Appendix E-1: Shionogi Protease Inhibitor S-217622 (Ensitrelvir)

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1 Trial Synopsis

Design:	Treatments are needed to improve outcomes among patients hospitalized for COVID-19, including direct-acting antiviral (DAA) agents to mitigate the pathology driven by ongoing viral replication. This trial will evaluate S-217622 (ensitrelvir), an anti-SARS-CoV-2 3C-like protease inhibitor (PI) developed by Shionogi & Co. Ltd. The study design is a randomized, placebo-controlled, multi-center international clinical trial that will evaluate the clinical efficacy of S-217622 when given in addition to standard of care (SOC) for inpatients with COVID-19. The SOC will be determined by local established guidelines and may include additional DAA (e.g., remdesivir) and immunomodulatory treatment strategies. Certain SOC treatments will be pre-specified prior to randomization.
Primary Endpoint:	The primary objective is to establish the safety and efficacy of S-217622 versus placebo when given in addition to SOC. The primary endpoint for this trial is the days to recovery scale assessed over 60 days (*DRS-60*). DRS-60 is a version of the STRIVE clinical recovery scale (CRS; see master protocol), which for this trial includes daily bins for time to recovery and also captures ongoing hospitalization and death. This corresponds to 63 ordered categories: categories 0 (best) through 60 reflect time to recovery, followed by categories for “alive, not recovered” and then “death” (worst).
Duration:	Participants will be followed for 60 days following randomization for the primary endpoint. Select secondary endpoints will also be measured.
Sample Size:	This Phase 3 trial is planned to provide 80% power to detect an OR of 1.30 in *DRS-60* for S-217622 versus matched placebo, both in combination with SOC. The planned sample size is 1500 participants. Sample size may be re-estimated before enrollment is completed based on an assessment of whether the pooled estimate of the distribution across the ordinal categories of the *DRS-60* is still consistent with adequate power for the hypothesized difference. A reassessment of the magnitude of the hypothesized difference, blinded to follow-up data, may also need to be made.
Population:	Adults (≥18 years) who have documented SARS-CoV-2 infection within 14 days of enrollment and are hospitalized for management of COVID-19. Inpatients at any disease stage will be eligible, including those not receiving oxygen as well as patients receiving oxygen supplementation via low-flow device, high-flow nasal cannula device, non-invasive ventilation, invasive mechanical ventilation or extracorporeal membrane oxygenation at enrollment.

Intervention:	Randomization to S-217622 plus SOC or matched placebo plus SOC in a 1:1 allocation. Study investigational agent/placebo (S-217622) will be administered as tablets with dosing of 375 mg (3 tabs) once on Day 0 and 125 mg (1 tab) once daily on Days 1-4. All participants will receive the full 5-day course, including those who are discharged from hospitalization prior to Day 4.
Stratification:	Randomization will be stratified by study site pharmacy and disease severity.
Monitoring:	An independent data and safety monitoring board (DSMB) will regularly review interim safety and efficacy data of this trial along with the conduct of other trials within the STRIVE protocol. A sponsor medical monitor will review blinded safety data. Pre-specified guidelines will be established to recommend early stopping of the trial for evidence of harm, futility, or substantial efficacy. The DSMB may recommend discontinuation of the investigational agent if the risks are judged to outweigh the benefits.

2 Introduction

2.1 Target Pathogen or Syndrome for This Trial

This is a trial of an investigational agent for patients infected with SARS-CoV-2 and manifested as a clinical syndrome termed coronavirus disease 2019 (COVID-19). First identified in late 2019, SARS-CoV-2 caused a serious pandemic, with at least 6 million dead and more than 500 million infected as of 26 April 2022. Excess mortality due to COVID-19 pandemic has been estimated in excess of 18 million [1]. After an initial infection in the upper airway, in a subset of patients more systemic infection occurs, primarily in the lung but with a wide range of extra-pulmonary effects described. To date, a variety of antiviral therapies are available for outpatients with COVID-19, including neutralizing monoclonal antibodies and direct-acting small-molecule antivirals. Among hospitalized patients, treatments utilized within standard care include corticosteroids as well as additional immunomodulatory therapy and the antiviral medication remdesivir (RDV) in some settings. Epidemiologic evidence suggests that among inpatients, viral replication persists and may contribute to the dysfunctional inflammatory/immune response that characterizes severe and critical COVID-19. Outcomes among hospitalized COVID-19 patients, including and especially those with critical disease, remain poor. Given the ongoing clinical need for improved treatments for hospitalized patients and the evidence for ongoing viral replication in this cohort, new antiviral agents are an important priority for additional testing.

2.2 Premise for Investigational Agent S-217622 (Ensitrelvir)

S-217622 (ensitrelvir) is a compound within the protease inhibitor (PI) class of direct-acting antiviral (DAA) medications, developed by Shionogi & Co., Ltd for the treatment

of COVID-19. The antiviral mechanism of S-217622 entails inhibition of SARS-CoV-2 3C-like protease (3CLpro). 3CLpro is a virally encoded enzyme that is critical to the SARS-CoV-2 life cycle, analogous to other obligatory virally encoded proteases (e.g., HIV Protease, HCV Protease). 3CLpro is the main coronavirus protease and processes the polyprotein that includes various replication proteins like the polymerase and helicase and 3CLpro itself.

S-217622 has demonstrated reduction in viral measures among patients with early COVID-19, as well as the potential for additive effects when given in combination with other antiviral agents with different mechanisms of action such as RDV. S-217622 (ensitrelvir) has emergency approval in Japan for the treatment of SARS-CoV-2 infection.

2.2.1 Anti-viral Therapies Among Patients with Early Stages of COVID-19 Disease

Clinical studies now support that pharmacologic inhibition of SARS-CoV-2 3CLpro (protease inhibitors [PI]), is an effective and promising strategy for treatment of COVID-19. Among non-hospitalized patients with COVID-19, recent data has demonstrated the efficacy of a novel PI targeting SARS-CoV-2 3CLpro. In a randomized, placebo-controlled trial of non-hospitalized high-risk patients with mild-to-moderate COVID-19 within 5 days of symptom onset, the combination of nirmatrelvir (300mg) and ritonavir (100mg) (nirmatrelvir-r, or 'Paxlovid') administered twice daily for 5 days led to an 89% reduction in hospitalization or death [2]. The event rate was 0.77% (8/1039) and 6.3% (66/1046) in the active and placebo groups, respectively (deaths were 0 and 12 in each group). The US FDA has issued an emergency use authorization for nirmatrelvir-r in the treatment of high-risk outpatients with mild to moderate COVID-19, with similar approvals under consideration in international settings. An important limitation of the clinical data on nirmatrelvir-r is that the study population was non-hospitalized, predominantly unvaccinated, and infected with viral variants prior to the emergence of Omicron. This trial will study a more contemporary hospitalized population with high vaccination rates.

Among hospitalized patients with COVID-19, it is currently not known whether PI targeting SARS-CoV-2 3CLpro improves clinical outcomes. The DAA drug RDV, which inhibits the SARS-CoV-2 RNA dependent RNA polymerase (RdRp), has demonstrated improved outcomes in some clinical trials, including shorter time to recovery (hospital discharge) [3] and need for new invasive mechanical ventilation [4]. However, in a large international pragmatic open-labeled clinical trial, RDV treatment had no effect on initiation of mechanical ventilation or all-cause mortality [5]. In this context, the use of RDV as standard care varies by region globally. The US NIH COVID-19 guidelines [6] issued a moderate strength recommendation for RDV use specifically among hospitalized patients receiving conventional low-flow oxygen supplementation, while other international guidelines do not recommend the use of RDV among hospitalized patients with COVID-19.

2.2.2 Importance of Anti-viral Therapy for COVID-19 Among Critically Ill Patients

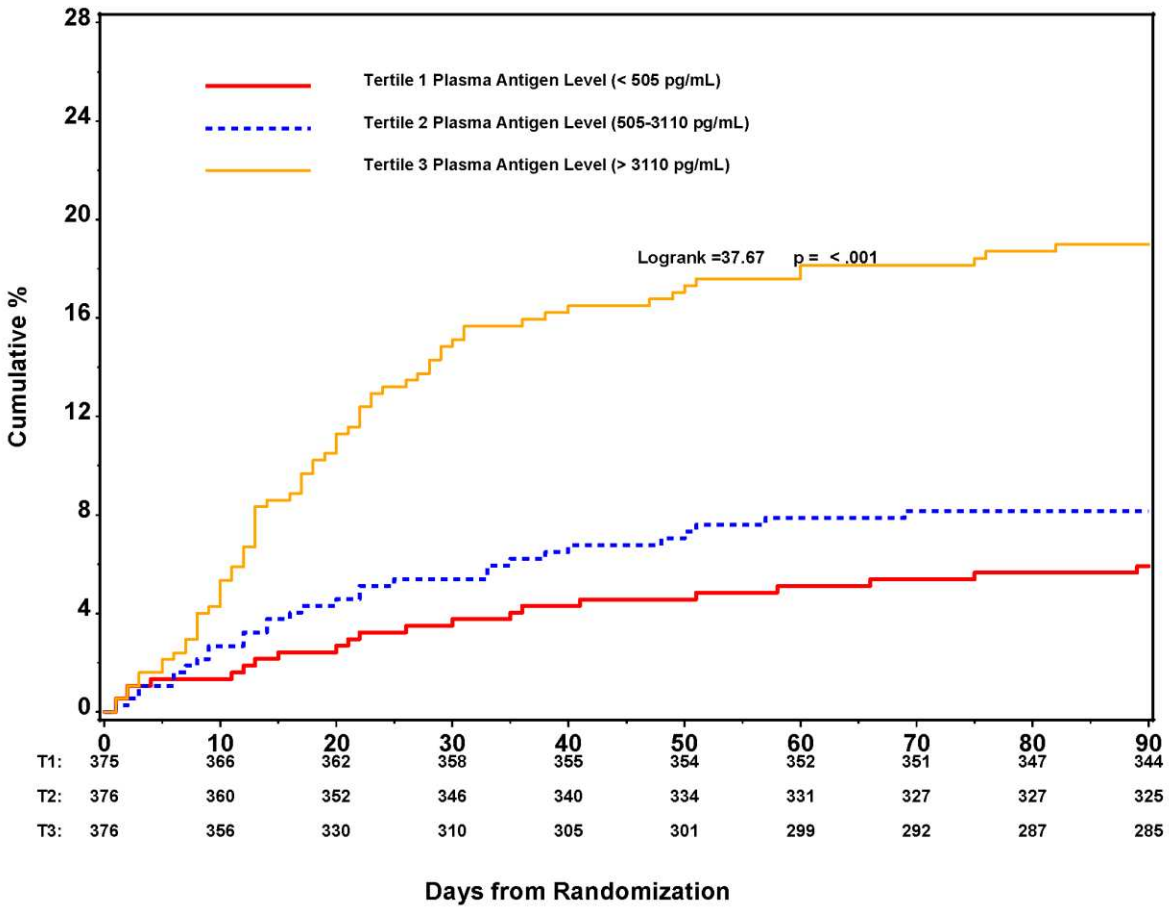
Whereas several antiviral agents have demonstrated efficacy among outpatients with COVID-19, and evidence from some (but not all) trials supports use of RDV among at

least some hospitalized patients with COVID-19, there remains an important therapeutic gap among hospital inpatients, including those who are critically ill from COVID-19. This clinical need may be well addressed by potent antivirals.

