Randomized Master Protocol for Immune Modulators for Treating COVID-19

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STATEMENT OF COMPLIANCE

Each institution engaged in this research will hold a current Federalwide Assurance (FWA) issued by the U.S. Office of Human Research Protection (OHRP) for federally funded research. The Institutional Review Board (IRB)/Independent or Institutional Ethics Committee (IEC) must be registered with OHRP as applicable to the research.

The study will be carried out in accordance with the following as applicable:

- All National and Local Regulations and Guidance applicable at each site
- The International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice, and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- United States (US) Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- US Food and Drug Administration (FDA) Regulations: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (IRBs), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), and/or 21 CFR 812 (Investigational Device Exemptions)

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) GCP guidelines.

Site Investigator Signature:

Signed: _____   Date: _____
                    Name and Title

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ACTIV-1 IM:
RANDOMIZED MASTER PROTOCOL FOR IMMUNE MODULATORS FOR TREATING COVID-19

1.   PROTOCOL SUMMARY

1.1.   ACTIV-1 IM – Synopsis

1.1.1.   *Study Overview*

ACTIV-1 IM is a master protocol designed to evaluate multiple investigational agents for the treatment of moderately or severely ill patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The research objectives are to evaluate each agent with respect to speed of recovery, mortality, illness severity, and hospital resource utilization. Each agent will be evaluated as add-on therapy to the standard of care (SoC) in use at the local clinics, including remdesivir (provided). The SoC may change during the course of the study based on other research findings. Comparisons of the agents among themselves is not a research objective.

The study population corresponds to moderately and severely ill patients infected with the coronavirus disease 2019 (COVID-19) virus. Recruitment will target patients already hospitalized for treatment of COVID-19 infection as well as patients being treated for COVID-19 infection in Emergency Departments while waiting to be admitted to the hospital. Patients both in and out of the ICU are included in the study population.

Enrollment is planned to begin when 2-3 agents have been selected for initial evaluation and are available for testing. Up to 5 agents may be evaluated in ACTIV-1 IM.

The study period is 29 days, with assessments on each day of the hospital stay. Patients will be followed after hospital discharge with periodic follow-up assessments through Day 29. There will also be a safety and clinical status assessment at 60 days. Treatment periods may vary by agent.

The trial is adaptive in that interim analyses are planned to assess the futility of each agent, with the goal of discontinuing those with lower probabilities of success to more effectively utilize trial resources for the remaining agents. Additionally, interim analyses are planned for early stopping for efficacy. Alpha spending functions are used to appropriately control the probability of making an erroneous conclusion at the interim and final analyses.

Safety monitoring will be performed throughout the trial, and formal stopping rules for each agent will be adopted. The Data and Safety Monitoring Board (DSMB) established for ACTIV-1 IM will have oversight responsibility for the study.

1.1.2.   *Enrollment Period*

Enrollment is expected to begin in September 2020. It is anticipated the enrollment may be completed in 4-6 months.

1.1.3.   *General*

ACTIV-1 IM is a master protocol designed to evaluate immune modulators for the treatment of moderately or severely ill hospitalized patients infected with COVID-19. Trial participants will be assessed daily while hospitalized. If the participants are discharged from the hospital prior to Day 29, they will have follow-up study visits at Days 8, 11, 15, 22, and 29. For discharged participants, it is preferred that the Day 8, 11, 15, and 29 visits are in person to obtain safety laboratory tests and blood (serum/plasma) samples for secondary research as well as clinical outcome data. However, infection control or other restrictions may limit the ability of the participant to return to the clinic. In this case, these visits may be conducted by phone, and only clinical data will be obtained. The Day 22 visit does not have laboratory tests or collection of samples and is conducted by phone. The Day 60 assessment will be conducted by phone.

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The effectiveness of each therapeutic agent as add-on therapy to SoC plus remdesivir (provided) will be evaluated based on the primary endpoint of time to recovery by Day 29. The sample size requirements are based on the ability to detect a moderate improvement in time to recovery (3-4 fewer days) for each agent (see Section 9.2). A total of 788 recoveries are required for each comparison to provide approximately 85% power to detect a recovery rate ratio of 1.25. Assuming 73% of participants achieve recovery in 28 days, consistent with the ACTT-1 results, the total sample size to evaluate 1, 2, and 3 agents in ACTIV-1 IM is approximately 1080, 1620, and 2160, respectively. Because each agent is being compared to SoC with no between-agent comparisons, no multiplicity adjustments for multiple agents are planned.

1.1.4.   *Study Population*

Hospitalized adults (≥18 years old) with COVID-19, including patients both in and out of the ICU. Patients seeking care for COVID-19 in an Emergency Department (ED) and waiting to be admitted to the hospital are included.

