathing, sore throat, body pain or muscle pain or aches, fatigue (low energy), headache, chills, nasal obstruction or congestion (stuffy nose),

nasal discharge (runny nose), nausea, vomiting, and diarrhoea. 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 4 consecutive days when all targeted symptoms are evaluated as resolved assessed according to the following rules.

- For the preexisting symptoms that were present prior to COVID-19 onset and considered by the participant to have worsened at baseline (Day 1 diary, completed prior to treatment 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 preexisting symptoms that were present prior to COVID-19 onset and considered by the participant not to have worsened at baseline (pretreatment 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 Absent.

  Severe or Moderate at baseline: Absent post-baseline

  Mild at baseline: Absent post-baseline

  Absent at baseline: Absent post-baseline

The estimand for the symptom duration outcome measure is defined by the following attributes:

Estimand description: The hazard ratio will be used to compare time (days) from start of intervention (S-217622 vs. placebo) until sustained resolution based on assessments for 4 consecutive days of targeted symptoms meeting the criteria stated above and being alive and not hospitalized for any reason by Day 29 among outpatient adults with SARS-CoV-2 starting intervention within ≤5 days of symptom onset..

The estimand is defined by the following attributes:

Target population: High- risk and low-risk outpatient adults with SARS-CoV-2 starting treatment within ≤5 days of symptom onset.

Variable/Outcome measure: Time (days) from start of S-217622 or placebo (Day 1) until sustained resolution for participants alive and never hospitalized by Day 29 based on assessments for 4 consecutive days of targeted symptoms meeting the criteria stated above.

Treatment condition: The randomized treatment (S-217622 or placebo) plus any locally provided standard-of-care, including COVID-19 mAb treatment, outpatient IV remdesivir, and oral antivirals.

Handling of intercurrent events: 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 26.

For 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), a treatment policy strategy will be used to evaluate treatment effects irrespective of the intercurrent event.

Population-level summary measure: The hazard ratio.

10.3.2. Key Secondary Outcome Measures

The following summarizes the key secondary efficacy outcome measures and the associated estimands under the placebo-controlled superiority design.

10.3.2.1. Key secondary virologic outcome: change from baseline in quantitative $\log_{10}$ SARS-Cov-2 RNA levels by PCR on NP swab at Day 4.

The estimand for the change from baseline in quantitative $\log_{10}$ SARS-CoV-2 RNA level by PCR on NP swab at Day 4 outcome measure is defined by the following attributes:

Estimand description: The difference in medians will be used to compare $\log_{10}$ SARS-CoV-2 RNA at Day 4 compared to baseline for S-217622 vs. placebo among outpatient adults with SARS-CoV-2 starting intervention within ≤5 days of symptom onset.

The estimand is defined by the following attributes:

Target population: High-risk and low-risk outpatient adults with SARS-CoV-2 starting treatment within ≤5 days of symptom onset.

Variable/Outcome measure: The change from baseline in quantitative log10 SARS-CoV-2 RNA level by PCR on NP swab at Day 4.

Treatment condition: The randomized treatment (S-217622 or placebo) plus any locally provided standard-of-care, including COVID-19 mAb treatment, outpatient IV remdesivir, and oral antivirals.

Handling of intercurrent events: 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 treatment effects irrespective of the intercurrent event.

Population-level summary measure: The difference in medians.

10.3.2.2. Key secondary clinical outcome:

The composite of 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. Hospitalization is adjudicated to be COVID-19-related as described in the adjudication committee charter.

The estimand for the composite of the COVID-19-related hospitalization (adjudicated) and all deaths regardless of occurrence outside of hospital or during hospitalization (not adjudicated) through Day 29 outcome measure is defined by the following attributes:

Estimand description: The risk ratio will be used to compare the cumulative probability of hospitalization (adjudicated) or death from Days 1 to 29 among outpatient adults with SARS-CoV-2 starting intervention within ≤5 days of symptom onset.

The estimand is defined by the following attributes:

Target population: High-risk and low-risk outpatient adults with SARS-CoV-2 starting treatment within ≤5 days of symptom onset.

Variable/Outcome measure: The cumulative proportion of hospitalization (adjudicated) or death from Days 1 to 29.

Treatment condition: The randomized treatment (S-217622 or placebo) plus any locally provided standard-of-care, including COVID-19 mAb treatment, outpatient IV remdesivir, and oral antivirals.

Handling of intercurrent events: For all 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 treatment effects irrespective of the intercurrent event.

Population-level summary measure: The risk ratio.

10.3.3. Additional Secondary Outcome Measures

10.3.3.1. Clinical: The composite of hospitalization from any cause or death from any cause 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.