Notably, evidence from the INSIGHT TICO trials suggest that a substantial number of patients presenting to hospital with respiratory failure from COVID-19 pneumonia lack neutralizing antibodies and/or have high viral load as measured by serum levels of nucleocapsid antigen (NC-Ag). In data from more than 2,400 patients from 5 TICO trials, nearly half of patients lacked neutralizing antibodies; this group had a 5-fold higher level of plasma antigen. Patients requiring non-invasive ventilation or HFNO (reflecting patients with early respiratory failure included within the target population for this trial) had a nearly 6-fold higher degree of plasma antigenemia.

Plasma NC-Ag levels were then analyzed for associations with mortality, pooling data from over 1100 patients in the control arms from 6 TICO trials. Figure 1 shows the mortality over time for the tertiles of NC-Ag levels at baseline; Unadjusted HR (Tertile 3 vs tertile 1): 3.46 [2.14-5.58], and adjusted HR (Tertile 3 vs tertile 1): 2.62 [1.62-4.25], when adjusted for age, gender, ordinal category at baseline

Figure 1: Mortality by Plasma Nucleocapsid Antigen Level Among Patients Hospitalized with COVID-19



In summary, these data suggest the ongoing importance of antiviral therapies in severe and critically ill patients with COVID-19 [7, 8]. In addition, the rising prevalence of baseline immune-suppression among critically ill patients with COVID-19 (observed, for example, within the INSIGHT TESICO trial) suggests the relevance of antiviral therapies in this patient population may increase.

2.3 Human Studies and Preclinical Information on Investigational Agent Treatment Effect and Safety

2.3.1 Preclinical efficacy and toxicology data

Efficacy Data: In-vitro, S-217622 shows strong antiviral activity via inhibition of the SARS-CoV-2 3CLpro, with a 50% inhibitory concentration (IC_{50}) of 0.0132 µmol/L. Two cell lines susceptible to SARS-CoV-2 infection that can be utilized to evaluate antiviral effects include VeroE6/transmembrane protease, serine 2 [TMPRSS2] and human embryonic kidney [HEK] HEK293T/angiotensin-converting enzyme 2 (ACE2)-TMPRSS2 cells. In both VeroE6/TMPRSS2 and HEK293/ACE2-TMPRSS2 cells, S-217622 inhibited cytopathic effects in a dose-dependent manner, with the half maximal (50%) effective concentration (EC_{50}) ranging from 0.12 to 0.50 µmol/L usingVeroE6/TMPRSS2 cells and 0.026 to 0.058 µmol/L using HEK293T/ACE2-TMPRSS2 cells. Additionally, the concentration achieving 50% of cytotoxicity (CC_{50}) of S-217622 for VeroE6/TMPRSS2 cells and HEK293T/ACE2-TMPRSS2 cells were >100 and 55 µmol/L, respectively. To investigate the antiviral efficacy of S-217622 against SARS-CoV-2 viral shedding in primary human airway epithelial cells (hAEC), MucilAir™ nasal cavity were infected with the clinical isolates of SARS-CoV-2 (hCoV-19/Japan/TY11-927-P1/2021) to determine the 90% maximal effective concentration (EC_{90}) value of S-217622 for this strain after the infection. The EC_{90} of S-217622 for SARS-CoV-2 in hAEC were 0.0514 and 0.117 µmol/L on Days 2 and 3 after the infection, respectively.

To evaluate in vivo efficacy, S-217622 was orally administered to female BALB/c mice infected with the hCoV-19/Japan/TY7-501/2021 strain at a dose of 0 (vehicle control: 0.5% methylcellulose aqueous solution), 8, 16, 32, or 64 mg/kg twice daily (every 12 hours) for 2 days, 8, 16, 32, or 64 mg/kg three times daily (every 8 hours) for 2 days, 16, 32, or 64 mg/kg once daily for 2 days, or 32 or 64 mg/kg once daily for 1 day. The first administration of S-217622 was performed 24 hours after virus infection. Lung virus titers decreased for twice-daily dosing in a dose dependent manner. In this study, PK parameters that predict decrease in lung viral titers 48 hours after the first administration were total time above the target plasma concentration (TimeHigh) (10 × protein-adjusted half maximal effective concentration [PA-EC_{50}]), area under the mean concentration curve until 48 hours after first administration ($AUC_{0\text{-}48hr}$)/PA-EC_{50}, plasma concentration at 48 hours after first administration (C_{48hr})/PA-EC_{50}, suggesting that maintaining a certain level of plasma concentration is important for exerting a sustained antiviral effect in the infected mouse model.

In-vitro susceptibility to SARS-CoV-2 omicron variant: VeroE6/TMPRSS2 cells and HEK293/ACE2-TMPRSS2 cells 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 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 variant lineages. Importantly, activity was also retained for a clinical isolate of the omicron SARS-CoV-2 variant.

Table 1: In Vitro Susceptibility of SARS-CoV-2 Variants to S-217622 (Ensitrelvir)

Half maximal (50%) effective concentration (EC_{50})	S-217622 (Ensitrelvir)	
	VeroE6/TMPRSS2 Cells	HEK293T/ACE2-TMPRSS2 Cells
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

Finally, when used in combination with other DAA agents (e.g., RDV, EIDD-1931 or PF-07321332) S-217622 showed additive effects on virus growth. In summary, these pre-clinical data support the premise that S-271622 has potent antiviral effect, which is robust against emerging viral lineages circulating clinically, and has potential to further improve outcomes when given in combination to standard treatments like RDV.

Toxicology Data from Animal Studies: No adverse effect was noted in rats during the 2-week and 4-week repeat-dose toxicity studies. The NOAEL was determined to be 1000 mg/kg/day. In the repeat-dose toxicity studies in monkeys the NOAEL was determined to be 10 mg/kg/day, both for the 2-week and the 4-week repeat-dose study. In the 2-week repeat-dose study animals showed decreased erythrocyte parameters and platelet counts, inflammatory changes in multiple organs with changes in blood inflammatory markers, decreased body weight and food consumption at doses above 50 mg/kg/day. Higher doses led to death/moribundity (1000 and 300 mg/kg/day) and vomiting (100 mg/kg/day and above). The causes of death were determined to be decreased food consumption, opportunistic infection and anemia. In the 4-week repeat-dose study animals showed decreased erythrocyte parameters, decreased body weight and food consumption, inflammatory changes in the muscular layer/fibrous membrane

of the gallbladder and in the muscular layer of the uterus with changes in blood inflammatory markers at doses above 30 mg/kg/day.

Fertility and Pregnancy: In rabbits, abnormal axial skeleton morphology and short tails were observed at 100 mg/kg/day or above (5.0 times relative to the expected clinical dose, based on AUC(0-24hr) in rabbits compared with humans at 375/125 mg). In addition, abortion was observed at doses of 100 mg/kg/day and low embryo-fetal viability was observed at dose of 300 mg/kg/day (7.4 times relative to the expected clinical dose, based on AUC(0-24hr) in rabbits compared with humans at 375/125 mg). In rats, no malformations or embryo-fetal lethality up to 1000 mg/kg/day (6.6 times relative to the expected clinical dose, based on $AUC_{(0\text{-}24hr)}$ in rats compared with humans at 375/125 mg).

2.3.2 Clinical Efficacy and Safety Data

Efficacy Data: S-217622 is being evaluated as part of a Phase 2/3 study conducted among non-hospitalized patients with mild-to-moderate COVID-19. The Phase 2b component evaluated virologic responses, clinical symptoms, and safety among 435 participants with ≥1 moderate or severe symptoms that were present ≤120 hours (5 days) prior to randomization to one of two doses or matched placebo. Study drug was administered once daily for 5 days, with the low dose regimen of 375 mg on 1st day and 125 mg on Days 2-5 (375/125 dose; n=114), with the high dose of 750 mg on 1st day and 250 mg on Days 2-5 (750/250 dose; n=116). Mean age was 36 years and >85% of the study population was previously vaccinated. Significant differences between active and placebo groups were present for viral load reduction at Days 2-9 of follow-up, with the largest difference at day 4. When compared to placebo, the decline in viral RNA level between baseline and day 4 was significantly greater for both the 375/125 dose (Diff in LS mean -1.3; 95% CI -1.57 to -1.03; p<0.0001) as well as the 750/250 dose (Diff in LS mean -1.21; 95% CI -1.48 to -0.94; p<0.0001). Patients also demonstrated a faster improvement in a respiratory symptom score with S-217622 treatment, at either dose when compared to placebo.

Safety Data: In the Phase 2b study, no deaths or serious treatment emergent adverse events (SAEs) were reported. Adverse events (AEs) leading to discontinuation of S-217622 were reported in 2 participants in the low dose group, and both were considered related. No severe treatment emergent AEs (TEAEs) were reported in either of the active study arms. Seven moderate AEs were reported, but most AEs were categorized as mild. The overall incidence of AEs deemed treatment-related was 13.6% (19/140 participants) in the low dose group, 22.1% (31/140 participants) in the high dose group and 5.0% (7/141 participants) in the placebo group. These AEs were predominantly laboratory defined and did not lead to clinical symptoms (e.g., transient reduction in HDL levels), and only clinical AEs will be assessed in this trial.

AEs that were reported in 2% or more of the participants in any of the treatment groups of part 2b were decreased high density lipoprotein (20.7% [29/140], 23.6% [33/140], and 2.1% [3/141] in the low dose group, in the high dose group, and in the placebo group, respectively), hypertriglyceridaemia (2.9% [4/140] in the high dose group), headache, diarrhea, back pain, and dyslipidaemia (2.1% [3/140] each in the high dose group),

blood creatine phosphokinase increased (2.8% [4/141] in the placebo group), upper abdominal pain and rash (2.1% [3/141] each in the placebo group).

AEs deemed treatment-related that were reported in 2% or more of the participants in any of the treatment groups were high density lipoprotein decreased (9.3% [13/140] and 15.7% [22/140] in the low dose and high dose groups, respectively) and dyslipidaemia (2.1% [3/140] in the high dose group). No treatment-related AEs were reported in 2% or more in the placebo group.

Safety Data on Rash and Possible Anaphylaxis: The information available on clinical rash AEs associated with S-217622 comes from Phase 1/2/3 clinical trials and post-marketing surveillance data in Japan. During a Phase 1 clinical trial of S-217622 conducted by Shionogi, a single rash event occurred that was not categorized as anaphylaxis which was noted on the participant's chest and lasted up to nine days. As a result of this event, rash was designated as an adverse event of special interest (AESI) in subsequent Phase 2/3 studies involving over 2000 participants. In these Phase 2/3 studies, there was no difference in the rate of rash between active and placebo arms. There is an ongoing Phase 3 outpatient clinical trial of S-217622 (ACTIV2d/SCORPIO-HR), with enrollment of over 1,000 participants to date. There have been no anaphylactic events reported at time of this protocol date in any of these trials.

Over 50,000 outpatients in Japan have been prescribed S-217622. In the post-marketing surveillance, three cases of rash involving anaphylaxis have been reported. There have been no other reports of anaphylaxis. **All of the rash events occurred within two hours of the first dose of S-217622**. The cases were all classified as anaphylaxis based on meeting major dermatologic criteria (e.g., generalized urticaria, pruritis and/or angioedema), with one case also involving hypotension. Two of the cases were taken to hospital for evaluation, admission, and management. All three cases have recovered. These three cases motivated the designation of new-onset rash as an AESI in the current trial (section 8.2).

