Supplemental materials

1 Protocol team structure

To oversee the implementation of this master protocol, a protocol team was formed including: Protocol co-chair(s)

- NIAID, Division of Clinical Research representatives
- INSIGHT University of Minnesota representatives
- INSIGHT International Coordinating Center representatives
- Representatives from collaborating trials networks (i.e. PETAL, CTSN and the VA)
- Representative from ACTIV-2 protocol team
- Representatives from the central specimen repository
- Representative from the drug distribution group
- Representatives from collaborating manufacturers of investigational agents
- Representatives from site investigators
- Community representative(s)

A core team consisting of the co-chair(s), ICC leaders, NIAID representatives, study statisticians, representatives from collaborating trials networks, and other representatives and the INSIGHT PI will also regularly convene to review study progress and address study conduct and administrative issues that arise.

2 Operationalisation of the primary endpoint

The TICO primary objective is to determine whether investigational agents are safe and efficacious compared with placebo when given with established standard of care (SOC). The primary efficacy endpoint is time to sustained recovery through day 90 i.e. when a participant is discharged from hospitalization to home and remains at home for at least 14 consecutive days. This patient-centred endpoint was chosen because of the extended duration of health impairment associated with COVID-19 [1-3]. The longer follow-up to capture this endpoint (compared to the common 28 days [4-6]) was designed to provide a more comprehensive assessment of the capacity of a therapeutic agent to speed recovery from COVID-19.

The TICO primary endpoint of sustained recovery is defined as 14 continuous days at home, where home is defined as the type or level of residence where the participant lived prior to their SARS-CoV-2 infection.

This approach avoids categorizing patients as recovered if they continue to have care needs beyond their pre-morbid state despite discharge from an acute care facility, or if they are re-admitted to hospital shortly after initial discharge. To operationalize the collection of this endpoint, a participant's 'home' is classified at enrolment (types of residences are defined below) and a participant's current location, and consecutive days spent at that location, is collected fortnightly during follow-up using a dedicated CRF.

There are seven possible categories for classifying home in the TICO study. They are:

Independent dwelling withOUT professional medical help - Participant is living in a house, apartment, flat, condominium independently (regardless whether alone or with family or friends; also regardless of any paid help such as housekeeping service, maid, gardener etc.).

Independent dwelling WITH professional medical help - Participant is living in a house of any form, apartment, flat, or condominium but is requiring visiting professional medical help (e.g., visiting nurse, physiotherapist, or other home healthcare personnel meant to provide medical or rehabilitation care in the home)

Community dwelling - Participant is homeless, living on the streets or undomiciled, or may be living in a shelter or hotel (including hotel stay for quarantine purposes).

Residential care facility - These are non-skilled nursing facilities where care and services are provided to assist with activities of daily living. If the nature of the services can be safely and effectively performed by a trained nonmedical person, the services will be considered residential care. Examples include assisted living facility, group home, low-level care facility, or other nonmedical institutional setting.

Other Healthcare facility - Skilled nursing facility (nursing homes), acute inpatient rehabilitation facilities (acute rehab), or other healthcare facility that provides onsite medical care above a residential care facility but with a lower intensity than provided in hospitals.

Long-term inpatient care hospital - Long-term acute care hospital (LTACH), long-term care hospital. Note: These are hospitals/facilities meant to provide longer term (typically >20-30 days) of acute-care services after discharge from the short-term acute care hospital. Services requiring this level of care may include mechanical ventilation, intensive wound care, intensive pain management. LTACHs are hospitals that specialize in the treatment of patients with serious medical conditions that require care on an ongoing basis but no longer require intensive care or extensive diagnostic procedures.

Short-term acute care hospital - Short-term acute care hospital (similar to the index/enrolling hospital). Most acute care hospitals fall into this category, regardless of the duration of hospital admission.

3 Sample size considerations for the initial futility assessment

The following assumptions were made in estimating the required sample size for the initial futility assessment, considering the marginal tests for each of the ordinal outcomes separately.

a. The primary analysis will be intention-to-treat.

b. A proportional odds model with indicators for the investigational agent group and baseline severity of illness as defined by the ordinal outcome will be used to estimate the odds ratio. The model will be stratified by study site pharmacy.

c. Type 1 error = 0.30 (1-sided) and power = 0.95.

d. The clinical status (% distribution for each pulmonary+ category) of participants in the placebo group at Day 5 is assumed as shown in the 3rd column Supplemental Table 4. Since both randomized treatment groups will receive remdesivir as standard of care (unless contraindicated), these percentages were estimated using Day 5 data from the ACTT1 trial for a subgroup of patients similar to the intended participants of this trial who were randomized to remdesivir.

e. We targeted an odds ratio (active/placebo) of 1.60 for a more favourable outcome. This corresponds to the % distribution of the clinical status of participants in the investigational agent group at Day 5 shown in the 2nd column in Supplemental Table 4. For example, the percentage of participants in the 2 most favourable categories would be increased to 56.7% in the group receiving the investigational agent from 45.0% in the placebo group (a 11.7% increase). Conversely, the percentage of participants in the 4 most severe categories would decrease to 22.7% from 32.0% in the placebo group. The same proportional improvement was assumed across the ordinal scale.

f. Based on the category percentages in **Error! Reference source not found.**, the estimated initial futility sample size with a single comparison between an investigational treatment and placebo is 293. This was increased to 300 to allow for some missing data at Day 5.

4 Sample size considerations for final assessment of efficacy

The following assumptions were made in estimating the required sample size for the final assessment of efficacy.

a. The primary analysis will be intention to treat. Gray's test with rho=0 will be used [7], with stratification by disease severity at entry for comparing each investigational agent to control for the primary endpoint of time to sustained recovery. Gray's test with rho=0 is the analogue of the log-rank test in the presence of competing risks; it is used here to account for the competing risk of death when analysing time to sustained recovery.

b. Type 1 error will be set at 0.025 (1-sided). This type 1 error will not be adjusted for the number of investigational agents being compared with placebo as each of the agents is expected to impact the primary endpoint through different mechanisms. If this is not the case, a type 1 error adjustment may be considered.

c. Power is set at 90% to detect a 25% increase in the rate of sustained recovery for the investigational treatment compared to placebo. This moderate efficacy is assumed considering the findings from ACTT-1 [8],and the percentage of patients in each baseline risk category of the ordinal outcome. Based on the results from ACTT-1 [8], we expect approximately 50% of patients enrolled after the initial futility assessment to be in the more severe strata (5 and 6 in the ordinal categories shown in Supplemental Table 4). However, all patients who are enrolled prior to the initial futility assessment are in the less severe strata at entry (categories 3 and 4 in Supplemental Table 4). These patients will also be part of the primary analysis. Thus, we assume that 40% of patients in the final analysis will be in the more severe strata; mortality is expected to be higher for patients in the more severe strata. Among surviving patients, we assume most will have met the criteria for sustained recovery.

d. With these assumptions for type 1 and type 2 error and a sustained recovery rate ratio of 1.25 for the investigational agent versus control, 843 sustained recoveries are needed [9, 10].

e. Given the duration of follow-up, we estimate that the sample size is slightly larger than the number of recoveries (i.e., we expect a low rate of loss-to-follow-up or deaths). For 2 groups, we assume that the sample size is approximately 20% higher than the number of recoveries, to account for deaths, a small number of withdrawals of consent, and a small number of patients remaining in the hospital at Day 90. Total sample size for 2 groups is approximately 1,000 (500 per group).

f. In order to observe 843 sustained recoveries among 1000 participants, and assuming 3% withdrawal of consent, at least 87% of participants (pooled across the two treatment arms) would have to achieve sustained recovery by Day 90. Assuming a recovery rate ratio of

1.25, this corresponds to 89.9% with sustained recovery among those randomized to the investigational agent, compared with 84.1% in the control group.

5 Randomization application

In order to facilitate randomizations to multiple possible agents, a flexible web-based randomization application was developed. The flexibility is accomplished with a database-driven approach pulling information from three tables: (i) randomisation table, which contains stratum specific schedules (as randomisation is stratified by pharmacy and disease severity stratum) for one or multiple agents; (ii) drug table, which contains agent availability and allows stopping/restricting randomisation to selected agents, and information describing the agent, including number of doses of the agent available at the site study pharmacy; and (iii) constraint table, which contains contraindications and information used to modify inclusion/exclusion criteria. Randomisation assignments will be obtained in sequence from pre-generated schedules stratified by pharmacy and disease severity stratum. Allocation will be 1:1 Active:Placebo for one agent, 2:1:2:1 Active A:Placebo A:Active B:Placebo B for two agents (A and B), and so on. Using permuted blocks with k agents, every k placebo assignments will include one agent specific placebo assignment per agent, and every k active assignments will include one per agent. Using the mass-weighted urn scheme [11], the underlying Active:Placebo sequence is generated to ensure an approximate 1:1 balance for each active versus pooled placebo comparison within strata throughout the trial.

The application can also vary allocation according to stratum (i.e. pharmacy or disease severity). With 2 agents, allocation for the less severe stratum might be 2:1:2:1 as above but if agent B has not advanced to Disease Stratum 2 (and can therefore not recruit individuals with high disease severity), for the more severe stratum allocation would be 1:1 Active A: Placebo A. Furthermore, the application allows a limited number of sites to allocate patients 2:1:2:1: Active A:Placebo A:Active B:Placebo B or 1:1 Active B:Placebo B initially

to obtain safety data for DSMB review for agent B while other sites randomize participants to only Active A; Placebo A until the safety review is complete.

6 Pharmacy set-up options

A number of pharmacy options are available to participating sites.

1. A single study site pharmacy serving multiple clinical sites within a close geographical area (e.g. the same city). Local site's clinical staff screen and randomise patient before ordering relevant study provided standard of care and placebo/agent from the study site pharmacy. Study provided standard of care and placebo/agent are made up and the placebo/agent is blinded at the study site pharmacy before being distributed to the local site clinical staff for administration.
2. A single study site pharmacy serving multiple local site pharmacies within a close geographical area. Local site's clinical staff screen and randomise patient before ordering relevant SOC and placebo/agent from the study site pharmacy. The study site pharmacy selects the appropriate number of vials of both study provided standard of care and placebo/agent. The study site pharmacy then arranges transport of the appropriate number of vials to the local site pharmacy At the local site pharmacy, the study provided standard of care and placebo are made up and the placebo/agent is blinded before being distributed to clinical staff for administration.
3. A traditional pharmacy set-up where the study site pharmacy only serves a single clinical site

7 Supplemental tables

Supplemental Table 1 Participating International Coordinating Centres (ICC), Clinical Sites and Site Coordinating Centres

INSIGHT Copenhagen ICC Centre of Excellence for Health, Immunity, and Infections (CHIP), Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark		
Site Name	**City**	**Country**
University Hospital Zurich	Zurich	Switzerland
Unité VIH/SIDA Genèva	Geneva	Switzerland
Johann Wolfgang Goethe Univ. Ho sp., Infektionsambulanz CRS	Frankfurt	Germany
Universitätsklinik Köln	Cologne	Germany
Universitätsklinikum Regensburg	Regensburg	Germany
Hvidovre University Hospital, Department of Infectious Diseases	Hvidovre	Denmark
Aarhus Universitetshospital, Skejby	Aarhus	Denmark
Odense University Hospital	Odense	Denmark
Aalborg Hospital	Aalborg	Denmark
Rigshospitalet, Department of Infectious Diseases	Copenhagen	Denmark
Nordsjællands Hospital, Hillerød	Hillerod	Denmark
Zealand University Hospital Roskilde	Roskilde	Denmark
Kolding Sygehus	Kolding	Denmark
Herlev-Gentofte Hospital	Hellerup	Denmark
Bispebjerg Hospital	Copenhagen	Denmark
Wojewodzki Szpital Zakazny	Warsaw	Poland
Hospital Universitari Germans Trias i Pujol (site and INSIGHT Site Coordinating Centre Spain)	Badalona	Spain

Hospital General Universitario Gregorio Marañón	Madrid	Spain
Hospital Clínic de Barcelona	Barcelona	Spain
Hospital Universitario La Paz	Madrid	Spain
Hospital Clínico San Carlos	Madrid	Spain
Hospital del Mar	Barcelona	Spain
Hospital Universitari Vall d'Hebron	Barcelona	Spain
Hospital Universitario de Bellvitge	Hospitalet de Llobregat	Spain
Hospital Universitario Arnau de Vilanova (Lleida)	Barcelona	Spain
AIDS and Clinical Immunology Research Center	Tbilisi	Georgia
Central City Clinical Hospital of Ivano-Frankivsk City	Ivano-Frankivsk	Ukraine
Karolinska University Hospital	Stockholm	Sweden
Capio Sankt Görans Sjukhus	Stockholm	Sweden
Uppsala University Hospital	Uppsala	Sweden
INSIGHT London ICC Medical Research Council Clinical Trials Unit at UCL, University College London, London, UK		
Site Name	**City**	**Country**
Hôpital Saint-Louis	Paris	France
Groupe Hospitalier Sud Île de France	Melun	France
Hopital Lariboisière	Paris	France
Ospedale San Raffaele S.r.l.	Milan	Italy
L. Sacco Hospital-Institue of Infectious and Tropical Diseases	Milan	Italy
INMI Lazzaro Spallanzani IRCSS	Rome	Italy
Bergamo Hospital	Bergamo	Italy
Royal Free Hospital	London	United Kingdom

Royal Victoria Infirmary	Newcastle upon Tyne	United Kingdom
Guy's & St. Thomas' NHS Foundation Trust	London	United Kingdom
MRC/UVRI Research Unit on AIDS (site and INSIGHT Site Coordinating Centre Uganda)	Entebbe	Uganda
St Francis Hospital, Nsambya	Kampala	Uganda
Gulu Regional Referral Hospital	Gulu	Uganda
Mulago Hospital Complex	Kampala	Uganda
Lira Regional Referral Hospital	Lira	Uganda
Masaka Regional Referral Hospital	Masaka	Uganda
CISPOC	Maputo	Mozambique
National & Kapodistrian University of Athens Medical School (INSIGHT Site Coordinating Centre Greece)	Athens	Greece
Attikon University General Hospital	Athens	Greece
1st Respiratory Medicine Dept, Athens University Medical School	Athens	Greece
AHEPA University Hospital	Thessaloniki	Greece
Dept of Critical Care and Pulmonary Medicine, Evangelismos General Hospital	Athens	Greece
Democritus University of Thrace	Alexandroupoli	Greece
3rd Dept of Medicine, Medical School, NKUA	Athens	Greece
St. Peters Tuberculosis Specialized Hospital	Addis Ababa	Ethiopia
INSIGHT Sydney ICC The Kirby Institute, University of New South Wales, Sydney, Australia		
Site Name	**City**	**Country**
Hospital General de Agudos JM Ramos Mejia	Buenos Aires	Argentina
CEMIC	Buenos Aires	Argentina
Hospital Italiano de Buenos Aires	Buenos Aires	Argentina
Hospital Profesor Bernardo Houssay	Buenos Aires	Argentina

NCGM	Tokyo	Japan
Fujita	Toyoake Aichi	Japan
Tan Tock Seng Hospital	Singapore	Singapore
Chennai Antiviral Research and Treatment Clinical Research Site (CART-CRS)	Chennai	India
Institute of Human Virology-Nigeria (IHVN)	Abuja	Nigeria
INSIGHT Washington ICC Veterans Affairs Medical Center and George Washington University, Washington, DC, USA.		
Site Name	**City**	**Country**
Washington DC VA Medical Center	Washington	United States
MedStar Health Research Institute	Washington	United States
Henry Ford Health System	Detroit	United States
Denver Public Health	Denver	United States
Cooper University Hospital	Camden	United States
West Haven VA Medical Center	West Haven	United States
Hennepin Healthcare Research Institute/HCMC	Minneapolis	United States
University of South Florida, Tampa General Hospital	Tampa	United States
SUNY Downstate Medical Center	Brooklyn	United States
Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center	Torrance	United States
Georgetown University	Washington	United States
UT Southwestern Medical Center	Dallas	United States
Parkland Health and Hospital Systems	Dallas	United States
Minneapolis VA Medical Center	Minneapolis	United States
University Hospitals Cleveland Medical Center	Cleveland	United States
University of Minnesota	Minneapolis	United States

Instituto de Infectologia Emílio Ribas - IIER	Sao Paulo	Brazil
Complexo Hospitalar Professor Edgard Santos	Salvador	Brazil
Instituto Nacional de Infectologia Evandro Chagas- INI	Rio de Janeiro	Brazil
Hospital Universitario Maria Aparecida Pedrossian	Campo Grande	Brazil
Socios En Salud Sucursal Peru	Lima	Peru
Hospital Nacional Hipolito Unanue	Lima	Peru
Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubiran (INCMNSZ)	Mexico City	Mexico
Instituto Nacional de Enfermedades Respiratorias Ismael Cosio Villegas (INER)	Mexico City	Mexico
Hospital General Dr. Manuel GEA Gonzalez	Mexico City	Mexico
Hospital General Dr. Aurelio Valdivieso	Oaxaca	Mexico

INSIGHT NIH-DCR ICC

Department of Clinical Research, National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

Country	**Country**	**Country**
Lincoln Medical Center	Bronx	United States
Maimonides Medical Center	Brooklyn	United States
CHRISTUS Spohn Shoreline Hospital	Corpus Christi	United States
Hendrick Medical Center	Abilene	United States
Hoag Memorial Hospital Presbyterian	Newport Beach	United States
Cotton O'Neil Clinical Research Center	Topeka	United States
CHRISTUS Good Shepherd Medical Center	Longview	United States
Velocity Chula Vista	Chula Vista	United States
Velocity San Diego	La Mesa	United States

Rhode Island Hospital	Providence	United States
The Miriam Hospital	Providence	United States
Memorial Healthcare System	Hollywood	United States
INSIGHT U.S. Department of Veterans Affairs (VA) research network ICC		
Site Name	**Site City**	**Country**
VA Greater Los Angeles Healthcare System	Los Angeles	United States
San Francisco VA Health Care System	San Francisco	United States
Miami VA Healthcare System	Miami	United States
Bay Pines VA Healthcare System	Bay Pines	United States
VA Palo Alto Healthcare System	Palo Alto	United States
Michael E. DeBakey VA Medical Center	Houston	United States
Southern Arizona VA Health Care System	Tucson	United States
North Florida/South Georgia Veterans Health Sysem	Gainesville	United States
Salem VA Medical Center	Salem	United States
VA San Diego Healthcare System	San Diego	United States
VA Loma Linda Healthcare System	Loma Linda	United States
Clement J. Zablocki Veterans Affairs Medical Center	Milwaukee	United States
Tennessee Valley Healthcare System	Nashville	United States
Sacramento VA Medical Center	Mather	United States
Portland VA Health Care System	Portland	United States
VA Providence Healthcare System	Providence	United States
VA Long Beach Healthcare System	Long Beach	United States
Saint Louis VAMC	Saint Louis	United States

Prevention and Early Treatment of Acute Lung Injury (PETAL) ICC Massachusetts General Hospital, Boston, USA		
Site Name	**Site City**	**Country**
Baystate Medical Center (site and ALIGNE Site Coordinating Center)	Springfield	United States
Beth Israel Deaconess Medical Center (site and Boston Site Coordinating Centre)	Boston	United States
Massachusetts General Hospital	Boston	United States
University of Mississippi Medical Center	Jackson	United States
UCSF San Francisco (site and California Site Coordinating Centre)	San Francisco	United States
Ronald Reagan UCLA Medical Center	Los Angeles	United States
Stanford University Hospital & Clinics	Stanford	United States
UC Davis	Davis	United States
UCSF Fresno	Fresno	United States
UCSF Medical Center at Mount Zion	San Francisco	United States
University of Colorado Hospital (site and Colorado Site Coordinating Centre)	Aurora	United States
National Jewish Health | St. Joseph Hospital	Denver	United States
University of Michigan Medical Center (site and Michigan Site Coordinating Centre)	Ann Arbor	United States
Montefiore Medical Center Moses Hospital (site and Montefiore-Sinai Site Coordinating Centre)	Bronx	United States
Montefiore Weiler	New York	United States
Banner University Medical Center Tucson	Tucson	United States
Cleveland Clinic Foundation	Cleveland	United States
University of Cincinnati Medical Center (site and Ohio Site Coordinating Centre)	Cincinnati	United States
Cleveland Clinic Fairview Campus	Cleveland	United States
Cleveland Clinic Marymount Campus	Cleveland	United States
Cedars-Sinai Medical Center	Los Angeles	United States

Oregon Health and Science University (site and Pacific Northwest Site Coordinating Centre)	Portland	United States
Swedish Hospital Cherry Hill	Seattle	United States
Swedish Hospital First Hill	Seattle	United States
UPMC Presbyterian	Pittsburgh	United States
UPMC Magee	Pittsburgh	United States
UPMC Shadyside	Pittsburgh	United States
Wake Forest Baptist Health (site and Southeast Site Coordinating Centre)	Winston-Salem	United States
Medical University of South Carolina	Charleston	United States
University of Kentucky	Lexington	United States
Virginia Commonwealth University Health System	Richmond	United States
Intermountain Medical Center (Site and Utah Site Coordinating Centre)	Murray	United States
University of Utah Hospital	Salt Lake City	United States
Utah Valley Regional Medical Center	Provo	United States
LDS Hospital	Salt Lake City	United States
Vanderbilt University Medical Center	Nashville	United States
Cardiothoracic Surgical Trials Network (CTSN) ICC Icahn School of Medicine at Mount Sinai, New York, USA		
Site Name	**City**	**Country**
Allegheny General Hospital	Pittsburgh	United States
Baylor College of Medicine	Houston	United States
Baylor, Scott and White Health	Dallas	United States
Cedars-Sinai Medical Center	Los Angeles	United States
CHI St. Vincent, Arkansas	Little Rock	United States
Duke University Hospital	Durham	United States

East Carolina Heart Institute	Greenville	United States
Emory University	Atlanta	United States
Inova Heart & Vascular Institute	Falls Church	United States
Lutheran Medical Group	Fort Wayne	United States
MH Mission Hospital	Asheville	United States
Mount Sinai Medical Center	New York	United States
New York University Langone Health	New York	United States
Northwell Health	Manhasset	United States
Ochsner Clinic	New Orleans	United States
Piedmont Healthcare	Atlanta	United States
Texas Heart Institute	Houston	United States
University of Louisville	Louisville	United States
University of Maryland	Baltimore	United States
University of Southern California	Los Angeles	United States
University of Virginia Health Systems	Charlottesville	United States
WakeMed Heart Center	Raleigh	United States
West Virginia University	Morgantown	United States
Dartmouth-Hitchcock Medical Center	Lebanon	United States
Hôpital Laval	Quebec	Canada

Supplemental Table 2 Agent specific information contained in separate appendices

Section	Key sub-sections
Introduction/Rationale for studying the agent 1	• Potential risks and benefits of agent • Motivation for agent selection with consideration of results from trials of other agents

Agent Specific Eligibility Criteria	n/a
Description of investigational agent	• Administration and duration • Formulation and preparation • Supply, distribution, and accountability • Contraindicated medications • Precautionary medications
Clinical and laboratory evaluations in addition to master protocol	• Timing • Special instructions
Clinical management issues	• Infusion-related reactions • Hypersensitivity • Pregnancy and breast-feeding considerations • Criteria for discontinuation of infusion

Supplemental Table 3 Safety Data Collection Schedule

	Infusion +2 hrs	Days 0-7	Day 14	Day 28	Day 90	Month 6, 12 and 18
Infusion-related reactions and symptoms	X					
Incident grade 3 and 4 clinical AEs			X[1]	X[1]		
Clinical AEs of any grade severity	X	X	X[2]	X[2]		
Targeted laboratory abnormalities of any grade		X (Day 5)				
Hospital admissions and deaths	Collected through to Month 18					
Serious AEs (including those reported as part of the pulmonary and pulmonary+ ordinal outcomes)	Collected through Day 90					
Unanticipated problems	Collected through Day 90					
Any serious adverse event related to study intervention	Collected through Day 90					

1. All grade 3 and 4 events since previous visit
2. All grade 1 and 2 events on the day of the visit only

Supplemental Table 4 Hypothesized percentage of participants in each category on Day 5 in the investigational agent and placebo groups based on aforementioned assumptions.

Pulmonary Plus Category	**Investigational Agent + Standard of Care**	**Placebo + Standard of Care**
1. No limiting symptoms due to COVID-19	3.2	2.0
2. Limiting symptoms due to COVID-19	53.5	43.0

3. Moderate end-organ dysfunction	20.6	23.0
4. Serious end-organ dysfunction	12.8	17.0
5. Life-threatening end-organ dysfunction	5.0	7.3
6. End-organ failure	4.5	7.0
7. Death	0.4	0.7
Total	100.0	100.0

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A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19

Short Title: Therapeutics for Inpatients with COVID-19 (TICO)

INSIGHT Protocol Number: 014 / ACTIV-3

NCT 04501978, EudraCT 2020-003278-37

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In collaboration with four International Coordinating Centers (ICCs) of the INSIGHT Network:

-Centre of Excellence for Health, Immunity and Infection (CHIP), Rigshospitalet, University of Copenhagen - Copenhagen, Denmark

-Medical Research Council (MRC) Clinical Trials Unit at University College London (UCL) - London, United Kingdom

-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)

And other research networks supported by NIAID (AIDS Clinical Trials Group [ACTG], Division of Clinical Research [NIH-DCR]), National Heart, Lung, and Blood Institute (NHLBI – Cardiothoracic Surgical Trials Network [CTSN] and Prevention and Early Treatment of Acute Lung Injury [PETAL]) and the US Department of Veterans Affairs

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1 Protocol Summary

DESIGN

TICO (Therapeutics for Inpatients with COVID-19) is a master protocol to evaluate the safety and efficacy of multiple investigational agents aimed at modifying the host immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, or directly enhancing viral control in order to limit disease progression.

Trials within this protocol will be adaptive, randomized, blinded and initially placebo-controlled. Participants will receive standard of care (SOC) treatment as part of this protocol.

The international trials within this protocol will be conducted in several hundred clinical sites. Participating sites are affiliated with networks funded by the United States National Institutes of Health (NIH) and the US Department of Veterans Affairs.

The protocol is for a phase III randomized, blinded, controlled platform trial that allows investigational agents to be added and dropped during the course of the study for efficient testing of new agents against control (i.e., placebo + SOC) within the same trial infrastructure. When more than one agent is being tested concurrently, participants will be randomly allocated across agents (as well as between the agent and its placebo) so the same control group will be used, when feasible. Randomization will be stratified by study site pharmacy and disease severity. There are 2 disease severity strata, defined as below:

Disease severity stratum 1: Absence of all of the following: stroke, meningitis encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, symptomatic congestive heart failure (NYHA class III or IV), arterial or deep venous thrombosis or pulmonary embolism, requirement for invasive mechanical ventilation, ECMO, mechanical circulatory support, vasopressor therapy, or new renal replacement therapy.

Disease severity stratum 2: Presence of at least one of the excluded conditions or treatments in disease severity stratum 1.

The primary endpoint is the time from randomization to sustained recovery, defined as being discharged from the index hospitalization, followed by being alive and home for 14 consecutive days prior to Day 90. The definition of home will be operationalized as the level of residence or facility where the participant was residing prior to hospital admission leading to enrollment in this protocol.

An independent Data and Safety Monitoring Board (DSMB) will regularly review interim analyses that summarize safety and efficacy outcomes. For agents with minimal pre-existing safety knowledge, the pace of enrollment will be initially restricted and there will be an early review of safety data by the DSMB. For the study of all agents, at the outset of the trial, only participants in disease severity stratum 1 will be enrolled. This more restricted enrollment will continue until approximately 300 participants are enrolled and followed for 5 days. The exact number will vary according to the speed of enrollment and the timing of DSMB meetings. Prior to expanding enrollment to also include patients in disease severity stratum 2 safety will be evaluated and a pre-

specified futility assessment by the DSMB will be carried out using 2 ordinal outcomes (see below) assessed at Day 5. The first ordinal outcome is a 7-category outcome largely based on oxygen requirements. The highest (worst) category that applies on Day 5 will be assigned. This outcome is referred to as the "pulmonary" ordinal outcome, with categories described below:

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen)
5. Non-invasive ventilation or high-flow oxygen
6. Invasive ventilation, extracorporeal membrane oxygenation (ECMO), mechanical circulatory support, or new receipt of renal replacement therapy
7. Death

The second ordinal outcome, also assessed at Day 5, captures the range of organ dysfunction that may be associated with progression of Coronavirus-Induced Disease 2019 (COVID-19), such as stroke and other coagulation-related complications. Again, the highest category that applies on day 5 will be assigned. Use of this outcome allows further characterization of the extra-pulmonary manifestations of COVID-19 and the capacity to identify agents that improve those extra-pulmonary manifestations. This outcome is referred to as the "pulmonary+" ordinal outcome.

The 7 categories of the pulmonary+ ordinal outcome assessed at Day 5 are:

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen) or any of the following: stroke (NIH Stroke Scale [NIHSS] ≤14), meningitis, encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, new onset congestive heart failure (CHF) NYHA class III or IV or worsening to class III or IV, arterial or deep venous thromboembolic events.
5. Non-invasive ventilation or high-flow oxygen, or signs and symptoms of an acute stroke (NIHSS >14)
6. Invasive ventilation, ECMO, mechanical circulatory support, vasopressor therapy, or new receipt of renal replacement therapy
7. Death

Both ordinal outcomes are used to assess futility because it is currently unclear whether the investigational agents under study will primarily influence non-pulmonary outcomes, for which risk is increased with SARS-CoV-2 infection, in part, through mechanisms that may be different from those that influence pulmonary outcomes.

For investigational agents passing this futility assessment, enrollment of participants will be expanded, seamlessly and without any data unblinding, to include participants in disease severity stratum 2 as well as those in disease severity stratum 1. Future interim analyses will be based on the primary endpoint of sustained recovery and will use pre-specified guidelines to determine early evidence of benefit, harm or futility for the investigational agent.

DURATION — Participants will be followed for 18 months following randomization. Primary and most secondary outcomes will be collected during the first 90 days of follow-up only. Follow-up beyond 90 days is planned because the half-lives of some agents indicate that potentially meaningful amounts may remain in the body after 90 days of follow-up. During the follow-up between 90 days and 18 months hospitalizations and deaths will be ascertained.

SAMPLE SIZE — This phase III trial is planned to provide 90% power to detect a 25% increase in the rate of sustained recovery for an investigational agent compared to placebo at the 0.025, 1-sided level of significance. This requires 843 primary events (i.e., participants who achieve sustained recovery). Randomization of 1,000 participants, equally allocated to each investigational agent and placebo, followed for 90 days is estimated to result in the required number of primary events. The event target may be achieved earlier if more than 1,000 participants are enrolled. Sample size will be evaluated periodically by study team members who are blinded to interim results and may be increased to maintain power for the hypothesized difference in sustained recovery between the investigational agent and placebo.

POPULATION — The study population consists of inpatient adults (≥18 years) who have had COVID-19 symptoms ≤ 12 days. Initially, approximately 300 participants in disease severity stratum 1 will be enrolled. Afterwards, based on the review by the DSMB of safety and futility, eligibility for randomization will be expanded to also include patients in disease severity stratum 2.

STRATIFICATION — Randomization will be stratified by study site pharmacy and also by disease severity stratum.

REGIMEN — Investigational agents suitable for testing in the inpatient setting will be prioritized based on in vitro data demonstrating activity against SARS CoV-2 entry or replication, preclinical data, phase I pharmacokinetic and safety data, and clinical data from other ongoing trials. The protocol will initially focus on agents for which there is a hypothesized benefit from passive immunization including use of neutralizing monoclonal antibodies.

MONITORING — An independent DSMB will review interim data on a regular basis and use pre-specified guidelines to identify agents with clear evidence of efficacy for the primary outcome, and if so recommend unblinding of the trial results for that agent. Conversely, the DSMB may recommend discontinuation of an investigational agent if the risks are judged to outweigh the benefits or if futility

assessments indicate that there is low probability that an investigational agent will achieve statistical significance for the primary endpoint of sustained recovery.