10.3.3.2. Virologic: Detectable SARS-CoV-2 by viral culture from NP swab at each of Days 4 and 8.

10.3.3.3. Virologic: Change from baseline in quantitative $\log_{10}$ SARS-CoV-2 RNA levels by PCR in NP swabs at Day 8.

10.3.3.4. Virologic: SARS-CoV-2 RNA levels by PCR in NP swabs below the LLoQ at each of Days 4 and 8.

10.3.3.5. Clinical (Supportive for Primary Symptom Duration Outcome): Time (days) from start of S-217622 or placebo (Day 1) until the first of 4 consecutive days that a participant reported return to usual (pre-COVID-19) health as recorded in a participant's study diary through Day 29.

10.3.3.6. Clinical: Participants having a score ≥2, ≥3, ≥4, ≥5, ≥6, ≥7, or ≥8 on the ordinal scale defined in Section 6.3.16 at each scheduled assessment time.

10.3.3.7. Clinical: Resting peripheral oxygen saturation as a quantitative measure and categorized as <96% vs. ≥96% at scheduled measurement times through Day 29.

10.3.3.8. Safety: New Grade 3 or higher AE through 29 days, and through 24 weeks (i.e., new in onset after starting study intervention or a worsening in severity after starting study intervention of an AE that had initial onset prior to start of study intervention).

10.3.3.9. Safety: New Grade 2 or higher AE through 29 days, and through 24 weeks (i.e., new in onset after starting study intervention or a worsening in severity after starting study intervention of an AE that had initial onset prior to start of study intervention).

10.3.3.10. Clinical: 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, SF36v2, and EQ-5D-5L).

10.3.3.11. Clinical: Participants dying from any cause during the 24 weeks of follow-up from and including the day of the first dose of S-217622 or placebo.

10.3.4. Other Outcome Measures

10.3.4.1. COVID-19 severity ranking based on self-reported symptom severity scores using study diary over time during the 29-day period from and including the day of the first dose of S-217622 or placebo and taking account of hospitalizations and deaths. For participants who are alive at 29 days and not previously hospitalized, the severity ranking will be based on their AUC of the daily total symptom score associated with COVID-19 over time (through

29 days counting Day 1 as the first day), where the total symptom score on a given day is defined as the sum of scores for the targeted symptoms in the participant's study diary (each individual symptom is scored as 0 if reported as absent, 1 if mild, 2 if moderate, and 3 if severe). Participants who are hospitalized or who die during follow-up through 29 days will be ranked as worse than those alive and never hospitalized as follows (in worsening rank order): alive and not hospitalized at 29 days; hospitalized but alive at 29 days; and died at or before 29 days.

10.3.4.2. New SARS-CoV-2 positivity among household contacts through to 29 days from start of S-217622 or placebo.

10.3.4.3. Emergence of viral resistance through to Day 29 (the definition of resistance will be defined at the time of laboratory analysis).

10.3.4.4. Laboratory markers (markers to be evaluated and times of evaluation are defined in Section 6.3.21).

10.4. Randomization and Stratification

Participants 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 low risk) for severe COVID-19.

10.5. Multiplicity Strategy

The primary hypothesis is based on the primary outcome measure. The hazard ratio will be used to compare time (days) from start of intervention (S-217622 vs. placebo) until sustained resolution based on assessments for 4 consecutive days of targeted symptoms and being alive and not hospitalized for any reason by Day 29 in the mITT population. 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, selected secondary outcome measures will be tested sequentially at the 2-sided 5% 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 on NP swab at Day 4
2. Adjudicated hospitalization due to COVID-19 or death due to any cause through Day 29

All tests performed higher in the hierarchy must be statistically significant at the 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 [25].

10.6. 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 4 consecutive days of targeted symptoms and being alive and not hospitalized for any reason by Day 29 in the mITT population.

A total of 1490 participants will be randomized into the study. Allowing for a 5% loss to follow-up, this is expected to provide 1414 participants completing the study. This will provide 88.5% power at the 5% significance level to detect a hazard ratio of 0.82 (equivalent to a median time to sustained symptom resolution of 11.5 days) when the placebo median time to sustained resolution is 14 days, assuming exponentially distributed times to symptom resolution.