Fertility and Pregnancy: There are no studies in pregnant woman. The potential risk of S-217622 in pregnant women is unknown. In this trial, patients who are pregnant or lactating will be excluded, and participants will agree to abstain from sexual intercourse that may result in pregnancy or agree to practice appropriate contraception. A non-hormonal method of contraception should be used during the 5 days of S-217622 (or placebo) treatment and through 30 days after the last dose of the investigational treatment (S-217622/placebo).

2.3.3 PK Data and Dosing Rationale

PK data from murine model and in vitro study: Results of a nonclinical pharmacology study using SARS-CoV-2-infected mouse model showed that initiation of treatment with S-217622 24 hours after acquisition of infection decreased lung viral titers in a dose-dependent manner, and that PK parameters that predict decrease in lung viral titers 48 hours after the first administration were: TimeHigh (10 × PA-EC_{50}), $AUC_{0\text{-}48hr}$/PA-EC_{50}, C_{48hr}/PA-EC_{50}, suggesting that maintaining a certain plasma concentration is important for exerting a sustained antiviral effect in the infected mouse model.

The PK/pharmacodynamic (PD) analysis of SARS-CoV-2-infected mouse model extrapolated that the estimated plasma concentration in human considering mouse PA-EC_{50} (2.09 µg/mL) and human PA-EC_{50} (1.61 µg/mL) adjustment associated with a 1-, 2-, and 3-log reduction in viral titers were 1.24, 6.09, and 23.7 µg/mL, respectively. These plasma concentrations are substantially higher than PA-EC_{90} (0.374 µg/mL) in primary human nasal epithelial cells, calculated from the EC_{90} (0.0623 µg/mL, preliminary study) and potency shift in human (x 6).

Dose rationale from Phase 1 data and PK/PD assumption: Since it is most beneficial to start antiviral drug therapy in the early phase after acquisition of SARS-CoV-2 infection, it was determined to set a loading dose to achieve the plasma concentration necessary for maximal viral suppression on the first day of intervention. Considering the clinical course from acquisition to onset of SARS-CoV-2 infection the appropriate duration of antiviral intervention was determined to be within 1 week, and the duration of treatment was determined to be 5 days to ensure adequate exposure for 7 days.

Results of a PK analysis of once daily, multiple-dose administration of S-217622 for 5 days, 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 in White participants (Study 2102T1211, Cohort R), showed that C_{24hr} on Days 1 and 5 were 19.0 and 28.9 µg/mL, respectively. The C_{24hr} on Days 1 and 5 exceeded the target concentration of a 2-log reduction (6.09 µg/mL) and a 3-log reduction (23.7 µg/mL) in viral titers (the estimated plasma concentration in humans considering potency shift adjustment associated with a 2-, and 3-log reduction in viral titers by PK/PD analysis in a SARS-CoV-2-infected mouse model), respectively. It also suggests that C_{24hr} on Days 1 and 5 at the loading dose 375 mg/maintenance dose 125 mg (12.2 and 16.9 µg/mL, respectively, Study 2102T1211, Cohort Q) would exceed the target concentration of a 2-log reduction (6.09 µg/mL). In addition, the ratios of C_{24hr} on Days 1 and 5 at the loading dose 750 mg/maintenance dose 250 mg to PA-EC_{90} (0.374 µg/mL) in primary human nasal epithelial cells were 51- and 77-fold, respectively, and those ratios on Days 1 and 5 at the loading dose 375 mg/maintenance dose 125 mg were calculated as 33-and 45-fold, respectively. The relative lack of food effect on S-217622 PK means that S-217622 can be dosed without regard to food.

2.4 Rationale for the Trial Intervention Dose and Duration

S-217622 is an oral anti-SARS-CoV-2 PI that does not require ritonavir co-administration The dose of 375/125 (375 mg on Day 0, followed by 125 mg daily on Days 1-4) is based on Phase 2b data above (section 2.3.2), where there was no appreciable difference in antiviral or clinical activity of the lower versus the higher dose.

3 Objectives and Endpoints

3.1 Primary Objective and Endpoint

The primary objective of this trial is to determine if a 5-day treatment course with S-217622, versus placebo, improves clinical outcomes for patients hospitalized for the management of COVID-19, when given in combination with standard care.

3.1.1 Primary Endpoint

The primary outcome for this trial is called the 'Days to Recovery Scale' assessed over 60 days (*DRS-60*). DRS-60 is a version of the STRIVE clinical recovery scale (CRS) that is described in the master protocol (section 4.1.4 and Table 4.1), which combines time to recovery with non-recovered clinical state and death into an ordinal outcome. For this trial, the DRS-60 version of the CRS includes daily bins for time to recovery with additional categories for alive, not-recovered and death.

The *DRS-60* assesses clinical recovery through Day 60 by combining 63 ranked categories. Categories 0 (best) through 60 correspond to the number of days from study entry to recovery, and the two worst categories are then "alive, not recovered" on Day 60, and death at any time through Day 60 (worst category). A participant is considered "recovered" when they return home and remain alive at home through Day 60. This means re-hospitalization or change of residence from home to a higher level of care would change the participant's status to "not recovered" and reset the clock.

Although categories 0-60 correspond to "days from study entry to recovery," the outcome differs from "time to (first) return-to-home," because the date of recovery is determined by the "last" return to home, including after a possible re-hospitalization or return to a higher level of care. Importantly, participants who die after an initial return home will not be counted as "recovered."

The construction of the DRS-60 is similar to "hospital-free days by Day 60," or "organ-support free days," ordinal outcomes that have been previously used in the study of critically ill patients and including within the REMAP-CAP COVID-19 trial [9, 10]. The exception is that the DRS-60 categories count the days from randomization to recovery rather than the days between recovery and Day 60. The categories of the DRS-60 are described in Table 2 below.

Table 2: Categories of the *DRS-60* ordinal primary outcome

***DRS-60* Category**	**Status at Day 60**	**Hospital-Free Days** by Day 60**
0 (best)	Recovered, and days from randomization to "recovery" * 0 (returned home on day of study entry)	60
1	1	59
2	2	58
3	3	57
…	…	…
59	59	1
60	60	0 (recovered on Day 60)
Alive, not recovered on Day 60	Alive, not returned to home, or in hospice care	0 (not recovered on Day 60)
Death (worst)	Death	-1 (death)

* Recovery date is the day the participant returned home and remained at home through Day 60

** Hospital-free days here refers to the number of days the participant was at home, alive, uninterrupted through Day 60.

"Recovery" is determined by return to home. Home is defined as the level of residence or facility where the participant was residing prior to onset of COVID-19 which led to the hospital admission (index hospitalization). Therefore, the day of recovery as defined in our primary endpoint does not necessarily reflect a return to normal health.

Residence or facility groupings to define home are: 1) **Independent/community dwelling** with or without help, including house, apartment, undomiciled/homeless, shelter, or hotel; 2) **Residential care facility** (e.g., assisted living facility, group home, other non-medical institutional setting); 3) **Other healthcare facility** (e.g., skilled nursing facility, acute rehabilitation facility); and 4) **Long-term acute care hospital** (hospital aimed at providing intensive, longer term acute care services, often for more than 28 days). A lower (less intensive) level of residence or facility will also be considered as home. By definition, "home" cannot be a "short-term acute care" facility. Participants previously residing in a "long-term acute care" hospital recover when they return to the same or lower level of care. Participants in hospice care are not eligible for the trial, and discharge from hospitalization into hospice care is not considered "return to home."

The primary comparison of S-217622 versus placebo will use the van Elteren test, a stratified version of the nonparametric Wilcoxon rank-sum test, with stratification by disease severity at entry (based on oxygen supplementation) [11]. To aid the interpretation of the treatment effect, additional descriptive statistics by treatment arm will include:

- Median (IQR) for days to recovery (categories of the DRS-60)
- Proportion of participants who died due to any cause by Day 60
- Proportion of participants who were alive and not recovered by Day 60
- Proportion of participants who were recovered by Day 60

To further quantify the treatment effect (to aid in the interpretation of the results for the primary comparison), the treatment effect on the DRS-60 will also be expressed as a summary odds ratio in a proportional odds model, comparing the odds of being in a better category for participants randomized to the investigational agent versus the placebo group. As secondary analyses, components of the primary ordinal outcome will be investigated, to support the interpretation of the treatment effect. This includes comparing the S-217622 group versus placebo for the proportion of participants who died at Day 60, for the proportion of participants who "were dead or not recovered" at Day 60, and for days to recovery (defined by categories 0-60 of the *DRS-60*). Details are described in the statistical analysis plan.

In summary, the DRS-60 combines information on the treatment effect on mortality, non-recovery by Day 60, and, for those who are recovered on Day 60, time to recovery.

3.1.2 Rationale for the Trial Primary Endpoint

The primary endpoint *DRS-60* includes mortality, non-recovered clinical status, and also discriminates time to recovery among those who are discharged from hospital, by incorporating ordinal categories that reflect participant recovery status over a 60-day follow-up period. The *DRS-60* is easy to ascertain and is patient-centered focusing on

the time and degree of recovery following severe disease. Thus, by considering time to recovery within the scale, this outcome has advantages over all-cause mortality by itself for a broad study population across all stages of COVID-19 severity among hospitalized patients. Of note, the day of recovery as defined in our primary endpoint does not necessarily reflect a return to normal health for all participants, as assessment of post-acute sequelae of COVID-19 is not a specific focus of the study.

3.2 Secondary Objectives and Endpoints

Secondary endpoints and subgroup comparisons are specified in the master protocol section 4.2.

Key secondary endpoints will be:

a) mortality (proportion of participants who died by Day 60);
b) a 3-category ordinal outcome, assessed at Day 60, with the following categories: recovered (alive and at home at Day 60), alive and not recovered, and dead;
c) days to recovery (corresponding to categories 0-60 of the *DRS-60*);
d) proportion of participants who died or required new invasive mechanical ventilation.

Additional secondary analyses are listed in the STRIVE master protocol, including time to all-cause mortality, time to (first) hospital discharge, a 7-level pulmonary ordinal scale assessed on Days 1-7, 14, 28, 42, and 60, Health-related quality of life by EuroQol (EQ-5D-5L) at the end of follow-up, and time to sustained recovery as defined in the TICO platform.

Key subgroup analyses in this trial will be:

a) disease severity (categories defined by supplemental oxygen use at study entry),
b) participants using RDV as part of SOC (pre-specified before randomization, see section 4.2; RDV-SOC subgroup),
c) immunocompromised status.

In addition to the full study cohort, the primary and secondary endpoints will also be explored specifically for the RDV-SOC subgroup.

3.3 Safety Endpoints

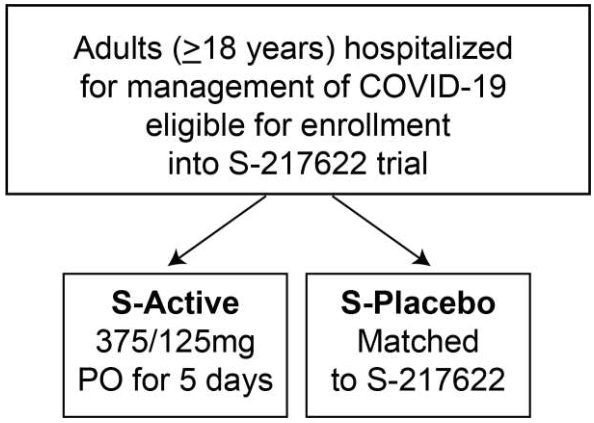
Safety endpoints are as specified in section 4.2 of the STRIVE master protocol. Important safety endpoints include mortality; a composite of death, SAEs, and protocol-defined anticipated clinical events (PDACEs) through Days 5, 28, and 60; a composite of death, SAEs, PDACEs, and grade 3 or 4 AEs, assessed through Days 5, 28, and 60; the components of the composite safety outcomes will also be summarized. In addition, AESIs (new-onset rash, see sections 2.3.2 and 8.2) will be summarized, and grade 1-4 AEs collected on Days 0-4, 7, and 14 will be summarized by grade and by type (based on MedDRA© coding).