For an investigational agent, if the trial is stopped early or if the trial continues until the pre-specified number of primary endpoints is reached, further enrollment of the investigational agent will be terminated if applicable, and the trial data for the investigational agent will be unblinded and reported with data through 90 days of follow-up. Follow-up of all participants will continue through 18 months using the data collection plan described in this master protocol.

A risk-based protocol monitoring plan will be developed to ensure participant safety, data integrity, and regulatory compliance during the conduct of the trial.

2 Introduction

2.1 Study rationale

COVID-19 is a respiratory disease caused by a novel coronavirus (SARS-CoV-2). While most cases are mild or asymptomatic, progressive disease can result in hospitalization, requirement for mechanical ventilation, and substantial morbidity and mortality.[1] While the most common mode of disease progression is progressive respiratory failure following the development of pneumonia, other severe complications including thrombosis and ischemia are increasingly recognized.[2,3]

Several clinical trials utilizing novel drugs and repurposing older agents have been implemented to investigate the treatment of adults hospitalized with severe COVID-19 (see section 2.2.7). Standard-of-care is hence rapidly evolving (see Appendix I for current recommendations).

Our understanding of the humoral immune response is evolving, with some evidence that responses are variable between individuals and delayed in some cases.[4] It may therefore be that viral replication leads to extensive tissue damage and inflammatory responses in the lungs and other organs before the development of neutralizing antibodies. Augmentation of the humoral immune response to SARS-CoV-2 infection using passive immunotherapy to SARS-CoV-2 in hospitalized patients with moderate to severe COVID-19 may thus improve the disease course and reduce the time to recovery.

2.2 Background

2.2.1 SARS-CoV-2 Infection and Coronavirus Disease 19 (COVID-19)

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. A novel coronavirus was rapidly identified by sequencing and named SARS-CoV-2, and the illness caused by infection with SARS-CoV-2 has been named COVID-19.[5] While SARS-CoV-2 mostly causes a mild respiratory illness, some individuals, particularly those who are elderly[6,7] and have comorbidities,[8] may progress to severe disease requiring hospitalization, mechanical ventilation in intensive care units, and death. As of 5 October 2020, less than seven months following the declaration of a pandemic on 11 March 2020 by the World Health Organization (WHO), there have been more than 35 million cases diagnosed and more than 1 million deaths worldwide.[1] Over 300,000 cases continue to be reported daily.[5]

2.2.2 Natural history of COVID-19

SARS-CoV-2 has a median incubation period of 4 days (interquartile range [IQR] 2-7 days)[9] and the mean serial interval defined as the time duration between a primary case-patient (infector) having symptom onset and a secondary case-patient (infectee) having symptom onset for COVID-19 was calculated as 3.96 (95% confidence interval [CI] 3.53–4.39) days.[10] COVID-19 illness is predominantly a respiratory disease typified by upper respiratory symptoms in mild cases and pneumonia, respiratory failure and acute respiratory distress syndrome (ARDS) in advanced disease. Initial symptoms typically involve the upper respiratory tract with cough, sore throat and malaise. Fever is present in approximately 44-98% of cases. Notably, persons with COVID-19 often experience loss of smell and taste.[11]

Complications of COVID-19 illness include cytopenias (lymphopenia, thrombocytopenia and anemia), and acute cardiac events (elevated troponin, changes on electrocardiogram),

acute renal injury and renal failure, liver impairment, and neurological events including acute cerebrovascular events, impaired consciousness and muscle injury and thrombotic events.

In most patients (approximately 80%) symptoms resolve without the need for intervention within five to seven days of symptom onset up to a maximum of 14 days. However, approximately 20% of patients show signs of clinical disease progression, most notably pneumonia, around day 3 to 8 following symptom onset. Other manifestations of disease progression include thrombotic episodes including stroke and myocardial infarction (MI). This resembles the documented 6-8 fold excess risk of thrombosis when patients are infected with influenza.[12]

A proportion of those who progress then further deteriorate, including with the development of ARDS around 1-5 days after pneumonic symptom onset.[6,13,14,15] Acute kidney injury necessitating dialysis and failure of other organs may also occur at this severe stage of disease.

Of the nearly 1,099 persons described in the Wuhan cohort, 16.0% had severe disease at presentation; 67 persons (6.1%) reached a composite primary endpoint of intensive care admission, mechanical ventilation or death.[9,16] As described below, outcomes for those requiring mechanical ventilation and with other manifestations of end-organ failure are poor, and approaches to prevent this late stage of the disease among those with early evidence of progression are critically needed.

Initially in this protocol, we aim to enroll patients hospitalized for medical management of COVID-19, close to the onset of clinical symptoms but without end-organ failure having developed (disease severity stratum 1). For agents passing the initial futility assessment eligibility for enrollment will be expanded so that patients with or without overt organ failure will be enrolled (patients in disease severity stratum 1 or 2). The majority of patients will have emerging evidence of pneumonia, but recognizing the expanding range of other organs involved in clinical progression of COVID-19, neither the inclusion criteria nor the outcomes used in in this trial are limited only to assessment of pneumonia.

2.2.3 Risk factors for clinical progression

Studies investigating risk factors for progression of COVID-19 and related hospital admission are currently few. Reports to date have predominately been based on individuals already hospitalized. These include a mix of descriptive information on the patients as well as estimates of associations between patient characteristics and disease severity. Older age has been found to be strongly related to greater severity[16,17,18] and poorer outcome as has the presence of conditions such as hypertension, diabetes and coronary heart disease.[14,16,18,19] Other risk factors identified include ethnicity[18], cigarette smoking[16,17,20] and high body mass index (BMI).[21,22,23,24] Gender has not shown a consistent relationship with disease severity.[16,18,25] However, reports of larger case series and cohorts suggest male gender is associated with an increased risk of hospitalization and mortality.[26,27,28] Specific symptoms at presentation that have notably been associated with greater likelihood of progression to more severe disease include shortness of breath and elevated body temperature.[16,29]

Patients with inborn errors of their interferon immunity or who have developed auto-antibodies that reduces this host-protective immunity appear to be at excess risk of disease progression.[30,31]

The COVID-19–Associated Hospitalization Surveillance Network (COVID-NET) report on 1,482 persons who were hospitalized in 14 states in the US in March 2020 show nearly 75% were aged over 50 years, and nearly 90% had at least one underlying comorbid illness.[32]

Based on 2.6 million users of the COVID Symptom Tracker App, predominantly in the United Kingdom, being older, obese, diabetic or suffering from pre-existing lung, heart or renal disease placed participants at increased risk of visiting the hospital with COVID-19.[33] Pre-existing lung disease and diabetes were consistently associated with a higher risk of requiring respiratory support.[33] A meta-analysis showed that cardiac injury as measured by a high sensitivity troponin was associated with higher mortality, higher need for intensive care unit (ICU) care, and severe COVID-19 disease.[34]

2.2.4 Hospitalization of people with COVID-19

Countries and jurisdictions differ in the clinical management of COVID-19 patients. Early in the epidemic, faced with small numbers of infected persons, some resource-rich countries such as Singapore elected to admit all persons with COVID-19 regardless of symptom severity to facilitate strict isolation. Admission for reasons of public health or quarantine, rather than medical management, continues to be a requirement in some countries, notably in Asia. Elsewhere, it is more common for those with mild illness to be advised to self-isolate at home, while only those severely unwell are admitted for medical management.

Thresholds for ICU management also differ globally and are likely to vary significantly even within individual countries at different stages of the epidemic. For example, during peaks of high incidence, procedures commonly performed only in ICU may be extended to other care areas, while patients who might otherwise have been considered for ICU admission may be palliated if clinical services are overwhelmed.

Mortality rates for those who develop end-organ failure requiring intensive support, including those admitted to ICU, differ widely. Among 1,591 ICU patients from Lombardy, the region in Italy hardest hit by COVID-19, 88% required mechanical ventilation and 11% noninvasive ventilation.[35] The ICU mortality rate was 26%. Of 1,043 patients with available data, 709 (68%) had at least 1 comorbidity, 509 (49%) had hypertension, and 21% had cardiovascular disease. Younger patients (≤63 years) compared to older patients, had lower ICU mortality and higher rates of discharge from ICU. The median length of stay in the ICU was 9 days, though 58% remained in ICU at time of report.[35] In the United Kingdom, of the 4,078 COVID-19 patients admitted into critical care with reported outcomes, 50.7% died in ICU; those requiring advanced respiratory support and renal support had worse outcomes.[36] These data underline the importance of attenuating the disease in its early phase prior to the development of end-organ failure.

For recovering hospitalized patients who still require supplementary oxygen, an emerging clinical practice is to discharge such patients and administer oxygen at their home until it is no longer required.

2.2.5 Viral kinetics of SARS-CoV-2 infection

Viral kinetic studies have demonstrated extensive SARS-CoV-2 viral replication in the pharynx just before and early after symptom onset.[37] Viral ribonucleic acid (RNA) shedding from the pharynx gradually wanes as symptoms resolve, but viral RNA is still detectable

weeks after symptom resolution.[37,38,39] Median duration of viral shedding was 20 days in survivors (longest 37 days), but SARS-CoV-2 was detectable until death in non-survivors.[7] Whether this is viable virus with the potential for continued transmission remains uncertain. RNAemia has been reported but is relatively rare.[38,40] Viral detection in sputum is higher and outlasts pharyngeal swabs in those with pneumonia.[41] Persons with asymptomatic disease clear their virus faster than symptomatic individuals.[42]

The contribution of ongoing viral replication to disease progression in the most severe stage of COVID-19 (i.e., on ventilator or ECMO) is unclear, but may be minor as we hypothesize that any organ damage from the infection may have occurred already and the predominant drivers of progression to severe disease/ARDS are those of the uncontrolled local and systemic immune response.

Case reports are emerging to suggest possible reinfection in patients who have recovered from SARS-CoV-2 infection.[43,44,45,46,47]

2.2.6 Immune responses to SARS-CoV-2 infection

Notwithstanding the observed high viral loads, and progression of viral shedding from the upper to lower respiratory tract in those with progressive disease, the humoral immune response to SARS-CoV-2 appears variable and may be slow. While data are still emerging, it appears that in a significant proportion of cases antibody responses are not yet evident at the time (day 5-7) when disease progression and hospitalization most commonly occur, supporting a role for supplementation of the antibody response at that time point.

For example, two large studies have described antibody responses (immunoglobulin G [IgG] and immunoglobulin M [IgM]). In the first, samples from 82 confirmed and 58 probable cases of COVID-19 in a cross-sectional analysis demonstrated IgG detection at a median of 14 (IQR 10-18) days after symptom onset, with IgM detected at a median of 5 days (IQR 3-6) after symptom onset. Antibodies were absent in around 22% of individuals at assessment (IgM), and IgM was most commonly absent in those assessed early (within 7 days of symptom onset).[48] In the second study of 262 patients who provided 363 samples, antibody levels were examined by days from symptom onset. IgM antibodies were detectable in just under 40% of patients at day 5-7, rising to 50% at day 8-10, while interestingly IgG was detectable in a slightly higher proportion at those time points: just over 50% at day 5-7, rising to 60% at day 8-10.[49] This series was drawn from hospitalized patients, but the severity of illness and relationships with disease outcomes were not described. Both studies show considerable individual variation in antibody kinetics. Further longitudinal studies are underway and will better characterize the kinetics of these responses in individuals.[50,51]

SARS-CoV-2 infection may also induce significant changes in elements of the cellular immune response. As the disease process progresses, the peripheral lymphocyte count typically declines. The depletion of peripheral lymphocytes likely reflects translocation to the pulmonary tissue. The extent that this influx is exclusively helpful to the host, or possibly may contribute adversely to disease severity is currently unclear. In severe cases this decline in CD4+ and CD8+ lymphocytes is also associated with an increase in activated CD4+ and CD8+ subsets, increases in key proinflammatory cytokines including interleukin 6 (IL-6), and increases in natural killer (NK) cells.[52,53] Trials assessing the use of various immunomodulatory agents with the aim of dampening this migration and systemic inflammation are underway, and may help to clarify this.

2.2.7 Current treatment strategies for COVID-19

Hundreds of clinical trials have been completed or are underway to study the safety and efficacy of treatments for COVID-19. Treatments being studied include direct anti-viral treatments, including repurposed drugs found in vitro to have activity against SARS-CoV-2; immune modulators especially in patients with advanced disease; drugs to reduce inflammation, including corticosteroids, and modifiers of other pathophysiological pathways implicated in disease progression, including potentially anticoagulants and anti-platelet agents.

As results of randomized trials for these and other treatments become available and treatment guidelines are updated, standard of care (SOC) for hospitalized patients with COVID-19 will change. This may influence the background treatment recommended (or required) by this protocol and/or second line or supportive care treatments recommended by the protocol. To accommodate this fast-moving field Appendix I (which outlines the SOC to be recommended in addition to investigational agent or matched placebo) will be regularly updated.

Of note, whereas evidence supports use of the interventions outlined in Appendix I, the most optimal approach to applying these interventions remains uncertain, and is the subject of ongoing trials.

2.2.8 Neutralizing Monoclonal Antibodies (nMAbs)

The ability to rapidly and urgently develop novel therapeutic nMAbs is best illustrated in the setting of the 2014-2016 Ebola epidemic. A triple monoclonal antibody (MAb) cocktail, ZMapp, which first showed efficacy in guinea pigs,[54] was tested in PREVAIL II, a randomized controlled trial of 72 patients.[55] This trial did not meet pre-specified efficacy threshold. Two phase I studies that separately explored a single nMAb against receptor-binding domain (RBD) Mab114[56] and a triple nMAb cocktail of REGN3470-3471-3479[57] showed linear pharmacokinetics and a good safety profile, with mild headaches in the latter. A large 1:1:1:1 randomised study of 681 patients compared ZMapp as control; remdesivir: single nMAb, Mab114 (Ansuvimab) and a triple cocktail of REGN-EB3, with the latter two showing superior results for day 28 mortality.[58] Four events in three patients were thought to be directly related to trial drug – 2 in the ZMapp arm and 1 in the remdesivir arm. Mab114 was granted breakthrough therapy designation by the US Food and Drug Administration (FDA) and REGN-EB3 was approved for the treatment of Ebola virus disease by the FDA.

SARS-CoV-2 and other pathogenic human coronaviruses encode four major structural proteins. The homotrimeric spike (S) protein is essential to viral attachment, fusion, entry and transmission and has two functional subunits - S1 subunit for virus-receptor binding and S2 subunit for virus-cell membrane fusion. S1 has an N-terminal domain (NTD) and a RBD.[59,60,61] During infection, SARS-CoV-2 first binds the host cell through interaction between its S1-RBD and the cell membrane receptor (angiotensin-converting enzyme 2 or ACE2 receptor) triggering conformational changes in the S2 subunit that results in virus fusion and entry into the target cell.[62] Other structural proteins include the envelope (E) protein encompassing the viral envelope, the membrane (M) protein protruding from the cell membrane, and nucleocapsid (N) protein covering the viral RNA. There are approximately 16 non-structural proteins (nsp1–16), and five to eight accessory proteins.[59] As the S glycoprotein is surface-exposed and mediates entry into host cells, it is the main target of neutralizing antibodies upon infection and the focus of therapeutic and vaccine design[62].

Most currently developed anti-SARS-CoV-2 nMAbs target the viral S protein, most commonly the RBD.[6364] The structural homology and cross-reactivity across the *Coronaviridae* have enabled knowledge translation from SARS-CoV-1 and MERS to SARS-CoV-2. Cross-reactivity has been exploited for immune protection. Promising human-derived nMAbs have been identified from previous SARS-CoV-1 patients and convalescing SARS-CoV-2 patients. After the SARS epidemic in 2003, two promising nMAb therapeutics were identified - CR3014 and CR3022.[65] CR3022 rather than CR3014 showed promise against SARS-CoV-2[66] but recent structure modelling showed that CR3022 binds to a cryptic epitope distal to the RBD, only accessible when the RBD is in the up conformation and at a specific angle,[67] thus limiting its application.

A new promising S309 antibody targeting the RBD, identified from a previous SARS-CoV-1 survivor, showed cross-reactivity against SARS-CoV-2 and an Fc variant with a longer half-life is in accelerated development.[61] Similarly, 18F3 and 7B11 against RBD were identified from SARS-CoV-1 patients.[68] Many papers have detailed identification and development of nMAbs from currently convalescing patients with SARS-CoV-2, all targeting the RBD including: CB6 which also has shown promise as a prophylaxis and therapeutic model in monkey studies[69]; P2B -2F6,[70] 311mab-31B5 and 311mab-32D4.[71]

Viral escape mutants may render the virus resistant to the neutralising effects of nMAbs.[72]

2.3 Investigational Agents

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) has formed an overarching “trial oversight committee (TOC)” for both ACTIV-2 (a parallel study assessing COVID-19 therapeutics in outpatients) and ACTIV-3 (this master protocol). The TOC will select agents for study in the two protocols. Members of the protocol team (non-voting) and NIAID are members of this committee. This committee reviews data for investigational agents and considers a number of factors including safety, in vitro potency against the virus, resistance, epitope and adequacy of antibody titers if the agent is an antibody, scale-up potential in general, and for completing the phase 3 trial in particular, and dose and route of administration.

The same DSMB will review interim data from ACTIV-2 and ACTIV-3 and this should facilitate early identification of safety concerns. The protocol team will inform the DSMB about emerging data that impacts the study design (e.g., the safety of the investigational agent being studied or SOC).

It is possible that agents from different sources will be combined at some point in the conduct of this master protocol. It is also possible that one agent will be identified as effective and then incorporated as SOC (providing there is good safety and adequate supply).

Information on dosing, administration, supply and distribution, matching placebo, and any special considerations as far as inclusion/exclusion criteria and safety monitoring for each investigational agent studied as part of this protocol is outlined in an appendix (see Appendix H), including known benefits and risk, justification for dosing, and administration. The appendix will also include whether any deviations from aspects of study procedures outlined in this master protocol will be needed. The informed consent will describe any risks associated with the investigational agents.

3 Risk/Benefit Assessment

3.1 Known Potential Risks

Potential risks of participating in this trial are those associated with the product, and these are described in an appendix and in the sample informed consent. Other risks include having blood drawn, intravenous (IV) catheterization, thrombosis, the volume of fluid infused, and breach of confidentiality.

3.1.1 Risks of Drawing Blood and IV Catheterization

Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the participant lie down and elevate his/her legs. Bruising at the blood collection sites may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken. IV catheterization may cause insertion site pain, phlebitis, hematoma formation, and infusate extravasation; less frequent but significant complications include bloodstream and local infections. The use of aseptic (sterile) technique will make infection at the site of blood draw or at catheterization less likely.

3.1.2 Risks of Anaphylaxis, Thrombosis and Fluid Overload due to Study Treatments

Infusions of investigational agents likely to be used in this protocol are generally well-tolerated, except in rare cases of existing allergy to the products infused. However, the volume of fluid infused may exacerbate pre-existing CHF. There is slight elevation in the risk of thrombosis with standard antibody therapy, and in some cases COVID-19 is associated with thrombotic complications. There is a theoretical risk that antibody infusion may worsen the disease course via antibody-dependent enhancement (ADE). ADE occurs if specific antibodies against a virus increase rather than decrease viral replication and hence worsen the disease course. ADE has been observed most clearly in the context of Dengue fever.[73] It is unclear if this phenomenon is present and/or clinically significant in COVID-19, but close monitoring of disease outcomes will be maintained during interim safety analyses.

3.1.3 Risks to Privacy

Participants will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the participant's PHI. All source records including electronic data will be stored in secured systems in accordance with institutional policies and government regulations.

All study data that leave the site (including any electronic transmission of data) will be identified only by a coded number that is linked to a participant through a code key maintained at the clinical site. Names or readily identifying information will not be released. Electronic files will be password protected.

Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected. Any publication from this trial will not use information that will identify study participants. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance and data analysis include groups such as the study monitor, other authorized representatives of the institutional review board (IRB), NIH, and applicable regulatory agencies (e.g. FDA).

3.2 Known Potential Benefits

While the trial is conducted to test the hypothesis that each investigational agent will reduce the risk of further disease progression or reduce the time to sustained recovery, the agents studied may or may not prevent these outcomes in any individual who participates in this trial. However, there is an anticipated benefit to society from a patient's participation in this trial, due to insights that will be gained about the investigational agent(s) under study as well as the natural history of the disease. While there may not be benefits for an individual, there will be benefits to society if a safe, efficacious therapeutic agent can be identified during this global COVID-19 outbreak.

4 Outcomes

This section describes the key outcome measures used in this phase III protocol. At the outset of the phase III trial for each investigational agent, only participants in disease severity stratum 1 will be enrolled. This more restricted enrollment will continue until approximately 300 participants are enrolled. Prior to expanding enrollment to include people in disease severity stratum 2, a pre-specified futility assessment by the DSMB will be carried out using two ordinal outcomes (see below) that are assessed at Day 5. This early futility assessment is designed to ensure some minimal level of activity for agents for which enrollment continues to the planned sample size of the phase III trial.

4.1 Ordinal Outcomes for Early Futility Assessments

Two ordinal outcomes will be used to assess futility after approximately 300 participants have been enrolled. Both outcomes are assessed 5 days after randomization (Day 5); the participant's highest (i.e. most severe) observed score on Day 5 is used.

The first ordinal outcome, referred to as the "pulmonary" ordinal outcome, is primarily defined based on oxygen requirements. The 7 categories of the pulmonary ordinal outcome are given below (see Protocol Instructions Manual [PIM] for criteria defining the categories and each of the conditions mentioned).

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen)
5. Non-invasive ventilation or high-flow oxygen
6. Invasive ventilation, extracorporeal membrane oxygenation (ECMO), mechanical circulatory support, or new receipt of renal replacement therapy
7. Death

The second ordinal outcome, referred to as "pulmonary+," also assessed at Day 5, captures extrapulmonary complications as well as respiratory dysfunction. The categories of the pulmonary+ outcome are defined below (see PIM for criteria defining the categories and each of the conditions mentioned).

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)

3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen) or any of the following: stroke (NIH Stroke Scale [NIHSS] ≤14), meningitis, encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, new onset CHF NYHA class III or IV or worsening to class III or IV, arterial or deep venous thromboembolic events.
5. Non-invasive ventilation or high-flow oxygen, or signs and symptoms of an acute stroke (NIHSS >14)
6. Invasive ventilation, ECMO or mechanical circulatory support; vasopressor therapy; or new receipt of renal replacement therapy
7. Death

The term ”usual activities,” in categories 1 and 2 for both outcomes, refers to activities of daily living that the participant was able to undertake prior to the current illness.

4.1.1 Rationale for two ordinal outcomes

There is as yet no consensus on the optimal endpoint for determining clinical benefit from COVID-19 therapies, including the constituent elements of the endpoint and the timing of its assessment after randomization. Both may differ depending on the target population and the nature of the treatment studied.

While the pulmonary ordinal outcome focuses on the pulmonary components of COVID-19, the pulmonary+ ordinal outcome captures the range of complications experienced by hospitalized patients with COVID-19. The pulmonary+ outcome recognizes that end-organ manifestations in addition to pneumonia and ARDS are increasingly emerging as significant contributors to morbidity, including morbidity resulting from the thromboembolic pathology of the disease. Emerging extrapulmonary events are also likely to affect the primary endpoint of sustained recovery. This ordinal outcome includes 7 well-defined mutually exclusive categories, each of which assesses further progression of disease, as well as recovery from COVID-19.

While the two ordinal outcomes are correlated, it is yet to be determined which of these two outcomes will best identify the investigational agents that, when given with SOC, have activity that merits advancement.

Day 5 was chosen for the timing of these ordinal outcomes for several reasons based on the following assumptions. The impact of the investigational agent on disease progression may not be immediate; a few days may be needed to see the effects on clinical outcomes as measured by each ordinal outcome. Also, transient treatment effects that are no longer present at Day 5 may be clinically less relevant. Assessment of the ordinal outcome at a later time point may result in a diminished treatment difference because spontaneous recovery from COVID-19 may have begun in many participants. Use of Day 5 to characterize the clinical severity of participants in 7 categories as studied here, results in a distribution of participants in the placebo group for the ordinal outcome that is sufficiently granular and not overly skewed to the most severe or least severe categories and, therefore, provides good power for comparing the two treatment groups (see section 6.3). Finally, an early time point of ascertaining the outcomes will facilitate more rapid interim analyses for these two ordinal outcomes.

4.2 Primary and Secondary Outcomes to Evaluate Efficacy and Safety

The primary endpoint is ***time from randomization to sustained recovery,*** defined as being discharged from the index hospitalization, followed by being alive and *home* for 14 consecutive days prior to Day 90.

Home is defined as the level of residence or facility where the participant was residing prior to hospital admission leading to enrollment in this protocol.

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 rehab facility); and 4) **Long-term acute care hospital** (hospital aimed at providing intensive, longer term acute care services, often for more than 28 days).

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 affiliated with a “long-term acute care” hospital recover when they return to the same or lower level of care.

Readmission from “home” may occur and if this occurs within 14 days of the first discharge to “home”, then the primary endpoint will not be reached until such time as the participant has been at home for 14 consecutive days.

Participants residing in a facility solely for public health or quarantine purposes will be considered as residing in the lowest level of required residence had these public health measures not been instated.

Some recovering patients are discharged from the hospital while still requiring continuous low flow supplementary oxygen to maintain satisfactory blood oxygenation for some period of time. Sensitivity analyses will be carried out using outcomes which are variations of the definition of sustained recovery. These outcomes will use definitions of sustained recovery that consider continuous use of supplemental oxygen reported during the 14-day period at home following discharge. These outcomes are cited as secondary endpoints.

4.2.1 Rationale for primary outcome

The primary outcome is intended to identify efficacy among the investigational agents.

Whereas mortality may be the most important outcome, the sample size to detect a plausible treatment effect for such an outcome would be much larger than outlined in this protocol and was judged not to be feasible to be the primary outcome. Nor was mortality considered to be the only relevant measure of efficacy in COVID-19.

The primary outcome is assessed during 90 days of follow-up, which is longer than for other trials of investigational agents for COVID-19, which are typically 28 days. The longer follow-up will allow better ascertainment of recovery from the longer-term consequences of the underlying disease, and hence the efficacy of the investigational agent. This is likely to be particularly true for patients who experience extra-pulmonary disease in conjunction with their COVID-19, and for patients enrolled while receiving care for life-threatening organ failure. It is also projected that excess mortality may still be observed beyond Day 28 until Day 90. All-cause mortality is an important secondary outcome (see below).

4.2.2 Secondary outcomes

In addition to the primary endpoint, several secondary efficacy endpoints will be assessed. These endpoints will be assessed for all participants enrolled.

1. All-cause mortality through 90 days of follow-up

2. Composite of time to sustained recovery and mortality through 90 days of follow-up

3. Time to discharge for the initial hospitalization

4. Days alive outside of a short-term acute care hospital up to day 90

5. Ordinal outcomes, pulmonary+ and pulmonary, on Days 1-7, and pulmonary ordinal outcome on Days 14 and 28

6. Clinical organ failure or serious infections defined by development of any one or more of the following clinical events through Day 28 (see PIM for criteria for what constitutes each of these conditions):

    a. Respiratory dysfunction:
        1. Respiratory failure defined as receipt of high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation or ECMO

    b. Cardiac and vascular dysfunction:
        1. Myocardial infarction
        2. Myocarditis or pericarditis
        3. CHF: new onset NYHA class III or IV, or worsening to class III or IV
        4. Hypotension requiring institution of vasopressor therapy

    c. Renal dysfunction:
        1. New requirement for renal replacement therapy

    d. Hepatic dysfunction:
        1. Hepatic decompensation

    e. Neurological dysfunction
        1. Acute delirium
        2. Cerebrovascular event (stroke, cerebrovascular accident [CVA])
        3. Transient ischemic events (i.e., CVA symptomatology resolving <24 hrs)
        4. Encephalitis, meningitis or myelitis

    f. Haematological dysfunction:
        1. Disseminated intravascular coagulation
        2. New arterial or venous thromboembolic events, including pulmonary embolism and deep vein thrombosis
        3. Major bleeding events (>2 units of blood within 24 hours, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding).

    g. Serious infection:

1. Intercurrent, at least probable, documented serious disease caused by an infection *other than* SARS-CoV2, requiring antimicrobial administration and care within an acute-care hospital.

7. A composite of death, clinical organ failure or serious infections (see above)

8. Outcomes assessed in other treatment trials of COVID-19 for hospitalized participants in order to facilitate cross-trial comparisons and overviews (e.g. 6- , 7-, and 8-category ordinal scales assessed at Days 1-7, 14 and 28; time to improvement in 1 or 2 categories of ordinal scale; time to best 3 categories of ordinal scale, and binary outcomes defined by improvement or worsening based on other ordinal outcomes)

9. A composite of cardiovascular events (outcomes listed above in items 6b1, 6e2 and 6e3) and thromboembolic events (item 6f2)

10. Safety and tolerability as measured by:
    a. A composite of grade 3 and 4 clinical adverse events, SAEs, clinical organ failure or serious infections (see item 6 above) or death through Day 5 (primary safety endpoint) and through Day 28 (the components of this composite will also be summarized)
    b. Infusion-related reactions of any severity and percentage of participants for whom the infusion was interrupted or stopped prior to completion
    c. A composite of SAEs, clinical organ failure or serious infections (see item 6 above) or death through Day 90
    d. Adverse events of any grade through Day 7
    e. Prevalence of adverse events of any grade at Day 14 and Day 28
    f. A composite of hospitalization readmissions or death through 18 months.

11. Change in antibody profile, overall titers of antibodies and neutralizing antibody levels from baseline to Days 1, 3, 5 and 28 and 90

12. Outcomes that consider home use of supplemental oxygen above pre-morbid oxygen use for sensitivity analyses for the primary outcome:
    a. Alive at home and no use of continuous supplemental oxygen for an uninterrupted 14 day period
    b. Alive at home for an uninterrupted 14 day period and no use of continuous supplemental oxygen at the end of the 14 day time period.

4.2.3 Rationale for secondary outcomes

Mortality and the composite of time to death or sustained recovery (see section 11.2 for the analysis of this outcome using a win ratio statistic)[74] are the two key secondary outcomes. An effective investigational agent should lead to a favorable trend for those these outcomes. Conclusive evidence for a treatment difference in mortality requires larger sample sizes than planned, and we expect that there is better power for detecting a treatment effect in the composite outcome than mortality.

Safety is assessed through a comprehensive review of data collected from baseline through follow-up. On day 0, during and immediately after the infusion, infusion-related reactions of any grade severity, and premature infusion termination are captured. From study entry through Day 28, deaths, grade 3 and 4 clinical adverse events, and the components of the

two ordinal outcomes assessed at Day 5 contribute to the safety assessment. A composite primary safety outcome is defined at Day 5. On Day 0 and Day 5, safety laboratory test results are reported, and grading determined (section 9.1). Finally, SAE's, SUSAR's, (re)admissions for acute care, organ disease, and organ dysfunction including supportive treatment hereof, are ascertained during the entire follow-up period.

The definitions of outcomes in different COVID-19 trials are evolving. It will be important to adequately capture data that enables the trial to "reconstruct" outcomes used in other trials.

Finally, continuous supplemental oxygen is increasingly prescribed for patients discharged from the hospital following treatment for COVID-19. Therefore, it will be important to carry out sensitivity analyses that consider home oxygen use in interpreting the results of the trial for the primary endpoint of sustained recovery.

5 Objectives

5.1 Primary Objective

The primary objective of this protocol is to determine whether investigational agents, initially focusing on those that are aimed at enhancing the host immune response to SARS-CoV-2 infection are safe and superior to control (e.g., placebo) when given with SOC for the primary endpoint of time to sustained recovery evaluated up to 90 days after randomization.

SOC may be modified (updated based on data from this or other trials) during the course of evaluating different investigational agents with this master protocol.

5.2 Secondary Objectives

Two key secondary objectives are to compare each investigational agent with control for all-cause mortality and a composite outcome which considers both time to sustained recovery and mortality.

Other secondary objectives are to compare each investigational agent with control for the secondary outcomes stated in section 4.

