Protocol

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This supplement contains the following items:

1. Original TICO protocol version 1.0, 27. July 2020, 90 pages
2. Original TICO statistical analysis plan (SAP) version 1.0, 06. Oct 2020, 41 pages

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

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Table of Contents

List of Tables

List of Figures

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. If an investigational agent shows superiority over placebo, SOC for the study of future investigational agents may be modified accordingly.

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 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.

This Phase III platform design includes 2 stages. In the initial stage (stage 1), safety will be evaluated and two intermediate outcomes will be assessed to determine whether an agent advances to stage 2. Treatments considered to have demonstrated unacceptable risks relative to benefits or those which do not reach the efficacy threshold for the stage 1 intermediate outcomes will not advance to stage 2 (i.e. randomization between that investigational agent and placebo will cease). In some cases, stage 1 may include 2 or 3 doses of the same investigational agent (considered as separate agents), and frequent pharmacokinetic sampling may be employed as necessary.

Investigational agents with reasonably well-established safety profiles and evidence of efficacy (i.e., at least equivalent to the criteria for advancement of an agent from stage 1 to stage 2) may enter the study directly into stage 2. Conversely, for agents with minimal pre-existing safety knowledge, pace of stage 1 enrollment will be initially restricted and there will be an early review of safety data by an independent Data and Safety Monitoring Board (DSMB). A Phase I dose escalation study for some agents may be indicated, and if so, the Phase I study would precede stage 1, and be carried out as a separate protocol.

Two ordinal outcomes, assessed at day 5, will be used in stage 1 to determine advancement of an agent to stage 2. The first ordinal outcome is a 7-category outcome largely based on oxygen requirements. The highest category that applies on day 5 will be assigned. This outcome is referred to as the “pulmonary” ordinal outcome, 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 respiratory dysfunction and 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 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

Two intermediate outcomes of potential activity in stage 1 are being assessed 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.

The stage 2 evaluation is a continuation of stage 1 for investigational agents that meet criteria for further evaluation. The primary endpoint of the Phase III trial, which is assessed during stage 1 and 2, is defined as the time from randomisation 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 end of follow-up. The definition of home will be operationalized as the level of residence or facility where the patient was residing prior to hospital admission leading to enrollment in this protocol.

DURATION — Participants will be followed for 90 days following randomization.

SAMPLE SIZE — For stage 1, 150 participants per group (i.e., investigational agent or placebo) will be randomized. For stage 2, a total of 500 participants per group will be randomized; this sample size includes participants enrolled in stage 1. There will be equal numbers of participants receiving a given investigational agent and control.

POPULATION — Stage 1: Inpatient adults (≥18 years) who have had COVID-19 symptoms ≤ 12 days and *without* any of the extrapulmonary conditions outlined in category 4 or 5 of the pulmonary+ 7-category ordinal outcome or end organ failure (i.e. the therapies included in category 6 of this outcome).

Stage 2: Inpatient adults (≥18 years) who have had COVID-19 symptoms ≤12 days, *with or without* end organ failure (any hospitalized patient being treated for COVID-19 who meets the eligibility criteria irrespective of pulmonary+ category).

STRATIFICATION — Randomization in both stage 1 and stage 2 will be stratified by study site pharmacy and in stage 2 also by severity of illness.

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 potential to advance from stage 1 to stage 2 of the trial. 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 and use pre-specified guidelines to determine whether an agent should be advanced from stage 1 to stage 2. Guidelines will also be provided to the DSMB for early evidence of sufficient activity of an investigational agent in stage 1 to advance to stage 2 before the required sample size is achieved, or, in the case of stage 2, early evidence of efficacy for the primary outcome. The DSMB may also recommend discontinuation of an investigational agent during stage 1 or 2 due to the risks being adjudged to outweigh the benefits and will consider futility assessments during both stages 1 and 2.

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 4 July 2020, less than four months following the declaration of a pandemic on 11 March 2020 by the World Health Organization (WHO), there have been more than 10 million cases diagnosed and more than 500,000 deaths worldwide.[1] Over 100,000 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.

In stage 1 of 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. In stage 2, patients with and without overt organ failure will be enrolled. 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 stages 1 and 2 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 in the literature. Reports to date have predominately been conducted in 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]

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.[30]

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 hospital with COVID-19.[31] Pre-existing lung disease and diabetes were consistently associated with a higher risk of requiring respiratory support.[31] 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.[32]

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.[33] 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.[33] 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.[34] These data underline the importance of attenuating the disease in its early phase prior to the development of end-organ failure.

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.[35] Viral ribonucleic acid (RNA) shedding from the pharynx gradually wanes as symptoms resolve, but viral RNA is still detectable weeks after symptom resolution.[35,36,37] 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.[36,38] Viral detection in sputum is higher and outlasts pharyngeal swabs in those with pneumonia.[39] Persons with asymptomatic disease clear their virus faster than symptomatic individuals.[40]

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.

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).[41] 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.[42] 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.[43]

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.[44,45] 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) 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 additional to investigational agent or matched placebo) will be regularly updated.

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,[46] was tested in PREVAIL II, a randomized controlled trial of 72 patients.[47] 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[48] and a triple nMAb cocktail of REGN3470-3471-3479[49] 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.[50] 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 has been granted breakthrough therapy designation by the US Food and Drug Administration (FDA) and REGN-EB3 is now under priority review for a new biologics license application 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.[51,52,53] During infection, SARS-CoV-2 first binds the host cell through interaction between its S1-RBD and the cell membrane receptor (angiotensin-converting enzyme ACE2 receptor) triggering conformational changes in the S2 subunit that results in virus fusion and entry into the target cell.[54] 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.[51] 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[54].

Most currently developed anti-SARS-CoV-2 nMAbs target the viral S protein, most commonly the RBD. 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.[55] CR3022 rather than CR3014 showed promise against SARS-CoV-2[56] 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,[57] 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.[53] Similarly, 18F3 and 7B11 against RBD were identified from SARS-CoV-1 patients.[58] 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[59]; P2B -2F6,[60] 311mab-31B5 and 311mab-32D4.[61]

2.3 Investigational Agents

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 III in particular, and dose and route of administration. The TOC will determine whether an agent should enter the Phase III trial of ACTIV-3 in stage 1 or 2, or whether the investigational agents should undergo Phase I testing before making that determination.

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 several agents from different sources will be combined at some point in the conduct of this master protocol – but not initially. It is also possible that one agent will be identified as effective in stage 2 of the protocol 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 aspects of study procedures outlined in this master protocol will need to be deviated from. 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 congestive heart failure. 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.[62] 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 2-stage Phase III design. The overall objective of stage 1 is to determine whether investigational agents identified for study should advance to stage 2. This will be accomplished by assessing intermediate measures of activity and safety. The evaluation of investigational agents which advance from stage 1 will be done with a larger number of participants; the study population in stage

2 also includes those enrolled in stage 1, who are followed for 90 days for the primary endpoint.

4.1 Stage 1 Outcomes to Evaluate Activity

Two intermediate outcomes to evaluate potential activity are used in stage 1. Both are ordinal categorical outcomes 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 stage 1 outcomes

The outcomes used in stage 1 are intended to identify activity, among the investigational agents examined in this early stage of the Phase III trial, meriting additional investigation.

Identification of activity may either constitute improvement of the disease state from baseline or prevention of additional progression.

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, recognizing 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 in stage 2 (time to 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 to stage 2.

Day 5 was chosen for the timing of the stage 1 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 with the planned sample size for stage 1 (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 Stage 2 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) L**ong-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.

4.2.1 Rationale for stage 2 primary outcome

The primary outcome used in stage 2 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. Time to 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 participants enrolled during both stages of the trial.

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. Change in National Early Warning (NEW) score from baseline to Day 5

7. Clinical organ failure 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. Congestive heart failure: 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.

8. A composite of death or clinical organ failure COVID-19-related events (see above)

9. 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)

10. A composite of cardiovascular events (outcomes listed above in items 7b1, 7e2 and 7e3) and thromboembolic events (item 7f2)

11. Safety and tolerability as measured by:
    a. A composite of grade 3 and 4 clinical adverse events, SAEs, or death through Day 5 (primary safety endpoint) and through Day 28
    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 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

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

4.2.3 Rationale for stage 2 secondary outcomes

Mortality and the composite of time to death or sustained recovery (see section 10.1.2 for the analysis of this outcome using a win ratio statistic)[63] 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 a 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 used in stage 1 (also assessed during stage 2) contribute to the safety assessment. A composite primary safety outcome is defined at Day 5. On days 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.

5 Objectives

5.1 Primary Objectives

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. This objective will be evaluated at the end of stage 2.

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.

Safety outcomes will be evaluated during both stage 1 and stage 2.

For stage 1, the primary objective 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 placebo for each of the two ordinal outcomes (pulmonary+ and pulmonary) when given with SOC.

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, 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 outcome category at entry, NEW score, and 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 be 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 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.

This Phase III platform design includes 2 stages. In the initial stage (stage 1), safety will be evaluated, and two intermediate outcomes (section 4.1) will be assessed to determine activity and seamless advancement to stage 2. Other efficacy outcomes and subgroups may also be considered by the independent DSMB in making their decision about advancement of investigational agents to stage 2.

Table 1 summarizes key design features of this 2-stage Phase III trial. These features are described in more detail in the remainder of this section and in section 7.

Table 1: Design Features of Master Protocol

Feature	Stage 1	Stage 2
Target population	- hospitalized with COVID-19 - symptoms ≤12 days - without end organ failure or dysfunction	- hospitalized with COVID-19 - symptoms ≤12 days - **with or** without end organ failure or dysfunction
Outcome	2 ordinal outcomes at day 5 (pulmonary+ and pulmonary)	Time to sustained recovery (primary)
Follow-up	90 days	90 days
Effect size and power	- OR=1.60 for favorable outcome - type 1 error=0.30 (1-sided) - power = 95%	- 25% increase in rate of recovery - type 1 error = 0.025 (1-sided) - power = 90%
Sample size for one (two) agents introduced together	300 (or 450)	1,000 (or 1,500) (includes 300 (450) from stage 1)

Figure 1 A Framework to Efficiently Study Multiple Candidate Agents: Placebo-controlled Comparisons on top of SOC

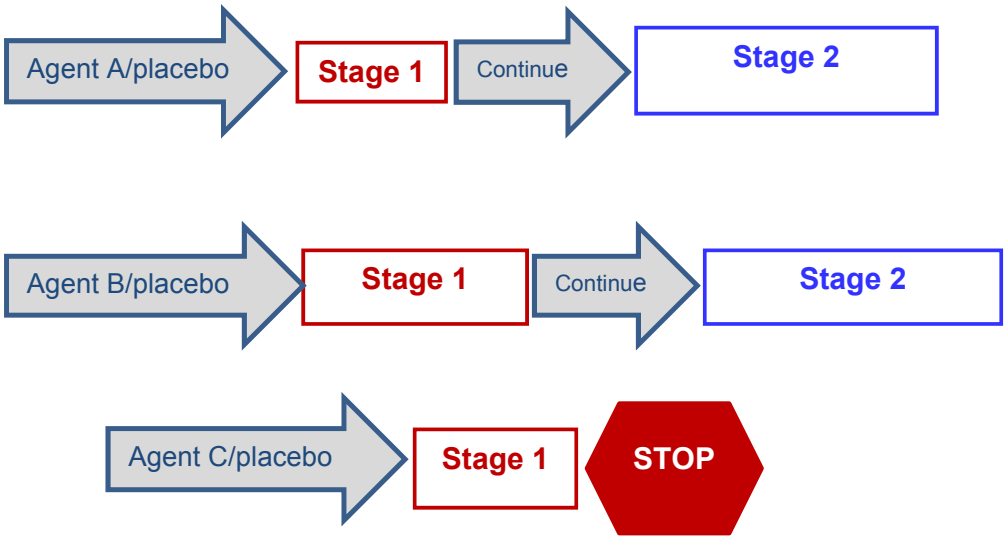

Figure 2 Two Pathways for Entry

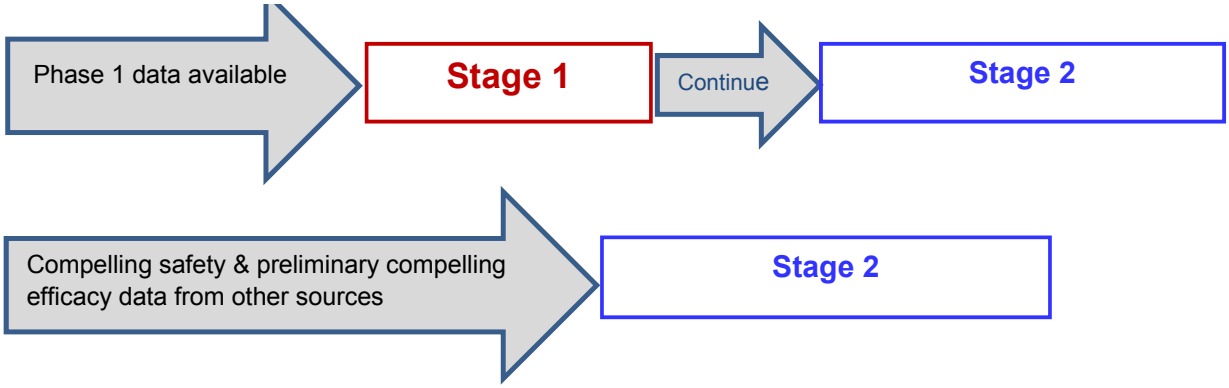

Figure 1 and Figure 2 illustrate other aspects of the 2-stage design. Investigational agents with a demonstrated unacceptable risk versus benefit profile or those which do not reach the efficacy threshold for the stage 1 intermediate outcomes will not advance to stage 2 (i.e., randomization between that investigational agent and placebo will cease, but follow-up for already enrolled participants will continue through 90 days in order to capture all relevant data). In some cases, stage 1 may include 2 or 3 potential doses of the same investigational agent (considered in stage 1 as separate agents), and frequent pharmacokinetic sampling may be employed. At most, only one of the doses will be advanced to stage 2, provided that the stated criteria for advancement are meet.