10.7. Data and Safety Monitoring

Monitoring of safety is described in Section 7.3. There will be 3 interim analyses of efficacy and safety data for review by the DSMB after approximately 25% (safety only), 50%, and 75% of the planned enrollment has been completed and followed through to Day 29 (or on a frequency as otherwise recommended by the DSMB). All available follow-up data concerning early treatment discontinuations, AEs, symptom resolution, all available virology data, and hospitalizations/deaths will be reviewed at each of these interim analyses. Early termination of enrollment and/or early release of interim results will be considered if efficacy is established based on the key secondary hospitalization/death outcome based on an O'Brien and Fleming stopping guideline implemented using a Lan and DeMets spending function. The initial analysis at 25% enrolled having completed their Day 29 study visit will be a safety analysis only (stopping earlier would limit the safety database size and utility).

A blinded sample size re-estimation may be undertaken at the timing of each interim efficacy analysis. This is to ensure that sufficient numbers of participants are achieving the primary outcome measure of sustained symptom resolution such that the study remains adequately powered.

Further details of the interim analyses and details of the blinded sample size re-estimation will be described in the DSMB SAP.

10.8. Analyses

A SAP will be developed that describes, in detail, the analyses to address the study's primary and secondary objectives. Separate SAPs will be developed to address the study's exploratory objectives; these may be developed after results addressing the primary and secondary objectives are available. The following provides an outline of the methods for the main comparisons between randomized groups, particularly for the primary outcome measure and associated estimands.

The main analyses involving randomized comparisons will include randomized participants who started S-217622 or placebo in the mITT population (an mITT approach). Exclusion of participants who did not start S-217622 or placebo should not introduce bias into the randomized comparison because of the use of a placebo. The clinical and virology analyses will use the mITT population, and the

safety analyses will use the Safety population.

For analyses of secondary and exploratory outcomes, statistical inference will be based on 95% CIs for effects comparing the S-217622 to placebo and associated 2-sided tests of no difference between groups using a 5% type I error rate.

The following sub-sections describe analyses of the primary and secondary outcome measures to address the study's primary and secondary objectives for the mITT and Safety populations.

10.8.1. Primary Outcome Measure

10.8.1.1. Based on the estimand definition for the symptom duration outcome, time (days) from the start of intervention (S-217622 or placebo) until sustained resolution will be compared using a Cox proportional hazards regression model to provide an estimate of the hazard ratio for treatment (S-217622 vs. placebo), along with a Wald CI and p-value. A Kaplan-Meier analysis where tabular summaries of the Kaplan-Meier curves providing the median, quartiles, and range will be provided for each treatment group. In addition, the Kaplan-Meier curves will be presented graphically. Time to sustained resolution is based on assessments for 4 consecutive days of targeted symptoms with Day 26 being the last day the outcome can be achieved. Follow-up will be censored at the appropriate number of days before the day of the last diary record for targeted symptoms if a participant is lost to follow-up or stops completing their diary. Participants who die or are hospitalized prior to Day 29 will remain in the risk-set to Day 26 and will be considered to have not had the symptom resolution event.

Sensitivity analyses on the primary outcome will include a Fine and Gray proportional hazards regression, which considers deaths and hospitalizations as competing events which are not eliminated and estimates a hazard ratio for treatment (S-217622 vs. placebo) based on the sub-distribution, along with a Wald confidence interval and p-value. Supplementary analyses will include restricted mean time to symptom resolution analysis (the restriction is to Day 26) and the generalized Wilcoxon test. Full details of these analyses will be included in the SAP. Supportive analyses will be carried out in a similar manner to the primary outcome for symptom resolution based on 2 and 6 consecutive days with Days 24 and 28, respectively, being the last day the outcome can be achieved.

10.8.1.2. Subgroup Analyses of the Primary Outcome Measure

The primary analyses described above will be applied to the subgroups of participants as described below:

- Risk status at enrollment: high, low
- Vaccination status: not vaccinated, completed primary series with last vaccine >3 months, completed primary series with last vaccine ≤3 months)
- Time from onset of COVID-19-related symptoms at baseline: ≤3 days, 4 to 5 days

- Sex at birth: male, female
- Geographic region: North America, South America, Europe, Africa, Asia
- 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

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 group.

10.8.2. Key Secondary Outcome Measures

10.8.2.1. For the virologic secondary outcome measure of the change from baseline in quantitative $\log_{10}$ SARS-CoV-2 RNA levels by PCR on NP swab at Day 4.population summary measure is the difference in medians. To adjust for any (chance) imbalance between the S-217622 and placebo groups at Day 1 and to increase precision, median regression will be used to obtain an estimate and associated 95% CI adjusted for $\log_{10}$ SARS-CoV-2 at Day 1. The median regression analysis will consider $\log_{10}$ SARS-CoV-2 RNA values below the LLoQ as censored measurements. 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 ACTIV-2/A5401, such missingness is expected to be no more than about 10%.

As a sensitivity analysis, an unadjusted estimate and associated 95% CI will also be obtained.