In addition, the primary endpoint of time to sustained recovery will be evaluated for subgroups defined by the following characteristics measured at enrollment:

- Disease severity as defined in the design for stratification
- Age
- Biological sex
- Race/ethnicity
- Type of residence/facility (home)
- BMI
- History of chronic conditions (cardiovascular disease, diabetes, asthma, chronic obstructive pulmonary disease, hypertension, hepatic impairment, chronic kidney disease, cancer)
- Geographic location
- Upper respiratory SARS-CoV-2 viral load
- SARS-CoV-2 neutralizing antibody level
- Duration of symptoms prior to enrollment

- Respiratory function scale
- Organ/respiratory dysfunction category based on each ordinal outcome (pulmonary+ and pulmonary)
- NEW score
- Disease progression risk score (defined using pooled treatment groups with the following baseline predictors of the primary outcome (sustained recovery): age, biological sex, duration of symptoms, ordinal category at entry, NEW score, and presence of chronic health conditions).

6 Study Design

TICO (Therapeutics for Inpatients with COVID-19) is a master protocol to evaluate the safety and efficacy of multiple investigational agents aimed at modifying the host immune response to SARS-CoV-2 infection, or directly enhancing viral control in order to limit disease progression. Master protocols can provide a more efficient approach to the evaluation of multiple experimental interventions for a single disease such as COVID-19 in a continuous manner.

The trial described in this master protocol is a phase III randomized, blinded, controlled platform trial that allows investigational agents to be added and dropped during the study for efficient testing of new agents against placebo within the same trial infrastructure. When more than one agent is being tested concurrently, participants will be randomized across agents, as well as to agent/control. This will allow rapid testing of multiple agents as the pooling of controls across agents requires fewer patients to be randomized to the matched control arm of each agent. However, this will only occur when feasible and when multiple agents are available to be tested at the same time. If an investigational agent shows superiority over placebo + SOC as initially defined, SOC for future investigational treatment evaluations will be modified accordingly.

Figure 1. A Phase III Platform Trial for Efficiently Evaluating Multiple Investigational Agents Over Time

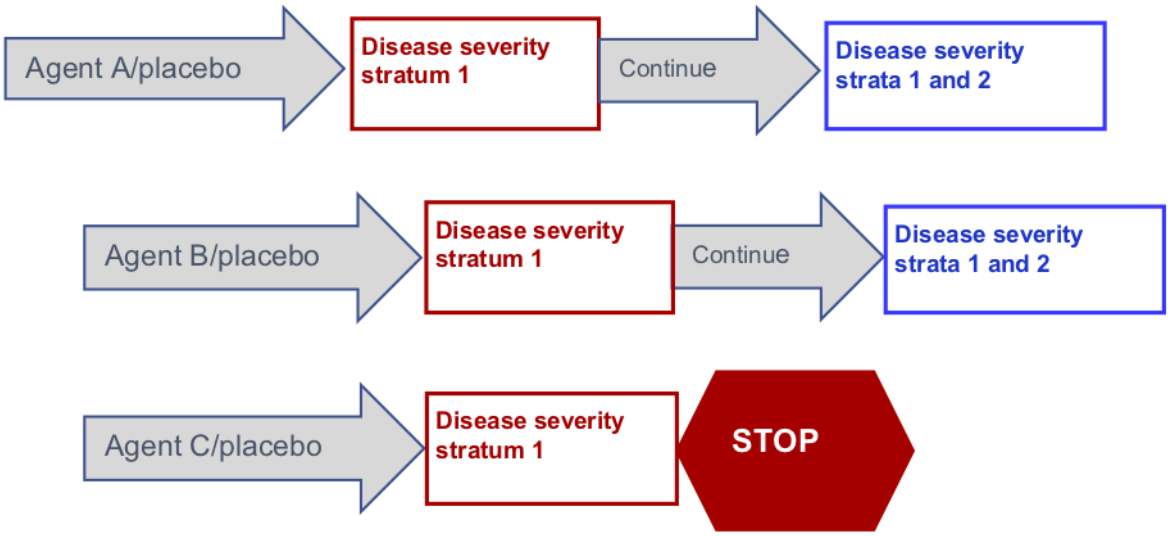

Figure 1 illustrates three aspects of the study design. Investigational agents may enter the trial simultaneously or sequentially. Agents B and C entered the trial simultaneously after agent A. During the time of overlapping randomization for the 3 agents, placebo is shared as described in section 6.1. All 3 agents share a placebo for part of the time in which patients in disease severity stratum 1 are enrolled. For a period of time participants in disease severity stratum 2 are only eligible for Agent A/placebo.

Agents which demonstrate an acceptable risk versus benefit profile in the initial cohort of participants in disease severity stratum 1 and pass the futility assessment based on the Day 5 ordinal outcomes continue enrollment with expanded eligibility criteria. This is illustrated by both agents A and B. Both agents advance to enroll participants in disease severity stratum 2 as well as 1. Agent A advances shortly before agent B.

Agent C illustrates an agent that did not pass the futility assessment in the initial cohort of patients in disease severity stratum 1. Enrollment stopped for agent C. Follow-up for the participants randomized (all in disease severity stratum 1) to agent C/placebo will continue through 18 months of follow-up in order to continue to assess safety and other outcomes.

In some cases, more than one dose of an investigational agent will be studied. For such agents, only one of the doses will be advanced to the expanded cohort that includes participants in disease severity strata 1 and 2.

6.1 Randomization and Stratification

Patients will be equally allocated to each investigational agent + SOC or to placebo + SOC. For example, for a study of a single investigational agent, participants will be randomized in a 1:1 ratio to the investigational agent + SOC or placebo + SOC. If a participant is eligible for two investigational agents, the allocation will be 1:1:1 to investigational agent A + SOC, agent B + SOC, or placebo + SOC. Because the two investigational agents (A and B) may require different placebos (for example, when infusion volumes differ), the 1:1:1 allocation ratio will be achieved through a two-step randomization procedure: in *step 1*, the participant is randomized 2:1 to “active” versus “placebo”; in *step 2*, the participant is randomized 1:1

to A versus B. With k agents, this can be viewed as an initial k:1 allocation to "active" versus "placebo", followed by a second, even allocation to one of the available agents (for example, if a participant was allocated to "placebo" in step 1, then the step 2 allocation will be 1:1 to "agent-specific placebo for A" versus "agent-specific placebo for B"). Sites will be informed of the specific investigational agent/placebo (e.g., A or B) to which the participant was randomized (see section 6.2). For the analysis, the concurrent agent-specific placebo groups will be pooled, resulting in a 1:1 allocation ratio for comparing each investigational agent versus the (pooled) placebo group.

If investigational agents are added or dropped, the allocation ratio to active versus placebo will be appropriately modified, and overall sample size will be recalculated as appropriate.

Randomization will be stratified by study site pharmacy (several clinical sites may share one study site pharmacy) and severity of disease at entry. The two strata that define disease severity are:

Disease severity stratum 1: Absence of all of the following: stroke, meningitis encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, symptomatic congestive heart failure (NYHA class III or IV), arterial or deep venous thrombosis or pulmonary embolism, requirement for invasive mechanical ventilation, ECMO, mechanical circulatory support, vasopressor therapy, or new renal replacement therapy.

Disease severity stratum 2: Presence of at least one of the excluded conditions or treatments in disease severity stratum 1.

Within each stratum, mass-weighted urn randomization[75] will be used to generate the active and placebo assignments. This will ensure throughout the trial placebo allocation near the intended ratio while also ensuring near equal numbers of active and matched placebo assignments to each agent.

If more than one investigational agent is being compared with placebo and they have different contraindications, consideration will be given to allowing participants to enter with randomization to each agent versus placebo separately as well as randomization to both agents. If the number of participants expected to have a contraindication is small, they will be excluded from the trial rather than establishing a separate randomization mechanism. Comparisons will be of each investigational treatment against its control arm. The control arm consists of all participants who were "at risk" of being randomized to the investigational agent but were randomized to a control group instead. This concept is relevant when the randomization includes investigational agents with different eligibility criteria or introduction into the platform trial at different time points. Formal randomization includes a matched placebo group for each agent, and the placebo groups will be pooled across agents, but only participants who 1) were eligible for the investigational agent under consideration, and 2) were randomized contemporaneously in a stratum will be included in the control group for a given agent.

The default randomization allocation to agent (or its placebo) for which a participant is eligible is as outlined above. However, in some circumstances this allocation ratio may be changed by the (blinded) protocol leadership based on an overall assessment of how the master protocol framework is able to produce relevant and novel findings most effectively.

6.2 Blinding

Investigational agents or placebo (as necessary) will be prepared by a pharmacist who is not blinded to the treatment assignment. All other study staff, including those at sites, and those in roles spanning multiple sites or spanning the protocol as a whole, will be blinded unless otherwise specified herein.

For investigational agents infused, blinding of the participant and clinical staff will be achieved by placing a colored sleeve over the infusion bags used for investigational agents and placebos. Placebo will consist of an isotonic crystalloid, referred to as an isotonic saline solution.

When more than one investigational agent is available for randomization, the clinical staff will be informed to which investigational agent/placebo the participant was randomly assigned for infusion, but they will be blinded to whether the random assignment was to the active investigational agent or matching placebo.

If the blind is broken for safety reasons, this will be recorded, and the protocol chair will be notified. In that situation, every attempt will be made to minimize the number of people unblinded. Specific unblinding procedures and instructions are found in the PIM.

6.3 Sample size assumptions

All sample size calculations are aimed at pairwise comparisons between a given investigational agent and its control arm. The following assumptions were made in estimating the required sample size for this phase III trial.

a. The primary analysis will be intention to treat. Gray's test with rho=0 will be used,[76] with stratification by disease severity at entry for comparing each investigational agent to control for the primary endpoint of time to sustained recovery (see section 4.2.1). Gray's test with rho=0 is the analogue of the log-rank test in the presence of competing risks; it is used here to account for the competing risk of death when analysing time to sustained recovery.

b. Type 1 error will be set at 0.025 (1-sided). This type 1 error will not be adjusted for the number of investigational agents being compared with placebo as each of the agents is expected to impact the primary endpoint through different mechanisms. If this is not the case, a type 1 error adjustment may be considered.

c. Power is set at 90% to detect a 25% increase in the rate of sustained recovery for the investigational treatment compared to placebo. This moderate efficacy is assumed considering the findings from ACTT-1 and the percentage of patients in each baseline risk category of the pulmonary ordinal outcome.[77] For an investigational agent that passes the initial futility assessment based on participants in disease severity stratum 1 that are initially enrolled, we expect approximately 50% of participants enrolled in the cohort expansion that includes both disease severity strata 1 and 2 to be in categories 5 or 6 of the ordinal outcome. Since most participants enrolled in the initial cohort will be categories 2, 3 or 4 of the ordinal outcome, we assume that 35% of patients in the final analysis will be in the more severe categories of the ordinal outcome; mortality is expected to be higher for participants in the more severe categories at entry. Among surviving patients we assume most will have met the criteria for sustained recovery.

d. With these assumptions for type 1 and type 2 error and a sustained recovery rate ratio of 1.25 for the investigational agent versus control, 843 sustained recoveries are needed.[78,79]

e. Given the planned 90 day follow-up for each participant, we estimate that the sample size is slightly larger than the number of recoveries (i.e., we expect a low rate of loss-to-follow-up or deaths). For 2 groups, we assume that the sample size is approximately 20% higher than the number of recoveries, to account for deaths, a small number of withdrawals of consent, and a small number of patients remaining in the hospital at Day 90. Total sample size for 2 groups is approximately 1,000 (500 per group).

f. In order to observe 843 sustained recoveries among 1000 participants, and assuming 3% withdrawal of consent, at least 87% of participants (pooled across the two treatment arms) would have to achieve sustained recovery by Day 90. Assuming a recovery rate ratio of 1.25, this corresponds to 89.9% with sustained recovery among those randomized to the investigational agent, compared with 84.1% in the control group.

Sample size will be re-estimated before enrollment is complete to determine whether the planned sample size of 1,000 participants followed for 90 days will yield the planned number of primary events. Sample size may be increased to achieve the event target in the planned follow-up of 90 days. A sample size increase may also be considered in order to achieve the event target before all participants are followed for 90 days.

6.4 Schedule of Assessments

Participants will be randomized and given their initial infusion on Day 0. All participants randomized will be followed through 18 months following randomization for collection of study data (Appendix B and section 9.1 for details).

6.5 Approach to Intercurrent Therapies and Clinical Trial Co-enrollment

In general, the study will take a pragmatic approach to the use of intercurrent, concomitant medications. Except for use of convalescent plasma, hyperimmune SARS-CoV-2 immunoglobulin or nMAb which is not permitted prior to entry or before Day 5, there are few restrictions.

Sponsor and/or protocol leadership may, based upon convincing new evidence, act in the interest of participant protection, and in avoidance of confounding, to exclude/dis-allow use of any specific concomitant therapy found to be reasonably contraindicated for a well-defined portion of the study population (see Appendix I). Such a determination may be made, communicated, and implemented by a Protocol Clarification Memo until it is reasonable to amend the protocol for other reasons.

Participants will be asked at screening to agree to refrain from participation in other clinical trials until at least the assessment at Day 5 except for certain trials approved by trial leadership. It is recognised that, in the case of progression during follow-up to life-threatening disease and end-organ failure (broadly categories 5 and 6 of the intermediate outcome measure; section 4.1) there will be considerable clinical concern, and participation in an additional clinical trial at that time will not be restricted.

The protocol leadership will make a determination on the appropriateness of a trial for which co-enrolment will be allowed.

Prior participation in clinical trials (except receipt of hIVIG, convalescent plasma or another nMAb) is not restricted, recognising for example that participants may have enrolled in a study for mild disease prior to progression and then may wish to participate in this study at the onset of progression.

All participants will be compared throughout follow-up, irrespective of use of concomitant treatments. Concomitant treatments will be recorded at baseline, Day 5 and Day 28. The study randomization and study site pharmacy stratification will balance the use of concomitant medications on average at baseline and these will be summarized with other baseline characteristics. Follow-up use of concomitant treatments may differ by treatment group reflecting different efficacy/safety of the study treatments and use of concomitant treatments will be summarized by treatment group.

7 Study Population

For each investigational agent, an estimated 1,000 COVID-19 participants will be enrolled at clinical trial sites globally. The time from screening (Day -1 or Day 0) to end of study for an individual participant is 18 months.

Patient eligibility must be confirmed by a study clinician named on the delegation log.

Initially, approximately 300 participants in the disease severity stratum 1 will be enrolled. For investigational agents passing an initial futility assessment for these participants, enrollment will be expanded, seamlessly and without any data unblinding, to include participants in disease severity stratum 2 as well as those in disease severity stratum 1.

Protocol inclusion and exclusion criteria are intentionally straightforward and are NOT subject to exception for even minor deviations by Study Medical Officers or by the Sponsor Medical Monitor.

7.1 Inclusion Criteria

1. Age ≥ 18 years;

2. Informed consent by the patient or the patient's legally-authorized representative (LAR)*;

3. SARS-CoV-2 infection, documented by a nucleic acid test (NAT) or equivalent testing within 3 days prior to randomization OR documented by NAT or equivalent testing more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection per the responsible investigator (For non-NAT tests, only those deemed with equivalent specificity to NAT by the protocol team will be allowed. A central list of allowed non-NAT tests will be maintained.);

4. Duration of symptoms attributable to COVID-19 ≤ 12 days per the responsible investigator;

5. Requiring admission for inpatient hospital acute medical care for clinical manifestations of COVID-19, per the responsible investigator, and NOT for purely public health or quarantine purposes.

***Continuing consent**

For participants whose consent was initially obtained from a LAR, but who subsequently regain decision-making capacity while in hospital will be approached for consent for continuing participation, including continuance of data acquisition. The consent form signed by the LAR should reflect that such consent should be obtained.

7.2 Exclusion Criteria

1. Prior receipt of
   - Any SARS-CoV-2 hIVIG, convalescent plasma from a person who recovered from COVID-19 or
   - SARS-CoV-2 nMAb at any time prior to hospitalization;

2. Not willing to abstain from participation in other COVID-19 treatment trials until after Day 5 (With the approval of study leadership, enrollment before or on Day 5 is permitted for individual trials.)

3. In the opinion of the responsible investigator, any condition for which, participation would not be in the best interest of the participant or that could limit protocol specified assessments;

4. Expected inability to participate in study procedures;

Prior to the initial futility assessment for an investigational agent, the following two additional exclusions (5 and 6) which define disease severity stratum 2 apply:

5. Presence at enrollment of any of the following:
   a. stroke
   b. meningitis
   c. encephalitis
   d. myelitis
   e. myocardial infarction
   f. myocarditis
   g. pericarditis
   h. symptomatic CHF (NYHA class III-IV)
   i. arterial or deep venous thrombosis or pulmonary embolism

6. Current requirement for any of the following:
   a. invasive mechanical ventilation
   b. ECMO
   c. mechanical circulatory support
   d. vasopressor therapy
   e. commencement of renal replacement therapy at this admission (i.e. not patients on chronic renal replacement therapy).

Exclusions that may be appropriate for an investigational agent studied are referenced in the relevant appendix (H) for the investigational agent. The contraindications for use of components of SOC are outlined in Appendix I and in the PIM.

7.3 Costs to Participants

There is no cost to participants for the research tests, procedures/evaluations and study product while taking part in this trial. Procedures and treatment for clinical care including

costs associated with hospital stay may be billed to the participant, participant's insurance or third party.

8 Study Product

Investigational agents and SOC treatment to be used are described in Appendices H and I, respectively.

9 Study Assessments and Procedures

9.1 Screening/Baseline and Follow-up Assessments

Data collection at each visit is outlined below and summarized in Appendix B. Day 0 refers to the day on which randomization occurs and on which the investigational agent/placebo is infused. Screening and randomization can be done in the same session. The term "baseline" refers to data that are collected prior to randomization.

9.1.1 Screening/Baseline Assessments

After obtaining informed consent, the following assessments are performed within 24 hours prior to randomization to confirm eligibility and to collect baseline data:

- Documentation of SARS-CoV-2 infection by NAT or equivalent testing that was performed within 3 days prior to randomization, OR documentation by NAT or equivalent testing more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection)

- A focused medical history, including the following information:
    - Demographics including age, gender, and type residence or facility prior to current illness (i.e. "home")
    - Day of onset of COVID-19 signs and symptoms
    - Components of ordinal outcomes
    - History of chronic medical conditions, including targeted conditions for outcome analysis
    - Targeted concomitant medications and SARS-CoV-2 vaccine trial participation

- A focused physical examination including height and weight

- Respiratory function scale

- Blood draw for local laboratory evaluations:
    - White blood cell count
    - Hemoglobin
    - Platelets
    - Lymphocytes
    - CRP
    - Serum creatinine
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)

- Vital signs for NEW score

- Plasma and serum specimens for central testing for SARS-CoV-2 antibody determination and storage for future related research (four 1.0 mL aliquots of serum and four 1.0 mL aliquots of plasma). Two 9 mL tubes, one SST and one EDTA, of blood (18 mL total) will be drawn in order obtain the 8 aliquots.

- Midturbinate nasal swab procedure for central determination of SARS-CoV-2 viral load
- Contact details (phone, e-mail or other types of contact) for the participant and at least two close relatives/friends, to ensure reliable data collection during follow-up in the trial.
- Urine or serum pregnancy test in women of childbearing potential who do not already have evidence of pregnancy

In some cases, it may not possible to draw blood for local laboratory assessments and storage and/or to obtain a midturbinate nasal swab for storage prior to the time of randomization. In these cases, the blood draw and swab collection can be obtained after the time of randomization but before the infusion of the blinded investigational agent/placebo.

The overall eligibility of the patient for the study will be assessed once all screening information is available. The screening process can be suspended prior to completion of the assessment at any time if exclusions are identified by the study team.

Participants who qualify will be randomized within 24 hours of consent and given the infusion of the blinded investigational agent/placebo. Immediately prior to randomization, the disease severity stratum of the participant should be verified.

On Day 0 following randomization the following are assessed:

- Adverse events of any grade severity present prior to the infusion
- Start and stop times of the infusion of the investigational agent/placebo and remdesivir
- Infusion-related reactions to the investigational agent/placebo
- Medication used prophylactically or therapeutically to manage infusion-related reactions
- New adverse events of any grade severity during and after the infusion

Participants should be monitored for at least 2 hours post infusion and have a final check 2 hours later. Participants who experience AEs during or after the infusion should be followed closely until the resolution of the AE.

9.1.2 Follow-up Assessments

Participants will be followed through 18 months following randomization for collection of study data (Appendix B). Clinical data will be collected on Days 0-7, 14, 28, 60, 90, 6 months, 12 months, and 18 months. These data will include discharge status, and interim changes in medical history (targeted to components of the intermediate ordinal outcomes and secondary endpoints). Local laboratory measurements will also be obtained on Day 5. Concomitant medications will be collected on Days 5 and 28, clinical (i.e., not limited to a laboratory abnormality) incident AEs of grade 3 and 4 severity through Day 28, and hospitalization readmissions and deaths through 18 months.

Both intermediate ordinal outcomes will be assessed on Days 1-7. Adverse events of any grade severity will be collected on Days 0-7. The pulmonary ordinal outcome will also be assessed on Days 14 and 28. On Days 14 and 28 AEs of any grade severity will also be

collected. Components necessary to determine the pulmonary ordinal outcome will be collected to allow the computation of the ordinal outcome for every day through Day 14.

At the time of discharge, the residence/place of living to which the participant was discharged and whether it was the type of residence (i.e. “home”) occupied at the time of onset of COVID-19 symptoms will be ascertained. All changes in this status (e.g., re-admission to another hospital or an intermediate care facility) will be collected at approximately 2 week intervals, starting with the day 14 visit, to assess when the participant meets the criterion for the primary endpoint of 14 consecutive days “home”. With this plan we will also address the secondary outcome of total days alive outside of a short-term acute care hospital.

For participants who are no longer hospitalized, in-person visits will be done on study Days 1, 3, 5, 28 and 90, when blood is collected. At each of these visits, plasma and serum specimens for central testing for SARS-CoV-2 antibody determination and storage (four 1.0 mL aliquots of serum and four 1.0 mL aliquots of plasma) will be obtained for future related research. Two 9 mL tubes, SST and EDTA, of blood (18 mL total) will be drawn in order obtain the 8 aliquots. If it is not possible to do an in-person visit on Day 3 or Day 5, the participant should be contacted to record the required clinical data on the study day and blood draws may be done one day earlier or one day later. In person research visits for participants at their residents or home health and mobile phlebotomy services may also be utilized to complete protocol-required data/specimen collection during follow-up.

For other visits on Days 7, 14, 42, 60, and 75, 6 months, 12 months, and 18 months, contact with the participant for study data collection may be performed by telephone or other electronic communication. Other information will be gathered, as outlined in Appendix B. This will include information on hospital readmissions (e.g., date of readmission, date of discharge, and reason for readmission) and deaths through 18 months. Safety data collection and reporting are described further in section 10.

9.1.3 Stored Samples and Future Research

The plasma and serum specimens collected as outlined above and the inoculum from the baseline mid-turbinate nasal swab will be stored at a central specimen repository in the US. In addition to the specified testing to be done per protocol, the specimens will be available for later use in research concerning COVID-19, SARS-CoV-2, and the impact of the study treatment. Proposed research utilizing these specimens will be reviewed and approved by the study scientific steering committee. Results of research tests on individual specimens will not be given to participants or their clinicians. Aggregate research results will be made available.

10 Safety Assessment

The safety evaluation of the study intervention includes several components, all of which will be regularly reviewed by the independent DSMB. For this protocol, the term “*study intervention*” refers to the investigational agent or placebo, and to study provided SOC treatment(s).

Infusion-related reactions of any grade are only collected for the blinded investigational agent/placebo. All other AEs are collected for the study intervention (either the blinded investigational agent/placebo or study provided SOC treatment).

The following information will be collected on eCRFs to evaluate safety:

- Infusion-related reactions of any grade severity during, or within 2 hours post-infusion of the investigational agent/placebo.
- Targeted laboratory results centrally graded for severity at Day 5.
- Clinical adverse events of any grade severity on Days 0-7, on Day 14 and on Day 28 (isolated laboratory abnormalities that are not associated with signs, symptoms, or a specific clinical diagnosis/syndrome are not collected).
- Clinical adverse events of grade 3 and 4 through Day 28 (isolated laboratory abnormalities that are not associated with signs, symptoms, or a specific clinical diagnosis/syndrome are not collected).
- Clinical events, including death, that are reported on eCRFs as part of the pulmonary+ ordinal outcome or as secondary outcomes through Day 90. These are considered as protocol specified exempt serious events (see 10.2.5) and are not reported on SAE eCRFs unless they are considered related to the study intervention (either the blinded investigational agent/placebo or a study-provided SOC treatment). Protocol exempt serious events are listed in section 10.2.5 and the PIM.
- Serious adverse events, including laboratory-only serious events, through Day 90 that are:
  - Related to the study intervention; or.
  - Not exempt from reporting on the SAE eCRF (events listed in section 10.2.5 are exempt).
- Unanticipated problems through Day 90.
- Deaths through 18 months.
- Hospital readmissions through 18 months.

An overview of safety data collected during the study is given in Table 1.

Table 1 Overview of Safety Data Collection

	Infusion +2 hrs	Days 0-7	Day 14	Day 28	Day 90	Months 6, 12 and 18
Infusion-related reactions and symptoms	X					
Clinical AEs of any grade severity		X	X	X		
Grade 3 and 4 clinical AEs from Day 7 through Day 28*			X	X		
Targeted laboratory abnormalities of any grade		X (Day 5)				
Hospital admissions and deaths		Collected through Month 18				
Targeted clinical events collected as study endpoints**	Collected through Day 90					
SAEs not exempt from reporting (i.e., not considered a protocol specified exempt event)	Collected through Day 90					
Any SAE related to study intervention	Collected through Day 90					
Unanticipated problems	Collected through Day 90					
* Grade 3 and 4 clinical AEs on Days 1-7 are reported each day; those occurring between Days 8 and 14 are reported at the Day 14 visit, and those occurring between Days 15 and 28 are reported at the Day 28 visit. ** see section 10.2.5 for protocol specified exempt serious events and the PIM						

Definitions and methods of reporting each type of event are given below.

10.1 Definitions

10.1.1 Adverse Event (AE)

An AE is any untoward or unfavourable medical occurrence in a study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with their participation in research, whether or not considered related to the research. If a diagnosis is clinically evident (or subsequently determined), the diagnosis, rather than the individual signs and symptoms or lab abnormalities, will be recorded as the AE.

In Appendix H details are outlined for each investigational agent under study of the following: specific AEs observed to be possibly associated with the agent in question, and how to monitor for, clinically handle and report such AEs, should they arise.

10.1.2 Criteria for Seriousness

Events are serious if they lead to one of the following outcomes:

- Death
- Life-threatening (i.e., an immediate threat to life)
- Hospitalization or prolongation of hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital abnormalities/birth defects
- Other important medical events that may jeopardize the participant and/or may require intervention to prevent one of the outcomes listed above

10.1.3 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience or outcome that is:

1. Unexpected in terms of nature, severity, or frequency in relation to:
   a. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents; and
   b. the characteristics of the population being studied; and
2. Possibly, probably, or definitely related to participation in the research; and
3. Places study participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized per the Investigator's Brochure(s) (IBs).

Furthermore, a UP could be an expected event that occurs at a greater frequency than would be expected based on current knowledge of the disease and treatment under study. The DSMB providing oversight to the study may make such an assessment based on an aggregate analysis of events.

10.1.4 Severity

The investigator will evaluate all AEs with respect to both seriousness (results in outcomes as above) and **severity** (intensity or grade). AEs will be graded for severity according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events* (also known at the DAIDS AE Grading Table; see Appendix D for the URL).

For specific events that are not included in the DAIDS AE Grading Table, the generic scale below is to be used:

Table 2 GENERIC AE GRADING SCALE

Grade 1	Events causing no or minimal interference with usual social and functional activities, and NOT raising a concern, and NOT requiring a medical intervention/ therapy.
Grade 2	Events causing greater than minimal interference with usual social and functional activities; some assistance may be needed; no or minimal medical intervention/therapy required.
Grade 3	Events causing inability to perform usual social and functional activities; some assistance usually required; medical intervention/therapy required.
Grade 4	Events causing inability to perform basic self-care functions; medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
Grade 5	Events resulting in death

10.1.5 Causality

Causality refers to the likelihood that the event is causally related to the study intervention. It will be assessed for SAEs and UPs. This assessment will be made for both the blinded investigational agent/placebo and any study-supplied SOC treatment using the following guidelines:

- Reasonable possibility: There is a clear temporal relationship between the study intervention and the event onset; **and** the event is known to occur with the study intervention or there is a reasonable possibility that the study intervention caused the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the event.

- No reasonable possibility: There is no evidence suggesting that the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

The causality assessment is based on available information at the time of the assessment of the event. The investigator may revise these assessments as additional information becomes available.

10.1.6 Expectedness

Expectedness will be assessed for SAEs using the Reference Safety Information section of the IBs for the investigational agent and any study-provided background therapy.

The expectedness assessment is based on available information at the time of the assessment of the event. The investigator may revise these assessments as additional information becomes available.

10.2 Schedule for Reporting of Specific Events

This section describes the schedule for reporting different types of safety outcomes on eCRFs as part of the protocol data collection plan. It is recognized that in the care of study participants, more information may be collected and recorded in the participant's medical record. The information collected in the medical record serves as source documentation of events (e.g., signs, symptoms, diagnoses) considered for reporting on eCRFs as part of protocol data collection.

10.2.1 Infusion-related reactions

Infusion-related signs/symptoms of any grade that are new or have increased in grade compared to their pre-infusion level are reported on the infusion eCRF checklist for the investigational agent/or matched placebo if they occur during or within 2 hours post infusion. Any infusion related reaction assessed as meeting SAE criteria will also be reported on an SAE eCRF.

10.2.2 Targeted Laboratory Abnormalities

Selected laboratory tests are reported from assessments made on Day 0 and Day 5. These values will be associated with a severity grade centrally using the laboratory test results reported on the eCRFs (using normal ranges when applicable), and with the DAIDS AE Grading Table.

Other laboratory abnormalities identified in the course of the participant's routine clinical care (e.g., an isolated elevated glucose level) are not reportable as AEs unless they are associated with signs or symptoms, or associated with a specific clinical diagnosis/syndrome (e.g., diabetic ketoacidosis), in which case the syndrome/diagnosis is reported on the appropriate adverse event eCRF. In addition, if an isolated laboratory test result meets SAE reporting criteria (e.g., the laboratory abnormality meets the criteria for a serious event as outlined in section 10.1.2), it should be reported as an SAE on the SAE eCRF.

10.2.3 Clinical adverse events of any grade severity on Days 0-7, 14 and 28

Beginning 2 hours post-infusion of the investigational agent or matched placebo, on Days 0-7, clinical AEs that are new or that have increased in grade compared to their pre-infusion level will be reported on eCRFs.

On Day 14 and on Day 28 AEs of any grade severity that the participant reports that day will also be collected on an eCRF.

These reportable AEs should be assessed for SAE/UP (sections 10.2.6 and 10.2.7) reporting on the SAE eCRF or for protocol specified exempt serious events (section 10.2.5) reporting on the eCRF documenting the hospital course.

This information supplements the data collected on Grade 3 and 4 events since the last study visit described in section 10.2.4.

10.2.4 Grade 3 and 4 clinical adverse events through Day 28

Adverse clinical events reaching Grade 3 or 4 severity level that occur between days 8 and 28 will be reported on an eCRF at the Day 14 and Day 28 visits. The date the event reached the indicated grade will be collected to permit time-to-event analyses.

These reportable AEs should be assessed for SAE/UP (sections 10.2.6 and 10.2.7) reporting on the SAE eCRF or for protocol specified exempt serious events (section 10.2.5) reporting on the eCRF documenting the hospital course.

10.2.5 Protocol specified exempt serious events

Protocol specified exempt serious events are listed below. These events are reported systematically on eCRFs as study endpoints during follow-up and are further defined in the PIM. They will NOT be reported on the SAE eCRF ***unless the investigator considered that there was a reasonable possibility that the study intervention (blinded investigational agent/ placebo or study-supplied SOC treatment) caused the event (see section 10.2.6)***. These events may occur during the initial hospitalization, lead to a re-admission, or occur in a later hospitalization during follow-up.