Advantages of this design are shown in Figure 1. Two investigational agents (A and B) initiate stage 1 at the same time and share a placebo group. Both advance from stage 1 to stage 2 but the advancement of A is faster than B. Randomization to C is initiated after B; placebo relevant to C includes only patients randomized after C is activated. C does not advance to stage 2.

Figure 2 shows the 2 pathways for entry into this Phase III trial. Treatments with reasonably well-established safety profiles and promising efficacy (with evidence considered to be at least equivalent to the criteria for advancement of a drug from stage 1 to stage 2) may enter the study directly into stage 2. Conversely, for treatments with minimal pre-existing safety knowledge, stage 1 enrolment will be initially restricted and may be paused until there is a review of safety data by the independent DSMB (e.g., a DSMB review may be scheduled after 50 participants have been randomized, 25 to the investigational agent).

If data from a Phase I study (e.g., dose escalation study) are not available, assistance with the development and conduct of such a study may be provided via a separate protocol (see Appendix G for a description of a Phase 1 protocol).

Participants may co-enroll in genomics or observational studies or may have been previously enrolled in studies of outpatients.

6.1 Randomization

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”). 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, where severity is defined as having a condition mentioned in exclusion criteria 5 or 6 (see section 7.2).

Within each stratum, mass-weighted urn randomization[64] 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.

In both stage 1 and stage 2, the comparison 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 and at participating sites 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 unblinded 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.

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.

6.3.1 Stage 1 Sample Size

The planned sample size for each pairwise comparison in stage 1 is 300 patients (150 patients in each group). A trial of a single investigational agent and matching placebo, randomized with 1:1 allocation, would require this sample size. If two investigational agents with matching placebos were simultaneously studied and enrollment began at the same time, the required sample size would be 450 (assumes that all participants are eligible for

both agents). In a trial like that, the two-step randomization procedure would result in a2:1:2:1 allocation (active A : placebo A : active B : placebo B) which gives 150 per group after pooling the placebo groups.

Stage 1 of the trial is powered to ensure that the DSMB has sufficient information to decide whether a specific investigational agent should be continued into stage 2, with expanded enrollment and expanded eligibility criteria. The stage 1 activity comparison (investigational agent versus control) uses two outcomes; both are ordered categorical outcomes with 7 categories, assessed on Day 5. One of the outcomes considers largely respiratory-related disease severity (pulmonary ordinal outcome), similar to the ACTT trial's ordinal endpoint,[65] while the second outcome also includes thrombotic, myocardial, and cerebral complications of COVID-19 (pulmonary+ ordinal outcome).

We expect that the pulmonary and pulmonary+ outcomes will be highly correlated, because the respiratory elements are common to both. In this case, tests comparing the investigational agent versus control would usually give similar results for both outcomes, in the sense that either $p<0.30$ for both, or $p>0.30$ for both. However, there is uncertainty. Data on non-pulmonary complications are emerging, and these outcomes may or may not have substantial impact on the rate of recovery through Day 90, the primary outcome. We developed the decision rule (see section 11.2) with two stage 1 intermediate outcomes because it is unclear to date, which of the two outcomes is better suited to select successful candidates for stage 2. As more knowledge accrues, the decision rules (and the ordinal outcomes) may be modified to improve efficiency and reliability.

Formal sample size estimates are based on the marginal tests for each of the two intermediate outcomes. In order to ensure a high probability that a truly active and potentially efficacious investigational agent advances to stage 2, we specify a power of 0.95 for each of the two marginal tests, with a (1-sided) type 1 error rate of 30%. While the high type 1 error rate will result in a fairly high probability (approximately 30%, see below) of advancing investigational treatments to stage 2 that are not effective, in stage 2 we plan to use aggressive futility boundaries to protect against enrolling too many patients to an investigational drug which is unlikely to be effective, along with more conservative type 1 error rate control.

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 activity in stage 1.[66,67] Also like this platform trial, a definitive outcome was used to assess efficacy at the end of stage 2. 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 stage 1.[66] A subsequent paper focused on the potential for estimation bias in selected and stopped treatments and concluded that its degree was generally small.[67]

As part of the development of this 2-stage platform trial, additional work was carried out to support the design. That work is briefly summarized below (personal communication).[68]

Like this protocol, Follmann and Proschan assumed a sample size of 300 for stage 1, the decision whether the investigational agent would proceed to stage 2 taking place when all 300 participants had completed Day 5, a sample size of 1000 for stage 2, a significance level of 0.30 (1-sided) and power of 0.95 for stage 1, and a significance level of 0.025 (1-sided) and power of 0.90 for the stage 2 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 a stage 1 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.[68]

For sample size calculations, we assume the same distribution across categories for both ordinal outcomes on Day 5 (pulmonary+ and pulmonary); while individual participants may fall into different categories for the two ordinal outcomes, we assume that the population proportions on Day 5 are roughly similar. Currently, no data are available that help estimate the impact of adding non-respiratory complications to the respiratory outcome categories. However, we anticipate that the two outcomes will be highly correlated, and the power calculations are robust relative to small changes to the hypothesized distribution in the placebo group.

The following assumptions were made in estimating the required sample size for stage 1, considering the marginal tests for each outcome 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 (OR). 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 in Table 2 below. Since both randomized treatment groups will receive remdesivir as SOC (unless contraindicated), these percentages were estimated using Day 5 data from the ACTT1 trial for a subgroup of patients similar to ours who were randomized to remdesivir.

e. We targeted an OR (active/placebo) of 1.60 for a more favorable 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 Table 2 below. For example, the percentage of participants in the 2 most favorable 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 Table 2, the estimated stage 1 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.

Table 2. 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 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 (forward the agent to stage 2 if one or both outcomes show superiority; forward only if both agents show superiority; some middle ground).

Table 3 below shows the power to identify (and advance to stage 2) 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 moved to stage 2 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 optimized for the intended approach to stage 1 (assuring that promising investigational agents are not stopped in stage 1).

Table 3. Power and type 1 error for the two-outcome decision rule to forward an investigational agent to stage 2, 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**
Move to stage 2 if one or both outcomes show superiority	0.98	0.39	0.97	0.36
Move to stage 2 if both outcomes show superiority	0.93	0.21	0.93	0.24

The sample size for stage 1 will be evaluated periodically using the category percentages for the pooled control group. These may change if, for example, additional treatments become SOC based on established efficacy, or if enrollment patterns change.

6.3.2 Stage 2 Sample Size

The following assumptions were made in estimating the required sample size for stage 2.

a. The primary analysis will be intention to treat. Gray's test with rho=0 will be used,[69] 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 ACTT1 and the percentage of patients in each baseline risk category of the ordinal outcome used in stage 1. Based on the results from ACTT-1,[65] we expect approximately 50% of patients enrolled in stage 2 to be in the more severe strata (5 and 6 in the ordinal categories shown in Table 2). However, all patients who are enrolled in stage 1 are in the less severe strata at entry (categories 3 and 4 in Table 2). 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 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.[70,71]

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). If 2 or 3 investigational treatments reach the end of stage 2, sample size estimates are 1,500 and 2,000, respectively.

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.

Like stage 1, sample size for stage 2 will be evaluated periodically.

6.4 Schedule of Assessments

Participants will be randomized and given their initial infusion on Day 0. Participants will be followed through Day 90 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 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. However, 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 considerable clinical concern, and participation in an additional clinical trial at that time will not be restricted.

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.

The planned analyses are by intention to treat. 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

The number of COVID-19 participants per group is projected to be 150 in stage 1 and to be 500 in stage 2; participants in stage 1 contribute also to stage 2. These participants will be enrolled at clinical trial sites globally. The estimated time from screening (Day -1 or Day 0) to end of study for an individual participant is 90 days.

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

The inclusion and exclusion criteria for stages 1 and 2 are identical with one exception. Participants with end organ failure or dysfunction are not eligible for stage 1 but are eligible for stage 2.

This plan was chosen because the goal of stage 1 is to quickly establish whether investigational agents have sufficient activity to advance them to stage 2. That decision is based on intermediate outcomes that are assessed at Day 5, a time period following treatment that was considered too early to assess potential benefit among participants with end organ failure.

Protocol inclusion and exclusion criteria are intentionally straightforward and are NOT subject to exception for even minor deviations, i.e., 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 PCR or other nucleic acid test (NAT) within 3 days prior to randomization OR documented by NAT more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection per the responsible investigator;

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**
Participants for whom 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;

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;

5. Women of child-bearing potential who are not already pregnant at study entry and who are unwilling to abstain from sexual intercourse with men or practice appropriate contraception through Day 90 of the study.

6. Men who are unwilling to abstain from sexual intercourse with women of child-bearing potential or who are unwilling to use barrier contraception through Day 90 of the study.

7. **[stage 1 only]** 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 congestive heart failure (NYHA class III-IV)

i. arterial or deep venous thrombosis or pulmonary embolism

8. **[stage 1 only]** Current or imminent 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 a positive PCR or other NAT for SARS-CoV-2 that was performed within 3 days prior to randomization, OR (documentation of a positive SARS-CoV-2 PCR or other NAT more than 3 days ago 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

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.

<u>On Day 0 following randomization record:</u>

- Adverse events of any grade severity 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
- 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 AE's 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 Day 90 following randomization for collection of study data (Appendix B). Clinical data will be collected on Days 0-7, 14, 28, 60 and 90. 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) AEs of grade 3 and 4 severity through Day 28, and SAEs through Day 90.

Both intermediate ordinal outcomes will be assessed on Days 1-4, 5 (stage 1 primary outcome), 6, and 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 the prevalence of 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. Components necessary for determination of NEW score and the respiratory function scale will be collected at baseline and Day 5, if the participant remains hospitalized.

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.

For other visits on Days 7, 14, 42, 60, and 75, contact with the participant for study data collection may be performed by telephone. However, 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), AEs, SAEs, and Unanticipated Problems (UPs). 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).

With the exception of infusion-related reactions of any grade, which 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).

Selected events will be reported to regulators and IRBs/ethics committees in addition to being regularly reviewed by the DSMB.

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

- Infusion-related reactions of any grade severity during and 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 or symptoms are not collected)..
- Incident clinical adverse events of grade 3 and 4 through Day 28 (isolated laboratory abnormalities that are not associated with signs of symptoms are not collected).
- Clinical events, including death, that are collected as part of the pulmonary+ ordinal outcome or as secondary outcomes through Day 90. These are protocol exempt events and are not reported as SAEs unless they are considered related to the study intervention (either the blinded investigational agent/placebo or a study-provided SOC treatment).
- Serious adverse events, including laboratory-only serious events, considered related to the study intervention through Day 90.
- Serious clinical adverse events that are not collected as part of the pulmonary+ ordinal outcome or as a secondary outcome through Day 90.
- Unanticipated problems through Day 90.
- Deaths through Day 90.

An overview of safety data collected during the study is given in Table 4.