Based on data previously obtained in the similar 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 1 group is observed). In this case, the analysis of the secondary outcome of percentage of participants with SARS-CoV-2 RNA below the LLoQ will become more important in interpreting possible treatment effects at that time.

10.8.2.2. For participants with adjudicated hospitalization due to COVID-19 or death due to any cause during the 29-day period from and including the day of the first dose of S-217622 or placebo, the ratio (for S-217622 group divided by placebo group) of the cumulative probability of hospitalization (adjudicated) or death from Days 1 to 29 will be calculated, where the event proportions will be estimated in each intervention group using the Kaplan-Meier estimator to account for participants lost to follow-up. A 2-sided 95% CI and associated p-value for the test of the risk ratio different from 1 between groups will then be obtained. Participants who prematurely discontinue the study, who are not

able to be contacted by the site to ascertain outcomes after discontinuation, will have follow-up censored at the time they were lost to follow-up.

Subgroup analyses for the key secondary outcome measures will be applied as for the primary outcome measure.

10.8.3. Additional Secondary Outcome Measures

Additional secondary outcome measures will not be adjusted for multiplicity; however, appropriate unadjusted p-values will be provided to provide context for the comparison of S-217622 vs. placebo for each outcome measure.

10.8.3.1. The proportion of participants with hospitalization or death due to any cause during the 29-day period from and including the day of the first dose of S-217622 or placebo will be analyzed in the same way as for the analysis of the key secondary outcome measure of hospitalization due to COIVD-19 or death from any cause through Day 29.

10.8.3.2. For the virologic outcome measure of detectable SARS-CoV-2 by viral culture on Day 4, comparison of S-217622 vs. placebo will be undertaken using the absolute difference of participants with detectable virus by culture with a 95% CI calculated using the normal approximation to the binomial distribution. The analysis of the similar outcome at Day 8 will be undertaken in the same way as for Day 4.

10.8.3.3. The analysis of the virologic secondary outcome measure of $\log_{10}$ SARS-CoV-2 RNA levels by quantitative PCR at Day 8 will be undertaken in the same way as for Day 4.

10.8.3.4. For the virologic secondary outcome measure of SARS-CoV-2 RNA levels by quantitative PCR in NP swabs below the LLoQ, comparison of S-217622 vs. placebo will be undertaken using the absolute difference in proportion of participants with RNA below the LLoQ on Day 4, with a 95% CI calculated using the normal approximation to the binomial distribution. The analysis of the similar outcome measure at Day 8 will be undertaken in the same way as for Day 4.

10.8.3.5. Analysis of time to self-reported return to usual (pre-COVID-19) health will be undertaken in the same way as the symptom duration primary outcome measure.

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

10.8.3.7. Analysis of 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 virology outcome measure of quantitative $\log_{10}$ SARS-CoV-2 RNA. Analysis of the proportion of participants with resting peripheral oxygen saturation ≥96% will be undertaken for each scheduled measurement

time in the same way as the analysis of the virology outcome measure of SARS-CoV-2 RNA below the LLoQ.

10.8.3.8. Analysis of an indicator variable for a new Grade 3 or higher AE through 29 days, and through 24 weeks (coded as 1 if participant developed a new Grade 3 or higher AE, and 0 otherwise). 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, a time variable for study day of first Grade 3 or higher AE or censoring (earlier of Day 29 or day of last contact with participant) will be created. Kaplan-Meier methods will be used in each intervention group (S-217622 or placebo) to estimate the cumulative proportion of participants having a Grade 3 or higher AE through Day 29 taking account of censoring due to loss to follow-up, which is assumed to be non-informative.

10.8.3.9. Analysis of new Grade 2 or higher AEs through 29 days, and through 24 weeks, will be undertaken in the same way as for the secondary safety outcome measure of new Grade 3 or higher AEs.

10.8.3.10. Measures of psychological health, functional health, and health-related quality of life in participants through the end of study follow-up will be analyzed based on data obtained using survey instruments, post-acute COVID-19 Questionnaire, SF36v2, and EQ-5D-5L. The change in overall and domain specific scores adjusted by baseline scores at each timepoint will be summarized.

10.8.3.11. 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 secondary outcome measure of death or hospitalization by Day 29.

10.8.4. Standard Safety Analyses

The Safety population will be used for safety analyses.

10.8.4.1. Adverse Events

All AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) using Medical Dictionary for Regulatory Activities (MedDRA). Of reported AEs on the eCRF, AEs reported after the initial dose of randomized study intervention will be used for analyses.