The following are **protocol specified exempt serious events.** As noted above, these events are not reported on the SAE eCRF unless they are considered related to the study intervention (blinded investigational agent/placebo or study provided SOC).

- Death
- Stroke
- Meningitis
- Encephalitis
- Myelitis
- Myocardial infarction
- Myocarditis
- Pericarditis
- New onset of worsening of CHF (NYHA class 3 or 4)
- Arterial or deep vein thromboembolic events
- Respiratory failure defined as receipt of high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation or ECMO
- Hypotension requiring vasopressor therapy
- Renal dysfunction requiring renal replacement therapy
- Hepatic decompensation
- Neurologic dysfunction, including acute delirium and transient ischemic events
- Disseminated intravascular coagulation
- Major bleeding events
- Serious infections

10.2.6 Reportable SAEs

Reportable SAEs for this study are serious events that are:

- Related to the study intervention; or.
- Not exempt from reporting on the SAE eCRF (events listed in section 10.2.5 are exempt).

Deaths, life-threatening events, and other SAEs considered potentially *related to the blinded investigational agent/placebo or study-supplied SOC treatment*, irrespective of whether the event is mentioned above as a protocol specified exempt serious event, that occur from the time of infusion of the study intervention through the Day 90 visit must be recorded by sites on the SAE eCRF **within 24 hours of site awareness**.

Suspected unexpected serious adverse reactions (SUSARs) are reportable SAEs that are assessed as related to a study intervention and are unexpected per the Reference Safety Information of the IB for that intervention. SUSARs are reported from the INSIGHT Safety Office to applicable regulators in an expedited fashion. SUSARs that result in death or are immediately life-threatening are reported to regulators within 7 calendar days of receipt. All other SUSARs are reported to regulators within 15 calendar days. The INSIGHT Safety Office will generate a Safety Report for each SUSAR for distribution to investigators and other parties. Investigators are responsible for submitting Safety Reports to their overseeing IRB/EC per requirements.

SAEs that are not protocol specified exempt serious events and that are not related to the study intervention (blinded investigational agent/placebo or study-supplied SOC treatment) must be reported on the SAE eCRF within 3 days of site awareness.

SAEs are followed until the outcome of the SAE is known. If the outcome of an SAE is still unknown at the time of the final follow-up visit, the outcome will be entered in the database as “unknown.”

10.2.7 Unanticipated Problems (UPs)

UPs must be reported via the appropriate eCRF to the INSIGHT Safety Office no later than 7 calendar days after site awareness of the event. Investigators are responsible for submitting UPs that are received from the sponsor to their overseeing IRB/EC. Investigators must also comply with all reporting requirements of their overseeing IRB/EC.

10.2.8 Deaths

All deaths are reported on the eCRF for deaths. Deaths considered **related to the study intervention** (blinded investigational agent/placebo or study-supplied SOC) must **also** be reported as an SAE.

10.2.9 Pregnancy

Female participants who are or become pregnant

If required by the agent-specific appendix for the study agent to which the participant has been randomized, the investigator will collect pregnancy information on any female participant who is or becomes pregnant while participating in this study.

The participant will then be followed to determine the outcome of the pregnancy and reported on the Pregnancy Outcome eCRF.

Male participants with partners who become pregnant

The following is only applicable if required by the agent-specific appendix for the study agent to which the participant has been randomized. If an investigator learns that a male participant’s partner has become pregnant while the male participant is in this study, the investigator is asked to attempt to obtain information on the pregnancy, including its

outcome, after obtaining consent from the pregnant partner. The outcome of the pregnancy will be reported on the Pregnancy Outcome eCRF.

10.3 Medical Monitor

A Medical Monitor appointed by the sponsor will be responsible for reviewing all SAEs, making an independent assessment of causality and expectedness, preparing sponsor safety reports, and communicating as needed with the DSMB and the Investigational New Drug (IND) holder through the study safety office or other mechanism mutually agreed to and documented.

10.4 Halting Enrollment for Safety Reasons

The sponsor medical monitor or the DSMB may request that enrollment be halted for safety reasons (e.g., unacceptably high rate of infusion-related reactions or other unanticipated AEs). If the study is temporarily halted or stopped for safety reasons, IRBs/ethics committees will be informed. The IND holder and sponsor, in collaboration with the protocol chair and the DSMB, will determine if it is safe to resume the study. The sponsor will notify the Site Investigators of this decision. The conditions for resumption of the study will be defined in this notification. The Site Investigators will notify their local IRBs/ethics committees of the decision to resume the study.

11 Statistical Analyses and Monitoring Guidelines

This section describes the analysis for primary and secondary outcomes of the trial. A more detailed statistical analysis plan (SAP) has been developed as a separate document. The SAP for each investigational agent may be updated by the blinded statisticians prior to unblinding for a specific treatment comparison.

Comparisons between each investigational agent and concurrent controls will be by intention to treat unless otherwise stated. Safety comparisons will be carried out on participants who received a complete or partial infusion of the investigational agent unless otherwise specified. It is anticipated that all study site pharmacies serving active sites will be randomizing all agents under study at any given time, but if this is not the case, comparisons will be restricted to the set of controls enrolled at study site pharmacies where the drug was available for randomization. Specifically, the control group for an investigational agent will consist of those participants who could have been randomized to the agent, but were randomized to a control group instead (i.e., randomized to the matched control group of one of the agents included in the randomization). Agents will be compared to controls, but not to each other, unless explicitly specified in the analysis plan.

All analyses will utilize 2-sided tests with a 5% significance level unless otherwise noted.

11.1 Analysis of the Primary Efficacy Endpoint

The evaluation for the primary efficacy outcome of the phase III trial, time to sustained recovery through Day 90, will be based on Gray's test with rho=0.[80] The test will compare the investigational agent versus the control group by intention to treat, and will be stratified by disease severity at entry and study site pharmacy. Gray's test compares the cumulative incidence functions for *sustained recovery* between the treatment groups, taking into account the "competing risk" of death in analysing *sustained recovery*. Gray's test with rho=0 is the analogue of the log-rank test in the presence of competing risks. Cumulative incidence functions for *sustained recovery* will be estimated by treatment group using the Aalen-Johansen estimator,[81] and the recovery rate ratio (RRR) (investigational agent

versus control) for *sustained recovery* will be estimated using the Fine-Gray method,[82,83] stratified by disease severity at entry and study site pharmacy; the RRR will be estimated as a point estimate with a 95% CI. The Aalen-Johansen estimator for cumulative incidence functions is the analogue of the Kaplan-Meier estimator in the presence of competing risks. The Fine-Gray method is the competing risks equivalent of Cox proportional hazards models; the RRR compares the cumulative incidence rates of *sustained recovery* between the study arms, and is a sub-distribution hazards ratio. Analyses for the *sustained recovery* endpoint require methods that take into account the competing risk of death, as participants may die before ever achieving *sustained recovery*. The "sustained recovery" outcome requires knowledge of a participant's residence status for at least 14 days after arriving "home" (as defined in section 4.2); since all participants are hospitalized at study entry, it takes at least 15 days to attain this outcome.

Sensitivity analyses for the primary endpoint comparisons will include consideration of home oxygen used as described in section 4.2.2.

11.2 Analyses of Secondary Efficacy Endpoints, Safety Outcomes, and Subgroups

Mortality is a key secondary outcome; time to death will be compared between the investigational agent versus control using a log-rank test, stratified by disease severity and study site pharmacy; the hazard ratio will be estimated using a stratified Cox proportional hazards model, and the proportion of participants who died by fixed time points (for example, Day 28 or Day 90) will be estimated using Kaplan-Meier estimates. To supplement the separate analyses of *time to sustained recovery* and *time to death*, the two endpoints will be analyzed jointly using the "win ratio" method[74] for the composite outcome of time to recovery or death. At a given time point (Day 90), the win ratio statistic ranks participants' outcomes into three ordered categories, death, alive but not achieved sustained recovery, alive and achieved sustained recovery, and ties are broken by time since randomization. So, time to death is first used to determine the winning group (i.e., longer time to death), then time to sustained recovery is used to determine the winning group (i.e., shorter time to recovery): in this manner these conflicting outcomes can be combined into a composite while recognizing the importance of mortality. Matching on baseline disease severity will be used to estimate the win ratio statistic. This combination of time to sustained recovery and time to death is also a key secondary analysis.

The primary safety outcome is a composite of grade 3 or 4 events, SAEs, clinical organ failure or serious infections, or death through Day 5, and tests for differences between treatment arms will be conducted with a Cochran Mantel Haenszel test stratified by study site pharmacy and disease severity at study entry, comparing the proportion of participants who had experienced any of these events by Day 5. Treatment differences for each of the components of this composite outcome will also be summarized. This composite safety outcome will also be assessed at Day 28 and Day 90. Proportions of participants who experienced any of these events will be compared using stratified Cochran Mantel Haenszel tests and logistic regression. Time to event analyses will also be used to summarize this composite safety outcome. SAEs and grade 3/4 events will be classified by system organ class according to MedDRA®.

Safety analyses also include infusion reactions collected during or within 2 hours after the infusion of the investigational agent or placebo. Proportions of participants who experienced infusion reactions or prematurely terminated infusions will be summarized by study arm, and Cochran Mantel Haenszel tests will be used to test for differences across arms.

Several other secondary efficacy outcomes will also be investigated. The models will include an indicator for treatment group, and stratify by study site pharmacy and disease severity at study entry as appropriate. Time from study entry to discharge from the hospital admission during which randomization took place will be analyzed using the same methods as described above for time to sustained recovery. Readmissions will be summarized using methods for recurrent events (i.e. those who are readmitted will reenter the risk set).

Both the pulmonary and pulmonary+ ordinal outcome will be assessed on Days 1 through 7; the pulmonary ordinal outcome will also be assessed at Days 14 and 28. Proportional odds models will be used to compare treatment groups for each ordinal outcome. These models will control for study site pharmacy and categories of the pulmonary+ ordinal outcome at baseline. A test for the proportional odds assumption across cumulative categories and stratification covariates will be performed by testing for separate slopes (a partial proportional odds model). In addition, cumulative probabilities of the ordinal outcome categories will be compared between treatment groups using logistic regression models.

Clinical organ failure is a composite of many different organ-specific events, listed in section 4.2.2, item 7. This outcome will be summarized as part of both safety and efficacy analyses. The incidence of organ failure, serious infection or death through Day 28 will be compared between arms using the log-rank test and Cox proportional hazards models. In addition, specific components (e.g., cardiac and vascular dysfunction, or the composite of cardiovascular outcomes and thromboembolic events described in section 4.2.2, item 10) will be analyzed using time-to-event analyses under competing risks, as described above for the primary analysis of sustained recovery. Proportions of participants who experienced organ failure, serious infection or death will be summarized and compared between treatment arms using stratified Mantel Haenszel tests, overall and for specific organ dysfunctions.

Longitudinal models for the logarithm of antibody titers will be fit using generalized estimating equation-based approaches to titers measured at baseline and Days 1, 3, 5, 28 and 90 and interactions between time and treatment group will be investigated to assess if the treatment effect changes over time. The same approach will be used to examine neutralizing titers should such data be available.

The impact of study arm on the primary efficacy (time to sustained recovery) and safety outcomes (composite of grade 3 or 4 events, SAEs, clinical organ failure or serious infections, or death through Day 5 and through Day 28, composite of SAE and death through Day 90) along with mortality will be assessed for subgroups defined by baseline characteristics, including demographics, social determinants, baseline classification of “home”, duration of symptoms at enrollment, clinical history and presentation (including disease severity stratum and pulmonary+ ordinal outcome at baseline), and tests for homogeneity of the treatment effect across subgroups will be carried out. Additionally, subgroup analyses will be conducted for subgroups formed by a disease progression risk score at baseline. The construction of this risk score will be revisited as new investigational agents move through the trial. Subgroup analyses will be interpreted with caution due to limited power and uncontrolled type I error.

11.3 Data Monitoring Guidelines for an Independent DSMB

An independent DSMB will review interim data and use pre-specified guidelines for early evidence of sufficient activity of an investigational agent that justifies continuing enrollment for the agent and expanding eligibility criteria to include participants in disease severity

stratum 2 as well as stratum 1. This assessment will be made by the DSMB when Day 5 data for approximately 300 participants in disease severity stratum 1 are available.

For agents which advance to enroll participants in both disease severity strata 1 and 2, the DSMB will continue to review interim data on a regular basis and use pre-specified guidelines to identify agents with clear evidence of efficacy for the primary outcome, and if so recommend unblinding of the trial results for that agent. Conversely, the DSMB may recommend discontinuation of an investigational agent if the risks are judged to outweigh the benefits or if futility assessments indicate that there is low probability that an investigational agent will achieve statistical significance for the primary endpoint of sustained recovery.

11.4 Rationale for Early Futility Analysis

The early futility analysis based on the intermediate outcome of efficacy using the pulmonary and pulmonary+ ordinal outcomes assessed at Day 5 will be carried out for approximately 300 participants entering the trial when only enrolling in disease severity stratum 1. The exact number may vary depending on the rate of enrollment and the timing of the DSMB meeting. The potential benefit of the investigational agents studied is expected to be greatest in this cohort and the Day 5 data provide an early assessment of activity to assess the potential for benefit in the expanded cohort of participants evaluated for the primary endpoint. This early futility analysis is based on Day 5 outcomes because too few primary endpoints of sustained recovery are expected when 300 participants with 5 days of follow-up are available. It allows resources for the platform trial to be more efficiently used by identifying agents early that have a low probability of being efficacious and stopping enrollment for those agents, while at the same expanding enrollment for promising investigational agents that have potential for showing efficacy with a larger sample size based on the primary endpoint.

The sample size of 300 participants in stratum 1 provides 95% power to detect an odds ratio (active/placebo) of 1.60 at the 0.30 (1-sided) level of significance. Data from the ACTT-1 trial (remdesivir group) were used to estimate the category percentages for the placebo group shown in Table 3 below. The percentages shown correspond to an odds ratio of 1.60 and are the basis for the sample size used for the early futility assessment.

Table 3. Hypothesized percentage of participants in each category on Day 5 in the Investigational agent and placebo groups based on aforementioned assumptions

Pulmonary+ Category	Investigational Agent + SOC	Placebo + SOC
1. No limiting symptoms due to COVID-19	3.2	2.0
2. Limiting symptoms due to COVID-19	53.5	43.0
3. Moderate end-organ dysfunction	20.6	23.0
4. Serious end-organ dysfunction	12.8	17.0
5. Life-threatening end-organ dysfunction	5.0	7.3
6. End-organ failure	4.5	7.0
7. Death	0.4	0.7

Total	100.0	100.0

The rationale for a 1-sided alpha level of 0.30 and power 0.95 is based on previous work for 2-stage cancer trials, where like this platform trial an intermediate outcome was used to assess early activity, and a definitive outcome was used to assess efficacy at the end of the trial. A re-analysis of 4 trials suggested a 1-sided significance level between 0.2 and 0.3 was optimal for making a good decision in the early futility assessment. A subsequent paper focused on the potential for estimation bias in selected and stopped treatments and concluded that its degree was generally small.[84,85]

As part of the development of this platform trial, additional work was carried out to support the design. That work is briefly summarized below (personal communication).[86]

Follmann and Proschan considered a 2-stage trial (where a drug would enter the 2nd stage once it had passed the futility assessment) and assumed a sample size of 300 for the initial stage, the decision whether the investigational agent would proceed to the 2nd stage taking place when all 300 participants had completed Day 5, a total sample size of 1000 for the trial, a significance level of 0.30 (1-sided) and power of 0.95 for the initial stage, and a significance level of 0.025 (1-sided) and power of 0.90 for the 2nd stage primary endpoint comparison. For simplicity, one ordinal outcome was assumed. With these assumptions, they showed that power with use of a stage 1 assessment was reduced only slightly from the power without the stage 1 review (0.87 versus 0.90). They cite two advantages to the approach used here compared to the standard phase III trial without an early evaluation: 1) more treatments can be evaluated; and 2) if one-half of the treatments are efficacious and one-half are not efficacious, 40% more efficacious treatments are identified.

11.5 Interim Analyses Guidelines

Stopping guidelines for use by the DSMB are described below. More specific guidance may be specified in the SAP. When several investigational agents are investigated in parallel, each agent will be compared to its corresponding, contemporaneously randomized pooled placebo group. Each investigational agent versus placebo comparison will be treated as a separate clinical trial; stopping boundaries will be derived to allow for multiple interim looks, but will not be additionally inflated to adjust for simultaneous analysis of multiple investigational agents, except when explicitly stated in the agent-specific protocol appendix and statistical analysis plan.

The DSMB will be asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference.

11.5.1 Early Assessment of Safety and Futility

For investigational agents with minimal pre-existing data, the pace of enrollment will be initially restricted and the DSMB will be asked to review safety data for the first 20 to 30 participants before increasing the pace of enrollment.

Subsequently the DSMB will carry out regular reviews of safety data reports. These reports will include summaries of lower grade AEs and infusion–related events as well SAEs and deaths, including the primary safety outcome. At the discretion of the DSMB, these reports will be prepared at a frequency they specify.

When approximately 300 participants have been enrolled and followed for 5 days, a futility assessment will be carried out. The criteria that will be used for the early futility assessment of each investigational agent are summarized below:

a. If the investigational agent is superior (i.e. 1-sided $p \leq 0.3$) to placebo for both ordinal intermediate outcomes, then enrollment for the agent will expand to complete the phase III trial.

b. If there is insufficient evidence for superiority versus control (i.e., 1-sided $p>0.3$) in each of the two outcomes, then stop randomization.

c. If there is evidence (1-sided $p \leq 0.3$) for an association for one endpoint and not the other, then the agent may or may not advance depending on the risk/benefit profile emerging from the data at this early stage. If the effect estimate for both outcomes is on the side of benefit, the preference would be towards advancing the agent and expanding enrollment to include disease severity stratum 2.

The DSMB will be asked to review whether the discordance is attributable to a positive or negative effect on extra-pulmonary organ dysfunction (the difference in the two ordinal scale categories, the conditions included in pulmonary+ but not in the pulmonary endpoint), and whether the same ordinal outcomes assessed on other days yield similar results, and weigh the risk/benefit profile. For example, if there is a significant positive effect on the pulmonary score and the lack of significant effect on the pulmonary+ score is driven by a lack of difference in the milder thrombotic symptoms in category 4 of the pulmonary+ scale (e.g. deep venous thrombosis) and there is no evidence of any raised risk of thrombosis overall, the agent will advance. Conversely, if the agent is superior to the control group with respect to the pulmonary outcome, but clearly inferior to the control group with respect to the pulmonary+ outcome or has a concerning safety profile, it will not advance. Analyses of the primary endpoint, “time to sustained recovery”, will also be provided to the DSMB, as supporting information.

After considering the aforementioned guidelines, the DSMB will be asked to consult with the Food Drug Administration before making their recommendation in order to consider any relevant external information.

The power and type 1 error of the complete decision rule considering both outcomes depends on the correlation between the two outcomes and on the DSMB’s assessment of discordant outcomes. Table 4 shows the power to identify an agent with an hypothesized OR=1.60 using the two-outcome decision rule, along with the simultaneous type 1 error, assuming correlations of r=0.8 and r=0.9 between the test statistics for the two outcomes. For example, if an agent is advanced when one or both of the outcomes show superiority, and assuming a correlation of 0.8, then an agent with OR=1.60 will be ”detected” and advanced with probability of 98% (power), while an ineffective agent would be advanced with probability of 39% (type 1 error). This balance between power and type 1 error is selected for the intended approach to making the early futility assessment.

Table 4. Power and type 1 error for the two-outcome decision rule to expand enrollment to strata 1 and 2 for an investigational agent for correlations of r=0.8 and 0.9 between the marginal test statistics for the two outcomes. OR=1.60, total sample size 300.

	r = 0.8		r =0.9	
Treatment of discordant intermediate outcomes	**Power**	**Type 1 error**	**Power**	**Type 1 error**
Expand enrollment if one or both outcomes show superiority	0.98	0.39	0.97	0.36
Expand enrollment if both outcomes show superiority	0.93	0.21	0.93	0.24

During the enrollment of approximately 300 participants in disease severity stratum 1, the safety reviews by the DSMB will include treatment comparisons of the safety outcomes described in section 4.2.2 that are measured in the first 28 days of follow-up. In addition, for each ordinal outcome at Day 5, a Haybittle-Peto boundary using a 2.5 standard deviation (SD) for the first 50 participants enrolled and 2.0 SD afterwards will used as a guideline for harm.

11.5.2 Monitoring Guidelines for the Primary Endpoint

As a guideline, asymmetric boundaries will be provided to the DSMB to monitor the primary endpoint (time to sustained recovery) for each pairwise comparison of investigational agent versus control. For monitoring overwhelming benefit of an investigational agent, the Lan-DeMets spending function analogue of the O'Brien-Fleming boundaries will be used; for monitoring harm for the primary endpoint, a Haybittle-Peto boundary using a 2.5 standard deviation (SD) for the first 50 participants enrolled and 2.0 SD afterwards will used as a guideline. The Lan-DeMets boundary used will be chosen to preserve a 1-sided 0.025 level of significance. For computing the Lan-DeMets boundary, the information fraction at each interim analysis will be the number of sustained recoveries at the interim analysis (divided by the number of sustained recoveries planned) (843). With this approach, less evidence will be required for crossing a boundary for harm than for benefit. To account for a possible delay in the ascertainment of the primary endpoint status, sensitivity analyses will be provided to the DSMB.

Futility analyses will be carried out. The aim of these analyses will be to consider whether an investigational agent should be discontinued due to a low probability of achieving statistical significance for the primary endpoint of sustained recovery at the completion of the 90 day follow-up. Conditional power calculations for time to sustained recovery will be presented under a range of scenarios. In the primary futility analysis, the treatment effect for the future, as yet unobserved follow-up will be assumed as hypothesized in the study design (RRR=1.25); in alternative scenarios, the treatment effect for future follow-up will be assumed to be similar to the observed effect, or more favourable for the investigational agent. Typical futility guidelines recommend stopping a trial when conditional power is below 10%-15%, with the higher value later in follow-up as measured by information time.[87] These analyses will be presented to the DSMB by the unblinded statisticians for each pairwise comparison.

12 Protection of Human Subjects and Other Ethical Considerations

12.1 Participating Clinical Sites and Local Review of Protocol and Informed Consent

This study will be conducted by major medical centers participating in INSIGHT and partnering networks. It is anticipated that potential participants will be recruited by the site investigators (and/or their delegates, as appropriate) and/or that positive SARS-CoV-2 laboratory testing will be used to enquire about potential enrollment. Information about this study will be disseminated to health care providers at enrolling sites.

Prior to the initiation of the study at each clinical research site, the protocol, informed consent form and any participant information materials will be submitted to and approved by a central/national IRB/EC and/or the site's local IRB/EC as required. Likewise, any future amendments to the study protocol will be submitted and approved by the same IRB(s) or EC(s). After IRB/EC approval, sites must register for this study before screening potential participants, and must register for any protocol amendments. Protocol registration procedures are described in the PIM.

12.2 Ethical Conduct of the Study

The study will be conducted according to the Declaration of Helsinki in its current version; the requirements of Good Clinical Practice (GCP) as defined in Guidelines, EU Clinical Trials Directive (2001/20/EC), and EU GCP Directive (2005/28/EC); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines; Human Subject Protection and Data Protection Acts; the US Office for Human Research Protections (OHRP); or with the local law and regulation, whichever affords greater protection of human subjects.

12.3 Informed Consent of Study Participants

Informed consent must be obtained (see sample in Appendix A) prior to conducting any study-related procedures. For patients who are incapacitated, informed consent may be obtained from a legally-authorized representative (LAR). Capacity will be assessed according to local standards and policies. Local standards and policies will also determine who is legally authorized to consent for an individual who is incapacitated. Should the individual regain capacity during the study, their direct consent should be obtained at the earliest opportunity.

Electronic consent may be used when a validated and secure electronic system is in place to do so, if in compliance with national legislation and approved by the local IRB/EC. Other methods of obtaining documentation of consent may be used when site staff are unable to be in direct contact with a potential participant or a legally-authorized representative due to infection-control restrictions. No matter how the participant's consent is obtained and documented, it is expected that consent will be preceded by research staff providing an explanation of the research and an opportunity for the participant (or their LAR) to have questions answered. Sites should follow all available local or national guidance on suitable methods for obtaining documentation of participant (or their LAR) consent.

12.4 Confidentiality of Study Participants

The confidentiality of all study participants will be protected in accordance with GCP guidelines and national regulations.

12.5 Regulatory Oversight

Sites in the US will conduct this trial under the terms of the IND and will adhere to FDA regulations found in 21 CFR 312, Subpart D. Sites in countries other than the US will not conduct the trial under the IND. As stated in Section 12.2 above, all sites will conduct the trial in accordance with the requirements of GCP as codified in their local law and regulation, under the oversight of their institution and competent regulatory authority.

As part of fulfilling GCP and FDA requirements for adequate trial monitoring, multiple modalities will be employed. The objectives of trial monitoring are to ensure that participant rights and safety are protected, to assure the integrity and accuracy of key trial data, and to verify that the study has been conducted in accord with GCP standards and applicable regulations.

A specific risk-based protocol monitoring plan will be developed. The plan will include strategies for central monitoring of accumulating data and will take into account site-level quality control procedures. On-site monitoring visits for targeted source document verification and review of regulatory and study pharmacy files will be conducted when possible, but these tasks will most likely need to be handled remotely during the pandemic. The monitoring plan will outline the frequency of this aspect of monitoring based on such factors as study enrollment, data collection status and regulatory obligations.

Therapeutics for Inpatients with COVID-19 (TICO) Master Protocol

Appendix A Sample Informed Consent form (not agent-specific)

Sample Informed Consent form

Short Title: Therapeutics for Inpatients with COVID-19 (TICO)

Sponsored by: The University of Minnesota (UMN)

Funded by: The National Institute of Allergy and Infectious Diseases (NIAID), US National Institutes of Health (NIH)

Full Title of the Study: **A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19**

CONSENT FOR PARTICIPATING IN AN NIH-FUNDED RESEARCH STUDY

SITE INVESTIGATOR: _____ PHONE: _____

ALL SITE INSTRUCTION THAT IS INCLUDED IN A TEXT BOX SHOULD BE REMOVED FROM THE SITE'S INFORMED CONSENT FOR PARTICIPANTS

US Office for Human Research Protections (OHRP) Requirements to be read by the sites:

PLEASE NOTE THAT THIS SAMPLE LANGUAGE DOES NOT PREEMPT OR REPLACE LOCAL IRB/EC REVIEW AND APPROVAL. INVESTIGATORS ARE REQUIRED TO PROVIDE THE LOCAL IRB/EC WITH A COPY OF THIS SAMPLE LANGUAGE ALONG WITH THE LANGUAGE INTENDED FOR LOCAL USE. LOCAL IRBs/ECs ARE REQUIRED TO WEIGH THE UNIQUE RISKS, CONSTRAINTS, AND POPULATION CONSIDERATIONS AS A CONDITION OF ANY APPROVAL. ANY DELETION OR SUBSTANTIVE CHANGE OF INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENT MUST BE JUSTIFIED BY THE INVESTIGATOR, APPROVED BY THE LOCAL IRB/EC, AND NOTED IN THE IRB/EC MINUTES. JUSTIFICATION AND IRB/EC APPROVAL OF SUCH CHANGES MUST BE FORWARDED TO THE INTERNATIONAL COORDINATING CENTER OR COLLABORATING NETWORK. SPONSOR-APPROVED CHANGES IN THE PROTOCOL MUST BE APPROVED BY THE LOCAL IRB/EC BEFORE USE UNLESS INTENDED FOR THE ELIMINATION OF APPARENT IMMEDIATE HAZARD. NEW INFORMATION SHALL BE SHARED WITH EXISTING SUBJECTS AT NEXT ENCOUNTER, WITH ALL NEW SUBJECTS PRIOR TO INVOLVEMENT, OR AS THE LOCAL IRB/EC MAY OTHERWISE ADDITIONALLY REQUIRE.

Key information:

We are asking you to join a research study about COVID-19. It is your choice whether or not you want to join. This form gives you information about the study that will help you make

PID: _____

your choice. You can talk about this with your doctor or family or anyone else you would like before you make your choice. Your choice will not affect the care you are getting for COVID-19.

Why are we doing this study?

We are studying experimental medicines to treat people with COVID-19. We are trying to find out if giving these medicines can help people in the hospital with COVID-19 get better and go home faster. We are also trying to see if they are safe. The medicines being tested in this study are not yet approved by the US FDA or any other government agency.

We are asking you to join the study because you are in the hospital with COVID-19.

What do you have to do if you decide to be in the study?

The study staff at your hospital will check to see if there is any reason you should not be in the study. They will check your medical history. They will look at tests commonly done for your condition.

We are testing different types of study medicines. If you join the study, you will be assigned by random chance – like flipping a coin or rolling dice – to get one of these study medicines or a salt-water placebo. You could be in any one of the groups below:

Investigational agent A

Investigational agent B

Placebo (a salt water solution that has no medicine in it)

Not all of the study medicines listed above may be available to you right now

If this is the case, then you will be told which ones are available.

You will have an equal chance of getting any of the available study medicines or the inactive placebo. If all of them are available, then you have a 1 in __chance of being in each of the groups listed above. *[Insert number of possibilities from the list above, including placebo, e.g. "3"]*

This means your chances of getting a study medicine instead of placebo are ___ out of ___, or __%. *[nsert the number of active possibilities from the list above, then the total number of possibilities, e.g., "2 out of 3." Then record the % to which that corresponds, e.g., "67%." Repeat the above for each possibility as an active treatment is eliminated.]*

Your doctor will not decide which group you are in and, just like you, will not know whether you are getting an experimental medicine or inactive placebo. None of the study staff will know whether you are getting a study medicine or the placebo.

PID: _____

We will tell you more about each study medicine you could get in a separate information sheet. You will be given an information sheet for each of the available study medicines.

You will get the study product through a plastic intravenous (IV) tube attached to a needle in your arm. This is called an infusion. The information sheets will tell you how much liquid the infusion will be and how long it should take.

The infusion is the only thing you will be given that is completely experimental.

The medicines we are studying can only be used in research. There are many treatments being studied for COVID-19, and some have received US FDA emergency approval or other types of approval to be used in some people with COVID-19. Your doctor and the study team will tell you about any treatment options you may have.

As part of the study, you will also get a drug called remdesivir (also called Veklury) for your COVID-19, unless your doctor thinks remdesivir would not be safe for you to take. Remdesivir is given once a day by infusion for up to 10 days while you are in the hospital, Remdesivir was shown in an earlier study to help people get better faster from COVID-19. Remdesivir is approved by the US FDA for treating COVID-19. It also has approval in other countries.

Any other medicines or treatments you get will be what you would usually get in this hospital for your condition. There may be some additional tests done just for the study. We will describe these below.

You will be in the study for 18 months. We will get most of the information for the study in the first 3 months.

We do not know what effects these study medicines may have on a pregnancy or unborn baby. There may be bad effects or no effects. If you decide to join the study, we strongly advise you to not have sex that could make you or a partner pregnant from thetimethat you sign this consent formfor some time after you have taken the study medicine. How long this will be depends on which study medicine you have been assigned to get. This may involve not having sex at all (abstinence), or you may use effective birth control (hormonal contraceptives like birth control pills or barrier methods with spermicide) to avoid pregnancy. Methods like rhythm, sympto-thermal or withdrawal are not considered effective for preventing pregnancy. We will tell you more about this requirement as part of telling you about each study medicine you could get. You should ask the study team about this if you have questions or concerns.

If you get pregnant during the study, please let your study team know as soon as possible. We may ask to follow you until your pregnancy is over, to see if there were any problems that may have been caused by any of the study treatments.

PID: _____

If your partner gets pregnant, please let your study team know as soon as possible. We may ask your partner to let us get basic information about her pregnancy.

You will also need to agree to not be in any other COVID-19 study for the first 5 days you are in this study. There may be exceptions to this requirement. We will tell you about any other studies you can be in during the first 5 days of this study so you can make a choice.