Table 4 Overview of Safety Data Collection

	Infusion +2 hrs	Days 0-7	Day 14	Day 28	Day 90
Infusion-related reactions and symptoms*	X				
Incident grade 3 and 4 clinical AEs			X	X	
Clinical AEs of any grade severity	X	X	X	X	
Targeted laboratory abnormalities of any grade		X (Day 5)			
Targeted clinical events collected as study endpoints*	Collected through Day 90				
Serious clinical AEs not reported as a study endpoint*	Collected through Day 90				
Unanticipated problems	Collected through Day 90				
Any serious adverse event related to study intervention	Collected through Day 90				
* see section 10.2.5 for specific events					

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, an 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 5 GENERIC AE GRADING SCALE

Grade 1	Symptoms causing no or minimal interference with usual social and functional activities
Grade 2	Symptoms causing greater than minimal interference with usual social and functional activities
Grade 3	Symptoms causing inability to perform usual social and functional activities
Grade 4	Symptoms causing inability to perform basic self-care functions, or 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 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 Data Collection and Reporting of Specific Events

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 collected 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 be reported as an SAE. Similarly, any grade 3 or 4 infusion related reaction will be collected as an AE from day 0 trough day 28.

10.2.2 Targeted Laboratory Abnormalities

Selected laboratory tests are performed at baseline and on Day 5. These values will be associated with a severity grade centrally using the laboratory test results reported on the eCRFs with normal ranges, and with the DAIDS AE Grading Table.

Other laboratory abnormalities identified in the course of the participant's clinical care are not collected as AEs (e.g., an isolated elevated glucose level) unless they are associated with a specific clinical diagnosis/syndrome, in which case they are collected if they meet the reporting criteria of one of the other safety outcomes. In addition, if an isolated laboratory test result meets SAE reporting criteria, it should be reported as an SAE.

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

On Days 0-7 clinical AEs of any grade severity will be collected unless the event is a protocol-specified exempt event (see section 10.2.5 below).

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

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 Incident Grade 3 and 4 clinical adverse events through 28

From Day 0 through Day 28, clinical events reaching Grade 3 or 4 severity level will be collected as AEs unless they are a protocol-specified exempt event (see section 10.2.5 below).

Any medical condition of grade 1 and 2 that is present at Day 0 will be collected as an AE if it increases to Grade 3 or 4 by Day 28.

Isolated laboratory abnormalities will not be collected on the eCRF for grade 3 and 4 events. However, if an isolated laboratory result meets SAE criteria, it should be reported as an SAE.

10.2.5 Protocol-specified exempt events

These events are listed in sections 4.1 and 4.2.2 and are collected systematically during study follow-up on eCRFs. They will not be reported as SAEs, even if they meet one or more of the criteria for seriousness, ***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***. 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 events** (unless considered related to the study intervention):

- 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 clinical AEs not reported as a study endpoint (section 10.2.5); and
- Any serious AE related to the study intervention

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 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 SUSAR summaries to their overseeing IRB/EC per requirements.

SAEs that are not protocol-specified exempt 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 (Day 90), the outcome will be entered in the database as “unknown.”

10.2.7 Unanticipated Problems (UPs)

UPs must also 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 become pregnant

The investigator will collect pregnancy information on any female participant who are or becomes pregnant while participating in this study.

The participant will be followed to determine the outcome of the pregnancy.

Male participants with partners who become pregnant

If an investigator learns that a male participant's partner becomes pregnant while the male participant is in this study, the investigator is asked to attempt to obtain information on the pregnancy, including its outcome. Information obtained on the status of the mother and child will be forwarded to the sponsor.

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 Evaluation

11.1 Data Analysis

More detailed statistical analysis plans will be developed for each investigational agent and will be finalized by the blinded statisticians prior to unblinding for a specific treatment comparison. All analyses will be intent to treat with comparisons to concurrent controls as described in section 6.3. 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.

11.1.1 Stage 1

The evaluation of the intermediate outcome of activity using the two ordinal outcomes for stage 1 will use proportional odds models with a 1-sided significance level of 0.3 for each ordinal outcome. These models will control for the two design stratification factors, baseline severity of illness and study site pharmacy. A test for the proportional odds assumption from a model that allows different slopes for the baseline covariates (a partial proportional odds model) will be performed. In addition, cumulative probabilities of the ordinal outcome categories will be compared between treatment groups using logistic regression models.

Evaluation of safety outcomes will focus on comparisons of the frequency of deaths, SAEs and grade 3/4 events between the investigational agent and the placebo group irrespective of attribution to the investigational agent. SAEs and grade 3/4 events will be classified by system organ class according to MedDRA®. Proportions and 95% CIs will be used to summarize the results; differences between treatment groups for the composite of grade 3/4 events, SAEs or death over the first 5 days of follow-up will be assessed with a Cochran Mantel Haenszel test stratified by study site pharmacy and by disease severity at baseline. There will be similar assessments of targeted toxicities across treatment arms if such toxicities are known or suspected based on phase 1 or stage 1 results for the agent under investigation or similar agents. Tests for the occurrence of each or of 1 or more of such toxicities will be based on the Cochran Mantel Haenszel test with stratification by study site pharmacy and disease severity (with a 2-sided significance level of 0.05). Infusion reactions and premature cessation of infusions (for investigational agents requiring infusion) will be summarized by arm and Cochran Mantel Haenszel tests stratified by study site pharmacy and disease severity will be used to test for differences across arms. Further efficacy and safety assessments may be considered.

11.1.2 Stage 2

The evaluation for the primary efficacy outcome for stage 2 of the Phase III trial, time to sustained recovery, will be based on Gray's test with rho=0.[69] 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,[72] and the recovery rate ratio (RRR) (investigational agent versus control) for *sustained recovery* will be estimated using the Fine-Gray method,[73,74] 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.

All analyses in stage 2 will utilize 2-sided tests with a 5% significance level. Similar to the primary analysis, all comparisons between the randomized treatment groups will be by intention to treat, unless noted otherwise.

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[63] 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. 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, 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. The composite of SAEs or death through Day 90 will be summarized using time-to-event methods as described above for mortality. Proportions of participants who experienced any of these events will be compared using stratified Mantel Haenszel tests and logistic regression.

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. The randomized treatment groups (investigational agent versus control) will be compared by intention to treat. 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 ordinal outcomes used in stage 1 will be assessed at Days 1 through 7; the pulmonary ordinal outcome will also be assessed at Days 14 and 28 and tests for differences between study arms will be conducted using proportional odds models.

Clinical organ failure is a composite of many different organ-specific events, listed in section 4.2.2, item 7. The incidence of organ failure 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 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 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, and 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 (i.e. type of residence or facility defined as “home”), duration of symptoms at enrollment, clinical history and presentation (including the disease severity stratum), 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 stage 2. Subgroup analyses will be interpreted with caution due to limited power and uncontrolled type I error.

11.2 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 in stage 1 that justifies advancement to stage 2 before the required sample size is achieved, or, in the case of stage 2, early evidence of efficacy for the primary outcome. The DSMB may also recommend discontinuation of an investigational agent during stage 1 or 2 for safety and will consider futility assessments during both stages 1 and 2.

General stopping guidelines for stage 1 and 2 treatment comparisons are described below. More specific guidance for specific investigational agents may be specified in the statistical analysis plan for that agent. When several investigational agents are investigated in parallel, each agent will be compared to its corresponding, contemporaneously randomized pooled placebo group. Using a pooled placebo group to assess activity or efficacy of multiple investigational agents is efficient. 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 criteria that will be used for advancing an investigational agent from Stage 1 to Stage 2 are:

a. If the investigational agent is superior (i.e. $p \leq 0.3$) to control for both ordinal intermediate outcomes, then advance agent to stage 2. The decision to advance an investigational agent before stage 1 is fully enrolled may be made at an interim review.

b. If there is insufficient evidence for superiority versus control (i.e., p>0.3) in each of the two outcomes, then stop randomization, agent does not continue to stage 2. During stage 1, the decision to stop an investigational agent for futility would typically occur after the stage 1 trial is fully enrolled, and all participants were followed for 5 or more days.

c. If there is a statistically significant ($p \leq 0.3$) 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 to stage 2, given that the decision to stop the investigational agent can be further considered as part of the planned safety and futility review in stage 2 follow-up.

   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 “time to sustained recovery”, the stage 2 primary endpoint will also be provided to the DSMB, as supporting information.

As a guideline, asymmetric boundaries will be provided to the DSMB to monitor the intermediate (stage 1) endpoint comparison and the primary (stage 2) endpoint (time to sustained recovery) comparison 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; 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. The Lan-DeMets boundary used will be chosen to preserve a 1-sided 0.30 (stage 1) or 0.025 (stage 2) level of significance. For computing the Lan-DeMets boundary, the information fraction at each interim analysis will be the number of participants who have completed 5 days of follow-up for stage 1 (divided by the planned sample size), and the number of sustained recoveries at the interim analysis (divided by the number of sustained recoveries planned) for stage 2. 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 in stage 2 (sustained recovery), sensitivity analyses will be provided to the DSMB.

Early futility analyses in stage 2 will use the observed treatment difference in the pulmonary and pulmonary+ ordinal outcomes assessed at Day 5 in addition to the primary outcome of 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, 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.[75] These analyses will be presented to the DSMB by the unblinded statisticians for each pairwise comparison.

As more experience is gained with the criteria for moving investigational agents from stage 1 to stage 2 and interim monitoring within each stage, guidelines to the DSMB may be modified based on this experience.

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.

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

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 discuss this information 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.

What is the research question we are trying to answer?

We are studying an experimental medicine [medicine name], made by [manufacturer]. We are trying to find out if giving this experimental medicine can help people in the hospital with COVID-19 have fewer bad effects from the disease, and if it may possibly help them get better and go home faster. We are also trying to see if it is safe.

This experimental medicine will provide antibodies that we think may work to fight COVID-19. We think this may possibly help, and we think this will be safe, but we are not sure and so we are doing this study.

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.

If you agree to be in the study, we will assign you to one of two study groups. This will be done by random chance -- like flipping a coin. You will have an equal chance (50/50) of getting either the experimental medicine, [medicine name], or an inactive salt solution, commonly called a placebo. Your doctor will NOT decide and will not know which of these two choices you will get. No one on the study staff will know whether you are getting the experimental medicine or the inactive placebo.

You will get the study product (either the experimental medicine or the placebo) only once, on the day you join the study (study Day 0). You will get it by an intravenous (IV) drip through a tube attached to a needle in your arm. This is called an infusion. The study product is [volume] of liquid. The infusion will take about [how many] minutes., It may sometimes take longer depending on how your body reacts to the infusion.

[Medicine name] is the only thing you will be given that is completely experimental. It is NOT approved by the United States Food and Drug Administration or any other regulatory body in the world, and its use is strictly limited to research.

As part of the study you will also get a drug called remdesivir once a day intravenously for up to 10 days while you are in the hospital, as care for your COVID-19, unless your doctor thinks remdesivir would not be safe for you to take. Remdesivir was shown in an earlier study to help people recover more quickly from COVID-19. Remdesivir has an “emergency use authorization” in the US and many other countries. This means that the regulatory authorities are allowing its use while the company that makes it is applying for approval, because there are so few medicines available to treat COVID-19.

PID: _____

Any other medications or treatments you will be given will be what you would usually receive in this hospital for your condition. There may be some additional procedures or testing done for study purposes. We will describe these below.

You will be in the study for 90 days. We will check on your health every day while you are in the hospital, and regularly after you leave the hospital.

If you leave the hospital after just a few days, we will ask you to either come back, or else possibly be visited by our staff in your home to draw a blood sample on day 3 and day 5 of the study. We will also need to take a blood sample from you on day 28 and day 90.

To be in the study, you will need to agree to not have sex that could make you or a partner pregnant for the entire 90 days you are in the study. This may involve not having sex at all (abstinence), or you may use effective contraception (hormonal contraception or barrier methods with spermicide) to avoid pregnancy. Methods like rhythm, sympto-thermal or withdrawal are not effective for the purpose of the study. You can ask the study team about this if you have questions or concerns.

If you become pregnant during the study, please let your study team know as soon as possible. We will 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.

If your partner becomes pregnant, please let your study team know as soon as possible. We will ask if we can get information about the pregnancy. If you and your partner are willing, we will ask for consent from your partner to obtain this information.

You will also need to agree to not participate in any other COVID-19 study for the first 5 days you are in this study.

We will need to do the following things with you, and gather detailed information at these times:

PID: _____

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 detection	• 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

Day 90 is the last day you will be in the study. If you are not completely well on day 90 we may ask to follow up with you after day 90 to see if you have gotten better.

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 if you are admitted there during the time you are in the study. We will contact them to be sure we know how you are doing.
- 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, so we can find out how you are doing.

PID: _____

We will send the information we collect 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 identifying 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 funding and space to do so, which we expect to be many years. There is more information below 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.

It is important to remember that half of the people in this study will get inactive placebo, and will not get the 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 so 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 is shown to be effective.

Why would you NOT want to be in the study?