The number of participants who experience at least 1 AE, death, other SAE, and AE leading to withdrawal will be counted for each treatment group. Kaplan-Meier methods will be used in each intervention group (S-217622 or placebo) to estimate the cumulative proportion of participants experiencing an AE. Treatment-related AEs will be summarized in the same manner as AEs described above.

The number and percentage of participants who experience AEs by MedDRA SOC and PT will be presented for each treatment group. The summary for timing of onset, severity, action taken with the study intervention, and outcome will be presented by SOC and PT. All AEs, including those occurring prior to the initiation of the study intervention, will be listed.

10.8.4.2. Vital Sign Measurement

For each of the vital sign measurements, summary statistics of observation and the change from baseline will be presented by treatment group for each scheduled timepoint. Baseline is defined as the last value obtained before the initiation of the study intervention.

10.8.4.3. Clinical Laboratory Analysis

For each of the laboratory tests, summary statistics of observation and the change from baseline will be presented by treatment group for each scheduled timepoint. Baseline is defined as the last value obtained before the initiation of the study intervention.

Qualitative laboratory test data at baseline and at scheduled timepoints will be classified according to test category, and the frequency of each pair will be presented in a 2-dimensional contingency table by treatment group.

11. PHARMACOLOGY PLAN

The pharmacology objectives are to determine and summarize the PK of S-217622. The relationships between exposure of S-217622 with laboratory markers and clinical outcomes will be explored.

The PK concentrations will be summarized and presented with PK population. The individual plasma S-217622 concentrations will be listed by study participants, 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 an appropriate manner. Plasma concentrations of S-217622 after the previous dose will be summarized for data at 60 and 90 minutes post dose on Day 1 and predose on Day 4 (concentration 24 hours after last dose, C_{24hr}) by time and day with N, mean, SD, and coefficient of variation (CV%, calculated by SD/Mean × 100); geometric mean (Geometric Mean) and coefficient of variation for geometric mean (CV% Geometric Mean); and median, minimum, and maximum values. The C_{24hr} is the plasma concentration of S-217622 within 20 to 28 hours after the previous dose.

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 should be described in the clinical study report (CSR).

An interim analysis will be conducted from the first 90 participants enrolled who have provided both Day 1 and Day 4 PK samples.

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/PD data analyses. When these analyses are performed, the analysis plan and its report will be prepared separately.

12. DATA COLLECTION AND MONITORING

12.1. Records to be Kept

Electronic CRF screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the Data Management Center. Participants will be identified by the participant identification number (PID) and study identification number (SID) provided by the IRT upon randomization.

12.2. Clinical Site Monitoring and Record Availability

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to, on-site visits to ensure the safety of study participants and data integrity [26]. Remote visits will be conducted according to the site's SOP, which will detail how the identity of participants will be verified at remote visits. The investigator will make study documents (e.g., consent forms, drug distribution forms, eCRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the FDA, the NIAID, the OHRP, the industry supporters or designee, and other local, US, and international regulatory entities for confirmation of the study data.

Data Quality Assurance: This study will be conducted according to the International Conference on Harmonisation (ICH) E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management. The sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

Role of Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. All eCRF information is to be filled in. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed. Investigative site personnel will enter participant data into CDMS. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data). Clinical data management will be performed in accordance with applicable sponsor or CRO standards and data cleaning procedures to ensure the integrity of the data, for example, removing errors and inconsistencies in the data. AE terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded

using the WHO Drug Dictionary (WHODrug).

13. PARTICIPANTS

13.1. Institutional Review Board/Independent Ethics Committee Review and Informed Consent

This protocol and the informed consent documents and any subsequent modifications will be reviewed and approved by the IRB or IEC responsible for oversight of the study. Informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 and US Title 45 CFR Part 46 shall be obtained from each participant before entering the study or performing any unusual or nonroutine procedure that involves risk to the participant. An informed consent template may be provided by the sponsor to investigative sites. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, and this fact will be documented in the participant's record.

13.2. Ethical Conduct of Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH Good Clinical Practice, and all applicable regulations.

13.3. Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the sponsor, ACTG, IRB/IEC, FDA, NIAID, OHRP, other local, US, and international regulatory entities as part of their duties, or the industry supporters or designee.

13.4. Study Discontinuation

The study may be discontinued at any time by the sponsor, ACTIV-2 Trial Oversight Committee, ACTG, IRB/IEC, FDA, NIAID, OHRP, or other country-specific government agencies as part of their duties to ensure that research participants are protected, or the industry supporters.

14. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporters prior to submission.

15. BIOHAZARD CONTAINMENT

As the transmission of SARS-CoV-2 and other pathogens can occur through contact with contaminated needles, respiratory secretions, blood, and blood

products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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