This is what you will be doing for the study:

Up to 1 day before you get study product	**Day 0 (the day you get study product)**	**Day 1, Day 3, Day 5**	**Day 2, Day 4 Day 6, Day 7, Day 14, Day 42, Day 60, Day 75**	**Day 28 and Day 90**
Informed consent (this document) Check to see how you are feeling Your medical history Contact information like telephone numbers and addresses for you and at least two close relatives or friends	Infusion of study product (the experimental medicine or else placebo) Whether you are taking certain medicines Blood tests to check your health (9 mL, about ½ tablespoon) Blood for future research (18 mL, about 1 tablespoon) A swab of your nose for virus	How you are feeling Blood for future research (18 mL, about a tablespoon) On Day 5, also whether you have taken certain medicines, and blood tests to check your health (9 mL, about ½ tablespoon)	How you are feeling (Days 2, 4, 6, 7, 14, 60) Update on return to home (Days 14, 42, 60, 75) These “visits” may take place by phone.	How you are feeling Blood for future research (18 mL, about a tablespoon) On Day 28, also whether you have taken certain medicines Update on return to home

If you leave the hospital after just a few days, we will ask you to come back to give a blood sample on Day 3 and Day 5 of the study. You might instead be visited in your home by a professional working for the study to get this blood sample. We will also need to take a blood sample from you on Day 28 and Day 90.

After Day 90, we will talk to you three more times by phone, at 6 months, 12 months, and 18 months, to see how you are doing and whether you have been in the hospital for any reason.

We may need to get some information from your medical record:

- By signing this consent, you agree to let us get information for this study from your medical record.
- By signing this consent, you are giving us permission to contact other hospitals or medical facilities you are admitted to while you are in the study. We will contact them to find out how you are doing.

PID: _____

- We will ask you to give us information about other people we can contact if we are not able to reach you after you leave the hospital. This is so we can find out how you are doing.

PID: _____

We will send the information you give us to the University of Minnesota (UMN) in the US where it will be stored and analyzed. In this information, only a code number, your year of birth, and a 3-letter code that the study staff chooses identifies you.

The study staff here at this site is responsible for keeping your information safe from anyone who should not see it.

We will send the blood and nose swab samples to a laboratory in the US for storage. We will keep them for as long as we have the money and space to do so. We expect this to be many years. There is more information later in this consent about how we will use these samples.

Why would you want to be in the study?

If you get the experimental medicine, it is possible it may help you get better, or that you may get home faster, but we do not know that.

Remember that some of the people in this study will get inactive placebo, and will not get any experimental medicine.

By being in this study, you will help doctors learn more about how to treat COVID-19 in people in the hospital. Because many people are getting hospitalized with COVID-19, this could help others. There may be a large health impact if a treatment proves to be safe and to work.

Why would you NOT want to be in the study?

If you do get one of the experimental medicines, it may not help. It may have harmful side effects.

What are the risks or side effects of the experimental medicines?

All treatments have risks and may cause side effects.

Any medicine can cause an allergic reaction. You may have an allergic reaction to the study treatment, including hives, trouble breathing, or other allergic responses. Allergic reactions like these are likely to be rare, but may be severe or life-threatening.

We will watch over you while you are being given the infusion of the study medicine and for at least 2 hours after the infusion is finished. We will give you medical care right away if you need it to treat any side effects from the infusion.

The fluid needed to give the experimental medicine or the placebo may overload your body if you have problems managing fluids due to COVID-19 or other conditions. We expect this to be rare.

There are discomforts and risks with blood draws and getting a swab of your nose. You will have these things done while you are in the hospital even if you are not in the study.

PID: _____

You may have some pain, bleeding, or bruising when a needle is put into your vein to draw blood or to give the study infusion. Getting your nose swabbed can be uncomfortable and you might gag. These discomforts and risks are not different from what you would have if they were done as part of your regular hospital care for COVID-19.

What if you are pregnant or breastfeeding?

[The following will vary depending on the agents being studied.]

If you are pregnant or breastfeeding, you can/cannot join this study.

Additional information:

Here is some additional information about the study that may help you make your choice about whether you want to be in the study.

The NIH, an agency of the US Federal government, is paying for this study.

We are required to follow all rules and regulations for human research as well as the laws of each country where the study is being done.

This study is taking place in several countries. We expect to enroll about 1,000 people around the world for each medicine we are studying.

You do not have to join this research study if you do not want to. If you choose to join the study, you can stop at any time. If you choose not to join or to stop, the medical care you are getting outside of the study will not change.

If we get any new information that might change whether you want to join or stay in the study, we will tell you right away.

If you do not want to be in this study, you will still get the usual care to treat COVID-19. However, you cannot get the study medicine, because it is experimental.

Vaccines against the virus that causes COVID-19 are starting to be available. It looks like people who have had COVID-19 do not have much chance of catching it again for at least 3 to 6 months. The US Centers for Disease Control and Prevention (CDC) recommends that people wait for at least 90 days after they've been given certain medicines before they get the vaccine. We do not know if the medicines we are studying change how you respond to the vaccine during that time.

What are the risks and benefits of taking remdesivir?

Remdesivir has been shown to help people who are in the hospital and moderately to severely sick with COVID-19 get better about 4 days faster than people who got a placebo. You may be given remdesivir to treat your COVID-19 even if you do not join this study.

PID: _____

The most common side effects of remdesivir included abnormal liver function tests, abnormal blood clotting tests, constipation, nausea, vomiting, decreased appetite, and headache. The abnormal liver function tests lasted longer than a few days in some people, but went back to normal within a few weeks or less.

Remdesivir might affect the way that other medications are processed by your body. They might stay in your body longer, or shorter, or at higher or lower levels. At the time this consent was written, one person in this study had an increase in the level of a medication in their blood that was considered by study doctors to be at least possibly related to having taken remdesivir. There did not appear to be any harm from this temporary change. You can ask the study team about this if you are concerned.

Some people have side effects after the infusion of remdesivir. Other people have no side effects. People can have allergic reactions to drugs, including hives, trouble breathing, or other allergic responses. Allergic reactions may be severe or life-threatening. This is very rare but is also a possible effect of any drug. We will monitor you closely while you are getting remdesivir. We will give you medical care right away to treat any side effects.

What are the costs to you?

We will give you the study treatment at no cost. We will pay for all clinic visits, lab work, and other tests that are part of this study.

[The next paragraph is for US sites only. Sites in other countries should delete the next paragraph and replace it with the language appropriate for your location.]

You, your insurance company, or some other third-party payer must pay for all other medicines and hospital costs.

Will you be paid to be in the study?

We will compensate you for your time and inconvenience participating in the study. *[Specific details to be completed by site.]*

What if you are hurt as part of this study?

If you are hurt because of being in this study, *[insert the name of the hospital/clinic]* will treat your injury right away. You or your insurance will have to pay for this treatment. The study cannot pay you or pay for any care for study-related injuries or for your illness.

[If the above is not true for your site, i.e., if trial insurance covers such cost, please replace the above with appropriate language.]

PID: _____

[The following section, up to "What happens to the blood and swab samples?", is for US sites only.]

A Declaration under the Public Readiness and Emergency Preparedness (PREP) Act was issued by the Secretary of the United States Department of Health and Human Services on March 10, 2020. This Declaration limits the legal rights of a subject participating in clinical studies utilizing COVID-19 countermeasures. Because this study is covered by the Prep Act Declaration, covered persons, such as the manufacturers, study sponsor, researchers, healthcare providers and others have liability immunity (that is, they cannot be sued by you or your family under the laws of the United States).

If you believe that you may have been harmed as a result of this research study, certain claims for serious injury or death caused by the countermeasure may be eligible for compensation through the Countermeasures Injury Compensation Program. This is a program set up by the United States Government.

Information about this program can be found at https://www.hrsa.gov/cicp/about/index.html or by calling 1-855-266-2427. If you are eligible for this program, you must file a claim within one year of the administration or use of the covered countermeasure.

What happens to the blood and swab samples?

We will send the blood and swab samples to a central laboratory in the United States. You and your doctor will **not** get the results of any tests done on these samples. We will **not** test your DNA (your genes). We will not sell your samples and they will not be used for research aimed at making money (commercial research). The laboratory where the samples are stored will not have any information that could identify you.

The blood samples will measure how many COVID-19 antibodies are in your blood. This will tell us how your immune system responded to your COVID-19. The swab sample will be used to see how much virus is in your body.

Any blood or swab samples that are left over after these tests will be stored at the central laboratory for as long as we are able to keep them. We hope to use these in the future to answer other questions about COVID-19, the virus that causes it, and how people respond to treatment. You and your doctor will **not** get any results from these tests. Some of the blood will also be given to the companies that made the study medicines to help them learn more about its effects.

You can withdraw your consent for us to keep these samples at any time. Let your study team know if you do not want the study to keep your samples anymore. We will make every effort to destroy all of your samples that are still at the central laboratory.

PID: _____

How do we protect your privacy?

We will take every reasonable step to keep your health information private and to keep anyone from misusing it.

Your information (data) and samples will not be identified by name, or in any other way, in anything published about this study.

We will do everything we can to keep your personal information private, but we cannot guarantee that nobody will get it. We may have to release your personal information if required by law.

These people may see your medical and research information:

- the *[insert the name of the hospital/clinic]* ethics committee (institutional review board [IRB]);
- the sponsor, the group paying for the research (US NIH), other study research staff and study monitors
- US and other participating countries' health regulatory agencies, including the US FDA.

They are committed to protecting your privacy.

As the research staff at *[inset the name of the hospital/clinic]*, we are required to make sure that people not involved with this study cannot see your research and medical information. We will keep your research files in a safe place and will handle your personal information very carefully.

Your study data are sent electronically to the UMN in the US through a secure system. By signing this consent, you agree to having your data sent to UMN. No information that could directly identify you is sent to UMN. This is called "pseudonymized data". UMN limits access to the data through security measures. No data breach or unauthorized access has ever occurred in this system. After the study is over, we will store the data securely for the period required by law.

We will share your study data with the US National Institutes of Health (which is paying for this study), and with regulators that oversee the study, including the US FDA. We are required by law to do this. We will also share your study data with the drug companies that provide the study medicines to help them develop the drugs.

UMN may share your data and samples with other people who study COVID-19. UMN will take out any information that could possibly identify you before sharing. This is called "anonymizing the data." We will not ask you for additional consent for this sharing. UMN will only share data and samples for research projects that are approved by the group that is conducting this study.

This study has a Certificate of Confidentiality from the US Federal Government. This means that UMN cannot share any data it has about you with national, state, or local

civil, criminal, administrative, legislative, or other authorities unless you specifically allow us to share it.

A description of this clinical trial is available at http://www.ClinicalTrials.gov, as required by law, and on the EU Clinical Trials Register (http://www.clinicaltrialsregister.eu/). These websites will not include your name or any other direct identifiers such as your contact information. These websites will include a summary of the results of this research once the study has been completed. You can search either website at any time.

[Note for US sites: The following brief HIPAA authorization is provided. Your site-specific consent should be modified to reflect the HIPAA authorization language requirements at your site.]

To do this research, we will collect and use your personal data, as described above and in any HIPAA Authorization Form we have given you. It is your choice whether you allow us to collect and use your data. However, you will not be able to be in this study if we cannot collect and use your data. Please tell us whether you agree to have us collect and use your personal data by placing your initials in front of your selection.

____**Yes**, I agree to the collection and processing of my personal data.

____**No**, I do not agree to the collection and processing of my personal data.

[The following section (up to "What if you have problems or questions?") is for countries subject to the GDPR or similar legislation requiring this information. It should only be included in consents for sites subject to such legislation. It will vary from place to place whether it must be in this consent document, a separate consent document, or an information sheet that does not require signature. The amount of information provided may be reduced to meet the requirements of a particular country (e.g., not all countries/ECs require an enumeration of all of a data subject's rights).]

What are your rights regarding your data?

The UMN is a public research university, and this study is mostly paid for by the US Federal government. UMN and the study funder require the sponsor (UMN) to follow regulations and policies that are meant to protect your privacy. UMN is also required to comply with the General Data Protection Regulation (GDPR), because it processes data obtained from people in Europe.

PID: _____

There is no specific authority overseeing the processing of data in the US. Any complaint you might have about the use of your data would be made to your national data protection authority.

The GDPR gives you additional rights which we will tell you about now.

Right to Information

You have the right to know what data about you is being processed. You can also get a free copy of this data provided.

Right to Correction

You have the right to correct any information about you which is incorrect or had become incorrect.

Right to Erasure/Anonymization

The sponsor is required under both EU and US law to retain data from research studies like this one for many years. However, you have the right to request that your personal data be completely anonymized. This is done by destroying the information at your study center that links your identity to the pseudonymized data held by the sponsor. This means that no one would ever be able to link the data held by the sponsor to you personally.

Right to Restriction of processing

Under certain conditions, you have the right to demand processing restrictions, i.e. the data may then only be stored, not processed. You must apply for this. Please contact your study physician or the data protection officer of the study center if you want to do so. This right may be limited if the restriction would affect the reliability of the study results.

Right to Data portability

You have the right to receive the personal data that you have provided to the study center. This will allow you to request that this information be transmitted either to you or, where technically possible, to another agency designated by you.

Right to Contradiction

You have the right to object at any time to any specific decision or action taken to process your personal data. This right is limited for data that have already been processed and may be limited if your objection would affect the reliability of the study results.

PID: _____

Right to Withdrawal of this consent

You may withdraw your consent at any time with effect for future data collection. This withdrawal may be in an informal or verbal communication to your investigator. If you withdraw your consent this will not affect the lawfulness of the data processing that has been or will be done with data collected up to the time you withdraw consent. Data already collected will be anonymized.

If you would like to use one of these rights, please first contact the person responsible for the data collection at your study center:

Person responsible for data collection at the study center:	
Name:	
Address:	
Phone:	
Email	

For concerns about data processing and compliance with data protection requirements you can also contact the data protection officer responsible for the study center:

Data protection officer responsible for the study center:	
Name:	
Address:	
Phone:	
Email	

In addition, you have the right to lodge a complaint with the competent authority if you believe that the processing of personal data concerning you is contrary to the GDPR:

Data protection authority responsible for the study center:	
Name:	
Address:	
Phone:	
Email	

What if you have problems or questions?

If you ever have questions about this study, or about the storage or use of your data or samples, or if you are hurt by being in the study, contact:

[name of the investigator or other study staff]

[telephone number of the above]

PID: _____

If you have questions about your rights as a research participant, you can call:

[name or title of person on the ethics committee (IRB) or other organization appropriate for the site]

[telephone number of the above]

PID: _____

Therapeutics for Inpatients with COVID-19 (TICO) Master Protocol

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE TICO STUDY

I have read this consent or have had it explained to me. I have had a chance to learn about each of the study medicines that I could be assigned to get. I have been given a copy of that information to keep. I believe that I understand the information. By signing and dating this consent, I am stating that I volunteer to join this study. I agree to have my data sent to and used by the sponsor as described in this consent. I understand that I do not waive any of my legal rights as a study participant by signing this consent. I understand that I will receive a copy of this signed and dated consent.

If you agree to be in this study, please sign and date below.

_____ Date: _____

Signature of participant

_____

Printed name of participant

_____ Date: _____

Signature of investigator/designee

_____

Printed name of investigator/designee

FOR ADULTS NOT CAPABLE of GIVING CONSENT

_____ Date: _____

Signature of Legally Authorized Representative (LAR)

_____

Printed name of LAR

PID: _____

_____

Relationship of LAR to Participant

(Indicate why the LAR is authorized to act as a surrogate health care decision-maker under state or applicable local law)

Witness to Consent Interview (if applicable)

On the date given next to my signature, I witnessed the consent interview for the research study named above in this document. I attest that the information in this consent form was explained to the participant, and the participant indicated that his/her questions and concerns were adequately addressed.

_____Date: _____

Signature of witness

_____

Printed name of witness

NOTE: This consent form, with the original signatures, MUST be retained on file by the Investigator of Record. A copy of the signed and dated consent must be given to the participant. A copy should be placed in the participant's medical record, if applicable.

If no-touch / electronic consent is used, the participant must be provided with a copy of the consent in a manner appropriate to the method used to obtain it. A record of the act of consent must also be appropriately retained in the participant's medical record.

Therapeutics for Inpatients with COVID-19 (TICO) Master Protocol

Appendix B Schedule of assessments

	Screen or Day 0	Day 0	Follow-up Study Day; shaded columns denote in-person visits															
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**	**75**	**90**	**6M**	**12M**	**18M**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+10**	**±14**	**±14**	**±14**
ELIGIBILITY & BASELINE DATA																		
Informed consent	X																	
Baseline medical (incl. duration of COVID-19) and social history	X																	
Baseline medications	X																	
Symptom-directed physical exam by the clinical team	X																	
Review SARS-CoV-2 test results	X																	
Local laboratory testing	X						X											
Urine pregnancy test or other documentation of pregnancy status	X																	
STUDY INTERVENTION																		
Randomization		X																
Study Drug/Placebo Administration		X																
Assess infusion completion and adverse reactions		X																
STUDY PROCEDURES																		
Clinical assessment for pulmonary ordinal outcome	X	X	X	X	X	X	X	X	X	X	X							
Clinical assessment for pulmonary+ ordinal outcome	X	X	X	X	X	X	X	X	X									
Vital signs for NEW score assessment	X																	
Respiratory function scale assessment	X																	
Hospitalization status					X		X		X	X	X		X		X	X	X	X
Changes in residence/facility										X	X	X	X	X	X			
Interim medical history									X	X	X		X		X			
Interim medications							X				X							

Clinical AEs of any grade on days indicated		X	X	X	X	X	X	X	X	X	X							
Clinical AEs reaching grade 3 or 4 severity through Day 28										X	X							
Research sample storage (plasma and serum)[2]		X	X		X		X				X				X			
Midturbinate swab for central SARS-CoV-2 viral load testing[2]		X																
SAEs and unanticipated problems			Report as they occur															
Deaths			Report as they occur															
Hospitalization Summary			Report upon hospital discharge															
Hospital Readmissions			Report upon hospital discharge															

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

[2] Blood draw and swab collection in some cases can be obtained after randomization but before the infusion. If it is not possible to do an in-person on Day 3 or Day 5, the blood draws may be done one day earlier or one day later (but the participant should be telephoned to record the clinical data on the indicated study day).

Appendix C INSIGHT 014 / ACTIV-3 protocol team

To oversee the implementation of this master protocol, a protocol team will be formed and include:

- Protocol co-chair(s)
- NIAID, Division of Clinical Research representatives
- INSIGHT University of Minnesota representatives
- INSIGHT International Coordinating Center representatives
- Representatives from collaborating trials networks
- Representative from ACTIV-2 protocol team
- Representatives from collaborating laboratory representatives
- Representatives from collaborating manufacturers of investigational agents
- Representatives from site investigators
- Study biostatisticians
- Community representative(s)

A core team consisting of the co-chair(s), ICC leaders, NIAID representatives, study statisticians, representatives from collaborating trials networks, and other representatives and the INSIGHT PI will also regularly convene to review study progress and address study conduct and administrative issues that arise.

Appendix D REFERENCES ON THE INSIGHT WEBSITE

The INSIGHT website (**www.insight-trials.org**) will maintain updated links to the following documents referenced in the INSIGHT 014 protocol and to other information pertinent to the study:

- DAIDS toxicity table: (https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables)

- INSIGHT Publications and Presentations Policy (http://insight.ccbr.umn.edu/resources/P&P_policy.pdf)

- Centers for Disease Control and Prevention (CDC) and European Centre for Disease Prevention and Control (ECDC) guidance on how to handle infection control measures (https://www.cdc.gov/sars/guidance/i-infection/healthcare.html and https://www.ecdc.europa.eu/en/publications-data/infection-prevention-and-control-and-preparedness-covid-19-healthcare-settings).

- Treatment guidelines, incl from NIH and WHO (https://www.covid19treatmentguidelines.nih.gov/, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management, https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/, https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation and https://www.ersnet.org/covid-19-guidelines-and-recommendations-directory)

Appendix E LIST OF ACRONYMS

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
ACTT	Adaptive COVID-19 Treatment Trial
ADE	antibody-dependent enhancement
AE	adverse event
ARDS	acute respiratory distress syndrome
CCP	convalescent plasma containing COVID-19 antibodies
CDC	Centers for Disease Control and Prevention (US)
CHF	Congestive heart failure
CI	confidence interval
COVID-19	Coronavirus-Induced Disease 2019
CTSN	Cardiothoracic Surgical Trials Network
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
EU	European Union
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
hIVIG	hyperimmune intravenous immunoglobulin from COVID-19 survivors
HR	hazard ratio
ICC	International Coordinating Center
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Institutional Ethics Committee

IgG	immunoglobulin G
IL-6	interleukin 6
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IQR	interquartile range
IRB	Institutional Review Board
IV	intravenous
IVIG	intravenous immunoglobulin
LAR	Legal Authorized Representative
mAb	monoclonal antibody
MI	Myocardial infarction
mL	milliliter
NAT	Nucleic acid test (to identify genomic material; some uses amplification)
NEW	National Early Warning
NIAID	National Institute of Allergy and Infectious Diseases, NIH (US)
NIH	National Institutes of Health (US)
NIHSS	National Institutes of Health Stroke Scale/Score
nMAb	Neutralizing Monoclonal Antibodies
OHRP	Office for Human Research Protections (US)
OR	odds ratio
PCR	polymerase chain reaction
PETAL	Prevention and Early Treatment of Acute Lung Injury
PHI	personal health information
PIM	Protocol Instruction Manual
RBD	receptor-binding domain
RNA	ribonucleic acid
SAE	serious adverse event
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TOC	trial oversight committee
UMN	University of Minnesota
UP	Unanticipated problem
US	United States of America
VA	Veterans Administration
WHO	World Health Organization

Appendix F National Early Warning (NEW) Score

Criteria	Point Value
Respiratory Rate (breaths per minute)	
≤8	+3
9-11	+1
12-20	0
21-24	+2
≥25	+3
Oxygen Saturation (%)	
≤91	+3
92-93	+2
94-95	+1
≥96	0
Any Supplemental Oxygen	
Yes	+2
No	0
Temperature in °C (°F)	
≤35.0 (95)	+3
35.1-36.0 (95.1-96.8)	+1
36.1-38.0 (96.9-100.4)	0
38.1-39.0 (100.5-102.2)	+1
≥39.1 (≥102.3)	+2
Systolic BP	
≤90	+3
91-100	+2
101-110	+1
111-219	0
≥220	+3
Heart Rate (beats per minute)	
≤40	+3
41-50	+1

51-90	0
91-110	+1
111-130	+2
≥131	+3
AVPU	
A	0
V, P, or U	+3

AVPU – Alert, Voice, Pain, Unresponsive.

Appendix G Phase I Studies as Part of this Master Protocol

It is anticipated that novel investigational agents entered into this master protocol will have enough safety and dosage data available by studies outside the master protocol, to enable them to move directly intoal this protocol. *In some instances, sufficient safety and dosage data will not be available, and the investigational agent will first require a safety evaluation in the form of a phase I dose escalation and dose determination before moving into the main master protocol.*

A separate protocol for the Phase I study will be developed for each individual investigational agent as a stand-alone document with its own consenting procedure, and included here as Appendix G1, G2, etc.

In this appendix, we describe the overarching framework as to how safety will be evaluated in a Phase I dose escalation study, with the understanding that additional details will be required as agents identified as being of interest for the master protocol but with insufficient prior safety data for entry into the master protocol.

The dose escalation study described below provides a framework for a Phase I dose escalation but a number of design parameters have been left intentionally unspecified because they will depend on the specific investigational agent under consideration and the current status of the master protocol. *Key scientific decisions regarding other design parameters including the number of dose levels to be investigated, the definition of dose-limiting toxicities (DLTs), and the appropriate target population will be determined by the protocol leadership together with the overarching ACTIV-2/3 TOC in collaboration with the drug developer and study statisticians.* Efforts will be made to harmonize these across study products, while allowing for learning from prior evaluations and also the incorporation of any issues predicted to be critical for a specific agent. This information will be included as new sub-appendices (H1, H2, etc.) in addition to other information regarding the new agent when it is entered into the master protocol for stage 1 evaluation.

a. Dose Escalation

The goal of the Phase I component is to identify the maximum tolerated dose (MTD) of the investigational agent, defined as the maximum dose with probability of dose limiting toxicity (DLT) less than a specific pre-specified threshold. The basic framework of the Phase I component will be a dose escalation study where initial study participants are treated at the lowest dose and subsequent participants are treated at progressively higher dose levels until the MTD is identified. Dose finding will be guided by the continuous reassessment method (CRM). Briefly, the CRM is a Bayesian adaptive Phase I trial design first proposed in O'Quigley, et al[88]) and later modified by Piantadosi, et al[89] and Goodman, et al.[90] The CRM is a model-based design that relies on a simple, one-parameter model for estimating the probability of DLT at each dose and uses the estimated probabilities of DLT at each dose to guide dose escalation. For this trial, we will model the probability of DLT using the power model:

$$P(\text{DLT} \mid \text{dose} = j) = d_j^{\exp(\alpha)}$$

Where *j* is the dose level and $(d_{-1}, \ldots, d_J)$ is the "skeleton" for the probability of DLT at each dose and the probability of DLT is estimated by estimating the α parameter.

For the purposes of this appendix, the number of doses or the specific skeleton are unspecified.

Dose finding in the CRM begins by treating the first cohort of three subjects at the initial dose level. After the toxicity outcomes for the first cohort are observed, the posterior distributions for the probabilities of DLT are updated. The next cohort is treated at the current estimate of the MTD, defined as the dose level with estimated probability of DLT (posterior mean) closest to the target probability of DLT, under the restriction that untried dose levels may not be skipped when escalating. This process continues until the maximum sample size is reached or until a pre-specified number of consecutive cohorts are treated at the same dose level, whichever comes first. The dose level with estimated probability of DLT (posterior mean) closest to the target probability at study completion is declared the MTD, and that dose may be carried forward to the master protocol. If at any point in the study, the posterior probability suggests that the lowest dose level is excessively toxic, the trial will terminate for excess toxicity. The specific threshold for determining excess toxicity will be determined when a new treatment is entered into the Phase I portion of the master protocol.

b. Other considerations in dose determination

It is possible that the MTD determined using the above may be higher than the optimal dose for evaluation in the next protocol stages. At present, correlative markers of clinical activity in COVID-19 are not well understood. As these markers (for example, but not limited to, SARS-CoV-2 viral load) are better understood, the above framework could also accommodate an approach allowing comparison of identified predictive biomarkers across two or more tolerable doses with the goal of identifying recommended doses for subsequent clinical evaluation that are below MTD. For example, MTD and one or more tolerable dose levels below MTD could be evaluated with respect to performance against the biomarkers, with a view to identifying a tolerable dose below MTD that is predicted to be effective, to carry forward to the next stage of evaluation in the master protocol (stage 1). This biomarker comparison would be secondary to the MTD determination.

c. Definition of DLTs and Sample Size

The dose escalation study described above provides a framework for a Phase I dose escalation but a number of design parameters, including the definition of DLTs and the sample size, have not been specified. These depend on the specific investigational agent under consideration and the current status of the main master protocol. Efforts will be made to harmonize DLT definitions across study products, while allowing for learning from prior evaluations and also any toxicities predicted to be critical for a specific agent. Other design parameters, including the sample size, will similarly be determined by the protocol team's study statisticians in collaboration with the drug developer to achieve desired operating characteristics.

d. Population

Given the early phase of evaluation, this population is likely to differ from the population in the master protocol, which includes hospitalized patients with varying stages of progression. Accurate determination of toxicity of an agent in early clinical phase is likely to be more challenging in patients with significant clinical progression. Consideration may therefore be given to restricting enrollment to patients with the lowest risk of clinical

progression within a hospitalized population, or to populations that are not in need for hospitalization except for the purpose of participating in the Phase I study.

e. Study Sites

While it is anticipated that the main master protocol will enroll participants at a large number of sites in multiple countries, it is anticipated that sites for Phase I studies will be much more restricted. Sites will be selected based on Phase I expertise, including ideally the availability of dedicated Phase I clinical evaluation units. While multiple sites may participate in Phase I studies during the life of the master protocol, for individual agents it is anticipated that in most cases evaluation will be performed at a single site. This will streamline integration of toxicity assessments into the CRM and the dose escalation process. In certain circumstances two or more sites may participate together in evaluation of a single Phase I agent, in which governance structures to facilitate rapid communication of toxicity data between sites and to the oversight team will be established.

f. **Relationship Between Phase I and the Master Protocol**

Agents evaluated in Phase 1 may or may not proceed to the master protocol, depending on results of the Phase 1 evaluation and review by the ACTIV steering committee. At a minimum, evaluation in Phase I will be used to determine the following key elements required for evaluation in the main master protocol should the agent proceed.

- Dose(s) for evaluation for later stages. In master protocol, up to three doses maybe evaluated.
- Any required specific exclusion and inclusion criteria, over and above the general criteria outlined in the main master protocol (this will be informed by toxicity and other agent characteristics in Phase I).

While the focus of Phase I evaluation will be safety and dose determination, markers of clinical efficacy including the ordinal endpoint at Day 5 may be assessed and information will be collected up to 90 days as in the main master protocol will also be collected to inform the clinical development of these agents.

While these data will be used to identify the correct dose or doses to investigate in the master protocol, the Phase 1 study will be distinct, and the data will not be incorporated into the master protocol.

Appendix H Neutralizing monoclonal antibody.

This appendix will include the following information for each nMAb studied. The rationale for studying the agent, justification for entry into the master protocol, and the description and administration of the agent. Also, as appropriate, specific AEs observed to be possibly associated with the agent in question, and how to monitor for, clinically handle and report such AEs, should they arise. Changes in endpoint, SOC, inclusion and/or exclusion criteria, sample size estimation and approach to interim analyses and data analyses will also be included if appropriate for the investigation of the nMAb in question relative to what is stated in the master protocol. Finally, the text will also clarify whether the manufacturer of investigational agent plans to pursue licensure in the countries where the trial will occur, should the investigational agent be demonstrated in the trial to have overall benefit.

Introduction/Rationale for studying the agent

  - Potential risks and benefits of agent
  - Motivation for agent selection with consideration of results from trials of other nMAbs
- Agent-specific eligibility criteria
- Description of investigational agent
  - Administration and duration
  - Formulation and preparation
  - Supply, distribution, and accountability
  - Contraindicated medications
  - Precautionary medications
- Clinical and laboratory evaluations in addition to master protocol
  - Timing
  - Special instructions
- Clinical management issues
  - Infusion-related reactions
  - Hypersensitivity
- Pregnancy and breast-feeding considerations
- Criteria for discontinuation of infusion
- References

Appendix I Standard of Care

I1. Overview

Currently, there are no licenced treatments for COVID-19. One investigational agent, remdesivir, is now accepted by several countries' regulatory bodies for use as part of routine care; in the US, FDA has been granted the drug an Emergency Use Authorization. Considering the number of randomized trials being conducted to study treatments for COVID-19, it is likely that other effective treatments will be identified during performance of this master protocol.

When treatments for COVID-19 are demonstrated to have safety and efficacy, those treatments should be considered in designing new studies. Depending on the scientific question, an experimental treatment will be coupled with or compared to a known effective treatment. When such known effective treatments are incorporated into both arms, they are called "background therapy" or standard of care (SOC). In this case, the scientific question addressed is whether a new treatment added to an already effective treatment is superior to the established effective treatment alone.

SOC may include general supportive care appropriate to the participant's clinical status, and specific therapeutic agents, and measures to reduce risk of SARS-CoV-2 transmission to the participant and health care givers.

As stated in section 5.1, the objective of this protocol is to evaluate investigational agents - aimed at enhancing the host immune response to or impair replication of SARS-CoV-2 infection - for safety and efficacy compared to placebo control, when all eligible participants receive background therapy that is considered effective. Consistent with precedent, we refer to background therapy as standard of care (SOC). All participants will receive an investigational agent (initially a nMAb) + SOC vs. placebo + SOC.

Below, principles for defining SOC are provided, and recommendations and guidance on SOC are given. Whether an individual SOC treatment is provided by the trial or not is based on multiple factors, including clinical and scientific considerations. In some cases, the decision to administer an SOC treatment is left entirely to the research participant's primary medical team.