Since only half of the people in this study will get the experimental medicine, you may not receive it. Even if you do get the experimental medicine, it may not be useful, or it may have harmful side effects, so being in the study would not be of any direct help to you.

What are the risks or side effects of the study treatment?

All treatments have risks and may cause side effects. These may happen to you from the study treatment.

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

You will be monitored very closely while you are being given the infusion of the study product and for at least [time period] after the infusion is finished. We will give you prompt medical care if needed to treat any side effects from the infusion.

PID: _____

Investigational agent A…safety [tbd]. It has been studied in …[tbd] There were no/or some and describe serious problems that occurred in people because they got investigational agent. [to be completed for each investigational agent]

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 associated with blood draws and obtaining 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. These discomforts and risks are no different from what you would experience if they were performed as part of your regular hospital care for COVID-19.

What if you are pregnant or breastfeeding?

If you are pregnant or breastfeeding, you can still join this study. However, we do not have any information about how either the study medicine or remdesivir may affect your baby. The risks to a pregnant woman or an unborn baby may possibly be serious. Please take this into account as you make your decision about whether to 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 comply with all rules and regulations for human research as well as the laws of each country where the study is taking place.

This study is taking place in several countries. We expect to enroll about 1,012 people around the world.

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 now 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 [medicine name], because it is experimental.

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 to get better about 4 days faster than people who got a

PID: _____

placebo. You may be given remdesivir to treat your COVID-19 even if you do not join this study.

The most common side effects of remdesivir included abnormal liver function test results, abnormal blood clotting test results, constipation, nausea, vomiting, decreased appetite, and headache. The abnormal liver function tests lasted longer than a few days but came back to normal levels during the study.

Some people may have some side effects after the infusion of remdesivir. Other people may 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. You will be monitored closely during the infusions, and short-term medical care will be provided 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 UNITED STATES SITES ONLY. SITES IN OTHER COUNTRIES SHOULD DELETE THE NEXT PARAGRAPH.

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

SITES OUTSIDE THE UNITED STATES: Please replace the paragraph above with language appropriate for your location

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: _____

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 determine the level of virus 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 company that made the study medicine to help them learn more about its effects.

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

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.

PID: _____

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". Access to the data at UMN is limited through security measures, and no data breach or unauthorized access has ever occurred in this system. After the study is over, the data will be stored securely for the period required by law.

Your study data will be shared with the US National Institutes of Health (which is paying for this study), and with regulators that oversee the study, including the US FDA, as required by law. Your study data will also be shared with the drug company that provides the study medicine to help them develop the drug.

UMN may share your data and specimens with other people who study COVID-19. UMN will remove any information that could possibly be used to 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 specimens 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 will be available at http://www.ClinicalTrials.gov,and on the EudraCT website (https://eudract.ema.europa.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. Please tell us whether you agree to have us collect and use your personal data by placing your initials in front of your selection.

PID: _____

____**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.

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.

[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 funded primarily by a grant from the US Federal government. UMN and the study funding source 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.

There is no specific independent supervisory 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 would like to inform you about below.

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

PID: _____

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.

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 until 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	

PID: _____

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]*

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: _____

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE TICO STUDY

I have read the consent or have had it explained to me. I believe that I understand the information. By signing this consent, I am stating that I want to join this study. 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 the signed and dated consent.

If you agree to be in this study, please sign 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

_____

Relationship of LAR to Participant

PID: _____

(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

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 subject, and the subject 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.

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**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+10**
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[2]	X						X								
Respiratory function scale assessment[2]	X						X								
Hospitalization status					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 - prevalence on days indicated		X	X	X	X	X	X	X	X	X	X				
Incident Clinical AEs of grade 3 and 4 severity										X	X				
Research sample storage (plasma and serum)		X	X		X		X				X				X
Midturbinate swab for central SARS-CoV-2 viral load testing		X													

SAEs and unanticipated problems		Report as they occur
Deaths		Report as they occur
Hospitalization Summary		Report upon hospital discharge

[1] Screening must be performed within 24 hours of randomization.
[2] This information will be collected while hospitalized only, as data will not be available in outpatients.

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 into stage 1 of this and possible also other master protocols as deemed relevant. *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 stage 1 of 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 stage 1 are identified 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[76]) and later modified by Piantadosi, et al[77] and Goodman, et al.[78] 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 next stage of evaluation in the master protocol (stage 1). 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 later stages of the 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 stage 1, 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 stage 1 of the main master protocol, up to three doses maybe evaluated.
- Any required specific exclusion and inclusion criteria for later stages, 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 (used for stage 1 evaluation in the master protocol) and capture of information 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 the way the agent enters this master protocol framework (see Figure 2), 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),[65] 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[79] (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)[80]. 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.[83]

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 H1: LY3819253 (LY-CoV555) – version 1.0 (16th July 2020)

The content of this appendix is confidential and should only be viewed by persons covered by the CDA entered between Lilly and NIAID in relation to the ACTIV-3 study.

This appendix provides detailed information pertaining to the study of this investigational agent. If not stated otherwise, the text in the master protocol gives the approach that will be taken to study this agent.

H.1.1. Introduction and rationale for studying the agent

LY3819253 is a neutralizing immunoglobulin G (IgG)-1 monoclonal antibody (mAb) to the receptor binding domain (RBD) of the S protein of SARS-CoV-2 being developed as a potential treatment and prophylaxis for COVID-19. This antibody blocks S protein attachment to human angiotensin-converting enzyme 2 (ACE2) receptors, preventing subsequent viral entry into human cells and viral replication. This is expected to result in a clinically important decrease in viral replication, mitigating the severity of disease in patients in who ongoing viral replication is an important driver of COVID-19 pathophysiology.

LY3819253 is made by Lilly Research Laboratories, Eli Lilly and Company, in partnership with AbCellera Biologics Inc. (AbCellera; Vancouver, Canada), and is derived from a person, who recovered from SARS-CoV-2 infection.

Whereas one antiviral agent (remdesivir) has been demonstrated to have clinical benefit in the target population for this trial and is now part of standard-of-care (see Appendix I), it is plausible that additional antiviral effects from LY3819253 in combination with the antiviral agent may provide additive, if not synergistic, antiviral effects and hence, contribute to improvement in time to sustained recovery.

Lilly is evaluating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3819253 in participants hospitalized for COVID-19, in a randomized, placebo-controlled, double-blind, sponsor-unblinded, single-ascending-dose, Phase 1, first in human study (Study J2W-MC-PYAA [PYAA]) (NCT04411628)(1). Lilly is also evaluating the safety, tolerability, PK and PD of LY3819253 in a phase 2, randomized, double-blind, placebo-controlled, dose ranging study in non-hospitalized participants with mild to moderate COVID-19 Illness (Study J2W-MC-PYAB [BLAZE-1]) (NCT04427501)(2). Both studies are ongoing and preliminary safety, tolerability, PK and PD data from these may inform the dose level administered in this study.

H1.1.1 *Potential risk and benefits from LY3819253*

Anticipated risk is considered low, based on the known mechanism of action for human derived neutralizing antibodies in acute viral disease states. LY3819253 is a highly specific mAb directed at foreign (non-human) epitope(s). The complementarity determining regions (CDRs) of the mAb were derived from B lymphocytes of a naturally convalescent SARS-CoV-2-infected patient and, thus, have undergone natural positive and negative selection pressures in vivo, unlike humanized antibodies generated in

mice. Therefore, off-target binding and tissue cross-reactivity are considered unlikely, which is further supported by the absence of binding to membranes of human tissue in a tissue cross-reactivity study.

Potential risks for infusion of an IgG1 mAb directed toward a microbial pathogen are mostly associated with either infusion-related immediate and non-immediate hypersensitivity reactions, or infusion-related cytokine release syndrome. Signs and symptoms of infusion-related immediate hypersensitivity reactions may include, but are not limited to: anaphylaxis, angioedema, bronchospasm, chills, diarrhea, hypotension, itching, skin rash, shortness of breath, urticarial, tachycardia, and throat irritation or chest tightness. Additional signs and symptoms associated with cytokine release syndrome may also include fever, headache, myalgia, nausea, and vomiting.

The single infusion in this study will be administered at a controlled rate, the study participants will be monitored closely, and adjustments in the infusion rate will be made and/or the infusion paused or stopped as well as any supportive measures instituted as per local practice, if indicated.

A theoretical risk is that LY3819253 may cause antibody-dependent enhancement (ADE) of viral replication (section 3.2). This is based on responses observed to some monoclonal antibody therapies used in other unrelated viral diseases, Dengue and Zika virus infections. Unlike ADE associated with Dengue and Zika virus infections, this phenomenon has not been clearly established for coronavirus infections, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and has not been reported to date with SARS-CoV-2. Additionally, limited experience with the use of convalescent serum as a treatment for patients with severe COVID-19 has not indicated safety concerns (3). LY3819253 will be administered to patients at sufficiently high dose levels to neutralize SARS-CoV-2 and avoid sub-neutralizing concentrations in the presence of virus that are typically associated with ADE. Both *in vitro* and *in vivo* (non-human primate) experiments have been completed, and no evidence of ADE of infection was observed at sub-neutralizing concentrations of LY3819253.

The potential benefit of LY3819253 is, that the clinical course of COVID-19 may be improved, which may include a faster recovery from COVID-19.

In Study PYAA, 24 adult participants were randomized and received either LY3819253 or placebo through 03 July 2020. A total of 18 participants received LY3819253 (6 participants each receiving either 700 mg, 2800 mg or 7000 mg) and 6 received placebo.

Based on preliminary data from the data cutoff date of 03 July 2020 in Study PYAA, LY3819253 has been well tolerated by participants and no deaths, serious adverse events (SAEs) or discontinuations due to adverse events (AEs) have been reported. No AEs of infusion-related reaction (IRR) considered to be related to LY3819253 by the Principal Investigator (PI) have been reported in this study. Overall, the frequency of treatment-emergent adverse events (TEAEs) in Study PYAA was 23 in 10 participants dosed with LY3819253 (across all doses) or placebo. There were a similar number of

TEAEs across all groups. Most TEAEs reported were mild to moderate in severity. There have been no dose-limiting safety issues identified. Of the data received to date, PK/PD were within expected limits.

In Study PYAB, 26 adult participants entered and were randomized to receive either placebo or LY3819253 at doses of 700 mg or 2800 mg (the 7000mg cohort was initiated on 03 July 2020). Based on the data cutoff date of 03 July 2020, no deaths, SAEs or discontinuations have been reported. The study remains blinded.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of LY3819253 may be found in the Investigator's Brochure, Participant Information Leaflet, and/or Development Safety Update Report.

Given the data on LY3819253 from the on-going Phase 1 and Phase 2 studies, the well-described safety profile of other therapeutic monoclonal antibodies, and the limited disease directed therapeutic options for patients with COVID-19 illness, the overall benefit-risk assessment of this study is considered favorable.

H1.1.2 *Motivation for agent selection by the ACTIV Trial Oversight Committee (TOC)*
The Lilly antibody LY3819253 discovered in partnership with AbCellera was identified from over 400 antibody sequences isolated from blood of a convalescent SARS-CoV-2 infected patient and is a very high affinity binder of the receptor binding domain (RBD) of the viral S-protein. In live virus neutralization *in vitro* assays, LY3819253 has very high potency against SARS-CoV-2. Based on current information available to the TOC, LY3819253 appears to have an excellent potency profile among the RBD antibodies available. Further, the Lilly data demonstrate binding to both the ACE-2-interacting and the resting state of the RBD, neutralization across multiple strains of live virus, and binding across RBD known mutations of SARS-CoV-2, which provides encouraging evidence of a low risk of viral reactivation.

LY3819253 has an open IND, and a single-ascending-dose study in hospitalized patients has already begun (NCT04411628). The Lilly strategy, assuming safety and tolerability, is, to rapidly advance into efficacy studies in hospitalized and ambulatory patients. Clinical trial materials are sufficient to support the general investigative plan, and Lilly will begin drug substance commercial manufacturing at risk at their Branchburg, NJ site with plans for drug product manufacturing at their parenteral fill facility in Indianapolis, IN.

Lilly's statement regarding plans for licensure: Lilly is a global pharmaceutical company and attempts to bring important medical breakthroughs to as many patients in as many countries as possible. It would therefore be our general intent to pursue licensure in countries where the trial occurs. In the case of the COVID-19 pandemic, the actual decision to pursue licensure will be impacted by other factors which may include: status of the COVID pandemic in the country and medical need, availability of other therapies including vaccines, available drug supply and other supply feasibility issues, and other regulatory considerations.

H1.1.3 Justification for dose chosen for LY3819253

The dose levels of LY3819253 administered in this study are informed by Study J2W-MC-PYAA (PYAA) and J2W-MC-PYAB (BLAZE-1). In both studies, 700, 2800, and 7000 mg doses are being evaluated. Based on safety results from the studies mentioned above, the dose to be used is 7000 mg irrespective of body weight.