4 Trial Design

4.1 Trial Design Overview

This is a randomized trial of S-217622 versus matched placebo among patients hospitalized for management of COVID-19 receiving no oxygen supplementation, low-flow oxygen supplementation, HFNC, NIV, IMV, or ECMO. The trial treatment intervention is given in addition to SOC as background treatment(s).

Figure 2: Trial Design Schematic



4.2 Trial Design Rationale and Justification

The approach and rationale for elements of the overall study design can be found in section 6 of the STRIVE master protocol.

The use of a placebo control is appropriate to answering the study question for this trial. Standard of care (SOC) as defined by local guidelines and utilized at the clinical sites is permitted in the background for both treatment groups in the trial. This includes the antiviral treatment RDV as well as immunomodulatory treatments recommended by local guidelines. When corticosteroids are indicated as SOC, an alternative to dexamethasone will be used to avoid DDI with S-217622 (see section 6.3.2).

RDV use as part of SOC varies by region globally. For this reason, the trial will define a subgroup based on whether remdesivir (RDV) is intended to be part of SOC treatments (RDV-SOC versus not), and this will be will pre-specified prior to randomization based on the intention to use RDV. The RDV-SOC group thus includes participants who either: a) have already been administered RDV prior to randomization, or b) are anticipated to start RDV as part of SOC following randomization, guided by the clinical care team.

4.3 Randomization and Blinding

An overview of the approach to stratification can be found in the STRIVE master protocol (section 6.3.4). Stratification will occur by study site pharmacy and disease severity, defined as a) no O2 or low-flow oxygen, b) HFNC/NIV, or c) IMV/ECMO.

For participants enrolled into this trial, randomization will be 1:1 allocation to S-217622 plus SOC or matched placebo plus SOC. For participants eligible for simultaneous co-enrollment into other trials within the STRIVE platform, the randomization assignment to S-217622 versus placebo will be independent of the other trials, and placebo groups will not be shared.

Blinding will be accomplished by use of a matched-placebo pill administered daily for 5 days (see section 6.3 of the master protocol for additional details).

4.4 Enrollment in other Trials within STRIVE Master Protocol

The principles for co-enrollment in this trial will follow those specified within section 6.1.1 of the STRIVE master protocol. Co-enrollment in other trials will only be allowed where a co-enrolling trial has been approved by STRIVE leadership for co-enrollment. Design implications of co-enrollment (e.g., timing between randomizations), will be evaluated and approved by STRIVE scientific steering committee and network leadership. Details of such co-enrollment authorization will be managed, maintained, and communicated by the STRIVE Data Coordinating Center. Where appropriate, the statistical analysis plan (SAP) will specify any analytic modifications relevant to co-enrollment.

4.5 Sample Size Assumptions

The primary outcome is the DRS-60, an ordinal outcome with 63 categories that combines information about mortality and time to recovery. The outcome is assessed on Day 60. The two worst categories are “death” and “alive, not recovered (on Day 60).” Participants who are alive and “recovered” on Day 60 fall into one of 61 ranked categories, labelled (0-60) by the number of days from randomization to recovery. For example, a participant who achieved “recovery” on Day 10 and did not relapse (i.e., was not re-hospitalized or transferred to a level of care more acute than home) or die would be in category “10” at Day 60. The best possible category is “0,” for participants who recovered on the day of randomization. A participant is considered “recovered” when they fulfill all three of the following conditions: **1)** discharged from the hospital, **2)** returned to home, and **3)** remained at home, uninterrupted, through Day 60.

With the requirement that “recovery” precludes rehospitalization or death, the DRS-60 ordinal outcome is similarly constructed to “hospital-free days by Day 60”, or “organ-support free days,” ordinal outcomes that have been previously used in the study of critically ill patients and including within the REMAP-CAP COVID-19 trial [9, 10]. The difference is that the DRS-60 categories are ordered from best to worst and count the days from randomization to recovery rather than the days between recovery and Day 60. An example of possible probability distributions across the categories of the DRS-60 is illustrated in Figure 3, which shows a side-by-side bar graph for the hypothesized distributions in the S-217622 and placebo groups that were used for the sample size estimation of the current trial.

The primary analysis for the treatment comparison will use the van Elteren test, a stratified version of the nonparametric Wilcoxon rank-sum test, stratified by disease severity at study entry [11]. Because the Wilcoxon rank-sum test is identical to the

score test using a proportional odds model, the sample size calculations are using a proportional odds model for the DRS-60, with an indicator variable for the treatment effect. Because power calculations require assumptions on the size of the treatment effect, the treatment effect is expressed as summary odds ratio, comparing the odds of being in a better category for participants randomized to the investigational agent versus the placebo group.

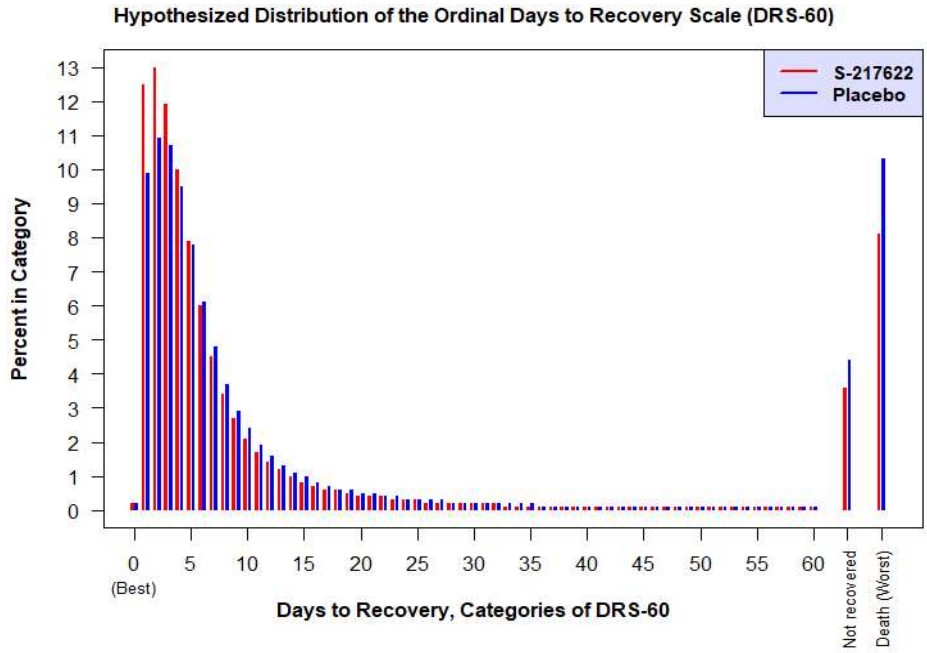
A sample size of 1500 participants (750 in each arm) is sufficient to detect an OR of 1.30 for the treatment difference between the S-217622 versus the placebo group with 80% power, using a two-sided test with a 5% significance level.
Sample size estimates used the following assumptions:

a. The investigational agent and placebo groups are of equal size (1:1 randomization).
b. The primary analysis will be modified intention to treat (mITT). The analysis population includes all participants who received any of the blinded investigational agent or placebo (full or partial). Because the treatment assignment is blinded and the study is placebo-controlled, restricting the analysis to the mITT cohort should not introduce bias.
c. The Type 1 error is set at 0.025 (one-sided).
d. Treatment groups will be compared for the *DRS-60* using a proportional odds model with an indicator variable for treatment group. The treatment effect is expressed as summary odds ratio, coded such that OR>1 favors the investigational agent.
e. Power is set at 80% to detect a clinically meaningful odds ratio of 1.30 comparing the investigational treatment versus control.
f. The total sample size needed to accrue the required number of events depends on the underlying distribution across the ordinal categories. Figure 3 below illustrates the hypothesized distribution across the 63 categories of the *DRS-60* in the placebo group, and the distribution in the investigational group that corresponds to an OR of 1.3. Table 3 describes the hypothesized distribution in the placebo group and the corresponding distribution for the S-217622 group under the assumption of proportional odds with OR=1.3 and OR=1.35; here, the 61 ordinal categories for patients who recovered were pooled into 7 categories, plus categories “death” and “not recovered.” The hypothesized distribution in the control group is based on the assumption that 15% of the participants will enter the study without requiring supplemental oxygen, 65% will require low-flow oxygen, 12% HFNC/NIV, and 8% require mechanical ventilation or ECMO. For participants who do not require supplemental oxygen and those who require low-flow oxygen, the distributions across the *DRS-60* categories were estimated from the pooled placebo groups in six ACTIV-3/TICO trials. The distribution for participants on IMV/ECMO at study entry were derived from the ACTIV-3b/TESICO trial. The hypothesized distribution for participants who require HFNC or NIV were estimated from pooled data of the TICO and TESICO trials. Table 4 shows the estimated distributions within the subgroups by oxygen requirement, and the derivation of the hypothesized distribution in the placebo group.
g. Under assumptions a-f, sample size is 1378 to detect an odds ratio of 1.3 with 80% power. The total sample size is inflated by 9% to account for some participants not receiving any of the blinded study treatment/placebo, loss to follow-up, and missing

data, for a total sample size of 1500. Total sample size to detect an odds ratio of 1.35 is 1054, inflated by 9% to 1148.

A sample size of 1500 participants (750 in each arm) is sufficient to detect an OR of 1.30 with 80% power; a total sample size of 1148 is sufficient to detect an OR of 1.35.

Figure 3. Hypothesized probability distribution across the 63 categories of the *DRS-60 in the S-217622 (ensitrelvir) (red) and placebo (blue) groups, assuming OR=1.3.**



* The best category is “0” for participants who recovered on the day of randomization, followed by categories 1-60 for the number of days from randomization to recovery, followed by 2 categories for “alive, not recovered” and “death” (worst category).

Figure 3 above shows the hypothesized probability distribution for the placebo group (blue) across the 63 ordered categories of the primary outcome (DRS-60), as well as the probability distribution of the S-217622 group (red) that corresponds to the hypothesized OR of 1.3 compared with the placebo group. The probability distribution in the placebo group was estimated from the ACTIV-3/TICO and the ACTIV-3b/TESICO trials; details are described below.

Table 3 below presents the hypothesized distribution across the ordinal categories of the *DRS-60* in the placebo group, the distributions in the investigational agent group corresponding to ORs of 1.30 or 1.35, and sample sizes needed to detect the difference. Here, the 61 categories for the number of days from randomization to recovery were pooled into 7 categories, with the bins chosen such that the probabilities across the bins are approximately similar. Sample size is inflated by 9% to account for some participants not receiving any of the blinded study treatment/placebo, losses to follow-up, and missing data.