I2. Guiding principles for inclusion of measures as part of SOC

The SOC will be regularly updated based on review of the scientific literature and updated authoritative treatment guidelines on this topic. The standard for including one or more measures as SOC, includes a careful review of the existing literature and current guidelines (see Appendix D). As for therapeutic agents, those having been shown to be clinically effective in properly powered phase III or phase IV trials (i.e., high quality/level 1 evidence) and with a reasonable safety profile will be considered by the protocol team for inclusion, if recommended by at least one major treatment guideline. This evaluation may also lead to a statement that one or more agents are either not recommended or should not be used as part of SOC. As knowledge will likely continue to accumulate rapidly, the protocol leadership team may occasionally decide to include or exclude an intervention as part of

SOC before it is recommended in at least one major treatment guideline. In such cases, the relevant literature that lead to the determination will be cited.

The use of a given SOC intervention may apply to all or to a subgroup of the participants in the master protocol based on available evidence – the subgroup may be defined based on severity of disease, a clinical or laboratory defined feature, or a clinically or laboratory defined contraindication for using the SOC treatment. An SOC agent may be mandated for participants (required for protocol entry); mandated where not contraindicated (participants may enter if that SOC is unsuitable, and not receive that SOC); or recommended subject to clinical discretion. SOC may be protocol-supplied where mandated.

The master protocol acknowledges that there may be local variation in the clinical availability of one or more agents chosen to be part of mandated protocol-supplied SOC from site to site. While acknowledging risks of inadvertent coercion, the importance of the scientific question (how candidate agents perform against the background of the current SOC treatments) is a crucial, high-priority question. There is no possible way to answer the question of efficacy against the background of an already proven effective agent without providing the agent – if not readily available - within the trial.

I3. Current SOC in the master protocol:

I3.1 Remdesivir Background Therapy

Based on the findings of the Adaptive COVID-19 Treatment Trial (ACTT),[91] remdesivir will be provided to all study participants as SOC unless contraindicated for an individual patient. As in the ACTT trial, remdesivir will be administered as a 200 mg IV loading dose, followed by a 100 mg once-daily IV maintenance dose while hospitalized up to a 10-day total course. Participants taking remdesivir prior to randomization will continue their daily remdesivir infusions while hospitalized up to a 10-day course and possibly longer should evidence emerge to support this. The primary medical team has discretion to plan for 5 days duration in patients that do not require mechanical ventilation or ECMO. If as part of clinical care a patient has received a loading dose of remdesivir before randomization, the loading dose will not be repeated. Details relating to contraindications, dosing, and monitoring of remdesivir are included in the Protocol Instructions Manual [PIM].

I3.2 Dexamethasone and Other Corticosteroids

Based on the preliminary findings of the RECOVERY trial (https://pubmed.ncbi.nlm.nih.gov/32678530/and in line with NIH treatment guideline (Appendix D), it is recommended to consider initiation of corticosteroid therapy in participants with COVID-19 who are mechanically ventilated and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated**.** In patients with minimal oxygen need, however, special consideration weighting benefits vs potential risk should be given whether to initiate a corticosteroid. Corticosteroids may increase the probability of reactivating latent infections including herpes viruses and tuberculosis, hyperglycemia, hypernatremia, secondary infections, and may delay clearance of SARS-CoV-2. In participants not requiring supplementary oxygen, it is recommended not to initiate a corticosteroid. As the RECOVERY trial was performed at or near sea level, for patients enrolled at altitude, investigators and clinicians may appropriately avoid corticosteroid administration in patients receiving modest flow rates of supplemental oxygen. Treatment

with a corticosteroid is recommended for a total of 10 days, using doses outlined in this table.

Corticosteroid name	Daily dose
Dexamethasone	6 mg PO or IV
Prednisone	~40 mg PO
Methylprednisolone	~32 mg IV
Hydrocortisone	~160 mg IV

I3.3 Other Supportive Care

All participants will be given *supportive care* for most complications of severe COVID-19 including: pneumonia, hypoxemic respiratory failure/ARDS, sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalization, including secondary bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy. Links to details of such care can be found in Appendix D. Supportive care components of SOC include lung-protective ventilation for patients who require invasive mechanical ventilation[92] (high quality evidence) and prone positioning for mechanically ventilated patients with more than moderate ARDS (high quality evidence), treatment with anti-bacterial agents for patients believed to have bacterial infection (high quality evidence), guidelines-compliant management of sepsis when it is present (moderate quality evidence)[93]. Use or non-use of extra-corporeal life support (ECLS) is not mandated as part of SOC; nor is any specific approach to renal replacement therapy.

Consideration should be given to the use of pharmacological thromboprophylaxis (thrombosis prevention) in line with local clinical guidelines for hospitalized patients as appropriate for an individual participant, in addition to approaches to maintain mobility and minimize other thrombotic risks. Standard approaches to thromboprophylaxis supported by high quality evidence include the use of low molecular weight heparin (for example, enoxaparin 0.5m/kg daily), which is the preferred agent in some COVID-19 treatment guidelines. However other standard approaches in accordance with local and institutional guidelines and the medical circumstances of an individual participant may also be considered, including the use of low (prophylactic) dose unfractionated heparin (high quality evidence). Specialist advice should be sought for participants with pre-existing prothrombotic states, or who are pregnant.

I3.4 Cautions and Contraindications

Remdesivir is recommended not to be combined with (hydroxy)chloroquine. The effectiveness of remdesivir may be reduced if combined with (hydroxy)chloroquine, and hence it is not advisable to combine these two medications.[94]

It is not recommended to use high dose chloroquine (600 mg twice daily) as SOC due to excess harm and not demonstrable benefit. (Hydroxy)chloroquine has no documented clinical benefit, and hence not recommended for use as SOC.

I3.5 SARS-CoV-2 Infection Control

Minimum standards of protection to *reduce the risk of SARS-CoV-2 transmission* from trial participants to research personnel, participants in other trials, or patients treated in the same facility can be found in links displayed in Appendix D.

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Appendix J References

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Statistical Analysis Plan

Version 2.1

Therapeutics for Inpatients with COVID-19 (TICO)

A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19

Clinicaltrials.gov identifier: NCT04501978
EudraCT number: 2020-003278-37

Version	Date	Who	Comments
1.0	06 October 2020	BG	TICO ACTIV-3 INSIGHT 014 Protocol v1.0, 27 July 2020 Investigational agent: LY-Cov555
2.0	28 January 2021	BG	TICO ACTIV-3 INSIGHT 014 Protocol v2.0, 3 November 2020 and v3.0, 7 January 2021 Investigational agents: Vir-7831; BRII-196 and BRII-198; AZD7442
2.1	22 February 2021	BG	Added detail to win ratio analyses and risk score specifications

Contents

1 Introduction

1.1 Objective of the Statistical Analysis Plan

The objective of this statistical analysis plan (SAP) is to provide a description of the general analytic strategy and the statistical methods that will be used to analyze the data for the TICO (Therapeutics for Inpatients with COVID-19) Phase III randomized, blinded, controlled, platform trial. This SAP applies to versions 2 and 3 of the TICO protocol. In version 2, two investigational agents are being studied, a SARS-CoV-2 neutralizing monoclonal antibody (nMAb) (Vir-7831) which is being developed by Vir Biotechnology (Vir) (San Francisco, CA) and GlaxoSmithKline (GSK) (Brentford, U.K.), and two nMAbs given sequentially (BRII-196 and BRII-198) which are being developed by Brii Biosciences (Durham, NC and Beijing). In protocol version 3, a third investigational agent is added, AZD7442, which is a combination of two nMAbs by AstraZeneca (Cambridge, U.K.). Participants are followed for death or re-hospitalization up to month 12 in version 2, and up to month 18 in version 3. Otherwise, the protocol versions are identical. The nMAbs are given by single infusion, or two sequential infusions for BRII-196 and BRII-198.

The primary objective of the platform trial is to determine whether investigational agents that are aimed at enhancing the host immune response to SARS-CoV-2 infection are safe and superior to control (e.g., placebo) when given with standard of care (SOC) for the primary endpoint of time to sustained recovery evaluated up to 90 days of follow-up.

In the platform trial, several agents may be investigated in parallel, or staggered with overlapping times; investigational agents may be added or dropped. When more than one agent is being tested concurrently, participants will be randomly allocated across agents (as well as between the agent and its matched placebo), and the control group is pooled across the concurrently randomized, agent-specific matched placebo groups. Thus, each investigational agent and the corresponding pooled control group form their own randomized trial, and several agents may (at least partially) share their pooled control groups.

This SAP:

- Provides a short description of the study design (sections 1.2-1.4)
- Describes goals of the interim reviews by the independent DSMB and the planned format of the review meetings (section 2)
- Describes the planned data analyses presented in the reports to the DSMB (sections 3-13). General analysis principles are summarized in section 3, safety analyses are described in section 7, efficacy analyses in section 8, and interim monitoring guidelines in section 9.
- Describes data summaries to be provided regularly to study leadership to aid in monitoring trial conduct and data quality; these data summaries will be pooled across treatment groups, and will be restricted to enrolment, baseline data, and summaries of data completeness and study conduct.

As needed, the overall SAP for TICO will be updated by the blinded study statisticians; it is planned to update the SAP in parallel with protocol amendments.

1.2 Description of the Study Design

This section is adapted from Section 1 of the TICO protocol versions 2.0 and 3.0.

Design
TICO is a master protocol to evaluate the safety and efficacy of multiple investigational agents aimed at modifying the host immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, or directly enhancing viral control in order to limit disease progression.

Trials within this protocol will be adaptive, randomized, blinded and initially placebo-controlled. Participants will receive standard of care (SOC) treatment as part of this protocol. If an investigational agent shows superiority over placebo, SOC for the study of future investigational agents may be modified accordingly.

The protocol is for a phase III randomized, blinded, controlled platform trial that allows investigational agents to be added and dropped during the course of the study for efficient testing of new agents against control (i.e., placebo + SOC) within the same trial infrastructure. When more than one agent is being tested concurrently, participants will be randomly allocated across agents (as well as between the agent and its placebo). For analysis, placebo groups of concurrently randomized agents will be pooled; therefore, control groups may overlap for different agents.

Randomization will be stratified by study site pharmacy and disease severity. There are 2 disease severity strata, defined as below:

- **Disease severity stratum 1:** Absence of all of the following: stroke, meningitis encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, symptomatic congestive heart failure (NYHA class III or IV), arterial or deep venous thrombosis or pulmonary embolism, requirement for invasive mechanical ventilation, ECMO, mechanical circulatory support, vasopressor therapy, or new renal replacement therapy.
    - Per FDA recommendation, none of the three investigational agents in version 3 of the protocol can be used in patients on high-flow oxygen or non-invasive ventilation. Therefore, all reference to “disease severity stratum 1” in this SAP also excludes such patients.

    - Initially, only patients in disease severity stratum 1 are eligible for enrolment, as described below.

- **Disease severity stratum 2:** Presence of at least one of the excluded conditions or treatments in disease severity stratum 1.

The **primary endpoint** is the time from randomization to sustained recovery, defined as being discharged from the index hospitalization, followed by being alive and home for 14 consecutive days prior to Day 90. The definition of home will be operationalized as the level of residence or facility where the participant was residing prior to hospital admission leading to enrollment in this protocol.

An independent Data and Safety Monitoring Board (DSMB) will regularly review interim analyses that summarize safety and efficacy outcomes. For any agent, at the outset of the

trial, only participants in disease severity stratum 1 will be enrolled. This more restricted enrollment will continue until approximately 150 participants per study arm are enrolled and followed for 5 days. At this point, the DSMB will carry out a pre-specified assessment of futility, based on two 7-category ordinal outcomes (pulmonary and pulmonary+), assessed at Day 5. The pulmonary and pulmonary+ outcomes are described in Appendix A. Safety of the investigational agents will also be assessed.

For investigational agents passing this initial futility assessment, enrolment of patients in disease severity stratum 1 will continue, and it is planned to also expand enrollment, seamlessly and without any data unblinding, to include participants in disease severity stratum 2. The expansion to include more severely ill participants will be subject to recommendations by the FDA and the DSMB based on safety considerations.

After the initial futility assessment is passed, future interim analyses will be based on the primary endpoint of sustained recovery and will use pre-specified guidelines to determine early evidence of benefit, harm or futility for the investigational agent.

Primary Objective
The primary objective of this protocol is to determine whether investigational agents, initially focusing on those that are aimed at enhancing the host immune response to SARS-CoV-2 infection are safe and superior to control (e.g., placebo) when given with SOC for the primary endpoint of time to sustained recovery evaluated up to 90 days after randomization.

Duration
Participants will be followed for 18 months following randomization in version 3 of the protocol, 12 months in version 2. Primary and most secondary outcomes will be collected during the first 90 days of follow-up only. Follow-up beyond 90 days is planned because the half-lives of some agents indicate that potentially meaningful amounts may remain in the body after 90 days of follow-up. After 90 days through the end of follow-up, hospitalizations and deaths will be ascertained.

Sample size
This phase III trial is planned to provide 90% power to detect a 25% increase in the rate of sustained recovery for an investigational agent compared to placebo at the 0.025, 1-sided level of significance. This requires 843 primary events (i.e., participants who achieve sustained recovery). Randomization of 1,000 participants, equally allocated to each investigational agent and placebo, followed for 90 days is estimated to result in the required number of primary events. The event target may be achieved earlier if more than 1,000 participants are enrolled. Sample size will be evaluated periodically by study team members who are blinded to interim results on treatment difference and may be increased to maintain power for the hypothesized difference in sustained recovery between the investigational agent and placebo.

Population
The study population consists of inpatient adults (≥18 years) who have had COVID-19 symptoms ≤ 12 days. Initially, enrollment is restricted to disease severity stratum 1. After a pre-specified review by the DSMB for safety and futility, when approximately 150 participants

are enrolled per study arm, eligibility for randomization will be expanded to also include patients in disease severity stratum 2, subject to recommendations by the FDA and DSMB.

Stratification
Randomization is stratified by study site pharmacy; once enrolment is expanded to also include disease severity stratum 2, randomization will also be stratified by disease severity stratum.

Monitoring
An independent DSMB will review interim data on a regular basis for safety and efficacy. An initial futility assessment will be performed after the first 300 participants (150 in the active and 150 in the placebo arms) are enrolled and have Day 5 data; this initial assessment is based on two ordinal outcomes (pulmonary and pulmonary+ outcomes at Day 5). Afterwards, the DSMB will use pre-specified guidelines to identify agents with clear evidence of efficacy for the primary outcome and, if so, recommend unblinding of the trial results for that agent. Conversely, the DSMB may recommend discontinuation of an investigational agent if the risks are judged to outweigh the benefits or if futility assessments indicate that there is low probability that an investigational agent will achieve statistical significance for the primary endpoint of sustained recovery.

For an investigational agent, if the trial is stopped early or if the trial continues until the pre-specified number of primary endpoints is reached, further enrollment of the investigational agent will be terminated if applicable, and the trial data for the investigational agent will be unblinded and reported with data through 90 days of follow-up. Follow-up of all participants will continue through 18 months (12 months in version 2.0 of the protocol) using the data collection plan described in the master protocol.

1.3 Randomization

The randomization is described in section 6.1 of the protocol.

Patients will be equally allocated to each investigational agent + SOC or to placebo + SOC. For example, for a study of a single investigational agent, participants will be randomized in a 1:1 ratio to the investigational agent or placebo. If a patient is eligible for two investigational agents, the allocation will be 1:1:1 to investigational agent A, agent B, or placebo. Because the two investigational agents (A and B) may require different placebos (for example, when infusion volumes differ), the 1:1:1 allocation ratio will be achieved through a two-step randomization procedure: in *step 1*, the participant is randomized 2:1 to “active” versus “placebo”; in *step 2*, the participant is randomized 1:1 to A versus B. With k agents, this can be viewed as an initial k:1 allocation to “active” versus “placebo”, followed by a second, even allocation to one of the available agents (for example, if a participant was allocated to “placebo” in step 1, then the step 2 allocation will be 1:1 to “matched placebo for A” versus “matched placebo for B”). For the analysis, the concurrent agent-specific placebo groups will be pooled, resulting in a 1:1 allocation ratio for comparing each investigational agent versus the (pooled placebo) control group. If investigational agents are added or dropped, the allocation ratio to active versus placebo will be appropriately modified, and sample size will be recalculated as appropriate.

Randomization will be stratified by study site pharmacy (several clinical sites may share one pharmacy) and severity of disease at entry; the two disease severity strata are defined in section 1.2 of this SAP.

If more than one investigational agent is being compared with placebo and they have different contraindications, it is possible that a participant is eligible only for a subset of agents.

Comparisons will be of each investigational treatment against its control arm. The control arm consists of all participants who were "at risk" of being randomized to the investigational agent but were randomized to a control group instead. This concept is relevant when the randomization includes investigational agents with different eligibility criteria, when agents are introduced into the platform trial at different time points, or randomization to one of the agents is halted temporarily. Formal randomization includes agent-specific matched placebo groups, and the placebo groups will be pooled across agents, but only participants who 1) were eligible for the investigational agent under consideration, and 2) were randomized contemporaneously and at participating sites will be included in the control group for a given agent. At the time of randomization, for each participant, indicator variables will be set that record whether an agent was included in the randomization for that participant (e.g., indicator A=1, indicator B=1, indicator C=0 if the participant was eligible to be randomized to agents A and B, but not C). The pooled control group for agent A then consists of all participants who were randomized to (any) placebo, and for whom indicator A=1.

1.4 Sample Size Estimates

The planned sample size for each pairwise comparison is 1,000 participants (500 participants in each group). The sample size is sufficient to detect a recovery rate ratio (RRR) of 1.25 for time to sustained recovery with 90% power, using a one-sided test with a significance level of 0.025. The treatment groups are compared using Gray's test with ρ=0, the competing risks analogue of the log-rank test.

Sample size calculations are described in detail in Section 6.3 of the protocol.

Blinded sample size re-estimation will be carried out before enrollment is complete to determine whether the planned sample size of 1,000 participants followed for 90 days will yield the planned number of 843 primary events. The blinded sample size re-estimation does not involve unblinding of the treatment difference. It will be based on the pooled outcome data. Sample size may be increased to achieve the event target in the planned follow-up of 90 days. A sample size increase may also be considered in order to achieve the event target before all participants are followed for 90 days.

When 300 participants (150 per study arm) are enrolled and have Day 5 outcome data, an early futility assessment is planned. This assessment will be based on two ordinal outcomes, denoted as "pulmonary" and the "pulmonary+"; both are ordered categorical outcomes with 7 categories, assessed on Day 5 (the outcomes are described in Appendix A). Treatment groups will be compared using proportional odds models. With 300 participants, the early futility assessment is powered to detect a summary OR=1.60 with power of 95%, using a one-sided test with significance level of 0.30.[1] Given the two-outcome decision rules, an investigational

agent with a summary OR=1.60 at Day 5 for both outcomes, would pass the futility assessment with a power between 93% and 98%, and a type I error between 0.21 and 0.39.

2 Interim DSMB Reviews: Goals and Format

Each investigational agent versus control will be reviewed as a separate clinical trial; separate data reports will be prepared for each investigational agent and the corresponding randomized (pooled) placebo group.

Goals of the interim reviews:

- Protect the safety of study participants.
- Advise on stopping or modifying the trial for efficacy, for patient safety in case of emerging data on harm, or for futility.
- After the first 300 participants are enrolled (150 participants per arm; all in disease severity stratum 1), advise on continuing the trial, and on expanding the study population to include more severely ill patients (disease severity stratum 2).
- Review the conduct of the trial
- If an investigational agent is stopped (due to efficacy, safety, or futility), the DSMB may be asked to advise on the timing of unblinding the data, in case the unblinding of the shared pooled placebo group may impact the integrity of the ongoing trial for another agent (section 14).

The DSMB will conduct frequent safety reviews. For an investigational agent with minimal pre-existing data, the first safety review will be conducted after 20-30 participants have been enrolled (10-15 per study arm) and Day 5 data are available, before increasing the pace of enrollment. Subsequent reviews will be timed according to the recommendations of the DSMB and study leadership. After the early futility review when 300 participants are enrolled (150 per study arm), further futility reviews would be expected to occur at approximately 50% and 75% information time (the number of observed sustained recoveries as a proportion of the targeted number of 843 events).

The DSMB may request interim reports that are focused on safety at any time.

Review meetings for each agent will typically consist of an Executive session (optional; closed), open session, closed session, and a second open session to give feedback to study leadership (optional). If several agents are reviewed at the same meeting, agents will be reviewed consecutively, either with a sequence of open and closed sessions, or with one open session and one closed session (provided there are no unblinding conflicts).

Masking of treatment group labels in interim reports: In the open reports, any data reports will be pooled across the two treatment groups (the specific investigational agent and its pooled control group as described above). In the closed reports, treatment group labels will masked; for example as “Group A” versus “Group B”. The treatment group labels will be consistent across all analyses and over subsequent reports. The DSMB will be unmasked to the treatment group labels.

Open report to the DSMB
The open reports for each investigational agent versus placebo comparison will contain:

- A synopsis of the trial design and current status of the platform trial
- Responses of the study team to DSMB requests
- A summary prepared by the study leadership
- Data summaries for enrolment, eligibility violations and protocol deviations, baseline characteristics
- Summary reports for data completeness and study conduct, pooled across treatment groups.
- Emerging external data, e.g., results of phase I or II trials on the investigational agent, will also be provided to the DSMB by the study leadership. This is usually included with the open report, but may be shared confidentially if needed.

All data summaries in the open report will be pooled across the investigational agent and placebo control. The open reports will be prepared by the blinded statisticians in cooperation with the unblinded statisticians. In addition to the DSMB, open reports will be provided to the study team, and posted on the website for access by study investigators.

While the study is ongoing, summaries by treatment group, and comparisons of the investigational agent versus placebo are restricted to the confidential closed report to the DSMB. Additionally, all summaries of follow-up data other than the data completeness and study conduct reports (pooled across the two treatment groups) will be restricted to the confidential closed report. For the **planned sample size re-estimations prior to completion**, the pooled number of primary events and the pooled event rate will be provided to the blinded study statisticians and study leadership. On a case-by-case basis, other pooled follow-up data may be provided if explicitly approved by the DSMB.

Closed report to the DSMB
All data summaries in the closed report will be by (masked) treatment group. The closed reports for a full review will contain:

- Specific data summaries requested by the DSMB or study leadership
- Data summaries in the open report, by treatment group (enrollment, baseline characteristics, eligibility violations)
- Data summaries to assess safety of the investigational treatment, described in sections 6 and 7. Data summaries for the primary “efficacy outcomes” and selected secondary outcomes will also be included in each report, because these data contain information about the risk/benefit profile of the investigational agent. Analyses are described in section 8.
- Data summaries on data completeness and study conduct, described in section 10
- Interim monitoring boundaries for efficacy or harm (section 9)
- Futility analyses (sections 9.2 and 9.4)
- Listings of grade 3 and 4 adverse events, serious adverse events (SAE), clinical organ failure and serious infections (PSEE), unanticipated problems (UP), suspected unexpected serious adverse reactions (SUSAR), and deaths.

Data reports will follow a similar format for all investigational agents. Each agent will have a small assigned team of unblinded statisticians, with 2-3 alternating teams when 2 or more agents are investigated in parallel. The unblinded statistician teams will cooperate in

designing the master layout for the data reports and will serve as each other's backup when needed. The unblinded statisticians will be unblinded to several investigational agents in the platform trial; those for which they serve as primary statisticians, and those for which they serve as backup or advisory statisticians.

3 Analysis Principles

Each investigational agent versus control will be treated as a separate clinical trial; data reports will be for one "target" investigational agent and its corresponding randomized (pooled) control group. Investigational agents will not be directly compared against each other, unless explicitly stated in the agent-specific data analysis plan and agreed upon by all stakeholders. Therefore, in the event that several investigational agents are included in the platform trial in parallel, the pairwise comparisons of each agent versus control will **not** be adjusted for potential inflation of Type I error "due to multiple comparisons".

Comparisons will be of each investigational treatment against its (pooled) control arm.

Analysis populations:

- Comparisons for safety outcomes will be by modified intention-to-treat. The modified intention-to-treat analysis is restricted to participants who received a complete or partial infusion of the investigational agent/placebo; participants who did not receive any of the investigational agent/placebo are excluded.
- Comparisons for efficacy endpoints will be by intention-to-treat, unless otherwise stated. Sensitivity analyses by modified intention-to-treat will be carried out for primary outcomes and key secondary outcomes.

Pooled control group: As stated in section 1.3 above, the control arm for any investigational agent will be pooled across the agent-specific control groups for all agents that concurrently participated in the randomization. Specifically, the pooled control group for investigational agent A consists of all participants who might have been randomized to agent A but were randomized to a placebo group instead. This concept is relevant when a participant is eligible to be randomized to more than one investigational agent, and agents were introduced into the platform trial at different time points or have different eligibility criteria.

In order to identify the pooled control group for each investigational agent correctly, the randomization application is setting indicator variables at the time of randomization for each participant that record whether an agent was included in the randomization (e.g., indicator A=1, indicator B=1, indicator C=0 if the participant was eligible to be randomized to agents A and B, but not C). The pooled control group for agent A then consists of all participants who were randomized to (any) placebo, and for whom indicator A=1.

Therefore, only participants who 1) were eligible for the investigational agent under consideration, 2) were randomized contemporaneously and at participating sites, and 3) were randomized to placebo will be included in the control group for a given agent.

Descriptive statistics will be reported overall and by randomized group. For categorical outcomes, the number and percent in each category will be reported; percentages will be of

non-missing values, if data are not complete. Continuous variables will be summarized by median (interquartile range [IQR]) and/or mean (SD). Continuous variables may be categorized (e.g., age may be broken into categories to investigate the distribution across age groups).

Stratification: Tests comparing the investigational agent versus control for primary outcomes and key secondary outcomes will be stratified according to the planned randomization strata (disease severity and site pharmacy), provided participant numbers are sufficiently large. In this analysis plan, "stratification by disease severity" refers to the two disease severity randomization strata described in section 1.2. Initially, participants are enrolled only in disease severity stratum 1, until the investigational agent has passed the initial futility assessment (when 300 participants are enrolled for the pairwise comparison; 150 per study arm) and has been approved to expand enrolment to include participants from both strata 1 and 2. In this SAP, we use the notation "stratification by disease severity and site pharmacy" to denote the following:

- For analyses that include only participants in disease severity stratum 1, analyses will be stratified by site pharmacy.
- For analyses that include participants in both disease severity strata, analyses will be stratified by site pharmacy within each disease severity stratum; this means, the maximal possible number of strata is twice the number of site pharmacies. For analyses where stratification is implemented through addition of indicator variables for strata to the model, the strata would be defined through main effects for disease severity, for site pharmacy, and the interaction between disease severity and site pharmacy.

Because there are many site pharmacies, some strata may be small, particularly early in the trial. In order to avoid loss of power, any stratum that contains too few participants (less than 10-20 participants or events) should be pooled with other strata (of the same disease severity, and preferably within the same country or geographical region). Thus, several small strata may be pooled together, or pooled with a larger stratum.

For time-to-event analyses, if strata are too small for fitting separate baseline hazard functions, strata may be added as a categorical covariate to models instead. Whenever possible, however, analyses should be stratified by disease severity (with separate baseline hazard functions).

For **binary outcomes**, probabilities will be compared between the investigational agent and its control group using Cochran-Mantel-Haenszel tests (CMH) or logistic regression. If the numbers are sufficiently large, CMH tests will be stratified according to the planned randomization strata (disease severity and site pharmacy), as described above under "stratification". Odds ratios (OR) with 2-sided 95% confidence intervals (CI) will be estimated using logistic regression models.

For longitudinally measured binary outcomes, the treatment effect through follow-up will be estimated with 95% confidence intervals using generalized estimating equations (GEE) with a logit link function; the treatment effect is estimated via the interaction between the indicator for treatment group and the indicator for follow-up (versus baseline) visits. When there is more than one follow-up visit, "visit number" (day) may be included as categorical variable in the model, for variance reduction; alternatively, "time" may be included as a continuous variable.

Ordered categorical outcomes (pulmonary and pulmonary+) will be compared between treatment groups using proportional odds models, and the summary OR will be estimated with

a 2-sided 95% CI.[2] Additionally, to aid the interpretation, the ordinal outcome will be dichotomized according to cumulative probabilities of the ordered categories, comparing treatment groups for proportions of participants in category 1, in the "best 2 categories", "best 3 categories", etc.; these comparisons will be performed using logistic regression (or stratified CMH tests).

Models will be adjusted for the baseline categories of the pulmonary+ outcome and for study pharmacy, by including the corresponding indicator variables in the model.

- If the number of observations is too small to adjust for both categorical covariates, preference will be given to the adjustment for the pulmonary+ category at baseline. Site pharmacy categories may be collapsed as described above under "stratification".
- For the initial futility analysis (after 150 participants per arm have Day 5 data), the adjustment for the pulmonary+ categories and pharmacy will be additive.
- For key analyses, unadjusted OR estimates will also be provided as sensitivity analyses.

The validity of the proportional odds assumption will be assessed by testing for heterogeneity in the log ORs (for the treatment effect) across the dichotomized cumulative ordered categories in the corresponding logistic regression model (partial proportional odds model, test for "unequal slopes").

- The primary sensitivity analysis testing the proportional odds assumption will compare the unadjusted proportional odds model for the treatment comparison (null model) versus a partial proportional odds model that allows for "unequal slopes" across the dichotomized cumulative categories (i.e., when testing the proportional odds assumption for the treatment comparison with respect to the pulmonary outcome on Day 5, the model will allow for heterogeneous ORs across the Day 5 pulmonary categories) as well as across the stratification covariates (i.e., the baseline pulmonary+ categories and site pharmacy strata) (full partial proportional odds model).

Continuous outcomes will be compared between treatment groups using ANCOVA models for comparing means, if the ANCOVA model assumptions hold. If the distributions of the continuous outcomes are skewed, outcomes may be transformed, or compared between treatment groups using rank-based methods, such as the Wilcoxon test, or quantile (median) regression.

Comparisons between treatment groups for a continuous outcome will be adjusted for baseline values of the outcome, for the purpose of variance reduction, unless there are concerns over model stability with such an adjustment. For this purpose, the baseline value will be included as covariate in the model (e.g., ANCOVA, linear mixed models).

To estimate the treatment effect for longitudinally measured continuous outcomes, the outcome will usually be defined as "change from baseline" (difference at follow-up visit minus baseline value). The treatment effect through follow-up will then be estimated with 95% confidence intervals using generalized estimating equations (GEE) with an indicator for treatment group, or, in the case of Gaussian responses, the corresponding mixed effects models with random effects for participants. When there is more than one follow-up visit, "visit number" (day) may be included as categorical variable in the model, for variance reduction; alternatively, "time" may be included as continuous variable. Models will also be adjusted for the baseline values of the outcome variable.

Time-to-event outcomes will be summarized with Kaplan-Meier estimates for cumulative probabilities over time, and compared between treatment groups using log-rank tests or Cox proportional hazards models, or the corresponding competing risk analogues when death is a competing risk for the outcome. In particular, the primary endpoint of "time to sustained recovery" will be analyzed taking into account the competing risk of death. The following competing risk methods will be used:

- Aalen-Johannsen estimator for the cumulative incidence function (analogue to the Kaplan-Meier estimate)[3]
- Gray's test with ρ=0 (analogue to the log-rank test)[4]
- Fine-Gray estimates and tests for the sub-distribution hazard ratio (analogue to the Cox proportional hazards model).[5,6]

The proportional hazards assumption will be tested by adding an interaction term for time by treatment group to the model. The cumulative proportions of participants who experienced the event will also be compared at given time points (specified in secondary objectives, e.g., at 28 days); in this case, the cumulative proportions will be estimated using Kaplan-Meier estimates or the competing risks analogue, and/or as proportion of participants who reached the time point (e.g., time since randomization $\geq$ 28 days).

The **administrative follow-up time** is defined as the minimum of (cut date minus randomization date) or the analysis time period. For example, the analysis time period for the primary endpoint of *sustained recovery* is 90 days, and the analysis time period for the important safety endpoint, the composite of *grade 3 and 4 events, SAEs, organ failure, serious infection or death*, is 5 days or 28 days. The **administrative censoring date** is the earlier of the cut-date of the dataset, or randomization date plus analysis time period.