The projected human half-life is expected to be in the 2-4 weeks range.

This dose is selected to minimize potential concerns about underdosing and thus failing to detect an efficacy signal for an efficacious therapy. There are no significant safety concerns about using the 7000 mg dose, as side effects in antibody therapy are not generally dose-dependent.

H1.2. Agent specific eligibility criteria

In addition to those outlined in the master protocol.

H1.2.1 Inclusion Criteria

1) Non-pregnant female participants who are of reproductive potential and male participants who are able to father a child must abstain from male/female sexual intercourse or agree to use two forms of effective contraception, where at least one form is highly effective (less than 1% failure rate), for the entirety of the study and for 90 days after investigational agent is administered.

   Highly effective methods of contraception (less than 1% failure rate) include, but are not limited to:
   - combination oral contraceptives
   - implanted contraceptives
   - intrauterine devices

   Effective methods of contraception include, but are not limited to:
   - diaphragms and cervical caps with spermicide
   - cervical sponges
   - condoms with spermicide

   NOTE:
   - Use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.
   - Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception.
   - Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), and withdrawal are not acceptable methods of contraception.

   Participants not of reproductive potential are eligible without requiring the use of a contraceptive method. Participant-reported history is acceptable documentation of surgical sterilization and menopause.

Participants with pregnant partners should use condoms during vaginal intercourse through 90 days after investigational agent administration.

Participants should refrain from sperm donation through 90 days after investigational agent administration.

NOTE: Reproductive potential is defined as patients who have reached menarche, who have not been post-menopausal for at least 12 consecutive months with follicle-stimulating hormone (FSH) ≥ 40 IU/ml or 24 consecutive months if an FSH is not available, who have not undergone surgical sterilization, who do not have other clinical condition that could induce amenorrhea, who are not taking medications such as oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs) or chemotherapy that could induce amenorrhea. Individuals with permanent infertility due to an alternate medical cause (e.g. Mullerian agenesis, androgen insensitivity), investigator discretion should be applied.

H1.3. Description of investigational agent

H1.3.1. Administration and duration

See the PIM and Pharmacy Procedures for details. See also section H1.5 below for guidance on the clinical management of the infusion, including infusion-related reactions.

The infusion rate may be reduced as deemed necessary, if an infusion reaction is observed. Participants will be closely monitored every 30 minutes during the infusion and for at least 2 hours after completion of the infusion. Additional monitoring may be necessary based on clinical judgement of the study investigator(s) and/or site staff, and in accordance with the master protocol. The site must have resuscitation equipment, emergency drugs and appropriately trained staff available during the infusion and for at least 2 hours after the completion of the infusion.

If a participant has not already received the relevant dose of remdesivir at the day of enrolment, and has no contraindications to start remdesivir, it is recommended (but not required) that the relevant dose of remdesivir is infused after the infusion of LY3819253 /placebo is completed.

H1.3.2. Formulation and preparation

LY3819253 is provided in vials of 20 ml solution containing 700 mg antibody each. LY3819253 must be stored between 2ºC and 8ºC.

A total of 10 vials is required for dosing of the agent at 7000 mg (see table H1.1). Placebo is normal saline. The study medication is prepared by a unblinded pharmacist at the local pharmacy. To ensure blinding of the participant and clinical staff a colored sleeve will be placed over the infusion bags used (see PIM and Pharmacy Procedures).

LY3819253 should be prepared and dispensed as soon as possible after randomization. Infusions should be completed within 4 hours after the infusion has been prepared by the pharmacist.

Table H1.1. Study medication overview.

Intervention Name	Placebo	LY3819253
Dose Formulation	0.9% sodium chloride solution	Solution
Dosage Level(s) (mg)	Not applicable	7000
Route of administration	IV infusion	IV infusion
Use	Placebo	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Commercially available 0.9% sodium chloride solution	From Lilly
Packaging and Labeling	Commercially available 0.9% sodium chloride solution	Study Intervention will be provided in glass vials and will be labeled appropriately

H1.3.3 Supply, distribution, and accountability

Procedures for ordering and accepting drug, for maintaining inventory of LY3819253, and for breaking the blind in the event of a medical emergency will be described in the Pharmacy Procedures.

H1.3.4. Contraindicated medications

No medication is known to be contraindicated in patients receiving the investigational agent. Whenever a concomitant medication or the study agent is initiated or a dose changed, investigators must review the concomitant medication's prescribing information and the relevant protocol appendix/appendices, as well as the most recent package insert, Investigator's Brochure, or updated information from DCR, NIAID to obtain the most current information on drug interactions, contraindications, and precautions.

H1.3.5. Precautionary medications

The clinical site should have necessary equipment and medications for the management of any infusion reaction (see section H1.5 below).

Premedication for infusions is not planned. However, if an infusion reaction occurs during administration or if the participant has a medical history suggesting a potential benefit from premedication, the study investigator(s) should determine the appropriate premedication.

The investigators and sponsor may decide to recommend premedication, if the frequency of infusion reactions among participants warrants it. If minor infusion reactions are observed, administration of acetaminophen, 500 mg to 1000 mg, antihistamines and/or other appropriately indicated medications may be given prior to

the start of infusions for subsequent participants. The decision to implement premedication for infusions in subsequent participants will be made by the investigator and sponsor and recorded in the study documentation. Any premedications given will be documented as a concomitant therapy.

H1.4. Clinical and laboratory evaluations

H1.4.1 Timing of Assessments

Appendix B outlines the clinical and laboratory monitoring. Assessment and reporting of AEs (section 10.1.1), SAEs (section 10.1.2) and unanticipated problems (section 10.1.3) and their severity, causality (section 10.1.5) and expectedness (section 10.1.6) is performed as outlined in the relevant section of the master protocol.

H1.4.2 Immunogenicity Assessments

At the visits specified in the master protocol (Days 0, 28, and 90) venous blood samples will be collected to determine antibody production against LY3819253. Immunogenicity may be assessed by a validated assay designed to detect ADAs in the presence of LY3819253 at a laboratory approved by Lilly. Antibodies may be further characterized for their ability to neutralize the activity of LY3819253. Remaining volume from the PK sample may also be used for immunogenicity assessments as needed.

H1.4.3. Pharmacokinetic Assessments

At the visits specified in the master protocol (Days 0, 1, 5, 28, and 90) venous blood samples will be collected to determine LY3819253 serum concentration for pharmacokinetic assessment. The PK/Immunogenicity assessment will require 2mL of the serum collected, as described in the Master Protocol Appendix B as “Research Sample Storage”. PK samples may be assessed by a validated assay at a bioanalytical lab designated by Lilly. The PK assessment will use the same 2ml serum aliquot specified in the Immunogenicity assessment section above (4.2). Analysis of samples from placebo-treated subjects is not planned. Remaining sample used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate.

H1.5. Clinical management issues

All participants should be monitored closely for 2 hours after the infusion, as there is a risk of infusion reaction and hypersensitivity (including anaphylaxis) with any biological agent.

H1.5.1. Symptoms and Signs

Symptoms and signs that may occur as part of an infusion reaction, include, but are not limited to, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

Infusion-related reactions’ severity will be assessed and reported using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected version 2.1 (July 2017) (Table H1.2).

Table H1.2. Overview of severity grading of infusion-related reactions.

Parameter	Mild	Moderate	Severe	Severe and Potentially Life-threatening
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized Urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Cytokine Release Syndrome[a]	Mild signs and symptoms AND Therapy (that is, antibody infusion) interruption not indicated	Therapy (that is, antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (for example, requiring pressor or ventilator support)

a = A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

Source: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)(4).

H1.5.2. Site Needs

The clinical site should have necessary equipment, medications, adequately qualified and experienced staff with appropriate medical cover for the management of any infusion reaction, which may include, but is not limited to, oxygen, IV fluid, epinephrine (/adrenaline), acetaminophen (/paracetamol) and antihistamine.

The pharmacy must use amber-colored Ultraviolet Light-Inhibiting (UVLI) protective bags to place over the infusion bag. The pharmacy will be provided with labels to be placed on the IV bag before dispensing (refer to the Pharmacy Procedures).

The pharmacy is required to provide normal saline and IV bags, similarly shrouded.

H1.5.3. Management of Infusion Reactions including Discontinuation

Investigators will use their clinical judgement and standard of care to evaluate and manage all infusion reactions. If an infusion reaction occurs, then supportive care should be used in accordance with the signs and symptoms. If a severe and potentially life-threatening infusion reaction occurs with LY3819253 /placebo, its use should be permanently discontinued.

If a participant is not infused with LY3819253 /placebo or the complete infusion is not given, all follow-up procedures and reporting's outlined in the master protocol (Appendix B for overview), should be adhered to as indicated.

H1.5.4. Adverse Events of Special Interest (AESI)

The following are AESIs for the agent LY3819253 or placebo for LY3819253:

- Infusion-related reactions
- Allergic/hypersensitivity reactions

H1.6. References

1. https://clinicaltrials.gov/ct2/show/NCT04411628 (PYAA trial)
2. https://clinicaltrials.gov/ct2/show/NCT04427501 (BLAZE-1 trial)
3. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A. 2020;117(17):9490-6.
4. https://rsc.niaid.nih.gov/clinical-research-sites/grading-severity-adult-pediatric-adverse-events-corrected-version-two-one (DAIDS AE severity grading; link also outlined in appendix D)

Statistical Analysis Plan

Version 1.0

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

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. The primary objective of the platform trial is to determine whether investigational agents that are aimed at supplementing the host immune response to SARS-CoV-2 infection are safe and superior to control (e.g., placebo + standard of care [SOC]) for the primary endpoint of time to sustained recovery evaluated over 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.

The platform design includes 2 stages. In the initial stage (stage 1), safety will be evaluated and two intermediate outcomes will be assessed to determine whether an agent advances to stage 2. In stage 2, eligibility and enrollment will be expanded, and the study is powered for the clinical primary outcome of time to sustained recovery.

This SAP:

- Provides a short description of the two-stage, multi-arm 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 3-11). Primary analyses for stage 1 and guidelines for continuing an investigational agent to stage 2 or stopping for safety are described in section 7. Primary analyses for stage 2 and guidelines for stopping an investigational agent for safety, early proof of efficacy, or for futility are described in section 8. General analysis principles are summarized in section 3.
- 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.

More detailed SAPs may be developed for individual investigational agents and included as an appendix. The agent-specific analysis plans may be updated, and will be finalized by the blinded statisticians prior to unblinding for a specific treatment comparison. As needed, the overall SAP for ACTIV-3 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 version 1.0.

Design

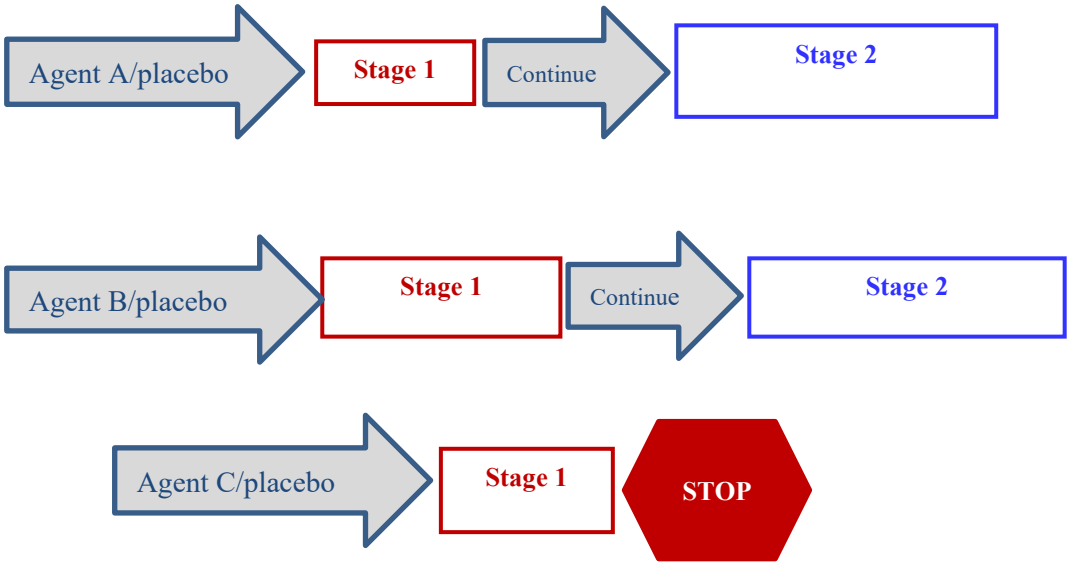
TICO is a master protocol to evaluate the safety and efficacy of multiple investigational agents aimed at modifying the host immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, or directly enhancing viral control in order to limit disease progression.