Table 3: Hypothesized Distribution of Clinical Status Across Pooled Categories of the *DRS-60* ordinal scale

	Hypothesized Distribution (Percent of Participants in Each Pooled Category)		
Pooled DRS-60 Categories* (assessed at Day 60)	**Investigational agent + SOC, OR=1.30**	**Investigational agent + SOC, OR=1.35**	**Placebo + SOC**
Days from randomization to recovery**			
0-2 (best)	25.7	26.4	21.0
3-4	21.9	22.2	20.2
5-7	18.4	18.2	18.7
8-10	8.2	8.1	9.0
11-15	6.1	6.0	6.9
16-30	5.5	5.3	6.5
31-60	2.6	2.5	3.0
Alive, not recovered	3.6	3.5	4.4
Death (worst)	8.1	7.8	10.3
Total Sample Size***	**1500**	**1148**	

* The DRS-60 is an ordinal outcome with 63 categories: 61 categories for participants who recovered by Day 60, ranked by the number of days from randomization to recovery (recovery is the start of an uninterrupted period at home through Day 60, a relapse resets the clock), and two categories for participants who did not recover: "alive, not recovered at Day 60," and "death." Probabilities for pooled categories are presented.

** A participant is recovered if they are alive, discharged from the hospital, at home, AND don't require supplemental oxygen above their pre-COVID-19 level.

*** Sample size was inflated by 9% to account for the possibility of missing data.

Table 4: Hypothesized distribution of the placebo group across pooled categories of the DRS-60, derived from estimated distributions by disease severity.

	Hypothesized Distribution in Placebo group (%)					
	Distribution by Disease Severity (%)					
Pooled DRS-60 categories	**No O2**	**Low-flow O2**	**HFNC/ NIV**	**IMV/ ECMO**	**Weighted average**	**Placebo Group (Est.)***
Days from study entry to recovery						
0-2 (best)	35.3	23.8	2.4	0	21.0	21.0
3-4	19.1	23.1	9.8	0	19.0	20.2
5-7	19.1	21.9	20.8	4.8	20.0	18.7
8-10	4.4	9.8	10.8	8.5	9.0	9.0
11-15	5.5	4.0	9.4	6.9	5.1	6.9
16-30	3.7	6.3	8.0	10.6	6.5	6.5
31-60	5.5	3.5	4.6	13.8	4.8	3.0
Alive, not recovered	3.7	2.6	8.3	14.3	4.4	4.4
Death (worst)	3.7	5.1	25.7	41.3	10.2	10.3
Pct. of study population	**15%**	**65%**	**12%**	**8%**	**100%**	**100%**

The methodology for deriving the hypothesized distribution in the placebo group is described below. Table 4 above presents assumptions about the composition of the study population across four subgroups by oxygen requirement at study entry (last row): 15% of participants require no supplemental oxygen at study entry, 65% low-flow oxygen, 12% HFNC or NIV, and 8% IMV or ECMO. The probability distributions in the first two subgroups were estimated from the placebo groups of 6 ACTIV-3/TICO trials (columns 2-3). Data from the ACTIV-3b/TESICO trial were used to estimate the distribution for participants who required IMV/ECMO (column 5), and data from the TICO placebo groups and the TESICO trial were pooled to estimate the distributions for participants who require HFNC or NIV (column 4). Using these estimated distributions within subgroups by oxygen requirement, the distribution in the placebo group for the current trial was estimated in two steps. First, a weighted average of the distributions for the four disease severity subgroups was calculated (column 6, weights are given in the last row of columns 2-5). The percentages in the worst 2 categories (not recovered at Day 60, death by Day 60) were used as estimates for the corresponding categories of the DRS-60. Second, the conditional probabilities for participants who recovered (categories 1 through 60) were estimated by fitting a unimodal probability distribution over the ranked categories 1-60 for “days to recovery” that had similar (although not identical) probabilities for the pooled categories in Table 4 as the weighted average distribution. The resulting probabilities for the fit are summarized in the last column. The fit used a parametric stable distribution with 4 parameters.[12] The additional step of fitting a unimodal distribution was necessary because the raw relative frequencies across 60 categories were noisy due to sparse data, particularly among participants with longer times to recovery (fewer days recovered). As a last step, because no participants in the TICO and TESICO studies were identified as discharged from the hospital to home on the day of randomization (category “0”), while hypothesized distributions should have positive probabilities for each category, we assumed that 0.2% of participants would fall into category “0,” and decreased the hypothesized probability for category “1” by this number.

5 Trial Population

5.1 Target Population

The target population for this trial is the population specified within the master protocol who are admitted for the management of COVID-19 at any disease stage, such as patients requiring no oxygen supplementation, low-flow oxygen supplementation, oxygen via high-flow nasal canula (HFNC), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO).

5.2 Trial-specific Eligibility Criteria

The eligibility criteria for STRIVE are listed in section 7.2 of master protocol.

For this trial, additional ***inclusions*** not outlined in the master protocol include:

1. Confirmation of SARS-CoV-2 infection by nucleic acid test (NAT) or equivalent non-NAT test [list of approved tests is in the PIM] collected within the prior 14 days.

2. Onset of symptoms attributable to SARS-CoV-2 infection occurred within 14 days before randomization.
3. Hospitalized for the management of COVID-19, with signs and/or symptoms suggestive of lower respiratory tract infection.

For this trial, additional ***exclusions*** not outlined in the master protocol include:

1. Allergy to investigational agent or vehicle
2. Use of a concomitant medication that is contraindicated due to a drug-drug interaction with S-217622 (see section 6.3 and protocol instruction materials)
3. Moderate to severe hepatic impairment (i.e., Child-Pugh class B or C) or acute liver failure.
4. Known estimated glomerular filtration rate (eGRF) <30 mL/min/1.73m^2
5. Continuous renal replacement therapy or chronic dialysis
6. Current pregnancy
7. Current breastfeeding and unwillingness to defer breastfeeding for 30 days after the last dose of investigational agent.
8. Women of child-bearing potential who are unwilling to abstain from sexual intercourse with men or practice appropriate contraception through 30 days from the last dose of the investigational agent.
9. Men who are unwilling to abstain from sexual intercourse with women of child-bearing potential or to use barrier contraception through 30 days from the last dose of the investigational agent.

6 Investigational Agent(s) and Standard Care

6.1 Formulation, Dosing and Administration of Investigational Agent

Detailed descriptions for interventional agent distribution, accountability, storage, preparation, and administration can be found within trial specific Pharmacy Procedures and Protocol Implementation Manual (PIM) specific to this trial.

Table 5 shows a summary of study medication. S-217622 tablets are round-shaped tablets containing 125 mg S-217622 free base. The tablets contain mannitol, croscarmellose sodium, hydroxypropyl cellulose, colloidal silicon dioxide, microcrystalline cellulose, and magnesium stearate as excipients. The recommended storage conditions and expiry date, where required, are stated on the drug product label.

Table 5: Study Medication Overview

Intervention Name	Placebo	S-217622 (ensitrelvir)
Dose formulation	Tablet; formulation: mannitol, microcrystalline cellulose, magnesium stearate	Tablet; protease inhibitor of SARS-CoV-2 3CLpro
Dosage level(s) mg	N/A	375 mg loading dose on Day 0 followed by 125 mg daily on Days 1 through 4
Route of administration	Oral or enteral	Oral or enteral
Use	Placebo	Experimental
IMP or NIMP	IMP	IMP
Sourcing	Shionogi	Shionogi
Packaging and labeling	Wallet, containing 7 tablets	Wallet, containing 7 tablets

This trial will randomize participants to one of the following dosing regimens:

- Active treatment group: multiple doses of S-217622, corresponding to 375 mg (125 mg tablet × 3) once on Day 0, followed by 125 mg (125 mg tablet × 1) on Days 1 to 4 once daily. The full 5-day dosing course is to be continued/completed if discharged prior to Day 4.
- Placebo group: multiple doses of placebo, corresponding to 3 tablets once on Day 0, followed by one tablet on Days 1 to 4 once daily. The full 5-day dosing course is to be continued/completed if discharged prior to Day 4.

Guidance on dosing schedule interruptions is provided within the PIM.

Premedication prior to administration of investigational agent is not planned.

6.2 Pharmacokinetics (PK) of S-217622 (Ensitrelvir)

See investigational brochure (IB) for detailed description of pharmacokinetics and drug-drug interactions for investigational agent S-217622 studied in this trial.

Single Dose: Following a single dose of S-217622 (suspension) 20 to 2000 mg in the fasted state, the median of T_{max} of S-217622 ranged 1.50 to 4.00 hours, the geometric mean of C_{max} ranged from 1.70 to 96.9 µg/mL, the geometric mean of $AUC_{0\text{-}inf}$ ranged from 91.44 to 6346 µg·hr/mL, and the geometric mean of $t_{1/2,z}$ ranged from 42.2 to 48.1 hours. The exposures (C_{max} and AUC) increased in an almost dose-proportional manner in the fasted state across the dose range from 20 to 2000 mg.

Multiple Dose: S-217622 (suspension) was administered to Japanese and white healthy adult male participants by once-daily multiple doses at 375 mg on Day 1 and 125 mg on Days 2 to 5. S-217622 (suspension) was also administered to Japanese healthy adult male participants at 750 mg on Day 1 and 250 mg on Days 2 to 6. The C_{max} and $AUC_{0\text{-}\tau}$ increased in a dose-dependent manner on each Day (Days 1 and 5) following multiple doses of S-217622 once daily in Japanese healthy adult male participants. In Japanese and White healthy adult males who received once-daily multiple doses of S-217622 suspension 375 mg on Day 1 and 125 mg on Days 2 to 5, the ratios of C_{max} and $AUC_{0\text{-}\tau}$ in White versus in Japanese were 0.77 and 0.72, respectively, on Day 1 and 0.87 and

0.86, respectively, on Day 5, indicating slightly decreased exposure in White compared with in Japanese.

S-217622 (tablets) was administered to Japanese healthy adult female participants by once-daily multiple doses of S-217622 375 mg on Day 1 and 125 mg on Days 2 to 5 or 750 mg on Day 1 and 250 mg on Days 2 to 5. The C_{max} and $AUC_{0-\tau}$ increased in a dose proportional manner on Day 1 and Day 5. On Day 5 following multiple dose 375/125 mg, the geometric mean of $t_{1/2,z}$ was 51.4 hours. On Day 5 following multiple dose 750/250 mg, the geometric mean of $t_{1/2,z}$ was 48.7 hours.

PK parameters following once daily multiple doses of S-217622 (tablets) at dose 375/125mg in the fasted state (White healthy adult male and female participants) on Day 5 include geometric means of C_{max} was 24.8 μg/mL, $AUC_{0-\tau}$ was 475.5 μg· hr/mL and $t_{1/2,z}$ was 57.6 hours.

Effect of Food: The geometric least squares mean ratio (fed/fasted) of C_{max} of S 217622 was completely contained within the range of 0.8000 to 1.2500, suggesting that C_{max} of S-217622 were comparable between the fasted and fed states. The food intake increased the AUC_{0-last} and AUC_{0-inf} by 24.4% and 24.5% with the upper limits of 90% CIs which were slightly higher than 1.2500. The median T_{max} in the fed state was 6.00 hours and was delayed compared to that in the fasted state (2.50 hours). These results showed that there was no clinically meaningful difference in the exposure of S-217622 between the fasted and fed states.

Impact of pH on absorption: From pH-solubility profile and food effect study results, it is concluded that pH variation within the gastrointestinal environment has low impact on the absorption of S-217622.

Dosing via dispersion solution: Compatibility and stability data support administration of tablets as dispersion solution for participants who may not be able to tolerate oral tablets. S-217622 or matching placebo may be administered as a dispersion solution, either via enteral access (orogastric or nasogastric tube) or by mouth. See protocol implementation manual for details on approach for administering S-217622 or placebo as a dispersion solution.