> **Comment:** The notion of "administrative censoring" is important in time-to-event analyses in the presence of competing risks. For example, the Fine-Gray method for estimating the sub-hazard ratio for sustained recovery can be approximated by using a Cox proportional hazards model where follow-up time for participants who died prior to achieving sustained recovery is not censored at death, but at the administrative censoring date.

Censoring for time-to-event analyses

For **interim** analyses, the type of censoring used will depend on the data collection schedule.

- If the reporting of the endpoint is data-driven (e.g., SAEs and deaths are reported as they occur), then follow-up is censored at the administrative censoring date, at the date of withdrawal, or loss to follow-up, whichever occurs earliest.
- If the date of the event is elicited retrospectively at fixed study visits spaced more than one week apart (e.g., "sustained recovery"), follow-up will be censored at the last day the endpoint status was ascertained.
- Sensitivity analyses will be provided for key analyses when the outcome status is uncertain.

For **final** analyses, follow-up will be censored on the last day the outcome status was ascertained.

Adverse events (AEs) will be classified by system organ class according to MedDRA®[1] (currently version 23.1 [September 2020] is used; when new versions are implemented, items are recoded). AEs will be graded according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, *Corrected Version 2.1 (July 2017)* (also referred to as the *DAIDS AE Grading Table*).[7] Cause of death will also be coded according to MedDRA®.

The number and percent of participants with grade 1-4 AEs will be summarized by day and grade, and by MedDRA® System Organ Class and grade. The percentage of participants with AEs will be compared between treatment groups according to grade cut-offs, e.g., "percent of participants with any AE", "percent of participants with grade 2 or higher AEs", etc., using CMH tests. The total number of events and median (IQR) of events per participant will also be summarized.

Additionally, the incidence of grade 3 and higher AEs will be summarized (number and percent of participants), and compared between treatment groups using time-to-event methods.

Significance level, two-sided tests: Unless noted otherwise, statistical tests and confidence intervals will be 2-sided, confidence intervals will have approximate 95% coverage probability, and test results with P-values $\leq$ 0.05 will be considered "significant". Percentages will be reported to at least one decimal place. P-values will be given to 2 significant figures.

Cut-date for interim reviews: Analysis data sets will be frozen (locked) several days (or weeks) prior to the review date, to allow the unblinded statisticians time to prepare a consistent report. The cut-date may be earlier than the date of the data freeze, to allow for lag time in the reporting of events. Early in the trial, the cut date and freeze date will be very close to the review date, to ensure timely safety reviews.

4 Enrolment and Eligibility

For the open report, the following enrolment and eligibility summaries will be provided:

- Enrolment over calendar time: plot by day or week, cumulative and increments.
- Enrolment by site pharmacy and by country: number (%)
- Eligibility: number (%) and reasons for eligibility violations

These summaries will be provided overall, and by disease severity randomization stratum.

For the closed report, enrolment and eligibility violations will be summarized by treatment group.

[1] The Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA® is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

5 Baseline Characteristics

Baseline characteristics will be based on information collected on baseline and screening forms. For the open report, baseline characteristics will be summarized pooled across the two treatment groups (investigational agent and the "pooled" control group as described in section 2 above).

For the closed report, baseline characteristics will be summarized by treatment group.

The following baseline characteristics will be reported; unless noted otherwise, categorical variables will be summarized with numbers (%) in each category, and continuous variables will be summarized with median (IQR); in the open report, in addition, the mean (SD) and range may be provided.

- Demographics
  - Age: distribution in categories 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, ≥80 years; and summary as continuous variable
  - Sex at birth: number (%) male, female
  - Ethnic group: number (%) Asian, Black, Latino/Hispanic, White, other
  - Type of residence ("home")
  - Country of enrolment
- COVID-19 related characteristics
  - Duration of symptoms prior to enrolment
  - Use of remdesivir prior to enrolment
  - Pulmonary and pulmonary+ ordinal outcomes, number (%) in each category
  - NEWS: summary as continuous variable
  - Respiratory function scale (modified Borg dyspnea scale; continuous outcome)
  - Disease severity randomization stratum (for investigational agents that enrol in both strata), number (%) in each category
  - Receipt of SARS-CoV-2 vaccination, and type of vaccine (and if received as part of a blinded clinical trial, in which case the vaccine may be active or control)
- Other clinical characteristics
  - Concomitant treatments
  - Corticosteroid use will be summarized overall, and separately by oxygen requirement at baseline (no supplemental oxygen, < 4 L/min, conventional supplemental oxygen $\geq$ 4 L/min, high-flow oxygen or mechanical ventilation/ECMO)
  - History of chronic conditions (cardiovascular disease, diabetes, asthma, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, hepatic impairment, cancer, or immunosuppressive disorder [HIV, and other than HIV])
  - Prior cerebrovascular event
  - Prior myocardial infarction (MI)
  - Requirement of continuous chronic supplemental oxygen
  - BMI (<30, 30-39.9, 40+)
  - Pregnancy (not applicable to protocol versions 2 and 3)
- Laboratory values: as continuous outcomes, and number (%) of grade 3 or 4 abnormalities according to the *DAIDS AE Grading Table.*

Some biomarkers will be measured centrally from stored samples, for example, SARS-CoV-2 antibody levels and SARS-CoV-2 viral RNA. If these measures are available, they will be included in interim reports.

6 Administration of Study Treatment

These data are an important part of the safety review, with particular emphasis on infusion-related reactions and symptoms occurring during or within up to 2 hours after the infusion. These reactions and symptoms will be graded according to the DAIDS AE Grading Table.

The administration of study treatment is also an essential element of study conduct. Several summaries, pooled across treatment groups, will be included in the open report or provided to study leadership. Any summaries of adverse events or infusion-related reactions are restricted to the closed report.

Each investigational agent is administered as a one-time infusion. The following statistics will be used to summarize the infusion in each treatment group (active and control):

- Number and percentage of participants receiving complete infusion, partial infusion, infusion paused but resumed for complete infusion, or not infused (comparison by intention-to-treat).
- Number and percentage of participants with infusion-related reactions and symptoms (reported during the infusion or within 2 hours after the infusion), by grade. (Closed report only)
- Number and percentage of participants with an incident AE, SAE, UP or SUSAR on Day 0 during or after the infusion, overall and by oxygen requirement category at time of infusion (oxygen requirement at baseline, unless updated information is available; categories: no supplemental oxygen, < 4 L/min, conventional supplemental oxygen $\geq$ 4 L/min, high-flow oxygen or mechanical ventilation/ECMO). Types of AEs will be summarized by system organ class and by grade. (Closed report only)
- Number and percentage of participants who received:
    - Prior to infusion, medication to prevent infusion reactions, and type of medication
    - During or within 2 hours after infusion, medication to treat infusion reactions, and type of medication (Closed report only)
- Among participants infused, the day of infusion (same day as randomization, next day, > 1 day after randomization), and time between randomization and beginning of infusion (median hours, IQR).
- Among participants receiving full infusion, duration of infusion (median minutes, IQR).
- Time from vial puncture (beginning of preparation of the study agent by the pharmacist) to the end of the infusion, and number and percent of participants for whom the agent-specific time window was exceeded.
- Remdesivir:
    - Number and percent of participants who received (any) remdesivir, and number of days remdesivir was administered: median, IQR, distribution. (Closed report only)
    - Number and percent of participants who received remdesivir prior to the day of randomization, overall and by number of days prior
    - On the day of randomization: Number and percent of participants who received remdesivir prior to the investigational agent; after the investigational agent; no remdesivir.

Treatment groups will be compared by mITT (excluding participants who did not receive any investigational agent/placebo), unless specified otherwise. The treatment comparisons will be performed using the methods described in section 3 for binary and continuous outcomes (stratified CMH test for comparing percentages, and Wilcoxon rank-sum test [or quantile regression for comparing medians], respectively).

Selected summaries will also be provided separately for the two disease severity strata.

Analyses specific to BRII-196 and BRII-198
The investigational agent by Brii Bio consists of two nMAbs (BRII-196 and BRII-198) that are administered as consecutive one-time IV infusions.

- The infusion status,
  - complete infusion, partial infusion, or not infused
  - for those where infusion was paused for adverse reaction, whether the infusion was later completed,

  will be summarized overall, and separately for BRII-196 and BRII-198. The order of infusion for BRII-196 and BRII-198 will be described.

7 Safety Analyses

The planned timing of safety reviews is described in section 2. An overview of the safety data collection is provided in Appendix C.

Analysis cohort: Safety analyses will be carried out on participants who received a complete or partial infusion of the investigational agent (modified intention-to-treat [mITT]), unless otherwise stated.

A comprehensive safety review includes:
- Comparison of the treatment groups for the primary safety endpoint, its components, and analyses of secondary safety outcomes (described in this section)
- Analyses of infusion-related reactions and symptoms, described in section 6
- Evaluation of the “efficacy outcomes” (the pulmonary and pulmonary+ ordinal outcomes early in follow-up, and time to sustained recovery), which contain important safety information.

In addition to the full DSMB reviews, more frequent, shorter safety reports may be provided to the DSMB, for example, weekly safety reports early in the trial.

This section describes the primary safety outcome, and the analyses of AEs, SAEs, UPs, SUSARs, and deaths. Comparisons between treatment groups will be stratified by study pharmacy and by disease severity at study entry (as described in section 3 under “stratification”).

In order to streamline the reporting of events, it was decided that certain protocol-specified exempt events (PSEE) are *not reported as SAEs*, unless they are considered related to the study treatment by the investigator. While the PSEEs in this protocol are similar in severity to SAEs, PSEEs are reported not on the SAE eCRF, but are reported as study endpoints on

various other eCRFs. The *clinical organ failure or serious infections* composite outcome, described in Appendix B, is the composite of all PSEEs.

The following safety and tolerability outcomes will be analyzed; models will be stratified by disease severity and study site pharmacy, as described in section 3 under "stratification", unless noted otherwise:

- The **primary safety endpoint** is a composite of incident grade 3 or 4 clinical adverse events, SAEs, clinical organ failure or serious infections (PSEE), or death through Day 5. The number and proportion of participants experiencing one of these events up through Day 5 will be tabulated, and treatment groups will be compared using a CMH test stratified by study site pharmacy and by disease severity at study entry.
    - Mortality will be analyzed as a key secondary outcome, see below.
    - The individual components of the composite outcome will be summarized.
    - Sensitivity analyses for the primary safety outcome: For interim analyses, while the trial is still enrolling, treatment groups will also be compared for time to event through Day 5 using a log-rank test, stratified by site pharmacy and disease severity at study entry; the HR will be estimated with a 95% CI using a Cox proportional hazards model, and the cumulative proportion of participants with events over the first 5 days in each treatment group will be estimated using Kaplan-Meier curves.

- All-cause mortality through follow-up will be analyzed using time-to-event methods. Cumulative proportions of participants who died in each treatment group will be estimated using Kaplan-Meier estimates, and summarized in tables (proportion of participants who died by Days 5, 7, 14, 28, 60, 90, month 6, 12, and 18) and figures (Kaplan-Meier curves with pointwise 95% CIs). Treatment groups will be compared for time to death using log-rank tests, stratified by study site pharmacy and disease severity, and an overall HR will be estimated with 95% CIs using stratified Cox proportional hazards models.

- Cause of death will be MedDRA® coded and summarized by treatment group.

- The following composite endpoints will be analyzed using time-to-event methods (cumulative proportions of participants with events will be estimated using Kaplan-Meier curves with pointwise 95% CIs; treatment groups will be compared using log-rank tests; numbers and percent of participants with events will be summarized by treatment group, and overall HRs with 95% CI will be estimated using Cox proportional hazards models):
    - Composite of incident grade 3 or 4 clinical adverse events, SAEs, clinical organ failure or serious infection, or death through Day 28
        - Components of the composite endpoint will be also be summarized, overall and by system organ class. Proportions of participants who experienced any of these events by Day 28 will be compared using stratified CMH tests and logistic regression.
    - Composite of SAEs, clinical organ failure, serious infection, or death through Day 28 and Day 90
    - Composite of hospital re-admission or death through 18 months

- Treatment groups will be compared for the incidence of non-pulmonary events in the pulmonary+ ordinal outcome that are not part of the pulmonary outcome, through Day 5 and

Day 7 (using time-to-event methods, with death as competing risk). These events are shown in red in Appendix A.

- AEs, SAEs, and UPs will be classified by MedDRA® system organ class. AEs will be graded for severity according to the *DAIDS AE Grading Table*. Grade 1-4 clinical AEs will be reported at baseline (Day 0 prior to infusion of the investigational agent), Day 0 after the infusion, Days 1-7, and on Days 14 and 28.

  The number and percent of participants with AEs will be summarized by day (Day 0 separately prior and after the infusion) and grade, and by system organ class and grade. Comparisons between treatment groups will be for the proportion of participants with AEs of a given grade or higher (i.e., any grade, grade 2+, grade 3+, grade 4). The treatment comparisons will be performed using stratified CMH tests or logistic regression.
  - For comparisons by day, the proportion of participants with any grade AEs will be compared for Days 0 (after infusion) through 7, and on Days 14 and 28.
  - For comparisons by grade, the proportion of participants who experienced any grade AEs (grade 2+ AEs, etc.) between Day 0 (after the infusion) through Day 7 will be compared.
  - For the comparison by system organ class, CMH tests will be performed if the number of participants with AEs is sufficiently large. System organ classes may be split up into MedDRA® preferred terms (PT) for system organ classes where the treatment difference is significant.

  Other clinically meaningful AE groupings (beyond system organ class) may be developed by the study team, who are blinded to the treatment effect.

- In addition to any grade AEs through Day 7, grade 3 and 4 clinical AEs are being reported through Day 28. The number and percent of participants with incident grade 3 or 4 AEs through Day 28 will be summarized, overall and by system organ class, and compared between treatment groups using stratified CMH tests. (A grade 3 or 4 AE is considered "incident" if the event was not present at baseline or increased to grade 3 or 4 from grades 1 or 2.)

  To illustrate the time course, the incidence of *grade 3 or 4 AEs or death* through Day 28 will be summarized by treatment group using Kaplan-Meier estimates of the cumulative incidence functions (CIF).

- Infusion-related reactions and symptoms during infusion or within 2 hours after infusion of the investigational agent or placebo, and infusion cessation prior to completion will be tabulated and compared between treatment groups; analyses are described in section 6.

- Treatment groups will be compared for the proportion of participants who developed *organ failure or serious infections* through Day 28 and through Day 90, overall and by individual components, using stratified CMH tests. Individual components of this composite outcome will be tabulated.

- Subgroup analyses: The impact of study arm on the primary safety outcome (composite of grade 3 or 4 events, SAEs, clinical organ failure, serious infections, or death through Day 5) and other important safety outcomes will be assessed for subgroups defined by baseline

characteristics, including demographics, duration of symptoms at enrollment, baseline classification of "home", clinical history and presentation (including disease severity stratum and pulmonary+ ordinal outcome at baseline), and tests for homogeneity of the treatment effect across subgroups will be carried out. Outcomes and methods for subgroup analyses are described in detail in section 8.4.

- Treatment groups will be compared for incidence of a composite of cardiovascular and thromboembolic events, a subset of the organ failure outcome (items 6b1, 6e2, 6e3, and 6f2 in Appendix B). Time-to-event methods will be used that take into account the competing risk of death (as described in section 3, using Aalen-Johansen estimates for the cumulative incidence functions, and Gray's and Fine-Gray's methods to compare treatment groups and estimate the sub-hazard ratio).

- Treatment groups will be compared for mean changes in laboratory test values from baseline to Day 5, and for incidence of grade 3 and 4 laboratory abnormalities at Day 5 (new abnormality or increase in grade). Laboratory tests are conducted locally, and include serum creatinine, AST/SGOT or ALT/SGPT, WBC, hemoglobin, platelet counts, lymphocyte counts, and C-reactive protein. Statistical methods are described in section 3.

- Participants who are pregnant are not eligible for enrolment. For participants who become pregnant, pregnancy outcomes will be summarized.

- In addition to the safety outcomes specified in the platform protocol, other targeted safety outcomes for specific investigational agents may be specified in appendices to the protocol. Analyses will be specified in the corresponding agent-specific appendix to this SAP.

Listings of SAEs, clinical organ failure and serious infections (PSEE), incident grade 3 and 4 AEs, UPs, SUSARs, and deaths (with cause of death) by treatment group will be provided at each DSMB meeting, with new events highlighted. The listings will include important baseline characteristics, such as age, sex, and disease severity (pulmonary outcome category) at study entry.

Further safety assessments may be considered.

Corticosteroid use will be monitored; concomitant medication use is collected at baseline and at Day 5.

- Corticosteroid use (any use at baseline or Day 5) will be summarized by treatment group and by oxygen requirement (worst category through Day 5: no supplemental oxygen, < 4 L/min, conventional supplemental oxygen $\geq$ 4 L/min, high-flow oxygen or mechanical ventilation/ECMO).
- Corticosteroid use on Day 5 will be summarized by treatment group and by oxygen requirement (worst category on Day 5, as above).

8 Efficacy Analyses

Analysis cohort: Comparisons between each investigational agent and its concurrently randomized (pooled) controls will be by intention-to-treat (ITT) unless otherwise stated.

8.1 Primary Efficacy Endpoint and Primary Analysis

The **primary efficacy outcome** of the trial is "time from randomization to *sustained recovery* through Day 90". *Sustained recovery* is defined as being discharged from the index hospitalization, followed by being alive and *home* for 14 consecutive days.

> **Comment:** The shortest possible time to sustained recovery is 14 days (this would require the patient to be discharged from the hospital on the day of randomization), and a patient would have to be discharged from the index hospitalization no later than Day 76 to achieve *sustained recovery* by Day 90.

Definition of *Home* for the primary endpoint:
According to the protocol, section 4.2, *Home* is defined as the level of residence or facility where the participant was residing prior to hospital admission leading to enrollment in this protocol.

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 rehab facility)
4) **Long-term acute care hospital** (hospital aimed at providing intensive, longer term acute care services, often for more than 28 days).

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 affiliated with a "long-term acute care" hospital recover when they return to the same or lower level of care.

Readmission from "home" (to a higher level of care) may occur and if this occurs within 14 days of the first discharge to "home", then the primary endpoint will not be reached until such time as the participant has been at home for 14 consecutive days.

Participants residing in a facility solely for public health or quarantine purposes will be considered as residing in the lowest level of required residence had these public health measures not been instated.

Primary analysis
The investigational agent will be compared to the (pooled) control group for *time to sustained recovery through Day 90* by intention-to-treat, using Gray's test with $\rho=0$.[4] The test will be stratified by disease severity at entry and by site pharmacy (as described in section 3 under "stratification"). Gray's test compares the cumulative incidence functions for *sustained recovery* between the treatment groups, taking into account the "competing risk" of death in analyzing *sustained recovery*. Gray's test with $\rho=0$ is the competing-risks analogue of the log-rank test.

Comment: Comparisons will be presented such that recovery rate ratios (RRR) >1 denote superiority of the investigational agent.

Analyses for the *sustained recovery* endpoint require methods that take into account the competing risk of death, as participants may die before ever achieving *sustained recovery*. The *sustained recovery* outcome requires knowledge of a participant's residence status for at least 14 days after arriving "home" (as defined above).

- The cumulative incidence functions for sustained recovery will be estimated by treatment group, using Aalen-Johansen estimators.[3] The estimates will be plotted over time, and tabulated at selected time points (days 15, 21, 28, 42, 60, 75, 90). The Aalen-Johansen estimator for a cumulative incidence function is the analogue of the Kaplan-Meier estimator in the presence of competing risks.

- The recovery rate ratio (RRR) for time to sustained recovery of the investigational agent versus control will be estimated, as a point estimate with a 95% CI, using the Fine-Gray model, stratified by disease severity at study entry and study site pharmacy.[5,6] The corresponding p-value for RRR=1 versus the two-sided alternative will be calculated. The Fine-Gray method is the competing risks equivalent of Cox proportional hazards models; the RRR compares the cumulative incidence rates of *sustained recovery* between the study arms and is a sub-distribution hazards ratio.

- To aid in the interpretation of the estimated treatment difference, the median days to sustained recovery (through Day 90) will be estimated for the investigational agent and the control group. Medians will be compared using the Wilcoxon rank sum test or quantile (median) regression. Participants who die at any time up to Day 90 will be assigned 91 days.

Censoring:

- Participants who are alive but have not experienced sustained recovery will be censored at the last date the endpoint status was ascertained (for interim analyses as well as the final analysis).
- For interim monitoring, two sensitivity analyses will be performed:
  1. Follow-up for time to sustained recovery will be censored *administratively* at the cut-date for the current report or Day 90, whichever comes first, with last known endpoint status carried forward. For participants who died, this type of censoring is integrated into Gray's test; using a log-rank test would require carrying forward the "not recovered" status for participants who died, up to the administrative censoring date.
  2. Administrative censoring as described above will be applied, with the modification that participants who have been discharged from the hospital, were "home" at the latest date when residence was ascertained (but for < 14 days), and, if they have remained there, would have been at home for 14+ days by the cut-date, will be imputed as having experienced *sustained recovery* (achieved on day 14 at home).

  Participants who withdrew consent or were lost to follow-up will be censored at the date of withdrawal or the last date the endpoint status was known, respectively.

In the first sensitivity analysis, the "not recovered" status is carried forward to the administrative censoring date; in the second analysis, "sustained recovery" is assumed at the earliest possible date. The first analysis potentially underestimates the rate of recovery, whereas the second analysis overestimates the recovery rate. In all analyses for time to sustained recovery, death is treated as competing risk.

Ascertainment of sustained recovery

The date of discharge from the index hospital will be recorded. Irrespective of the timing of the hospital discharge, there will be patient contact approximately every two weeks, on Days 14, 28, 42, 60, 75, and 90, either at a scheduled clinic visit or through phone contact. At these time points, a) vital status, and b) the location of the participant over time will be recorded, to assess whether the participant had been "at home" for 14 days. Therefore, the outcome status of sustained recovery will usually be ascertained within 3 weeks or less of the date the outcome was achieved.

- To illustrate the status of the primary endpoint, the recovery status of participants will be described over time with the following categories (at interim reviews):
  1. At home for 14+ days (reached the primary endpoint of sustained recovery)

  Did not reach sustained recovery, and:

  2. At home, < 14 days
  3. Discharged from the hospital, but not at home
  4. Hospitalized
  5. Dead
  6. Primary endpoint status unknown.

  The proportions of participants in each of the 6 categories will be summarized over time, by treatment group (stacked bar graphs and tables). In this analysis, both "sustained recovery" and "death" are absorbing states.

Assessment of model assumptions

- The trial was powered to detect an RRR of 1.25 with 90% power; this requires 843 sustained recoveries among the 1000 participants by Day 90. The rate of recoveries will be monitored, overall and within the two disease severity strata. Deviations of the observed distribution from the hypothesized distribution in the control arm will be monitored, and the impact on the power of the trial will be assessed. Prior to the completion of the trial for the investigational agent, sample size will be re-estimated by the blinded statisticians on the study team, based on the pooled rate of *sustained recovery*.

- The Fine-Gray model assumes that the sub-distribution rate ratio for *sustained recovery* is constant over time, similar to Cox proportional hazards models. The assumption of constant RRR will be tested by including an interaction effect between time and treatment indicator.

Sensitivity Analyses

- As sensitivity analyses, the primary comparison will be repeated after excluding participants who did not receive any of the investigational agent/placebo (modified intention-to-treat).

- Sensitivity analyses for the primary endpoint comparisons will include consideration of home oxygen above pre-morbid oxygen use (described in section 4.2.2 item 12 of the protocol). For these sensitivity analyses, *sustained recovery* will be re-defined as:
    a. "Discharged to home, alive at home without use of continuous supplemental oxygen for an uninterrupted 14 day period"
    b. "Discharged to home, alive at home for an uninterrupted 14 day period, and no supplemental oxygen use a the end of the 14 day period"
- If the RRR is not constant (test described under "assessment of model assumptions" above), as a sensitivity analysis, the RRR will be estimated within time periods, for example, Day 14-28, Day 29-60, Day 61-90.
- Additional sensitivity analyses are described under "censoring" above.

8.2 Key Secondary Outcomes

- Mortality is a key secondary outcome; analyses are described in section 7.

- To supplement the separate analyses of time to sustained recovery and time to death, the two endpoints will be analyzed jointly using the "win ratio" method for the composite outcome of time to recovery or death.[8] The win ratio will be calculated using the matched pairs method described in Pocock (2012).[8] Pairs will be formed by ranking the participants in each treatment group according to a risk score, described in section 12.2, and pairing the participants in groups A (here referring to the investigational drug) and B (referring to control) with equal ranks. Details are given below.

    - If both treatment groups have the same number of observations, the win ratio is calculated as follows:
      Step 1: Calculate the risk score for all participants, and order participants by the risk score in each treatment group. If needed, break ties at random. Each participant forms a "matched pair" with the participant of equal rank order in the other treatment group.
      Step 2: For each pair, determine whether the participant in group A wins, loses, or neither:
      a. *Compare pairs for time to death, for all pairs where one or both participants died.* If the participant in group A died, wins and losses are computed as follows:
          - If the matched participant in group B has longer follow-up, then A loses and B wins.
          - If the matched participant in group B has shorter follow-up and is alive at the censoring date, then neither group wins.

      Repeat for pairs where the participant in group B died.
      b. *Compare remaining pairs for time to sustained recovery*.
          - If A achieved sustained recovery, and time to sustained recovery is longer for B, then A wins and B loses; vice versa for B.
          - If A achieved sustained recovery, and B was censored without reaching sustained recovery before A reached sustained recovery, then neither group wins; vice versa for B.
          - Otherwise, neither group wins.

Step 3: Calculate the win ratio as the number of wins in group A divided by the total number of pairs with a win or a loss in group A. Calculate the 95% CI for the win ratio and p-value as described in Pocock (2012).[8]

- If one treatment group has more participants than the other, select $|n_A - n_B|$ participants at random from the larger group and delete. Calculate the win ratio, 95% CI and p-value for the resulting matched pairs. Repeat the random selection of observations to delete 501 times; identify the matched pairs data set that corresponds to the median win ratio; the final values of the win ratio, 95% CI and p-value are those calculated from this data set.
- If both treatment groups have the same number of observations, but some ranked risk scores are tied within a treatment group, a similar process may be used to repeat the random breaking of ties, with the final win ratio chosen as the median over repeated random tie breaks.

With this approach, time to death is first used to determine the winning group (i.e., longer time to death), then time to sustained recovery is used to determine the winning group (i.e., shorter time to recovery): in this manner, the win ratio combines these conflicting outcomes into a composite while recognizing the importance of mortality.

8.3 Other Secondary Outcomes

The protocol defines a number of secondary endpoints in addition to the two key endpoints described in section 8.2 above. These analyses will be carried out for the final report. Selected secondary endpoints may also be analyzed for interim monitoring reports, to help evaluate the safety and efficacy of the investigational agent.

Below, the secondary outcomes from section 4.2.2 of the protocol are cited, with a short description of the analysis methods. For each outcome, the treatment groups will be compared by intention-to-treat, stratified by disease severity at study entry and by site pharmacy, as described in section 3 under “stratification”.

- Time to discharge for the initial hospitalization. Treatment groups will be compared using time-to-event methods that take into account the competing risk of death, similar to the analyses for time to sustained recovery described in section 8.1.
  - Hospital readmissions will be summarized using methods for recurrent events (i.e. those who are readmitted will re-enter the risk set).[9]
- Days alive outside of a short-term acute care hospital up to day 90. For this analysis, the “last-off” method will be used, i.e., days from the latest hospital discharge to day 90 will be counted. A person who dies within 90 days will be assigned a value of 0, consistent with the approach taken in trials of intensive care-based interventions. We will present the median days by group and test the hypothesis of no difference between arms with a Wilcoxon rank sum test.
  - For interim analyses, only participants who have reached Day 90 (administrative follow-up for those who died) will be included, to avoid bias. Alternatively, a shorter time period may be used.

- Pulmonary+ and pulmonary ordinal outcomes on Days 1-7, and the pulmonary ordinal outcome on Days 14 and 28. The proportion of participants in each category of the pulmonary and pulmonary+ outcomes will be summarized over time (both outcomes at days 1-7, the pulmonary outcome also at Days 14 and 28); at each of those days, treatment groups will be compared using proportional odds models as described in section 9.1; the proportional odds models will be adjusted for the categories of the pulmonary+ outcome at baseline and for study site pharmacy. If participants in both disease severity strata are enrolled, the models will also be adjusted for the interaction between disease severity stratum and pharmacy.

  Additionally, the ordinal outcomes will be dichotomized ("category 1", "best 2 categories" through "best 5 categories"), and proportions will be compared between treatment groups at selected time points using logistic regression. For these analyses, the key dichotomized outcome considers the "best 2 categories", which is similar to the "recovery" outcome in the ACTT-1 trial.

- *Clinical organ failure or serious infections*, defined by development of any one or more of the clinical events listed in Appendix B, through Days 28 and 90. The development of *organ failure or serious infections* will be analyzed as a binary outcome, and the proportions of participants who developed *organ failure, serious infections or death* will be compared across arms using stratified CMH tests, overall and for individual components.

- A composite of death, clinical organ failure, or serious infection through Days 28 and 90 (see Appendix B). Treatment groups will be compared using standard time-to-event methods, since death is part of the outcome and not a competing risk. (Also described in section 7 as safety analysis).

- Outcomes assessed in other treatment trials of COVID-19 for hospitalized participants in order to facilitate cross-trial comparisons and overviews (e.g. 6- , 7-, and 8-category ordinal scales assessed at Days 1-7, 14 and 28; time to improvement in 1 or 2 categories of ordinal scale; time to best 3 categories of ordinal scale, and binary outcomes defined by improvement or worsening based on other ordinal outcomes). We will try to match the analyses in the other trials, to get results that can be compared. These analyses will not be performed for interim reports to the DSMB, unless requested.

- A composite of cardiovascular events (outcomes listed in items b1, e2 and e3 in Appendix B) and thromboembolic events (item f2). Time to event methods will be used that take into account the competing risk of death, e.g., Gray's test to compare treatment groups.

8.4 Subgroup Analyses

As stated in the protocol, subgroup analyses for the primary efficacy outcome (time to sustained recovery), the primary safety outcomes (composite of grade 3 and 4 events, SAEs, clinical organ failure, serious infections, or death through Day 5 and Day 28, composite of SAEs, clinical organ failure, serious infections, or death through Day 90), and for time to death will be performed to determine whether and how the treatment effect (active versus control) differs qualitatively across various subgroups defined at baseline, and whether there are safety concerns in specific subgroups.

Subgroup analyses will also be carried out for the Pulmonary and Pulmonary+ ordinal outcomes on Day 5.

Key subgroup analysis are by disease severity and by the categories of the pulmonary+ outcome at baseline; other important subgroups include subgroups by duration of symptoms prior to enrollment, by age and by pre-existing conditions.

Subgroup analyses will be performed by the following baseline factors:

- Disease severity (categories of the pulmonary+ outcome at study entry, randomization stratum). This subgroup analysis will be used at interim analyses after expansion of enrollment to assess if the treatment effect varies across the severity strata.
- Duration of symptoms prior to enrollment
- Age (18-49, 50-59, 60-69, 70-79, 80+)
- Biological sex
- Race/ethnicity
- Geographic location
- Residence (home) at the time COVID-19 symptoms developed
- Body mass index (BMI)
- History of chronic conditions (cardiovascular disease, diabetes, asthma, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, hepatic impairment, or cancer)
- SARS-CoV-2 vaccination status at baseline.

When SARS-CoV-2 viral load, antibody, and antigen levels are available, subgroups will also be considered by upper respiratory SARS-CoV-2 viral load, by antibody level, by neutralizing antibody level, and by antigen level at baseline. The lab tests to be conducted and the analysis plan for these endpoints are currently under discussion.

Subgroup analyses for the primary endpoint of time to sustained recovery will use the Fine-Gray model, stratified by disease severity at study entry, and by site pharmacy if the sample size permits. RRRs with 95% CIs comparing the investigational agent versus control will be estimated for each subgroup. Global tests for heterogeneity of the treatment effect across subgroups will be carried out, by adding the interaction between the subgroup indicator and the treatment group indicator to the model. In case the subgroup was formed by categorizing a continuous variable, the interaction term will be formed between the subgroup indicator and the continuous variable.