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.

Investigational agents may 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.

This Phase III platform design includes 2 stages, as illustrated in Figure 1 below. In the initial stage (stage 1), safety will be evaluated and two intermediate outcomes will be assessed to determine whether an agent advances to stage 2. Treatments considered to have demonstrated unacceptable risks relative to benefits or those which do not reach the efficacy threshold for the stage 1 intermediate outcomes will not advance to stage 2 (i.e. randomization between that investigational agent and placebo will cease). In some cases, stage 1 may include 2 or 3 doses of the same investigational agent (considered as separate agents), and frequent pharmacokinetic sampling may be employed as necessary.

Figure 1 A Framework to Efficiently Study Multiple Candidate Agents: Placebo-controlled Comparisons on top of SOC



Investigational agents with reasonably well-established safety profiles and evidence of efficacy (i.e., at least equivalent to the criteria for advancement of an agent from stage 1 to stage 2) may enter the study directly into stage 2. Conversely, for agents with minimal pre-existing safety knowledge, pace of stage 1 enrollment will be initially restricted and there will be an early review of safety data by an independent Data and Safety Monitoring Board (DSMB). A Phase I dose escalation study for some agents may be indicated, and if so, the Phase I study would precede stage 1, and be carried out as a separate protocol.

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. This objective will be evaluated at the end of stage 2.

Primary outcomes stage 1

Two ordinal outcomes, “pulmonary” and “pulmonary+”, assessed at Day 5, will be used to determine advancement of an agent from stage 1 to stage 2. Both outcomes have 7 categories. The “pulmonary” outcome is largely based on oxygen requirements. The categories of the “pulmonary+” outcome additionally include extra-pulmonary manifestations, such as coagulation related complications. The two outcomes are defined in Appendix Aof this SAP.

Two intermediate outcomes of potential activity in stage 1 are being assessed 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.

Primary endpoint stage 2

The stage 2 evaluation is a continuation of stage 1 for investigational agents that meet criteria for further evaluation. The primary endpoint of the Phase III trial, which is assessed during stage 1 and 2, is defined as the time from randomisation 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 end of follow-up. The definition of home will be operationalized as the level of residence or facility where the patient was residing prior to hospital admission leading to enrollment in this protocol.

Duration

Participants will be followed for 90 days following randomization.

Sample size

For stage 1, up to 150 participants per group (i.e., investigational agent or placebo) will be randomized. For the Phase III trial, a total of 500 participants per group will be randomized; this sample size includes participants enrolled in stage 1. There will be equal numbers of participants receiving a given investigational agent and control.

Population

Stage 1: Inpatient adults (≥18 years) who have had COVID-19 symptoms ≤ 12 days and *without* any of the extrapulmonary conditions outlined in category 4 or 5 of the pulmonary+ 7-category ordinal outcome or end organ failure (i.e. the therapies included in category 6 of this outcome).

Stage 2: Inpatient adults (≥18 years) who have had COVID-19 symptoms ≤12 days, *with or without* end organ failure (any hospitalized patient being treated for COVID-19 who meets the eligibility criteria irrespective of pulmonary+ category).

Stratification

Randomization in both stage 1 and stage 2 will be stratified by study site pharmacy and in stage 2 also by severity of illness.

Monitoring

An independent DSMB will review interim data and use pre-specified guidelines to determine whether an agent should be advanced from stage 1 to stage 2. Guidelines will also be provided to the DSMB for early evidence of sufficient activity of an investigational agent in stage 1 to advance to stage 2 before the required sample size is achieved, or, in the case of stage 2, early evidence of efficacy for the primary outcome. The DSMB may also recommend discontinuation of an investigational agent during stage 1 or 2 due to the risks being adjudged to outweigh the benefits and will consider futility assessments during both stages 1 and 2.

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.

Randomization will be stratified by study site pharmacy (several clinical sites may share one pharmacy) and severity of disease at entry, where severity is defined as having a condition mentioned in the stage 1 exclusion criteria 7 and 8 (see protocol section **Error! Reference source not found.**).

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.

In both stage 1 and stage 2, the comparison 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 in stage 1 is 300 patients (150 patients in each group). A trial of a single investigational agent and matching placebo, randomized with 1:1 allocation, would require this sample size. Stage 1 of the trial is powered to ensure that the DSMB has sufficient information early in the trial to decide whether a specific investigational agent should be advanced to stage 2.

The stage 1 activity comparison (investigational agent versus control) uses two outcomes, denoted as “pulmonary” and the “pulmonary+”; both are ordered categorical outcomes with 7 categories, assessed on Day 5. The sample size calculations are based on the marginal tests for each of the two outcomes, using proportional odds models to compare the treatment groups.[1] The total sample size of 300 participants is sufficient to detect a summary OR=1.60 with power of 95%, using a one-sided test with significance level of 0.30. Given the two-outcome decision rules, an investigational agent with a summary OR=1.60 at Day 5 for both outcomes, the power for advancing the agent to stage 2 would be between 93% and 98%, with a type I error between 0.21 and 0.39.

For stage 2, the planned sample size for each pairwise comparison is 1,000 participants (500 participants in each group), including the participants that had been enrolled in stage 1. 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 two-sided test with a significance level of 0.05. 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.

Prior to the completion of stage 2, **sample size may be re-estimated** based on the observed pooled rates of sustained recovery in the two disease severity strata, and the proportion of enrollment in the two disease severity strata. The sample size re-estimation will be performed by the blinded statisticians on the protocol team. The goal of the sample size re-estimation would be to preserve power to detect the hypothesized treatment effect, in case model assumptions used for the original sample size estimates were not fulfilled.

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.
- In stage 1, advise on promoting the investigational agent to stage 2, either when all participants have completed the Day 5 visit and the data for the co-primary interim outcomes are available, or earlier in case of overwhelming benefit. Advise on stopping the investigational agent (and agent-specific matched placebo) for harm, or not continuing the agent into stage 2 for lack of efficacy.
- In stage 2, advise on stopping or modifying the Phase III trial for efficacy, for patient safety in case of emerging data on harm, or for futility.
- 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 12).

The DSMB will conduct frequent safety reviews. Unless an investigational agent has extensive safety data from previous or other ongoing trials, the first safety review will be conducted after 20-30 participants have been enrolled, and Day 5 data are available for the first 10 participants randomized to the investigational agent. Subsequent reviews will be timed according to the recommendations of the DSMB and study leadership. In stage 1, reviews would be expected to occur after 75 and 150 participants, respectively, have been randomized to the investigational agent, or more frequently. Stage 2 efficacy reviews will occur frequently, and futility reviews would be expected to occur at approximately 50% and 75% information time (based on the primary endpoint of time to sustained recovery). **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, as is customary for DSMB panels reviewing several separate trials.

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. With each closed report, the DSMB will receive a separate, encrypted file that unmasks the treatment group labels. This procedure ensures that the DSMB has the full information to weigh benefit versus harm.

Open report to the DSMB

The open reports 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.

All data summaries in the open report will be pooled across treatment groups, except the allocation ratio between the active and (pooled) control groups. 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. 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, usually as part of the open report.

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 of stage 2**, the pooled number of primary events 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. Comparisons between treatment groups will be by intention-to-treat, with sensitivity analyses by modified intention-to-treat (excluding participants who did not receive any of the investigational agent/placebo) for primary and key secondary outcomes. 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, 7.2 and 8.2. 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 sections 7 and 8.
- Data summaries on data completeness and study conduct, described in section 9.
- Interim monitoring boundaries for the primary safety outcomes.
- Interim monitoring boundaries for efficacy when sufficient data has accrued (e.g., 20% information time).
- Futility analyses (section 8.3).
- Listings of grade 4 adverse events, serious adverse events (SAE), 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 (1 PhD statistician and 1-2 MS level statisticians will have the primary responsibility, with a second PhD statistician in an advisory role), 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 compared against each other, unless explicitly stated in the agent-specific data analysis plan and agreed upon by all stakeholders. Therefore, in case 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".

In both stage 1 and stage 2, the comparisons will be of each investigational treatment against its (pooled) control arm.

Analysis populations: Comparisons will be by intention-to-treat. Sensitivity analyses for primary outcomes and key secondary outcomes will include comparisons 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.

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 disease severity randomization strata, unless stated otherwise. Any stratum that contains too few participants (less than 20 participants or events) may be pooled with other strata (in the same disease severity category, preferably within the same country). Alternatively, "site pharmacy" may be added as a categorical covariate to models instead of fitting separate baseline hazard functions.

For **binary outcomes**, probabilities will be compared between the investigational agent and treatment groups 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). 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 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 CMH).

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").

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.

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 stage 2 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 in important safety endpoint, the composite of grade 3 and 4 events, SAEs, or death, is 5 days or 28 days. In particular, the administrative follow-up time is not censored at death.
The **administrative censoring date** is the earlier of the cut-date of the dataset, or (randomization date plus analysis time period).

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 23.0 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 prevalence of AEs (the number of participants with at least one event) will be

[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)

summarized by day and grade, and by MedDRA® System Organ Class and grade. 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.

General rules: 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
- For investigational agents in stage 2, cumulative and daily/weekly enrolment over time by disease severity stratum
- 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, enrollment and eligibility violations will be summarized by treatment group.

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. For interim reports, baseline characteristics will be compared between treatment groups using tests comparing proportions (CMH), means (ANCOVA models) or medians (Wilcoxon test) as appropriate.

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, the pooled data will also be summarized by mean (SD) and range.

- 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 in stage 2), number (%) in each category
  - Receipt of SARS-CoV-2 vaccination (active or control, if blinded)
- Other clinical characteristics
  - Concomitant treatments
  - History of chronic conditions (heart failure, diabetes, asthma, chronic obstructive pulmonary disease, hypertension requiring medication, renal impairment, hepatic impairment, cancer, immunosuppressive disorder [HIV, and other than HIV])
  - Prior cerebrovascular event
  - Prior myocardial infarction (MI)
  - Requirement of continuous chronic supplemental oxygen
  - BMI (<30, 30-34.9, 35+)
  - Pregnancy
- 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.

In case the 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, or not infused.
- 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. 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 (< 5 days, 5 days, > 5 days). (Closed report only)
  - Number and percent of participants who received remdesivir prior to the day of randomization, and number of doses (median, IQR).
  - 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 intention-to-treat, 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).

In stage 2, eligibility is expanded to include participants with more severe disease. To aid in monitoring safety, selected summaries will also be provided separately for the two disease severity strata.

In case an investigational agent is administered over several days, the following statistics will be used to summarize the administration of the study treatment (active and control):

- Number and percentage of participants receiving a complete course of treatment, partial duration of treatment, or no treatment.
- Number of days the treatment was administered: median, IQR, and distribution.
- Reasons for not receiving a full course of study treatment (e.g., discharge to home, or toxicities).

7 Stage 1 Analyses

The primary objective in stage 1 is to determine whether the investigational agent is safe and suitable to advance to stage 2. In the following, “active” or “agent” refers to the investigational agent plus SOC, and “control” or “placebo” refers to placebo plus SOC.

7.1 Stage 1: Primary Efficacy Analysis

The stage 1 efficacy comparison (active versus control) 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.[8] 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 advancing investigational agents to stage 2 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 advance agent to stage 2. The decision to advance an investigational agent before stage 1 is fully enrolled may be made at an interim review.

b. If there is insufficient evidence for superiority versus control (i.e., $p>0.3$) in each of the two outcomes, then stop randomization, agent does not continue to stage 2. During stage 1, the decision to stop an investigational agent for futility would typically occur after the stage 1 trial is fully enrolled, and all participants were followed for 5 or more days.

c. If there is a statistically significant ($p \leq 0.3$) 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 to stage 2, given that the decision to stop the investigational agent can be further considered as part of the planned safety and futility review in stage 2 follow-up.

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 "time to sustained recovery", the stage 2 primary endpoint, will also be provided to the DSMB, as supporting information.

Treatment groups will be compared by intention-to-treat. For each of the two ordinal outcomes, the 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 outcome at baseline (to adjust for baseline severity of illness).[2] The model will be stratified by site pharmacy. The tests 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 (denoting higher odds of more favorable disease categories in the group randomized to investigational agent compared with control), and the p-value ≤ 0.30. This level of type 1 error was specified in the protocol to ensure a high probability that a truly active and potentially efficacious investigational agent advances to stage 2. With a sample size of 300 (150 per treatment group), stage 1 of the study has 95% power to detect an OR of 1.60, under model assumptions described in section 6 of the protocol.