6.3 Drug-Drug Interactions (DDI)

S-217622 (ensitrelvir) is a CYP3A substrate, P-gp substrate, and BCRP substrate. S-217622 is also a **strong CYP3A inhibitor**, a P-gp inhibitor, a BCRP inhibitor, and an OAT3 inhibitor at dosing regimen 375/125 mg. Drug interactions can occur as a result of concomitant medications impacting S-217622 (increasing or decreasing S-217622 exposure), or as a result of S-217622 impact on concomitant medication exposure. Participants enrolling into the trial must be screened for clinically important drug-drug interactions (DDI). Investigators should review a participant's medication list, including prescription and OTC (e.g., herbals) medications, factoring in potential DDI issues related to either S-217622 or concomitant medications (including those recently discontinued). Information is available within the protocol implementation manual (PIM) and a web-based STRIVE S-217622 Drug Interaction Screening Tool developed to

provide important information on DDI at enrollment, during study, and at time of hospital discharge. Please note, the list of medications in the STRIVE web-based DDI tool is not comprehensive, and the tool is not intended to direct clinical management but to help inform clinical teams regarding management of study participants.

6.3.1 The Impact of Concomitant Medications on Exposure to the Investigational Agent S-217622 (Ensitrelvir)

S-217622 (ensitrelvir) is a CYP3A substrate, P-gp substrate, and BCRP substrate. The below sections review the impact of concomitant medications based on the impact the medication has on various metabolic pathways. For further information on properties of S-217622, please refer to investigational brochure (IB) for this trial (section 6.2.4 within the IB). **Additional trial specific resources are available within protocol instruction materials, including a web-based DDI screener tool to evaluate individual substrate medications that are prohibited or permitted during study.**

Strong CYP3A Inducers: An estimated ~20% of S-271622 is eliminated unchanged from urine; ~80% is metabolized. Of the proportion metabolized, the contribution of CYP3A to metabolism is approximately ~40%. When co-administered with S-217622, CYP3A inducers are expected to decrease S-217622 exposure. **Strong CYP3A inducers are prohibited.** Refer to the STRIVE DDI screener for any participant previously on or proposed to start a strong CYP3A inducer.

Moderate CYP3A Inducers: Moderate CYP3A inducers are also expected to reduce S-217622 exposure, but to a lesser extent compared to strong CYP3A inducers. Available data from PBPK modeling suggested that the AUC ratios of S-217622 with or without a moderate CYP3A inducer were 0.90 and 0.76 on Day 1 and Day 5, dosing day of S-217622, respectively. Based on these data and the predicted magnitude of impact (~20-30% decrease), **moderate CYP3A inducers are prohibited.** Refer to the STRIVE DDI screener for any participant previously on or proposed to start a moderate CYP3A inducer.

CYP3A Inhibitors: Since S-217622 is a substrate of CYP3A, it is also expected to be impacted by coadministration with CYP3A inhibitors. The resulting increase in S-217622 exposure from coadministration with strong 3A inhibitors is predicted to be less than 2-fold. **Strong CYP3A inhibitors are prohibited during study,** and the timing of restarting/starting may differ between medications (details specified in PIM and DDI guidance material)**.** Although co-administration of nirmatrelvir/ritonavir (Paxlovid) and S-217622 is prohibited from Day 0 to study Day 15, **nirmatrelvir/ritonavir use prior to randomization is permitted**.

Based on predicted PK exposures, **moderate CYP3A inhibitors are permitted** in the study, provided they are not prohibited by another pathway associated with a DDI.

P-gp and BCRP Inhibitors and/or Inducers: S-217622 is also substrate for P-gp and BCRP. Inhibitors and inducers for these transporters may fluctuate the plasma concentration of S-217622. Because S-217622 is orally well absorbed (bioavailability of 85.5% in rats), inhibitors of P-gp and BCRP may increase S-217622 absorption in the gastrointestinal tract to an insignificant extent. Coadministration with medication that are

inhibitors of P-gp and BCRP generally do not result in a clinically significant change in plasma S-217622 concentrations. Based on predicted PK exposures, **P-gp inhibitors and BCRP inhibitors are permitted** in the study, provided they are not prohibited by another pathway associated with a DDI.

6.3.2 The Impact of the Investigational Agent S-217622 (Ensitrelvir) on Exposure to Concomitant Medications:

S-217622 (ensitrelvir) is a strong CYP3A inhibitor, a P-gp inhibitor, a BCRP inhibitor, and an OAT3 inhibitor at dosing regimen 375/125 mg. Medications that are a substrate of any one of these pathways will have a DDI with S-217622. The below sections review the impact of S-217622 on potential concomitant medications based on the impact S-217622 has on various metabolic pathways. Additional trial specific resources are available within the PIM and web-based DDI screening tool.

In general, sensitive CYP3A substrates[1] and moderate-sensitive CYP3A substrates are prohibited during the trial. In addition, a small selection of sensitive substrates of either P-gp, BCRP, or OAT3 are also prohibited. Some of these prohibited medications can be held, switched to a preferred alternative, or may be permitted with a dosage adjustment, (e.g. dose reduction or application of dosage cap). The S-217622 investigational brochure (IB) provides detailed information about DDIs through various drug metabolism pathways, based on results of in-vitro and in-vivo studies. Refer to the STRIVE DDI screener tool for management of potential DDIs.

Impact of S-217622 (Ensitrelvir) as a Strong CYP3A Inhibitor: S-217622 (ensitrelvir) is considered a strong CYP3A inhibitor at 375/125 mg dose. Investigators must carefully screen participants for concomitant medications that are CYP3A substrates and therefore have clinically relevant drug interactions with strong CYP3A inhibitors (i.e., sensitive CYP3A substrates, and moderate-sensitive CYP3A substrates). **Sensitive and moderate-sensitive CYP3A substrates are prohibited** (unless specifically listed as a permitted medication in the DDI screener). Refer to the STRIVE DDI screener for any participant previously on or proposed to start a sensitive or moderately sensitive CYP3A substrate co-medication.

Corticosteroids. Many corticosteroids (including dexamethasone) are substrates of CYP3A. As a result of this DDI, dexamethasone exposure is significantly increased when co-administered with S-217622. In this trial, **dexamethasone use is prohibited through study Day 14** (can be started on Day 15) due to DDI. **When clinical management includes the use of corticosteroids (CS), an alternative to dexamethasone must be used, such as prednisolone, prednisone, and/or a non-corticosteroid immunomodulatory treatment (e.g., baricitinib).** Combination of immunomodulatory treatment is allowed in the trial.

The effects of multiple doses of S-217622 was evaluated on the PK of corticosteroids (dexamethasone or prednisolone). The effect of S-217622 on **dexamethasone**

[1] Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies (ref: Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers | FDA)

exposure is expected to be similar between 750/250 mg and 375/125 mg dosing strategies, as both are categorized as strong CYP3A inhibitors. The estimated effect of S-217622 dosing over 5 days on AUC of dexamethasone exposure is approximately 3.5 fold at Day 5, 2.4 fold at Day 9, and 1.6 fold at Day 14.

No clinically meaningful effect of S-217622 on the PK of prednisolone was observed, and no clinically meaningful DDI is expected with prednisone, so both **prednisolone and prednisone are permitted during the trial and are the recommended options when corticosteroids are indicated**. **Use of hydrocortisone is also permitted up to a maximum dosing of 100 mg q6 hours.** No DDI data are available for hydrocortisone, but risk for interaction is expected to be low for this dosing. A clinically significant DDI is predicted for methylprednisolone (increased AUC), and **methylprednisolone is prohibited** during the trial until study Day 15.

In summary, clinical teams should be informed of the potential increase in levels of dexamethasone due to DDI with S-217622 and informed of alternative corticosteroid(s). Please refer to the PIM for additional guidance on corticosteroid use.

Impact of S-217622 (ensitrelvir) as a P-gp inhibitor, BCRP inhibitor, and OAT3 inhibitor. Drug interaction study was performed with substrate cocktail containing digoxin (P-gp substrate), rosuvastatin (BCRP, OATP1B1 and OATP1B3 substrate), and metformin (OCT1 and MATE1 substrate). S-217622 (500 mg single dose) increased the C_{max} and $AUC_{0\text{-}inf}$ of digoxin by 2.17- and 1.31-fold, those of rosuvastatin by 1.97- and 1.64-fold, and those of metformin by 1.03- and 1.02-fold. Considering that plasma concentration of coproporphyrin-1, which is an endogenous biomarker of OATP1B1 and OATP1B3, did not change after a single dose of S-217622 500 and 1000 mg, S-217622 is a weak inhibitor for P-gp and BCRP. In addition, S-217622 has a weak inhibition potential for OAT3 (in vitro study). **Sensitive substrates, or substrates with narrow therapeutic index, of any of the following transporters are prohibited: P-gp, BCRP, or OAT3**.

Impact of S-217622 (ensitrelvir) on other pathways: S-217622 (ensitrelvir) is also a weak CYP2B6 inducer, but based on duration of therapy and weak effect, a clinically significant DDI is not expected. OCT-1 substrates and MATE-1 substrates are also not expected to have clinically significant DDI with S-217622. **CYP2B6, OCT-1, and MATE-1 substrates are permitted** in this study, provided they are not prohibited due to another pathway.

Oncology agents: Due to the complexity of drug interactions and patient specific considerations, for participants receiving **anticancer agents** that are substrates of CYP3A, P-gp, BCRP, or OAT3 that have potential for DDIs with S-217622, consultation with the clinical specialist who is managing their antineoplastic medications is recommended to assess appropriateness for enrollment. Strong CYP3A inducers that are contraindicated due to the impact on S-217622 levels are reviewed above in section 6.3.1. Please refer to the web-based DDI screener for guidance on each individual drug.

Other DDI Considerations:

- Narrow therapeutic index drugs: Sensitive CYP3A substrates with a narrow therapeutic index that are contraindicated in the trial will need to be held for a longer duration compared to other substrates (see DDI screener and PIM for guidance).

- Implications from the impact of S-217622 (ensitrelvir) on multiple pathways. Medications that are a substrate of any one (or more) of these pathways are expected to have a DDI with S-217622: CYP3A, P-gp, BCRP, or OAT3. When considering DDIs through multiple pathways, sensitive substrates of multiple CYP3A, P-gp, BCRP, and OAT3 pathways are typically prohibited. As noted above, there are specific exceptions for certain medications that can be used when clinical monitoring is possible to mitigate adverse effects and inform dose adjustment (see DDI screener for guidance).
- Dose adjustments of substrates: Note that although pre-emptive dose adjustments for medications with DDIs are available in prescribing information for some substrates, pre-emptive dose adjustments are challenging to implement in a blinded study since the interaction will only be applicable to active S-217622 agent and not the placebo. For this trial, please check the STRIVE DDI screener for guidance on substrate drugs where dose adjustment is recommended and/or permitted during the study.

For further information when evaluating potential drug interactions, please refer to prescribing information for substrate drugs, or drug interaction information within the IB (section 6.2.4).

Summary of prohibited medication substrates (see DDI Screener and PIM for specific details on individual medications):

- Strong or moderate CYP3A inducers
- Sensitive CYP3A substrates and moderate-sensitive CYP3A substrates are prohibited and must be held or switched to a preferred alternative medication for a specified duration during the trial. However, some prohibited medications may be permitted with concurrent dosage adjustment (e.g., dose reduction or application of dosage cap). Timing for resuming pre-enrollment medication and dosing varies by medication.
- Certain P-gp, BCRP, and OAT3 substrates, when categorized as sensitive substrates and substrates with a narrow therapeutic index.
- Strong CYP3A inhibitors. The timing of restarting/starting varies by medication; details are provided in DDI screener.

