Medicines Control Authority of Zimbabwe

Clinical Trials Registry

PUBLIC TITLE/ACRONYM	A Multicenter, Adaptive, Randomized, Controlled Trial Platform to Evaluate Safety and Efficacy of Strategies and Treatments for Hospitalized Patients with Respiratory Infections (STRIVE) Version 1.0 Dated 11 November 2022
Scientific Title	A Multicenter, Adaptive, Randomized, Controlled Trial Platform to Evaluate Safety and Efficacy of Strategies and Treatments for Hospitalized Patients with Respiratory Infections (STRIVE) Trial 1: Appendix E-1: Shionogi Protease Inhibitor (S-217622) Trial

Primary Sponsor Details

Sponsors *	International Network for Strategis Initiatives in Global HIV Trials(INSIGHT) represented by Medical Research Council (MRC) Clinical Trials Unit at University College London (UCL) - London, United Kingdom

Secondary Sponsor Details

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Countries of Recruitment *

	Institution
	International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)
	Medical Research Council (MRC) Clinical Trials Unit at University College London (UCL) - London, United Kingdom
	University of Minnesota (INSIGHT Statistical and Data Management Center (SDMC))
	Centre of Excellence for Health, Immunity and Infection (CHIP), Rigshospitalet, University of Copenhagen - Copenhagen, Denmark
	Hennepin Medical Center - Minneapolis, Minnesota
	The Kirby Institute, University of New South Wales - Sydney, Australia
	The Institute for Clinical Research at the Veterans Affairs Medical Center - Washington, D.C., United States of America (US)
	Medical Research Council (MRC) Clinical Trials Unit at University College London (UCL) - London, United Kingdom

Trial 1 :**106 sites open globally**

Trial 2: 31 Sites open globaly

Source of Funds US National Institute of Allergy and infectious disease (NIAID) and National institute of Health (NIH)

Health Condition(s) or Problem(s) Studied * Respiratory Infections and viral emergencies Trial 1 and Trial 2 focus is on SARS-COV 2 COVID-19

Medicine Name * S217622 and Abatacept

Quantity of medicine required * S217622 175 (125MG) TABLETS PLACEBO 175 TABLETS : Abatacept 175 (250mg) vials

7.0 PRINCIPAL INCLUSION CRITERIA *

Trial-1: Inclusion for the STRIVE Platform: 1. Age ≥18 years; **2**. Informed consent for trial participation; **3**. Hospital admission (or boarding in an emergency department or other area awaiting hospital admission) with signs and/or symptoms of a respiratory infection.

Additional Inclusion for Trial 1 (as described in Appendix E1): 1 Confirmation of SARS-CoV-2 infection by nucleic acid test (NAT) or equivalent non-NAT test 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.

Trial-2 Inclusion for the STRIVE Platform: 1. Age ≥18 years; **2**. Informed consent for trial participation; **3**. Hospital admission (or boarding in an emergency department or other area awaiting hospital admission) with signs and/or symptoms of a respiratory infection.

Additional Inclusion for Trial 2 (as described in Appendix E2):

1. Confirmation of SARS-CoV2 infection by nucleic acid test (NAT) or equivalent non-NAT test collected within 14 days of randomization.

2. Requiring hospitalization for the management of COVID-19.

3. Has evidence of COVID-19 pneumonia defined as either: a. Receiving supplemental low flow oxygen, >0 L/min and ≤2 L/min, with evidence of airspace disease on chest imaging (X-ray, computer tomography or ultrasound) OR b. Receiving supplemental low flow oxygen, >2 L/min and <10 L/min.

4. Currently receiving or planned to receive (ordered) one Immunomodulator drug (for example, a corticosteroid or baricitinib, but NOT abatacept) as part of treatment of COVID-19 prior to randomisation.

5. Has started supplemental oxygen for the treatment of COVID-19 within the past 5 calendar days. Patients on home oxygen are eligible if current oxygen flow rate is increased from pre-COVID-19 level and all other study criteria are met.

6. Investigator agrees that the pneumonia is due to COVID-19.

7.1 PRINCIPAL EXCLUSION CRITERIA *

Exclusion for the STRIVE Platform:

1.Patient expected to be discharged from hospital within 24 hours;

2. Medical condition other than acute respiratory infection (and its manifestations) that is likely to result in death within 7 days, Moribund condition, defined as prior cardiac arrest during this hospitalization and life expectancy less than 48 hours;

3. Patient undergoing comfort care measures only such that treatment focuses on end-of-life symptom management over prolongation of life;

4. Expected inability or unwillingness to participate in study procedures;

5. In the opinion of the responsible investigator, participation in a trial is not in the best interest of the patient

Additional Exclusion for Trial-1 (as described in Appendix E1)

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;

3. Moderate to severe hepatic impairment or acute liver failure;

4. Known estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2;

5. Continuous renal replacement therapy or chronic dialysis;

6. Current pregnancy. For women of reproductive potential: required documentation of a negative pregnancy test from within 24 hours; For women not of reproductive potential: Required note indicating the reason the patient is not considered to be of reproductive potential. Patient self-report is acceptable;

7. Current breastfeeding and unwilling to defer breastfeeding for 30 days after last dose of investigational agent;

8. Women of childbearing potential who are unwilling to abstain from sexual intercourse with men or practice appropriate contraception through 30 days from last dose of investigational agent;