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. Tests will be stratified by site pharmacy and adjusted for baseline severity, if numbers are sufficiently large. These analyses need to be interpreted with caution, because they are not adjusted for inflation of type I error due to multiple comparisons.

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.

Stage 1: Interim monitoring boundaries for superiority or harm

To monitor for benefit of an investigational agent, including the decision to advance an agent to stage 2, the Lan-DeMets spending function analogue of the O'Brien-Fleming boundaries will be used.[9,10] The Lan-DeMets boundary used will be chosen to preserve a 1-sided 0.30 (stage 1) level of significance. For computing the Lan-DeMets boundary, the information fraction at each interim analysis will be the number of participants who have completed 5 days of follow-up (divided by the planned sample size).

> **Comment:** If the cut date is less than 10 days before the data freeze date, the numerator of the information time will be calculated as number of participants for whom Day 5 data for the pulmonary outcome are available.

The monitoring boundary for harm is asymmetric, requiring less evidence to stop for harm than for superiority; a Haybittle-Peto boundary with a 2.5 standard deviation (SD) for the first 50 participants enrolled and 2.0 SD afterwards will used as a guideline for harm.

At each interim analysis after the first 50 participants are enrolled, and until stage 1 is fully enrolled (n=300), the following will be provided:

- Estimated summary ORs for the pulmonary and pulmonary+ outcomes, 95% CIs, p-values, at the current visit. These analyses will be by intention-to-treat and use the proportional odds model.[2] The model will be stratified by site pharmacy if the strata are sufficiently large, as described in section 3. Estimates of the proportions of participants in each of the categories on Day 5 by treatment group will be provided.
- Signed square root of the value of the CMH test statistic for OR=1 for the pulmonary and the pulmonary+ outcomes at Day 5, plotted over information time, at the current DSMB review, and the corresponding values of the test statistic presented at the previous reviews. The graph will also show the one-sided O'Brien-Fleming boundary, calculated with Lan-DeMets α-spending function (α=0.30) for superiority, and an asymmetric, Haybittle-Peto boundary for harm (2 standard deviations).[9,10] (Provided at full DSMB reviews after 100 participants are enrolled and have Day 5 data, or earlier at request of the DSMB; the monitoring boundary accounts for multiple views). The primary safety outcome to monitor for harm is a composite of grade 3 and 4 AEs, SAEs, or death through Day 5, as described in section 7.2 below.
- History of the estimated ORs at previous DSMB reviews, as presented, and recalculated with the current data (using the cut-date of the previous visits). The

latter provides information on the influence of a possible time lag in the reporting of outcome data. (At full DSMB reviews).

- Probabilities for dichotomized cumulative ordinal outcome categories (e.g., "best two categories" through "best five categories") at Day 5 will be compared between treatment groups using logistic regression models, stratified by site pharmacy. Estimated probabilities by treatment group, estimated ORs, 95% CIs and p-values will be reported.
- Comparison of the treatment groups for the stage 2 primary outcome, time to sustained recovery. Treatment groups will be compared using Gray's test. These analyses are described in section 8.1.

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

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**:
  - For the primary analysis, only participants with Day 5 data for the pulmonary outcome will be included. 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.
  - As sensitivity analysis, the ordinal outcome data will be imputed by last-carried-forward.
- **Final analyses** after completion of the trial:
  - For the primary analyses, 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. Additionally, the latest measured status of the pulmonary (or pulmonary+) outcome, and the date of the hospital discharge may be used in the imputations. 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.
  - As sensitivity analysis, only participants with Day 5 data will be included.

Sensitivity analyses

- As sensitivity analyses, the primary analyses will be repeated after excluding participants who did not receive any of the assigned investigational agent (active or control). This **modified intention-to-treat** 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 3 and Day 7 using similar methods, 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 cumulative ordinal categories in the

model; this corresponds to testing for separate slopes using a partial proportional odds model). In addition, non-proportionality with respect to stratification covariates (baseline ordinal categories and pharmacy) will be assessed. 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; however, the analyses of the dichotomized ordinal outcome categories help interpret the treatment effect.

- Stage 1 of the trial was powered 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 distribution in the control group used for the sample size calculations. 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. (At selected interim reviews, when enrollment nears completion).

7.2 Stage 1: Safety Analysis

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

A comprehensive safety review includes:

- Comparison of the treatment groups for the primary safety endpoint, with formal stopping boundaries, and analysis of secondary safety outcomes (described in this section)
- Analysis 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.

This section describes the primary safety outcome in stage 1, and the analysis of AEs, SAEs, UPs, and deaths. Comparisons between treatment groups will be by intent to treat. Tests will use a 2-sided significance level of 0.05, unless noted otherwise.

There is ambiguity in the definition of SAEs in version 1.0 of the protocol document, which will be addressed in an upcoming protocol amendment to version 2.0. 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. PSEEs are reported and summarized separately, as components of the *clinical organ failure* outcome, described in Appendix B. PSEEs are similar in severity to SAEs. The primary safety endpoint is defined as a *composite of incident grade 3 or 4 clinical AEs, SAEs, or death*. The ambiguity arises in whether PSEEs should be considered SAEs for the purpose of the statistical analyses. Following the letter of the protocol, we interpret "SAE" as event that is reported as a SAE. However, each analysis that includes SAEs only (without citing PSEE) will be complemented by the corresponding analysis that includes both SAEs and PSEEs.

The following safety and tolerability outcomes will be analyzed:

- The **primary safety endpoint** in stage 1 is a composite of incident grade 3 or 4 clinical events, SAEs, or death through Day 5. The number and proportion of participants experiencing one of these events by Day 5 will be tabulated, and treatment groups will be compared using a CMH test stratified by study site pharmacy. If the agent is

investigated in Stage 2 of the platform trial, the test will also be stratified by disease severity at baseline (randomization stratum).

- Mortality will be analyzed as a key secondary outcome, see below.
- The individual components of the composite outcome will be summarized.
- As sensitivity analysis, treatment groups will be compared for time to event (primary safety outcome) through Day 5 using a log-rank test, stratified by site pharmacy, 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.
- As sensitivity analysis, the primary intention-to-treat comparison will be repeated after excluding participants who did not receive the assigned study treatment (modified intention-to-treat).

- Analyses for the primary safety endpoint will be repeated for a composite of incident grade 3 or 4 clinical events, SAEs, organ failure (PSEE), or death through Day 5.

- All-cause mortality through day 90 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 3, 5, 7, 14, 28, 60, and 90) and figures (Kaplan-Meier curves with pointwise 95% CIs); treatment groups will be compared for time to death using log-rank tests, an overall HR will be estimated with 95% CIs using Cox proportional hazards models.
  - As sensitivity analysis, all-cause mortality will be analyzed by modified intention-to-treat, excluding participants who did not receive any of the investigational agent/placebo.

- 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, and overall HRs with 95% CI will be estimated using Cox proportional hazards models):
  - Composite of incident grade 3 or 4 events, SAEs, or death through Day 28
  - Composite of incident grade 3 or 4 events, SAEs, organ failure (PSEE), or death through Day 28
  - Composite of incident grade 3 or 4 events, SAEs, organ failure (PSEE), re-hospitalization, or death through Day 28
  - Composite of organ failure (PSEE) or death through Day 28
  - Composite of SAEs or death through Day 90
  - Composite of SAEs, organ failure (PSEE), or death through Day 28

- Treatment groups will be compared for the incidence of non-pulmonary outcomes in the pulmonary+ ordinal outcome by Day 5 (comparing proportions with events), and through 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 prevalence of 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 by intention-to-treat, using methods for binary data (CMH tests and logistic regression); comparisons will be for prevalence of events of a given grade or higher (i.e., any grade, grade 2+, grade 3+, grade 4).

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

- For investigational agents requiring a one-time infusion, 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 incidence of clinical organ failure (PSEE) defined by development of any one or more of the clinical events listed in Appendix B, through Day 28, and for a composite of cardiovascular and thromboembolic events. These analyses are described in section 8.5.

- Treatment groups will be compared for mean changes in laboratory test values from baseline to Day 5, and 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.

- 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, grade 4 AEs, UPs, SUSARs, and deaths (with cause of death) will be provided at each DSMB meeting, with new events highlighted. Further safety assessments may be considered.

7.3 Stage 1: Key Secondary Outcomes

Treatment groups will be compared by intention-to-treat for key secondary outcomes. Analysis methods used for binary outcomes, for continuous outcomes, and for time-to-event outcomes were described in section 3.

The following key secondary outcomes will be analyzed:

- All-cause mortality through 90 days of follow-up (analysis described in section 7.2 above).

- A composite outcome which considers both time to sustained recovery and mortality, through Day 90. Treatment groups will be compared using a win-ratio statistic, described in section 8.4 below.

7.4 Stage 1: Other Secondary Outcomes

The analysis of other secondary outcomes is described in section 8.5 below. The protocol lists these secondary outcomes for stage 2. However, several of these outcomes may help evaluate the safety and efficacy of the investigational agent early in the trial. Therefore, analyses of selected additional outcomes will also be provided in stage 1 of the trial.

7.5 Stage 1: Subgroup Analyses

Subgroup analyses will be carried out for the primary efficacy outcome (pulmonary and pulmonary+) and important safety outcomes (composite of grade 3 and 4 events, SAEs and death through Day 5 and Day 28, and mortality), when sufficient data have accumulated for meaningful analysis. 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.

Subgroup analyses are described in detail for stage 2, in section 8.6. Subgroup analyses in stage 1 follow the same principles, using the proportional odds models for the pulmonary and pulmonary+ outcomes, and Cox's proportional hazards models for time-to-event analyses of the safety outcomes. Important subgroups will be by duration of symptoms, age (< 65 versus 65+ years) and by pre-existing conditions.

Even if statistically significant, subgroup analyses will be interpreted with caution due to the uncontrolled type I error.

7.6 Stage 1 Analyses for Investigational Agents in Stage 2

When an investigational agent progresses to stage 2 of the trial, more participants will be enrolled, and eligibility will be expanded to include participants with more severe disease. The data summaries described in sections 7.1-7.3 will be continued.

Additionally, in order to assess whether the treatment effect varies by disease severity and to quantify the effect of the investigational agent in the expanded study population, subgroup analyses by disease severity (randomization stratum indicator) will be performed. In particular, for the pulmonary and pulmonary+ ordinal outcomes on Day 5, possible heterogeneity of the treatment effect across the severity strata will be assessed, as described for subgroup analyses in section 7.5 and 8.6.

8 Stage 2 Analyses

The primary objective in stage 2 is to determine whether the investigational agent is safe and superior to the control arm (e.g., placebo) when given with SOC, for the primary endpoint of time to *sustained recovery* evaluated 90 days after randomization.

If an investigational agent entered the master protocol in stage 1 and was approved to proceed to stage 2, all study participants who were enrolled in stage 1 are included in the analysis of stage 2.

All analyses in stage 2 will utilize 2-sided tests with a 5% significance level. Similar to the primary analysis, all comparisons between the randomized treatment groups will be by intention to treat, unless noted otherwise.

8.1 Stage 2: Primary Efficacy Analysis

The primary efficacy endpoint in stage 2 is time 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.

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); 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” (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 by intention-to-treat, using Gray’s test with ρ=0.[4] The test will be stratified by disease severity at entry and by 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 analyzing sustained recovery. Gray’s test with ρ=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, and the recovery rate ratio (RRR) (investigational agent versus control) for sustained recovery will be estimated using the Fine-Gray method, stratified by disease severity at entry and study site pharmacy; the RRR will be estimated as a point estimate with a 95% CI.[3,5,6] RRR>1 indicates superiority

of the investigational agent. 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 above); since all participants are hospitalized at study entry, it takes at least 15 days to attain *sustained recovery*.

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. This applies to participants who are alive but have not yet experienced sustained recovery. For participants who died, this type of censoring is integrated into Gray's test. With this analysis, the "not recovered" status will be carried forward.
  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, and may 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.

Stage 2: Interim monitoring boundaries for superiority or harm

The trial of an investigational agent in stage 2 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 2.0 SD will used as a guideline for harm.

At each interim analysis after the first 300 participants are enrolled, the following will be provided:

- Signed square root of the value of the test statistic for Gray's test with ρ=0, comparing the investigational agent versus the control group through Day 90, plotted over information time, at the current DSMB review, and the corresponding values of the test statistic presented at the previous reviews. The graph will also show the O'Brien-Fleming boundary with Lan-DeMets α-spending function. Boundaries will be shown for a one-sided test with α=0.025 for superiority of the investigational agent, and an asymmetric, Haybittle-Peto boundary for harm (2 standard deviations). The primary safety outcome to monitor for harm is a composite of grade 3 and 4 AEs, SAEs, or death through Day 5, as described in section 8.2 below.