1.1.5.   *Inclusion Criteria*

1. Admitted to a hospital or awaiting admission in the ED with symptoms suggestive of COVID-19.
2. Subject (or legally authorized representative) provides informed consent prior to initiation of any study procedures.
3. Subject (or legally authorized representative) understands and agrees to comply with planned study procedures.
4. Male or non-pregnant female adults ≥18 years of age at time of enrollment.
5. Has laboratory-confirmed (within 14 days prior to enrollment) SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen.
6. Ongoing illness of any duration, and at least one of the following:
   - Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
   - Blood oxygen saturation (SpO$_2$) ≤ 94% on room air, OR
   - Requiring supplemental oxygen, OR
   - Requiring mechanical ventilation or ECMO.
7. Women of childbearing potential must agree to either abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through Day 60.
8. Agrees to not participate in another interventional trial for the treatment of COVID-19 through Day 60.

1.1.6.   *Exclusion Criteria at Screening*

1. ALT or AST >5 times the upper limit of normal.
2. Estimated glomerular filtration rate (eGFR) <30 mL/min (including patients receiving hemodialysis or hemofiltration).
3. Neutropenia (absolute neutrophil count <1000 cells/μL) (<1.0 x 10^3/μL or <1.0 GI/L).
4. Lymphopenia (absolute lymphocyte count <200 cells/μL) (<0.20 x 10^3/μL or <0.20 GI/L)
5. Pregnancy or breast feeding.
6. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours.
7. Known allergy to any study medication.
8. Received cytotoxic or biologic treatments (such as anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], anti-IL-17, or T-cell or B-cell targeted therapies (e.g., rituximab), tyrosine kinase inhibitors including baricitinib, TNF inhibitors, or interferon within 4 weeks or 5 half-lives prior to screening. Steroid dependency defined as need for prednisone at a dose >10 mg (or equivalent) for >1 month within 2 weeks of screening is exclusionary. Note 1: Dexamethasone (at a dose of 6 mg per day for up to 10 days) is permitted for the treatment of COVID-19 in patients who are already mechanically ventilated and in patients who require supplemental oxygen at screening, but who are not mechanically ventilated in accordance with national guidelines. Note 2: Infusion of convalescent plasma is also allowed.
9. Based on medical history and concomitant therapies that would suggest infection, have suspected clinical diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening required).

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10. Based on medical history and concomitant therapies that would suggest infection, suspected serious, active bacterial, fungal, viral (including, but not limited to, active HBV, HCV, or HIV/AIDS).
11. Have received any live vaccine (that is, live attenuated) within 3 months before screening, or intend to receive a live vaccine (or live attenuated) during the study. Note: Use of non-live (inactivated) vaccinations is allowed for all participants.
12. Severe hepatic impairment (defined as liver cirrhosis Child stage C).
13. Current severe heart failure (New York Heart Association [NYHA] III-IV).
14. In the Investigator's judgment, the patient has any advanced organ dysfunction that would not make participation appropriate.

1.1.7. *Study Intervention*

Therapeutic agents will be evaluated as an add-on therapy to SoC. Participants will be randomly assigned to receive either SoC plus one of the test agents or SoC plus placebo. Randomization will proceed in two stages. At the first stage, each participant will be assigned to one of the sub-studies with equal probability. At the second stage, each participant will be assigned to either the test agent or its matching placebo in an n:1 ratio, where n = the number of agents currently active in the master protocol and for which the patient is eligible to receive. With three agents and SoC, for example, this procedure results in a randomization ratio of 1:1:1:1 if the patient is eligible to receive all three agents (see Section 6.2).

Inclusion of a placebo for each agent enables masking of study participants and clinical personnel to treatment assignment at the second stage. Data from patients receiving SoC plus placebo will be pooled across agents for comparative analyses and hypothesis testing.

If there are supply limitations on any product, the sub-study containing that product, or its matching placebo will be temporarily closed to enrollment.

The initial SoC will be remdesivir, based on the results of the ACTT-1 study. Participants will receive SoC as follows:

- Remdesivir will be administered as a 200 mg intravenous (IV) loading dose on Day 1, followed by a 100 mg once-daily IV maintenance dose for the duration of the hospitalization up to a 10-day total course.

Duration of SoC therapy:

- Remdesivir IV component – 5 to 10 days while hospitalized (see Section 6.1.2).

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1.1.8. *Schedule of Assessments*

<u>In addition to the table below</u>, please consult the appropriate appendix for each sub-study (Section 1.8 of Appendices 1, 2, and 3) for additional agent- and sub-study-specific assessments.