Summary of permitted medications (see PIM for details):

- Certain specified CYP3A or P-gp or BCRP or OAT3 substrates requiring monitoring
- Moderate CYP3A inhibitors
- P-gp inhibitors
- BCRP inhibitors
- CYP2B6, OCT-1, and MATE-1 substrates
- OATP1B1 and OATP1B3
- Any other drugs without known or suspected interactions with S-217622

6.4 Standard Care Treatments (Trial-specific Considerations)

Appendix F of the STRIVE master protocol describes the standard of care for hospitalized patients with COVID-19.

The use of remdesivir as part of SOC for hospitalized patients with COVID-19 varies by the severity of illness (i.e., disease stage) as well as by region globally. In this context, our approach to allow but not require RDV treatment is patient-centered and will increase generalizability of study findings broadly for different SOC practices.

Corticosteroids are commonly used within SOC for hospitalized patients with COVID-19. Dexamethasone use is contraindicated during this study, due to increased exposure when co-administered with S-217622 (see section 6.3.2). Prednisolone and prednisone are permitted and recommended as alternative corticosteroids. Hydrocortisone is also permitted up to dosing of 100 mg q6 hours.

Baricitinib, tocilizumab, sarilumab, enoxaparin, and heparin are not expected to have clinically relevant DDI, and use of these medications is permitted during this study. Remdesivir is a CYP3A substrate but is permitted in the study. Tofacitinib use is not permitted, given it is a CYP3A substrate that would require a dose decrease.

7 Risk/Benefit Assessment

Potential risks and benefits associated with participation in STRIVE protocol are reviewed in section 3 of the master protocol.

Potential risks from this trial: The investigational agent S-217622 has been associated with a low risk (~2%) for side effects in early clinical studies, including headache, diarrhea, abdominal pain, back pain and rash. There is also a low risk for laboratory changes in blood cholesterol levels that are not associated with symptoms. The potential risks from S-217622 exposure during pregnancy is unknown, and this trial tests and excludes pregnant women from enrollment. Women of child-bearing potential and men must agree to abstain from sexual intercourse with the opposite sex or practice effective contraception through 30 days from the last dose of the investigational agent.

Potential benefits from this trial: The trial is conducted to test the hypothesis that S-217622 improves clinical outcomes when given in addition to standard of care among hospitalized patients with COVID-19. It is possible that combining S-217622 with standard care may have added benefits. However, S-217622 may or may not benefit any individual who participates in this trial.

8 Assessment and Procedures

8.1 Summary of Trial-specific Data Collection and Specimens

A detailed listing of clinical and specimen data collection, along with specific visit schedules are reviewed in the STRIVE master protocol Section 9.3 and Appendix A.

This trial will utilize the study visit assessment Schedule A (see Table 8 below) for clinical data collection and Schedule C (see Table 9 below) for specimen collection.

8.2 Trial Specific Monitoring and Reporting of Safety Data

A detailed overview of safety data collection and reporting for trials is included in STRIVE master protocol Section 10.3. For data collection, this trial will utilize study assessment Schedule A, with additional collection of AEs and concomitant medications as specified in Table 8 below. Additional safety information specific to this trial will be collected on any pregnancy identified in a trial participant during the 60-day follow-up, including the pregnancy outcome.

Rash has been identified as an adverse event of special interest (AESI) for this trial. The case definition entails any new rash with initial onset following the administration of the first dose of study medication and anytime through 24 hours after the last dose. Additional guidance on continuing versus discontinuing S-217622/placebo medication in the context of a rash during study is included in the PIM.

Monitoring of this trial by the DSMB and guidelines for interim estimates of efficacy, futility, and safety are described within section 11 of the STRIVE master protocol and will be further specified in the trial-specific SAP. An early safety evaluation occurred after an initial cohort of 20-30 participants had Day 5 data available; the DSMB recommended that the trial continue as planned. Safety will be monitored frequently by the DSMB early in the trial. To preserve the integrity of the trial, blinding will be maintained whenever possible. The process for unblinding is reviewed in section 10.4 of the STRIVE master protocol and within the trial PIM.

8.3 Pharmacokinetic and Virology Measurements

In addition to important clinical endpoints assessed in this trial, there are important research questions related to pharmacokinetics (PK) of this investigational agent and the virology of SARS-CoV-2 infection, specifically among hospitalized patients.

Table 9 (below) presents the schedule of specimen collection that will be used for PK and virology measures.

8.3.1 Pharmacokinetic (PK) Measures

PK measures will include plasma levels of S-217622, assessed on Days 3 and 5. Planned sample size is approximately 100 participants (50 each for S-217622 and placebo groups), enrolled at select sites. Participating clinical sites will be required to follow specimen processing timelines and use of a refrigerated centrifuge. Specimens on Day 3 will be collected ≤2 hours prior to administration of S-217622 or placebo (dosed in AM); on Day 5, specimen collection will be approximately 24 hours after Day 4 dosing of study agent. Additional information on specimen collection supplies, processing, storage, and shipment are outlined in the STRIVE Laboratory Manual and PIM.

8.3.2 Virology Measures

Virologic assessments will be studied during the 5-day dosing and at Study Day 14 for evidence of continued suppression versus a persistence or rebound in viral levels. Specimens utilized will be collected as part of the STRIVE master protocol specimens,

with an additional set of blood and swab specimens collected on Study Day 14. The following virology measures are planned:

1. Plasma nucleocapsid antigen (NC-Ag) levels, on Day 0, 3, 5, and 14.
2. Viral load in nasal cavity, estimated by PCR, on Day 0, 5 and 14.
3. Viral sequencing and resistance testing, on selected cases.

Day 14 specimens are included in the schedule of specimen collection, but participants may opt out of Day 14 specimen collection (specified prior to randomization during the consenting process). Clinical sites should consider the ability to collect specimens after discharge from the hospital (e.g., at Day 14). Additional information on collection supplies, processing, storage, and shipment to the central biorepository will follow steps outlined in STRIVE Laboratory Manual and PIM.

Planned sample size is 600-800 participants (300-400 for each, S-217622 and placebo groups), with a minimum of 600 that have evaluable specimens at Day 14. The sample size estimates were driven to address two goals:

- *Primary goal:* Estimate the percentage of participants with detectable viral NC-Ag (or viral load in nasal cavity) on Day 14 within each treatment group with sufficient precision. Assuming low rates of participants with detectable viral load after the 5-day course of S-217622, Day 14 will assess the persistence of viral suppression.
- *Secondary goal:* Compare the S-217622 versus control groups for the proportion with detectable plasma NC-Ag levels and for detectable virus in the nasal cavity.

Table 6 Two-sided 95% confidence intervals for proportions with undetectable virus

Proportion with Detectable Virus	Sample Size within each treatment group and 95% CI		
	n=100	n=200	n=300
1.0%	0 – 3.0%	0 – 2.4%	0 – 2.1%
2.0%	0 – 4.7%	0.1 – 3.9%	0.4 – 3.6%
5.0%	0.7 – 9.3%	2.0 – 8.0%	2.5 – 7.5%

Table 6 provides two-sided 95% confidence intervals for estimated proportions, if the proportions to be estimated are 1%, 2%, or 5%, for a range of sample sizes. For example, if the proportion of participants with detectable viral load is 2%, a sample size of 300 would exclude proportions of higher than 3.6% or lower than 0.4%.

Table 7 below summarizes sample sizes needed to detect given differences in proportions with 80% power using a two-sided test with a significance level of 0.05. For example, a total of 568 evaluable samples is needed to detect a difference between 1% and 5% in the active and placebo groups, respectively. Larger sample sizes would be needed in order to detect similar differences within subgroups of participants, e.g., if analyses are restricted to participants who are immunosuppressed.

Table 7 Sample size needed to detect a difference in proportions with 80% power

Hypothesized proportion with detectable virus on Day 14		
S-217622 (ensitrelvir)	Placebo	Total sample size
2%	10%	274
1%	5%	568
0.5%	5%	412
1%	4%	848
0.5%	4%	562
1%	3%	1536
0.5%	3%	862

9 Data Analysis

Please refer to the master protocol for a detailed overview of the analysis plan for study endpoints assessed for all trials conducted within the STRIVE master protocol, including safety endpoints and data monitoring (sections 10 and 11 of master protocol). A formal statistical analysis plan (SAP) will be written and utilized for analysis of trial results.

9.1 Analysis of Trial Primary Outcome

The primary outcome is the DRS-60, an ordinal outcome with 63 categories, assessed at Day 60, where categories 0-60 include participants who are recovered by Day 60, with labels 0-60 according to the number of days between randomization and achieving "recovery", ranked by the number of days (0 is the best category) followed by 2 categories for participants who are not recovered: "alive, not recovered" and "death" (worst category). Ascertainment of the DRS-60 requires 60 days of follow-up for all participants who are alive by Day 60.

The primary analysis will be by modified intention to treat (mITT). The analysis population includes all participants who received any of the blinded investigational agent or placebo (full or partial). Because the treatment assignment is blinded and the study is placebo-controlled, restricting the analysis to the mITT cohort should not introduce bias.

The primary comparison of S-217622 versus placebo will use the van Elteren test [11], a stratified version of the nonparametric Wilcoxon rank-sum test, with strata by disease severity at study entry. Disease severity strata will be defined by oxygen requirement at study entry. The estimand of the primary comparison is the Mann-Whitney estimand, which reflects the probability that a randomly selected participant assigned to S-217622 has a better DRS-60 outcome than a random participant assigned to placebo, with ties broken evenly, among those who received at least one dose of the blinded study drug.[13]

The treatment effect will be described by several data summaries:

1. Recovery: Median (IQR) days to recovery (ranked categories of the DRS-60) will be computed in each treatment group.

2. All-cause mortality by Day 60: the proportion of participants who died by Day 60 will be summarized by treatment group.
3. The proportion of participants who died or were not recovered by Day 60 (alive and not recovered or dead).
4. Additionally, the treatment effect on the DRS-60 will also be summarized as an odds ratio (with 95% CI) from fitting a proportional odds model, comparing the odds of being in a better category for participants randomized to the investigational agent versus the placebo group. Specifically, the proportional odds model will include the treatment group indicator and disease severity at baseline as stratification covariate. A test for the proportional odds assumption across cumulative categories and the disease severity covariate will be performed by testing for separate slopes for the treatment effect in a partial proportional odds model. The summary OR in proportional odds regression is robust with respect to violation of the proportionality assumption. In order to further characterize the summary OR and any deviations from proportional odds, separate ORs will be estimated for different dichotomized definitions of improvement formulated from the components of the ordinal outcome (e.g., alive versus dead, recovered versus alive and not recovered or dead, etc.)

Missing data: Ascertainment of the DRS-60 requires 60 days of follow-up (except in the case of death), since it is possible that a participant is re-admitted to the hospital (or to a level of care more advanced than “home”) at any time after the initial discharge. Data completeness will be monitored throughout the conduct of the trial in order to minimize missing data. For the primary efficacy analysis at the completion of the trial, the DRS-60 will be imputed for participants with unknown DRS-60 status using multiple imputation; the multiple imputation methods will utilize partial information such as disease severity at baseline and last known recovery status. To assess the robustness of the estimate of the treatment effect, the treatment comparison without imputation will be provided as sensitivity analysis. The primary analysis will be restricted to the actually observed DRS-60 data, however, if two conditions are fulfilled: (1) the percentage of missing data is very low (<5%), and (2) the pattern of missing data is consistent with “missing at random.” In this case, multiple imputation would be expected to have little effect on the treatment effect estimates, and the treatment comparisons with imputed data will be provided as sensitivity analysis. Details of the imputation, as well as additional sensitivity analyses, will be described in the statistical analysis plan.