- Estimated cumulative incidence functions for sustained recovery at selected time points (days 15, 21, 28, 42, 60, 75, 90) by treatment group, using the Aalen-Johansen estimator; and the recovery rate ratio (RRR) with 95% CIs and p-values, estimated using the Fine-Gray model, stratified by disease severity at study entry and site pharmacy. The Aalen-Johansen estimators will also be plotted over time.

- History of the estimated RRRs for time to sustained recovery with 95% CIs and p-values (by Fine-Gray's method), 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 visits). The latter provides information on the influence of a possible time lag in the ascertainment of sustained recovery.

- To aid in the interpretation of the estimated treatment difference, the median days to sustained recovery 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 will be assigned 91 days.

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 be usually ascertained within 3 weeks or less of the date the outcome was achieved.

- As sensitivity analysis, we will analyze participants for whom the primary endpoint status is unknown, but who were discharged from the hospital to home 14 or more days prior to the cut-date, as having achieved sustained recovery at 14 days after discharge.

- 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

- Stage 2 of 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 RRR for *sustained recovery* is constant over time, similar to a Cox proportional hazards model. Based on prior studies in COVID-19, we anticipate that many participants achieve sustained recovery within 4-5 weeks, and that the treatment effect (RRR) is not constant over time. This assumption will be tested by including an interaction effect between time and treatment indicator.

Sensitivity Analyses

- As sensitivity analyses, the primary analyses will be repeated after excluding participants who did not receive any of the investigational agent/placebo (modified intention-to-treat).
- Sensitivity analyses with imputed primary endpoint status will be performed, described under "Ascertainment of sustained recovery" above.
- If the RRR is not constant, as a sensitivity analysis, the RRR will be estimated within time periods, for example, Day 14-28, Day 29-60, Day 61-90.

8.2 Stage 2: Safety Analyses

The safety analyses in stage 2 are largely similar to those described in section 7.2 for stage 1 of the trial. However, in stage 2, eligibility criteria are expanded, and the comparisons between treatment groups will be stratified by disease severity at study entry (randomization stratum) in addition to site pharmacy.

Comparisons between treatment groups will be by intention-to-treat. Tests will use a 2-sided significance level of 0.05, unless noted otherwise.

The following safety and tolerability outcomes will be analyzed:

- The **primary safety endpoint** is a composite of grade 3 and 4 events, SAEs, or death through Day 5. Treatment groups will be compared for time to first event, using a log-rank test, stratified by disease severity at study entry and site pharmacy. The cumulative proportion of participants with an event will be estimated using Kaplan-Meier curves, by treatment group. The hazard ratio (HR) will be estimated with a 95% CI using a Cox proportional hazards model with an indicator for treatment group, stratified by disease severity and site pharmacy.
    - The individual components of the composite outcome will be summarized.

- Sensitivity analysis will be performed as described in section 7.2, including analyses by modified intention-to-treat.

- Analyses for the primary safety endpoint will be repeated for a composite of incident grade 3 or 4 clinical events, SAEs, organ failure (PSEE), or death through Day 5.

- All-cause mortality through day 90 will be analyzed using time-to-event methods, as described in section 7.2, stratified by disease severity at study entry, and by site pharmacy if event numbers permit. This is a key safety endpoint. Cause of death will be MedDRA® coded, and summarized by treatment group.

- Other safety analyses will be conducted as described in section 7.2 for the stage 1 analyses, including the following outcomes:
  - A composite of grade 3 or 4 AEs, SAEs or death through Day 28
  - A composite of grade 3 or 4 AEs, SAEs, organ failure (PSEE), or death through Day 28
  - A composite of incident grade 3 or 4 events, SAEs, organ failure (PSEE), re-hospitalization, or death through Day 28
  - A composite of grade 4 AEs, SAEs or death through Day 28
  - A composite of organ failure (PSEE) or death through Day 28
  - A composite of SAEs or death through Day 90
  - A composite of SAEs, organ failure (PSEE), or death through Day 28
  - Prevalence of clinical AEs of any grade at baseline (Day 0 prior to infusion), at Day 0 after infusion, Days 1-7, and on Days 14 and 28; AEs will be summarized by grade and day, and by MedDRA® system organ class and grade.
  - Summaries of UPs and SUSARS, and listings of SAEs, UPs, SUSARs and deaths.
  - Infusion-related reactions and symptoms during or within 2 hours after the infusion of the investigational agent or placebo, and premature cessation of infusion (described in section 6).
  - Summaries of clinical organ failure (PSEE) (described in section 8.5 under “clinical organ failure”).
  - Change in laboratory test values from baseline to Day 5, and incidence of grade 3 and 4 laboratory abnormalities at Day 5.
  - Pregnancy outcomes

Further safety assessments may be considered.

8.3 Stage 2: Monitoring for Futility

Early futility considerations in stage 2 will include the pulmonary and pulmonary+ ordinal outcomes assessed at Day 5 (and at selected days through Day 28) in addition to the primary outcome of sustained recovery. These analyses are intended to inform the DSMB in deciding whether randomization to the investigational agent should be discontinued due to a low probability that a statistically significant effect on the primary endpoint of sustained recovery will be observed with 90 days of follow-up.

To assess futility, 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, as yet unobserved 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.

8.4 Stage 2: Key Secondary Outcomes

Mortality is a key secondary outcome; time to death will be analyzed as described in section 8.2 above.

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.[13] 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; ties are broken by time since randomization. The analysis will use matched pairs, with matching based on disease severity, presence of pre-existing conditions (COPD, asthma, diabetes, obesity, kidney impairment, hepatic impairment, heart failure, MI or other acute coronary syndrome, cancer, immunosuppressive disorder), age, sex, and country, with criteria for matching based on this ordering. This combination of time to sustained recovery and time to death is also a key secondary analysis.

8.5 Stage 2: Other Secondary Outcomes

The protocol defines a number of secondary endpoints in addition to the two key endpoints described in the previous section. These analyses will be carried out for the final report. Selected secondary endpoints may also be analyzed for the interim monitoring report, 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 (randomization stratum), and by site pharmacy.

- 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).[14]
    - Days alive outside of a short-term acute care hospital up to day 90. We will sum the number of days that each individual spends outside a short-term acute care

hospital up to 90 days. 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. This analysis will be undertaken only when complete follow-up data are available.

- 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 7.1.

  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 defined by development of any one or more of the clinical events listed in Appendix B, through Day 28. The development of organ failure through day 28 will be analyzed as a binary outcome, and compared across arms using logistic regression. These analyses will be supplemented by time to event based approaches when possible, overall and for individual components. Individual components of this composite outcome will be tabulated. The clinical organ failure events are protocol-specified exempt events (PSEE).

- A composite of death or clinical organ failure due to COVID-19-related events (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.

- 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.

- Change in National Early Warning (NEW) score from baseline to Day 5. Treatment groups will be compared for mean change using methods for continuous outcomes (ANCOVA models or Wilcoxon test), with baseline NEW score as covariate.

8.6 Stage 2: 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 and death through Day 5 and Day 28, composite of SAEs and death through Day 90), and for key secondary outcomes (including mortality) 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.

The protocol denotes the subgroup analysis by disease severity as “key subgroup analysis”; 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 (randomization stratum)
- 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)
- Modified Borg dyspnea scale
- Organ/respiratory dysfunction category based on each ordinal outcome (pulmonary+ and pulmonary)
- NEW score

If available, subgroups will also be considered by upper respiratory SARS-CoV-2 viral load, by antibody level, and by neutralizing antibody level at baseline.

Subgroup analyses for the primary endpoint of time to sustained recovery will use the Fine-Gray model, stratified by disease severity at study entry. 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 safety endpoints will use 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.

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 stage 2.

Subgroup analyses will not be adjusted for multiple comparisons; they are supportive to the primary endpoint analysis. Subgroup analyses will be interpreted with caution due to limited power and uncontrolled type I error.

9 Data Completeness and Study Conduct

According to the protocol, the intermediate ordinal outcomes for stage 1 (pulmonary and pulmonary+) will be assessed on days 0-7; the decision rules for advancing an agent to stage 2 are based on these outcomes on Day 5. The pulmonary outcome will also be assessed on Days 14 and 28. The stage 2 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. 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).

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:

- Number, percent and type of protocol deviations
- Expected and observed number (% of expected) of participants who completed visits on Days 1-7, 14, 28, 42, 60, 75, and 90.
- Ascertainment of the stage 1 (intermittent) primary outcomes: Expected and observed number (% of expected) of participants with outcome status for the pulmonary (Days 5, 14, and 28) and the pulmonary+ outcome (Day 5).
- Ascertainment of the stage 2 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.
- 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, disease severity stratum, receipt of study treatment, date of withdrawal, and reason of withdrawal.
- Length of follow-up: Median, IQR, range and distribution
- 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.

10 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.

11 Exploratory Analyses

11.1 Checking Assumptions for the Two-Stage Study Design

In stage 1 of this two-stage platform trial, estimated treatment differences in the pulmonary and pulmonary+ ordinal outcomes on Day 5 are used to identify promising investigational agents to be tested in stage 2 with the clinical outcome of “time to sustained recovery”. In exploratory analyses, data collected in stage 2 in will be used to re-assess the decision rules in stage 1. This includes the choice that the ordinal outcomes in stage 1 are being assessed on Day 5 (compared with Day 3 or Day 7), and whether both the pulmonary and pulmonary+ outcomes are needed. For example, we will develop models to predict the treatment effect in stage 2 based on the pulmonary and pulmonary+ outcomes in stage 1, and to develop a “risk score” for the stage 2 primary outcome.

These analyses require completed stage 1 and 2 follow-up for at least one investigational agent, preferably several agents. A detailed analysis plan will be developed at a later time, but before analyses start.

11.2 Disease Progression Risk Score

A disease progression risk score will be developed, using pooled treatment groups with the following baseline predictors of the primary outcome (recovery): age, biological sex, duration of symptoms, ordinal outcome category at entry, NEW score, and chronic health conditions. This risk score will be used for subgroup analyses for the stage 2 primary outcome of time to sustained recovery, and time to mortality, to investigate if the treatment effect differs between subgroups at lower versus higher predicted disease progression risk.

These analyses require completed stage 1 and 2 follow-up for at least one investigational agent. A detailed analysis plan will be developed at a later time, but before analyses start.

12 Unblinding of Treatment Comparisons

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. If an investigational agent advances to stage 2, **interim results from stage 1 will not be unblinded** until the trial for this investigational agent is concluded, in order to preserve the integrity of the trial.

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.

13 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).

14 References

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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

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 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 (MI)
    2. Myocarditis or pericarditis
    3. Congestive heart failure: 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-CoV-2, requiring antimirobial administration and care within an acute-care hospital.

Appendix C. Safety Data Collection

Table C-1. Overview of Safety Data Collection (protocol section 10).

	Infusion +2 hrs	Days 0-7	Day 14	Day 28	Day 90
Infusion-related reactions and symptoms	X				
Incident grade 3 and 4 clinical AEs[1]			X	X	
Clinical AEs of any grade severity[2]	X	X	X	X	
Targeted laboratory abnormalities of any grade		X (Day 5)			
Targeted clinical events collected as study endpoints[3]	Collected through Day 90				
Serious clinical AEs not reported as a study endpoint[4]	Collected through Day 90				
Unanticipated problems	Collected through Day 90				
Any serious adverse event related to study intervention	Collected through Day 90				
Death	Collected through Day 90				

1 Incident grade 3 or 4 clinical AEs will be reported through Day 28, with dates. Excludes protocol-specified exempt events. Medical conditions of grade 1 or 2 at baseline will be collected if they advanced to grade 3 or 4.
2 On the day of infusion of the investigational agent (Day 0), any grade clinical AEs that were not present pre-infusion or that worsened. The timing is recorded (during infusion or within 2 hours of infusion versus later). Excludes protocol-specified exempt events.
3 Protocol-specified exempt events.
4 Excludes protocol-specified exempt events. All deaths are reported as SAEs, irrespective of relatedness to study intervention.

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. 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
IV	Intravenous
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
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
RNA	Ribonucleic acid
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
US	United States of America
WHO	World Health Organization

Appendix E. Investigational Agent LY3819253 / LY-CoV555

The investigational agent LY381923 / LY-CoV555 is an IgG1 neutralizing monoclonal antibody (mAb) made by Lilly Research Laboratories, Eli Lilly and Company, in partnership with AbCellera Biologics, Inc. It is administered through a one-time infusion, on the day of randomization. Remdesivir is study-supplied, and is administered as background therapy in both study arms, referred to as standard of care (SOC).

Participants are randomized to *LY-Cov555* + *remdesevir* versus *placebo* + *remdesivir*.

No additional statistical analyses are specified.