Subgroup analyses for the primary safety endpoint at Day 5 will use logistic regression, stratified by disease severity at study entry, and by site pharmacy (if the sample size permits). Subgroup analyses for safety endpoints that are analyzed using time-to-event methods (those analyzed through Day 28 or longer) will use stratified Cox proportional hazards models, since death is part of the composite endpoints and not a competing risk. HRs will be estimated for each subgroup, and global tests of heterogeneity of the treatment effect will be carried out, as described above.

Subgroup analyses for the pulmonary and pulmonary+ ordinal outcomes on Day 5 will use proportional odds models, adjusted for pulmonary+ category at study entry and for site pharmacy.

Additionally, subgroup analyses will be conducted for subgroups formed by a disease progression risk score at baseline. The construction of this risk score will be revisited as data on the sustained recovery endpoint accumulate for new investigational agents.

Subgroup analyses will not be adjusted for multiple comparisons. Subgroup analyses will be interpreted with caution due to limited power and uncontrolled type I error.

9 Interim Monitoring Guidelines for the DSMB

Each investigational agent versus placebo comparison will be treated as a separate clinical trial; stopping boundaries will be derived to allow for multiple interim looks, but will not be additionally inflated to adjust for simultaneous analysis of multiple investigational agents, except when explicitly stated in the agent-specific protocol appendix and statistical analysis plan.

The DSMB will be asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference (unless a trial is stopped for futility).

9.1 Early Assessment of Safety

For investigational agents with minimal pre-existing data, the pace of enrollment will be initially restricted and the DSMB will be asked to review safety data for the first 20 to 30 participants before increasing the pace of enrollment.

Subsequently, the DSMB will carry out regular reviews of safety data reports. These reports will include summaries of infusion–related events, grade 1-4 AEs, SAEs, organ failure, serious infections, and deaths, including the primary safety outcome at Day 5, and Day 28. Event listings for incident grade 3 and 4 AEs, SAEs, organ failure and serious infections (PSEE), SUSARs, UPs and deaths will be provided (events that were reported since the previous review will be marked). Narratives will be provided for selected SAEs, SUSARs or UPs, particularly those judged related to study treatment. Analyses are described in section 7.

Monitoring boundary for harm:

- Until the first 300 participants are enrolled (150 per study arm) and the early futility analysis is conducted, the treatment groups will also be compared for the “pulmonary” and “pulmonary+” ordinal outcomes at Day 5, using a proportional odds model stratified by study pharmacy and pulmonary+ outcome category at baseline. A Haybittle-Peto boundary with 2.5 standard deviation (SD) for the first 50 participants enrolled and 2.0 SD afterwards will be used as a guideline for harm.

- After the study population is expanded to include disease severity stratum 2, these analyses are performed by disease severity stratum.

At the discretion of the DSMB, these safety reports will be prepared at a frequency they specify, for example, weekly. The DSMB may also request additional data summaries.

9.2 Early Assessment of Futility

9.2.1 Interim Monitoring Guidelines for Early Assessment of Futility

Early in the trial, enrolment is restricted to participants in disease severity stratum 1. When Day 5 data for the first (approximately) 300 participants (150 per study arm) are available, the DSMB will review interim data and use pre-specified guidelines for early evidence of sufficient activity of the investigational agent that justifies continuing enrolment for the agent and expanding eligibility criteria to include participants in disease severity stratum 2 as well as stratum 1.

The early futility monitoring uses two co-primary outcomes, denoted by “pulmonary” and “pulmonary+”, assessed on Day 5. Both are ordered categorical outcomes with 7 categories, described in section 4.1 of the protocol and in Appendix A to this SAP. The pulmonary outcome considers largely respiratory-related disease, similar to the ordinal outcome in the ACTT-1 trial.[10] The pulmonary+ outcome has the same categories for pulmonary complications (e.g., requirements for oxygen), and additionally includes extra-pulmonary outcomes such as thrombotic, myocardial, and cerebral complications of COVID-19.

Guidelines for the early futility assessment are as follows:

a. If the investigational agent is superior to placebo (i.e., $p \leq 0.3$ for a one-sided test) in both the pulmonary+ and pulmonary intermediate ordinal outcomes, then enrolment for the agent will expand to complete the trial.

b. If there is insufficient evidence for superiority versus control (i.e., one-sided $p>0.3$) in each of the two outcomes, then stop randomization.

c. If there is evidence (1-sided $p < 0.3$) for an association for one endpoint and not the other, then the agent may or may not advance depending on the risk/benefit profile emerging from the data at this early stage. If the effect estimate for both outcomes is on the side of benefit, the preference would be towards advancing the agent and expanding enrollment to include disease severity stratum 2.

   The DSMB will be asked to review whether the discordance is attributable to a positive or negative effect on extra-pulmonary organ dysfunction (the difference in the two ordinal scale categories, the conditions included in pulmonary+ but not in the pulmonary endpoint), and whether the same ordinal outcomes assessed on other days yield similar results, and weigh the risk/benefit profile. For example, if there is a significant positive effect on the pulmonary score and the lack of significant effect on the pulmonary+ score is driven by a lack of difference in the milder thrombotic symptoms in category 4 of the pulmonary+ scale (e.g. deep venous thrombosis) and there is no evidence of any raised risk of thrombosis overall, the agent will advance. Conversely, if the agent is superior to the control group with respect to the pulmonary outcome, but clearly inferior to the control group with respect to the pulmonary+ outcome or has a concerning safety profile, it will not advance.

Analyses of the primary efficacy endpoint, time to sustained recovery, will also be provided to the DSMB, as supporting information. These analyses are described in section 8.1.

After considering the aforementioned guidelines, the DSMB will be asked to consult with the Food Drug Administration before making their recommendation in order to consider any relevant external information.

9.2.2 Analyses of the Pulmonary and Pulmonary+ outcomes on Day 5

- Treatment groups will be compared by intention to treat.

- For each of the two ordinal outcomes, the number and percentage of participants in each of the categories on Day 5 will be tabulated, and the OR of the active versus control group will be estimated using a proportional odds model with indicators for the investigational agent group (active versus control) and for the categories of the ordinal pulmonary+ outcome at baseline (to adjust for baseline severity of illness).[2] The model will be stratified by site pharmacy.

  The summary tables will show the adjusted summary OR with 95% CI, estimated as described above, as primary analysis. In addition, the unadjusted summary OR with 95% CI will be shown as sensitivity analysis (estimated using a proportional odds model without adjustment for the pulmonary+ baseline category or site pharmacy). In the case that the adjusted OR differs substantially from the unadjusted OR, the reason for the deviation will be explored.

  Comments:
  - Results will be presented such that OR>1 favors the investigational agent, denoting higher odds of more favorable disease categories in the group randomized to investigational agent compared with control.

  - In order to avoid overestimating the proportion of participants who died, participants who died prior to Day 5 will only be included in the Day 5 summaries of the pulmonary and pulmonary+ outcomes if their time from randomization to cut-date is at least 5 days, and similarly for analyses on other days. Mortality is a key secondary endpoint and will be summarized cumulatively as an additional analysis.

- **For the initial futility analysis**, the tests comparing the investigational agent versus placebo will be performed using a (1-sided) type 1 error rate of 30%. This means, the investigational agent will be considered “superior” to the control with respect to the pulmonary (or pulmonary+) outcome, if the estimated summary OR is greater than 1, and the p-value $\leq$ 0.30.

  The summary reports will show the estimated summary OR with 95% CI, the signed Z-value for the test statistic comparing the treatment groups, and the one-sided p-value for superiority, calculated in the primary analysis (i.e., using the proportional odds model that is adjusted for the pulmonary+ category at baseline and stratified by site pharmacy, as described above). As sensitivity analysis, these values will also be calculated using the unadjusted proportional odds model and included in the summary report.

  Comment: At the recommendation of the FDA, patients requiring high-flow oxygen or mechanical ventilation (invasive or non-invasive) are currently not eligible for enrolment. Also,

prior to the initial futility assessment, eligibility is restricted to disease severity stratum 1. Therefore, adjusting the treatment comparison for the pulmonary+ outcome at baseline is identical to adjusting for the following categories defined by oxygen requirement:

- No supplemental oxygen (pulmonary+ category 2)
- Supplemental oxygen < 4 L/min (or < 4 L/min above premorbid requirements) (pulmonary+ category 3)
- Supplemental oxygen ≥ 4 L/min (or ≥ 4 L/min above premorbid requirements, but not high-flow oxygen) (pulmonary+ category 4)

- To supplement the overall summary odds ratios for the 7-category outcomes, each dichotomized definition of improvement that can be formulated from the components of the ordinal outcomes will be considered separately; for example, treatment groups will be compared for the proportions of participants in category 1 on Day 5, proportions in categories 1 or 2 ("best two categories"), in categories 1-3, etc. Proportions will be tabulated, and odds ratios for active versus control groups will be estimated with 2-sided 95% CIs using logistic regression models. These analyses need to be interpreted with caution, because they are not adjusted for inflation of type I error due to multiple comparisons.

- Subgroup analyses will be carried out for the Pulmonary and Pulmonary+ outcomes on Day 5, to supplement the early futility analyses. The goal is to determine whether the treatment effect differs across subgroups, and to aid the DSMB in considerations on whether there are safety concerns in specific subgroups. Principles for subgroup analyses are described in section 8.4; here, subgroup analyses are based on the proportional odds models. In particular, heterogeneity of the treatment effect across the baseline pulmonary+ categories will be assessed.

- After an investigational agent has passed initial futility assessment and enrollment has been expanded to include participants in disease severity stratum 2, treatment comparisons for the pulmonary and pulmonary+ outcomes on Day 5 continue, and will be performed separately for each of the two disease severity strata, to assess safety for the more severely ill participants in stratum 2.

Missing data: Unknown outcome status for the pulmonary or pulmonary+ outcomes on Day 5:

The following items describe how missing data will be treated for the primary analyses of the pulmonary or pulmonary+ outcomes on Day 5. As needed, these methods may be also applied to analyses at other time points (e.g., Day 7).

- **Interim analyses**:
  - Only participants with Day 5 data for the pulmonary outcome will be included for the Day 5 comparisons. The number and proportion of participants with unknown outcome status will be summarized.
    Comment: If the cut date is less than 10 days before the data freeze date, Day 5 data for the ordinal outcomes are considered "missing" only for participants with at least 10 days of administrative follow-up.

- **Final analyses** after completion of the trial:
  - If Day 5 data are missing for a substantial proportion of participants (e.g., more than 5%), multiple imputation will be used to impute missing Day 5 data for the

pulmonary and pulmonary+ outcomes. For the imputation, the following baseline covariates will be considered in addition to the indicator for treatment group: age, sex, country, duration of symptoms prior to enrollment, status of the ordinal pulmonary (or pulmonary+) outcome, and presence of comorbidities. Ten rounds of imputation will be used to estimate the summary odds ratio.

- The number and proportion of participants with missing data will be reported.

Sensitivity analyses

- As sensitivity analyses, the treatment groups will be compared by **modified intention-to-treat (mITT)** after excluding participants who did not receive any of the assigned investigational agent (active or control). This mITT analysis will be provided at important decision points, e.g., when the test statistic approaches the monitoring boundary, and for the final analyses after completion of the trial.
- Treatment groups will be compared for the pulmonary and pulmonary+ outcomes on Days 1-7, to monitor the consistency of the treatment effect over time.

Assessment of model assumptions

- For the pulmonary and pulmonary+ outcomes at Day 5, the proportionality assumption of the odds ratio will be assessed (by including the interaction between the treatment group indicator and indicators for the Day 5 cumulative ordinal categories in the model, as well as the interactions between the treatment group indicator and the indicators for the strata by baseline pulmonary+ categories and site pharmacy; this corresponds to testing for separate slopes using a partial proportional odds model, see section 3 under “ordered categories”). If there is evidence for non-proportionality, the summary odds ratio in the proportional odds model will still be used to quantify the treatment effect, and the analyses of the dichotomized ordinal outcome categories will be used to help interpret the treatment effect.

- The sample size of 300 (150 per study arm) is sufficient to detect a summary OR of 1.60 for the comparison of the investigational agent versus control for each of the two ordinal outcomes with 95% power. The power of the tests depends on the hypothesized OR and the hypothesized distribution in the control group used for the sample size calculations. At the time of the early futility review, the deviation of the observed distribution from the hypothesized distribution in the control arm will be assessed, and the impact on the power of the trial will be estimated.

9.3 Interim Monitoring Guidelines for the Primary Endpoint

This section describes the interim monitoring guidelines that apply after the investigational agent has passed the initial futility assessment (after approximately 150 participants per study arm are enrolled).

As a guideline, asymmetric boundaries will be provided to monitor the primary endpoint (time to sustained recovery) for overwhelming benefit or for harm. The trial of an investigational agent should be stopped for efficacy only if there is clear and convincing evidence of superiority of the agent versus the pooled control group with respect to the primary outcome, time to sustained recovery. For monitoring superiority, the Lan-DeMets spending function analogue of

the O'Brien-Fleming boundaries will be used, with a 1-sided 0.025 level of significance over multiple looks. For computing the Lan-DeMets boundary, the information fraction at each interim analysis will be the observed total number of sustained recoveries divided by the planned number of sustained recoveries (N=843).

The monitoring boundary for harm is asymmetric, requiring less evidence to stop for harm than for superiority; a Haybittle-Peto boundary with 2.5 SD for the first 50 participants enrolled and 2.0 SD afterwards will used as a guideline for harm. With this approach, less evidence will be required for crossing a boundary for harm than for benefit.

At each full interim review after the first 169 participants have achieved sustained recovery (20% information time), the following will be provided:

- Signed square root of the value of the test statistic for Gray's test with ρ=0, ("Z-value") comparing the investigational agent versus the control group for the primary endpoint through Day 90, plotted over information time, and the asymmetric monitoring boundaries: the O'Brien-Fleming boundary with Lan-DeMets α-spending function for superiority (one-sided test with α=0.025), and the asymmetric, Haybittle-Peto boundary for harm described above.

    - **Comment:** Test statistics for the primary treatment comparison will be coded such that the value of the test statistic > 0 favors the investigational agent. Thus, in case of harm, the Haybittle-Peto boundary with 2 SD of the normalized test statistic, is crossed if the Z-value for the test statistic is below -2, irrespective of information time.

    In addition to the current value of the test statistic, the corresponding values of the test statistic at the previous reviews will be plotted over information time, (1) as presented at the previous DSMB meetings, and (2) re-calculated with current data (using the cut-dates of the previous reports).

- History of the estimated rate ratios for time to sustained recovery with 95% CIs and p-values (by Fine-Gray's method), and normalized test statistic values and p-values for Gray's test at previous DSMB reviews, as presented, and recalculated with the current data (using the cut-date of the previous reports). The latter provides information on the influence of a possible time lag in the ascertainment of sustained recovery.

9.4 Interim Monitoring for Futility

After investigational agents have passed the initial futility assessment (based on the pulmonary and pulmonary+ outcomes at Day 5, assessed for the first 300 participants), further futility analyses will be based on the primary outcome of *time to sustained recovery*.. The aim of these analyses will be to consider whether an investigational agent should be discontinued due to a low probability of achieving statistical significance for the primary endpoint of sustained recovery at the completion of the 90 day follow-up.

Conditional power calculations for time to sustained recovery will be presented under a range of scenarios. In the primary futility analysis, it will be assumed that the treatment effect for the future, as yet unobserved follow-up will be as hypothesized in the study design (RRR=1.25). As secondary analysis, the treatment effect for future follow-up will be assumed to be similar to

the observed effect. Additional scenarios may be provided. Typical futility guidelines recommend stopping a trial when conditional power (assuming the originally hypothesized treatment effect for the future follow-up) is below 10%-15%.[11]

As a guideline, futility will first be assessed when 50% of the planned number of sustained recoveries have occurred, and a value of 15% will be suggested as a threshold for the conditional power. An additional assessment will take place at 75% of the events. Conditional power will be computed using Gray's test with ρ=0, the competing risk analogue of the log-rank test.[12]

Decisions to terminate an agent for futility will include a broad assessment of the risk/benefit trade-off in addition to these guidelines.

10 Data Completeness and Study Conduct

According to the protocol, the pulmonary and pulmonary+ outcomes will be assessed on days 0-7; the decision rules for at the initial futility assessment are based on these outcomes on Day 5. The pulmonary outcome will also be assessed on Days 14 and 28. The primary outcome, "time to sustained recovery", will be assessed through Day 90. Clinical data will be collected on Days 0-7, 14, 28, 60 and 90; mortality and re-hospitalizations will be assessed through 18 months. After hospital discharge, in-person visits are scheduled on Days 1, 3, 5, 28, and 90, when blood is collected (plasma and serum); other visits may be conducted by phone (Days 7, 14, 42, 60, and 75). The data collection schedule is included in Appendix D of this SAP.

Data completeness and study conduct reports will be provided by treatment group (for the closed report) and pooled across treatment groups (for the open report). Data summaries for the infusion of the investigational agent on Day 0 are described in Section 6; several of those reports are also relevant for monitoring study conduct and will be included in the open report or provided to study leadership, pooled across treatment groups.

The following data summaries will be provided to assess data completeness and study conduct:

- Number and percent of participants with protocol deviations, and type of protocol deviation
- Expected and observed number (% of expected) of participants who completed visits on Days 1-7, 14, 28, 42, 60, 75, and 90.
- Expected and observed number (% of expected) of participants with known outcome status for the pulmonary and the pulmonary+ outcomes on Day 5.
- Ascertainment of the primary outcome: Expected and observed number (% of expected) of participants with known status of "time to sustained recovery" at days 28, 60, and 90. To ascertain "sustained recovery", several elements are required: vital status; the status of hospitalization; if discharged, the status of the residence ("home" versus other).
- Expected and observed number (% of expected) of participants with known vital status at days 5, 14, 28, 60 and 90, and at months 6, 12, and 18.
- Number and percent of participants who withdrew consent or were lost to follow-up (no contact and unknown vital status for 45+ days).

- If substantial numbers of participants are lost to follow-up (e.g., more than 10% of participants), Kaplan-Meier estimates for the cumulative proportion of participants who are lost to follow-up over time, by treatment group, will be provided (closed report only).
- Listing of participants who withdrew consent, including dates of randomization, pulmonary+ category at baseline, receipt of study treatment, date of withdrawal, and reason of withdrawal.
- Length of follow-up: Median, IQR, range
- Collection of specimens: Expected and observed number (% of expected) of participants with specimens collected as specified by the protocol, by visit.
- Expected and observed numbers of participants with local laboratory data at baseline and on Day 5.

A visit counts as “expected” if the visit window has closed or the data have been received.

11 SARS-CoV-2 Antibody Levels

SARS-CoV-2 antibody levels will be determined centrally, from stored plasma samples, and thus may not be available at interim analyses. If data are available, analyses will be included in interim reports.

Treatment groups will be compared for change in antibody profile, geometric mean titers (GMT) of antibodies and neutralizing antibody levels from baseline to Days 1, 3, 5, 28, and 90, using ANCOVA models applied to log-transformed antibody levels; usually, $\log_{10}$ is used for antibody titers.

Longitudinal models for the logarithm of antibody titers will be fit using GEE-based approaches to titers measured at baseline and days 1, 3, 5, 28 and 90; the interactions between time and group will be investigated. In addition, GMTs of the antibody levels will be summarized and compared between treatment groups at each of the days, using ANCOVA models for the log-transformed antibody titers.

The same approach will be used to examine neutralizing titers when such data are available.

Additional lab tests are currently being planned, including measurement of SARS-CoV-2 viral load and antigen levels. Analysis plans will be developed when more information is available.

12 Exploratory Analyses

12.1 Associations Between the Pulmonary and Pulmonary+ Outcomes and Time to Sustained Recovery

At the early futility assessment when 300 participants (150 per study arm) are enrolled and have Day 5 data, estimated treatment differences in the pulmonary and pulmonary+ ordinal outcomes on Day 5 are used to identify promising investigational agents to continue to be studied with the clinical outcome of “time to sustained recovery”. In exploratory analyses, we

will investigate whether the early pulmonary and pulmonary+ outcomes on Day 5 are an adequate predictor for time to sustained recovery, to re-evaluate our initial futility decision rule.

- Associations between the pulmonary and pulmonary+ ordinal outcomes at Day 5 with time to sustained recovery will be estimated using Cox proportional hazards models, pooled across treatment groups. To illustrate these associations, median time to sustained recovery will be estimated by category of the ordinal outcomes on Day 5, using Aalen-Johansen estimates of the cumulative incidence function.

Ideally, the goal would be to evaluate the extent to which treatment differences in the pulmonary outcomes on Day 5 predict treatment differences in time to sustained recovery through Day 90. A detailed analysis plan will be developed at a later time.

12.2 Disease Progression Risk Score

A disease progression risk score, calculated at baseline, will be used to form subgroups of participants with low or high predicted risk for subgroup analyses for safety and efficacy outcomes, and to pair participants for the win ratio analyses described in section 8.2.

The risk score for a participant is defined as the estimated *probability that the Pulmonary outcome on Day 5 is in one of the categories 5, 6 or 7* (5=non-invasive ventilation or high-flow oxygen, 6=invasive ventilation, 7=death). The probability is estimated using a logistic regression model for the corresponding binary outcome (Pulmonary categories $\geq$5 vs <5 on Day 5) with the following baseline predictors: age, sex, Pulmonary category at baseline, days since symptom onset, NEW score, and indicator variables for the following risk factors: asthma/COPD, diabetes, CVD, heart failure, hypertension, HIV or other immune deficiency, and renal impairment. The risk score will be derived from the pooled data for the investigational agent/placebo groups. Thus, the risk score will be specific to each investigational agent.

13 Unblinding of Treatment Comparisons

For any investigational agent, trial results will be unblinded when the pre-specified number of primary endpoints is reached; results may be unblinded earlier upon the recommendation of the DSMB if the sponsor and study leadership concur. In this case, trial results for the investigational agent will be unblinded and reported with available data through 90 days of follow-up. After that, data collection will continue as outlined in the data collection plan; under protocol version 3.0, death and re-hospitalizations will be recorded through 18 months.

While the trial is ongoing, access to any data summaries by treatment group (investigational agent or control groups) will be restricted to the members of the DSMB, the DSMB's Executive Secretary, and the unblinded statisticians.

When the trial for an investigational agent is concluded, data for the investigational agent and the corresponding pooled control group will be unblinded and provided to the study team.

The timing of the unblinding of data for one agent may require consideration, if:

- the control group is substantially shared with another agent for which the trial is still ongoing, **and**
- pooled data on treatment outcomes for the ongoing trial are available to investigators.

In this case, the need for a speedy unblinding has to be balanced with maintaining trial integrity for other agents in the platform trial, and the DSMB will be consulted as to the timing of the unblinding.

14 Distribution of Reports

- Open report: ACTIV-3 leadership team; DAIDS Medical Officer; selected NIAID staff; representatives of the companies; and all recipients of the unblinded closed report. After the DSMB meeting, the open report and the DSMB summary statement will be posted to the trial's web site, open to all investigators.
- Closed report: DSMB members, Executive Secretary of the DSMB, unblinded statisticians.
- Web reports (accessible by all investigators and study staff):
    - Enrollment summaries by site and over time (updated daily)
    - Baseline characteristics
    - Selected summary measures on data quality and study conduct (pooled across treatment groups).
- Additionally, selected summary measures on study conduct will be provided to study leadership upon request (pooled across treatment groups).

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Appendix A. Definition of the Pulmonary and Pulmonary+ ordered categorical outcomes

The Pulmonary categorical outcome is primarily defined based on oxygen requirements. The categories of the Pulmonary+ outcome are similar, except that categories 4 and 5 also capture selected extra-pulmonary complications, highlighted in red below.

Pulmonary outcome	Pulmonary+ outcome
1. Can independently undertake usual activities with minimal or no symptoms	1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)	2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)	3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen)	4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen) or any of the following: stroke (NIH Stroke Scale [NIHSS] ≤14), meningitis, encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, new onset CHF NYHA class III or IV or worsening to class III or IV, arterial or deep venous thromboembolic events
5. Non-invasive ventilation or high-flow oxygen	5. Non-invasive ventilation or high-flow oxygen, or signs and symptoms of an acute stroke (NIHSS >14)
6. Invasive ventilation, extracorporeal membrane oxygenation (ECMO), mechanical circulatory support, or new receipt of renal replacement therapy	6. Invasive ventilation, ECMO, mechanical circulatory support, new receipt of renal replacement therapy, or vasopressor therapy
7. Death	7. Death

The term “usual activities”, in categories 1 and 2 for both outcomes, refers to activities of daily living that the participant was able to undertake prior to the current illness.

Appendix B. Definition of Clinical Organ Failure and Serious Infection

According to the protocol, section 4.2.2., *clinical organ failure* is defined by development of any one or more of the following clinical events (see PIM for criteria for what constitutes each of these conditions):

a. Respiratory dysfunction:
    1. Respiratory failure defined as receipt of high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation, or ECMO

b. Cardiac and vascular dysfunction:
    1. Myocardial infarction (MI)
    2. Myocarditis or pericarditis
    3. Congestive heart failure (CHF): new onset NYHA class III or IV, or worsening to class III or IV
    4. Hypotension requiring institution of vasopressor therapy

c. Renal dysfunction:
    1. New requirement for renal replacement therapy

d. Hepatic dysfunction:
    1. Hepatic decompensation

e. Neurological dysfunction
    1. Acute delirium
    2. Cerebrovascular event (stroke, cerebrovascular accident [CVA])
    3. Transient ischemic events (i.e., CVA symptomatology resolving <24 hrs)
    4. Encephalitis, meningitis or myelitis

f. Haematological dysfunction:
    1. Disseminated intravascular coagulation
    2. New arterial or venous thromboembolic events, including pulmonary embolism and deep vein thrombosis
    3. Major bleeding events (>2 units of blood within 24 hours, bleeding at a critical site [intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal], or fatal bleeding).

Serious infection is defined as:

g. Serious infection:
    1. Intercurrent, at least probable, documented serious disease caused by an infection *other than* SARS-CoV-2, requiring antimicrobial administration and care within an acute-care hospital.

Appendix C. Safety Data Collection

Table C-1. Overview of Safety Data Collection (protocol version 3, section 10).*

	Infusion +2 hrs	Days 0-7	Day 14	Day 28	Day 90	Months 6, 12, and 18
Infusion-related reactions and symptoms	X					
Clinical AEs of any grade severity		X	X	X		
Grade 3 and 4 clinical AEs from Day 7 through Day 28[1]			X	X		
Targeted laboratory abnormalities of any grade		X (Day 5)				
Hospital admissions and deaths		Collected through Month 18				
Targeted clinical events collected as study endpoints[2]	Collected through Day 90					
SAEs not exempt from reporting (i.e., not considered a protocol specified exempt event)[2]	Collected through Day 90					
Any SAE related to study intervention	Collected through Day 90					
Unanticipated problems	Collected through Day 90					

[1] Grade 3 and 4 clinical AEs on Days 1-7 are reported each day; those occurring between Days 8 and 14 are reported at the Day 14 visit, and those occurring between Days 15 and 28 are reported at the Day 28 visit.

[2] Protocol-specified exempt serious events (PSEE); these events are listed below. See section 10.2.5 of the TICO study protocol and the PIM for information on PSEE.

* In protocol version 2.0, the data collection is identical, except that hospital re-admissions and deaths are collected through Month 12 only.

Protocol-specified exempt events (protocol section 10.2.5)
The following events are protocol-specified exempt events. They are **not** reported as AEs or SAEs, **unless** the investigator considered that there was a reasonable possibility that the study intervention (blinded investigational agent/ placebo or study-supplied SOC treatment) caused the event.

- Death
- Stroke
- Meningitis
- Encephalitis
- Myelitis
- Myocardial infarction
- Myocarditis
- Pericarditis
- New onset of worsening of CHF (NYHA class 3 or 4)
- Arterial or deep vein thromboembolic events
- Respiratory failure defined as receipt of high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation or ECMO
- Hypotension requiring vasopressor therapy
- Renal dysfunction requiring renal replacement therapy
- Hepatic decompensation
- Neurologic dysfunction, including acute delirium and transient ischemic events
- Disseminated intravascular coagulation
- Major bleeding events
- Serious infections

Appendix D. Schedule of Assessments

Table D-1. Schedule of Assessments (protocol version 3.0, Appendix B).*

	Screen or Day 0	Day 0	Follow-up Study Day; shaded columns denote in-person visits															
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**	**75**	**90**	**6M**	**12M**	**18M**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+10**	**±14**	**±14**	**±14**
ELIGIBILITY & BASELINE DATA																		
Informed consent	X																	
Baseline medical (incl. duration of COVID-19) and social history	X																	
Baseline medications	X																	
Symptom-directed physical exam by the clinical team	X																	
Review SARS-CoV-2 test results	X																	
Local laboratory testing	X						X											
Urine pregnancy test or other documentation of pregnancy status	X																	
STUDY INTERVENTION																		
Randomization		X																
Study Drug/Placebo Administration		X																
Assess infusion completion and adverse reactions		X																
STUDY PROCEDURES																		
Clinical assessment for pulmonary ordinal outcome	X	X	X	X	X	X	X	X	X	X	X							
Clinical assessment for pulmonary+ ordinal outcome	X	X	X	X	X	X	X	X	X									
Vital signs for NEW score assessment	X																	
Respiratory function scale assessment	X																	
Hospitalization status					X		X		X	X	X		X		X	X	X	X
Changes in residence/facility										X	X	X	X	X	X			
Interim medical history									X	X	X		X		X			
Interim medications							X				X							
Clinical AEs of any grade, on days indicated		X	X	X	X	X	X	X	X	X	X							
Clinical AEs reaching grade 3 or 4 severity through Day 28										X	X							
Research sample storage (plasma and serum)[2]		X	X		X		X				X				X			
Mid*turbinate* swab for central SARS-CoV-2 viral load testing[2]		X																
SAEs and unanticipated problems			Report as they occur															
Deaths			Report as they occur															
Hospitalization Summary			Report upon hospital discharge															
Hospital Readmissions			Report upon hospital discharge															

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

[2] Blood draw and swab collection in some cases can be obtained after randomization but before the infusion. If it is not possible to do an in-person on Day 3 or Day 5, the blood draws may be done one day earlier or one day later (but the participant should be telephoned to record the clinical data on the indicated study day).

* In protocol version 2.0, the data collection is identical, except that hospital re-admissions and deaths are collected through Month 12 only.

Appendix E. List of Acronyms

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
ACTT	Adaptive COVID-19 Treatment Trial
ADE	Antibody-dependent enhancement
AE	Adverse event
ARDS	Acute respiratory distress syndrome
CHF	Congestive heart failure
CHF	Coronary heart failure
CI	Confidence interval
CIF	Cumulative incidence curve
CMH	Cochran-Mantel-Haenszel [test]
COVID-19	Coronavirus-Induced Disease 2019
CVA	Cerebrovascular accident
DSMB	Data and Safety Monitoring Board
ECMO	Extracorporeal membrane oxygenation
EU	European Union
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GEE	Generalized estimating equations
GMT	Geometric mean titer
HR	Hazard ratio
ICC	International Coordinating Center
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IgG	Immunoglobulin G
IL-6	Interleukin 6
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IQR	Interquartile range
IRB	Institutional Review Board
ITT	Intention-to-treat
IV	Intravenous
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	modified intention-to-treat
mL	Milliliter
NEW	National Early Warning [score]
NIAID	National Institute of Allergy and Infectious Diseases, NIH (US)
NIH	National Institutes of Health (US)
NIHSS	National Institutes of Health Stroke Scale/Score
NYHA	New York Heart Association
nMAb	Neutralizing Monoclonal Antibodies
OR	Odds ratio
PCR	Polymerase chain reaction
PIM	Protocol Instruction Manual
PT	Preferred term

PSEE	Protocol-specified exempt (serious) events
RNA	Ribonucleic acid
RR	Rate ratio
RRR	Recovery rate ratio
SAE	Serious adverse event
SARS-CoV-1	Severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAP	Statistical analysis plan
SOC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TOC	Trial oversight committee
UMN	University of Minnesota
UP	Unanticipated problem
U.S.	United States of America
WHO	World Health Organization

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