Timing of interim efficacy analyses: Interim efficacy analyses will be reviewed by the independent DSMB after approximately 25%, 50%, and 75% of the planned participants have been enrolled and followed for 60 days (to assess the DRS-60). The DSMB may request additional efficacy assessments. The Lan-DeMets interim monitoring boundaries for efficacy (master protocol, section 11.3.1) are designed with an alpha-spending function, to minimize inflation of type I error due to additional analysis time points. Details are described in the statistical analysis plan.

9.2 Trial-specific Secondary Objectives and Safety Outcomes

Analyses of secondary endpoints, safety outcomes, and subgroup comparisons are specified in the master protocol section 11.2. Unless specified otherwise, comparisons between treatment groups will be stratified by disease severity (or adjusted for disease severity by including severity as covariate).

The following analysis methods will be used for key secondary outcomes.

- Mortality. The proportion of participants who died by Day 60 (key secondary outcome) will be estimated within each treatment group using Kaplan-Meier estimates. Treatment groups will be compared for time to death using a log-rank test, stratified by disease severity. The hazard ratio (S-217622 versus placebo) will be estimated using a stratified Cox proportional hazards model; the estimand for this comparison is the hazard ratio of death through Day 60 among those randomized to S-217622 (numerator) versus placebo (denominator) who received at least one dose of the blinded study drug (mITT cohort). In addition to Day 60, the proportion of participants who died by fixed time points (for example, Day 28) will be estimated using Kaplan-Meier estimates.
- Three-category ordinal outcome assessed at Day 60, with categories “recovered (alive and at home at Day 60),” “alive and not recovered,” and dead: This outcome will serve to further characterize the relative effect of the treatment on recovery and on mortality. The proportions of participants in each of the three categories will be estimated by treatment group. Treatment groups will be compared using a summary odds ratio estimated with 95% CI in a proportional odds model. The model will include the treatment group indicator, and disease severity as stratification covariate. The estimand in this treatment comparison is the log-odds ratio (LOR), defined as the average of the cumulative log-odds ratios comparing the odds of being in a better category for participants randomized to S-217622 versus the placebo group (among those who received at least one dose of the blinded study drug [mITT cohort]), averaged over the two possible (cumulative) dichotomizations of the three-category ordinal outcome. If the proportionality assumption holds, this is the log-odds of being in a better category if randomized to the S-217622 group compared to the placebo group in the mITT cohort.[13, 14] The validity of proportional odds will be assessed. Separate ORs will be estimated for comparing “recovered” versus “not recovered or dead,” and “alive” versus “dead,” using logistic regression.
- Time (days) to recovery: The cumulative incidence functions for recovery (returned to home and remained home through Day 60) taking into account death as a competing risk will be estimated using the Aalen-Johansen method and compared using the Gray’s test with rho=0. The sub-hazard ratio for recovery will be estimated using a Fine-Gray regression model. The comparisons between treatment groups will be stratified by disease severity. For this analysis, “days to recovery” is defined by categories 0-60 of the DRS-60. This analysis will be performed at the completion of the trial, when the recovery status at Day 60 and the date of recovery are known for all participants. The estimand is the sub-hazard ratio (sHR) for recovery, i.e., the ratio of the sub-hazard of “recovery” in

the S-217622 group (numerator) over the sub-hazard in the placebo group (denominator), among those who received at least one dose of the blinded study drug.

- Proportion of participants who died or required new invasive mechanical ventilation: Analysis methods will be similar to those for comparing proportions of participants who died by Day 60. The estimand is the HR of having died or required new mechanical ventilation by Day 60 if randomized to the S-217622 group compared to the placebo group, among those who did not require invasive mechanical ventilation at study entry and who received at least one dose of the blinded study drug.

Several other secondary efficacy outcomes will also be investigated, including time to death, time to discharge from the index hospitalization, time to (first) return home, and time to sustained recovery (as defined in the TICO trials). The models will include an indicator for treatment group and stratify by disease severity at study entry as appropriate. Time to death analyses were described above. Time from study entry to discharge from the index hospitalization will be analyzed using the same methods as described above for time to recovery, as will time to return home and time to sustained recovery. Readmissions will be summarized using methods for recurrent events (i.e., those who are readmitted will reenter the risk set). Analyses for other secondary outcomes are described in the STRIVE master protocol.

Important safety outcomes are the composite of grade 3 or 4 events, SAEs, PDACEs, or death through Day 5, Day 28, and Day 60, as well as mortality and the composite of SAEs, PDACEs, or death. Tests for differences between treatment arms will be conducted using Mantel-Haenszel tests to compare proportions at Day 5, and using Cox proportional hazards models through Day 28 and Day 60; models will be stratified by disease severity at study entry. Cumulative proportions of participants experiencing these events will be summarized. Proportions of participants who experienced any of these events will be compared using stratified Mantel Haenszel tests and logistic regression. SAEs and grade 3/4 events will be classified by system organ class according to MedDRA©. The composite of grade 3 or 4 events, SAEs, PDACEs, or death will be summarized overall and by type, where type is defined by collections of Standardized MedDRA Queries (SMQs) and corresponding PDACEs, such as, for example, “embolic and thrombotic events,” “renal dysfunction,” or “respiratory failure.” These composite endpoints are described in detail in the study-specific SAP.

Safety analyses also include AESIs (new-onset rash, see section 8.2) and grade 1-4 AEs collected on Days 0-4 (the time period the blinded treatment was administered), on Day 7 and on Day 14. Proportions of participants who experienced AESIs will be summarized by study arm, overall and by grade. Proportions of participants who experienced AEs will be summarized by study arm and by grade for each day and pooled across Days 0-4. Mantel Haenszel tests stratified by disease severity at study entry will be used to test for differences across arms. AEs will also be summarized by MedDRA© system organ class for each of Days 0-4, 7, and 14.

Clinical organ failure is a composite of many different organ-specific events, listed in the STRIVE master protocol. This outcome will be summarized as part of both safety and efficacy analyses. Details are provided in the STRIVE master protocol.

The impact of S-217622 versus placebo on the primary efficacy (DRS-60) and important safety outcomes (mortality; composite of grade 3 or 4 events, SAEs, PDACEs, and death through Days 5, Day 28, and Day 60) will be assessed for subgroups defined by baseline characteristics, including disease severity, demographics, use of RDV, duration of symptoms at enrollment, clinical history and presentation, immunocompetence and vaccination status. Tests for homogeneity of the treatment effect across subgroups will be carried out. Subgroup analyses will be interpreted with caution due to limited power and uncontrolled type I error.

Blinded sample size re-estimation will be carried out before enrollment is complete to determine whether the planned sample size is sufficient to maintain an unconditional power of 80% to detect the hypothesized OR=1.3 for comparing S-217622 versus placebo, as described under sample size assumptions in section 4.5. **The sample size re-estimation does not involve any unblinding of the treatment difference and will be carried out by statisticians who are blinded to the treatment comparisons.** All outcome data used for the sample size re-estimation will be pooled across treatment groups. The re-estimation will be based on the estimated (pooled) distribution across the ordered categories of the DRS-60, baseline characteristics of the enrolled study population including disease severity at study entry, the number of withdrawals, adherence to the blinded study treatment, and the amount of missing data. The sample size re-estimation may also include re-assessment of the hypothesized size of the treatment effect (OR=1.3) based on external data, baseline data or pooled follow-up data; no data on the observed treatment difference will be used. The study-specific SAP will provide further detail.

10 Schedule of Events and Specimen Collection

Table 8: Clinical Time and Events Table (Schedule A)

	Screen or Day 0	Day 0	Follow-up Study Day:										
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+6**	**+13**	**+13**	**+17**	**+20**
ELIGIBILITY & BASELINE DATA													
Informed consent	X												
Baseline medical (incl. duration of illness) and social history	X												
Targeted baseline and prior medications[2] and vaccines	X												
Symptom-directed physical exam by the clinical team	X												
Review test results for specific viral infection	X												
Urine or serum preg. test or other documentation of pregnancy status for women of childbearing potential	X												
STUDY INTERVENTION													
Randomization		X											
Study drug/placebo administration		X	X	X	X	X							
Monitoring for adverse reactions[3]		X	X	X	X	X			X	X			
Monitor adherence of study agent		X	X	X	X	X							
STUDY PROCEDURES													
Pulmonary ordinal outcome assessment		X[4]	X	X	X	X	X	X	X	X	X	X	X
Local clinical laboratory testing		X[4]	X				X			X[5]			
Hospitalization status					X		X		X	X	X	X	X
Changes in residence/facility			X	X	X	X	X	X	X	X	X	X	X
Interim medical history									X	X	X	X	X
Medications[2]		X	X	X	X	X	X	X	X	X			
Clinical AEs reaching grade 3 or 4 severity		X	X	X	X	X	X	X	X	X	X	X	X
Clinical AEs reaching grade 1 or 2 severity		X	X	X	X	X			X	X			
EuroQol (EQ-5D-5L)													X
SAEs and unanticipated problems		Report as they occur											
AESI		Report as they occur (following first dose of blinded study drug and through 24 hours after the last dose of blinded study drug)											
Vaccinations for source of infection		Report when received											
PDACEs (master protocol, 4.2.3)		Report as they occur											
Deaths		Report as they occur											
Hospitalization summary			Report upon hospital discharge										
Hospital readmissions			Reported as a change in residence/facility										

[1] Screening must be performed within 24 hours of randomization.
[2] COVID-related medicines and other types of concomitant medications will be assessed prior to randomization, daily through Day 14 while hospitalized and on Day 5 and Day 14 after discharge.
[3] Clinical AEs of any grade will be collected through study Day 4, on study Day 7 and on Day 14
[4] Assessed prior to randomization
[5] Clinical labs will be assessed on Day 14, excluding participants that opt out to collection of Day 14 specimens. There is a +2 day visit window for Day 14 stored specimens and local labs. The +13 day visit window applies to additional data collected at the Day 14 visit.

Table 9: Stored Specimen Time and Events Table (Schedule C)

	Screen or Day 0	Day 0	Follow-up Study Day: shaded columns denote in-person visits										
Day	**−1/0**[1]	**0**	**1**	**2**	**3**[2]	**4**	**5**[2]	**6**	**7**	**14**[3]	**28**	**42**	**60**
Acceptable deviation (specific to specimen collection)	**0**	**0**	**0**	**0**	**+/-1**	**0**	**+/-1**	**+1**	**+6**	**+2**	**+13**	**+17**	**+20**
Research sample storage (plasma and serum)		X			X		X			X			
Airway swab for central determination of RNA levels		X					X			X			
Whole blood for genomics	X[4]												

[1] Screening must be performed within 24 hours of randomization.

[2] For sites supporting PK measures (see section 8.3), there is NO acceptable deviation from designated study day. Blood specimens on Day 3 will be collected ≤2 hours prior to administration of S-217622 (ensitrelvir) or placebo (dosed in AM), and Day 5 specimens will be collected approximately 24 hours after Day 4 administration of study agent.

[3] During the consenting process participants may opt out of planned Day 14 specimen collection (specified prior to randomization).

[4] Collected only once for participants who consent to optional collection of whole blood for host genetic analysis. This is not required for any trial. Consent for whole blood collection may be offered at the time of consent into the trial.

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