9. Men who are unwilling to abstain from sexual intercourse with women of childbearing potential or to use barrier contraception through 30 days from last dose of investigational agent;

10. Inability to take investigational agent in tablet form by mouth

Exclusion for the STRIVE Platform: **1.**Patient expected to be discharged from hospital within 24 hours;**2.** Medical condition other than acute respiratory infection (and its manifestations) that is likely to result in death within 7 days, Moribund condition, defined as prior cardiac arrest during this hospitalization and life expectancy less than 48 hours; **3.** Patient undergoing comfort care measures only such that treatment focuses on end-of-life symptom management over prolongation of life; **4.** Expected inability or unwillingness to participate in study procedures; **5.** In the opinion of the responsible investigator, participation in a trial is not in the best interest of the patient

Additional Exclusion for Trial-2 (as described in Appendix E2)

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

1. Oxygen requirement of 10 L/min or more of low flow oxygen (or equivalent if using Venturi mask, etc.), or requiring high-flow oxygen (HFNO), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV) or ECMO.

2. Received more than one baseline IM for treatment of the current COVID-19 infection at the time of trial enrollment (examples: corticosteroid, baricitinib, tocilizumab, anakinra, abatacept, or infliximab).

3. Participant anticipated to not meet all inclusion criteria within 24 hours of randomization in the opinion of the investigator.

4. Allergy to investigational agent.

5. Neutropenia: absolute neutrophil count <1000 cells/µL (<1.0 x 10^3/µL or <1.0 x 10^9/L) on most recent lab within 2 calendar days of randomization.

6. Lymphopenia: absolute lymphocyte count <200 cells/µL (<0.20 x 10^3/µL or <0.20 x 10^9/L) on most recent lab within 2 calendar days of randomization.

7. Known or suspected active or recent serious infection (bacterial, fungal, viral, or parasitic infection, excepting SARS-CoV-2) that in the opinion of the investigator could constitute a risk when taking investigational agent. Note: Broad spectrum empiric antibiotic usage does not exclude participation.

8. Known or suspected history of untreated tuberculosis (TB). TB diagnosis may be suspected based on medical history and concomitant therapies that would suggest TB infection. Participants are also excluded if they have known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening required).

9. Received any live vaccine (or live attenuated) within 3 months before screening or intend to receive a live vaccine (or live attenuated) during the trial. Use of prior non-live (inactivated) vaccinations is allowed for all participants, including any vaccine for COVID-19.

10. Pre-existing immunomodulation or immunosuppression that meets any of the following:

a. Participant has received abatacept for an indication other than COVID-19 within 5 half-lives (65 days) of enrollment (Abatacept elimination half-life is 13.1 days.)

b. Participant is receiving immune modulatory therapy for autoimmune, transplant management or another indication AND has one or more of the following:

i. evidence of active infection (other than COVID-19) or

ii. has required reduction in their immune modulatory therapy in the preceding 6 months due to infectious complication (routine reduction as SOC is not an exclusion) or

iii. has required intensification in immune modulatory therapy within the preceding 6 months due to organ rejection/worsening underlying disease status (e.g., intensification with an additional agent on top of usual immunosuppressive regimen).

c. Participant has recently received or is anticipated to require immune modulatory agents for their underlying disease including chemotherapeutic treatments likely to induce neutropenia or lymphopenia.

d. Participant has untreated advanced HIV (known CD4 <200 cells/mm^3 in the past 6 months) AND is not established on antiretroviral therapy.

11. Pregnancy or intention to become pregnant within 60 days of randomization.

12. Currently breastfeeding.

13. Co-enrollment in other trials not predetermined to be compatible with this trial.

14. In the investigator's judgment, the participant has any advanced organ dysfunction that would not make participation appropriate.

15.The treating clinician expects inability to participate in trial procedures or participation would not be in the best interests of the patient.

7.2 PRIMARY END POINTS *

Statistical analysis, primary endpoint and sample Size in trial-1: The primary outcome for this trial is called the 'Days to Recovery Scale' assessed over 60 days (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)." A participant is considered "recovered" when they fulfilled all three of the following conditions: 1) discharged from the hospital, 2) returned to home, and 3) remained at home, uninterrupted, through Day 60. A sample size of 1500 participants (750/arm) is sufficient to detect around a 30% better improvement compared to the placebo arm.

Statistical analysis, primary endpoint and sample Size in trial-2: 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)." A participant is considered "recovered" when they fulfilled all three of the following conditions: 1) discharged from the hospital, 2) returned to home, and 3) remained at home, uninterrupted, through Day 60. A sample size of 1500 participants (750/arm) is sufficient to detect around a 35% better improvement compared to the placebo arm.

9.0 DESIGN OF THE TRIAL

Type of trial *	Controlled
If controlled	
Randomised	Yes
Single Blind	
Double Blind	Yes
Parallel group	
Cross over	
Other	
If yes to other, specify	
If controlled, specify the comparator	Placebo
Other medicinal product(s)	Yes
Placebo	
Other	Yes
If yes to other, specify	Standard of Care
Other	

Expected Number of participants in Zimbabwe *	50
Total enrolment in each site: (if competitive enrolment, state minimum and maximum number per site.) *	Competitive recruitment min15- max25 per trial per site
Total participants worldwide *	3000

Time period for the trial *	2023-2025