Table 1-1. Schedule of Assessments (SOA)

Day +/- Window	*Screen* −1 or 1	*Baseline* 1	*Study Intervention Period* **Daily until hospital discharge***	*Follow-up Visits* **15**[7] ± 2	**22**[7] ± 3	**29**[7] ± 3	**60**[12] ± 5
ELIGIBILITY							
Informed consent	X						
Demographics & Medical History	X						
Review SARS-CoV-2 results	X						
STUDY INTERVENTION							
Randomization		X					
Administration of investigational agent		• Remdesivir+placebo: daily infusion until Day 10 or discharge.					
STUDY PROCEDURES							
Targeted physical exam	X						
Vital signs including SpO$_2$ [1]		X[4]	Daily until discharge[8,9]	X[9]		X[9]	
Clinical data collection [2]		X[4]	Daily until discharge[8,9]	X[9]	X[9]	X[9]	X[12]
Adverse event evaluation		X[4]	Daily until discharge[8,9]	X[9]	X[9]	X[9]	X[12]
Concomitant medication review		X[4]	Daily from Day -7 to Day 15 or until discharge[9]	X[9]			
SAFETY LABORATORY							
Safety hematology, chemistry and liver tests	X[3]	X[4,5,6,7]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized[6,7,9]	X[9]		X[9]	
Pregnancy test for females of childbearing potential	X[3]						
PHARMACOKINETICS							
Blood sample for pharmacokinetics[11]		X[11]	Day 8			X[11]	
RESEARCH LABORATORY							
Blood for serum and plasma (future secondary research)		X[4,10]	Day 3, Day 8 (all ± 1 day) if hospitalized	X[9]		X[9]	

Notes:

* *If participant is discharged from hospital a telehealth visit will be performed on Day 8 and 11 where applicable (without required blood draws) with assessment of clinical and vital status using the 8-point scale*

[1] *Vital signs include temperature, systolic blood pressure, heart rate, respiratory rate, O$_2$ saturation and level of consciousness. Vital signs collected as part of standard care may be used.*

[2] *Refer to Section 8.1.2 and 8.1.3 of the protocol for details of clinical data to be collected including ordinal score, NEWS, oxygen requirement, mechanical ventilator requirement, extrapulmonary manifestations, etc.*

[3] *Screening laboratory tests include: CBC with differential (including absolute neutrophil count and absolute lymphocyte count), ALT, AST, ALP, total bilirubin, direct bilirubin, creatinine (and calculate an estimated glomerular filtration rate (eGFR); the formula used is determined by the sites, but should be consistent throughout the study at each site), and*

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pregnancy test. Laboratory tests performed in the 48 hours prior to enrollment will be accepted for determination of eligibility.

[4] Baseline assessments should be performed within 24 hours prior to first study product administration. Results of Day 1 (baseline) laboratory assessment do not need to be reviewed to determine if initial study product should be given.

[5] Laboratory tests performed as part of routine clinical care in the 24 hours prior to first dose will be accepted for the baseline safety laboratory tests. Baseline may be the same as the screening laboratory tests.

[6] Safety laboratory tests include WBC with differential, hemoglobin, platelets, creatinine (with calculated eGFR), glucose, total bilirubin, direct bilirubin, ALP, ALT, AST, CPK-MB, Troponin, PT/INR, d-dimer, serum ferritin, and C-reactive protein.

[7] Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing. Window during hospitalization is ±1 day.

[8] Daily until hospital discharge or end of study, whichever comes first.

[9] In-person visits are preferred but recognizing quarantine and other factors may limit the participant's ability to return to the site for the visit. In this case, the visit may be performed by phone. If participant is still hospitalized during the follow-up period, they should get Day 8, 11, 15, 22, and 29 assessments along with the daily clinical data collection.

- If still hospitalized at Day 8, 11, 15, and 29 or returns to the site for an in-person visit: collect clinical data, vital signs, safety laboratory tests, and research laboratory samples (serum/plasma) as able. Concomitant medications will only be assessed through Day 15.
- If phone call only on Days 8, 11, 15, and 29 and all Day 22 visits: assess adverse events, clinical status (ordinal scale), readmission to a hospital, and mortality only. Concomitant medications will only be assessed through Day 15.

[10] Serum and plasma collected will be stored for future assessment of biomarkers of immune function including cytokines, and chemokines that may be associated with inflammation, anti-viral response, cytokine response syndrome (CRS) and secondary hemophagocytic lymphohistiocytosis (sHLH) during SARS-CoV-2 infection and genetic markers predicting disease progression and/or response to specific therapy. Final decision about the specific biomarkers will be determined later.

[11] Pharmacokinetic samples will be collected on select days, see **Table 8-2**, Section 8.2 of Master Protocol including for details on timing of sample collection. If the patient is discharged prior to the day of PK sample collection, a sample should be collected just prior to discharge.

[12] Telephone assessment of clinical and vital status using the 8-point ordinal scale, of re-hospitalization, and of AEs.

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Study Schema

2. INTRODUCTION

2.1.   Background

2.1.1.   *ACTIV-1 IM – Immune Modulators & Remdesivir Multi-arm Trial*

A preliminary review of data from ACTT-1 occurring after 606 recoveries and 103 deaths (approximately 67% of the 1,063 subjects enrolled) demonstrated that subjects that received remdesivir had a 31% faster time to recovery (11 vs 15 days, recovery rate ratio 1.312 (1.119, 1.541), p<0.001), and a decrease in mortality (8.0% vs 11.6%, p = 0.059). The DSMB asked that the sponsor be unblinded early given the public health implications of the results as well as the implications for the design and conduct of ACTT-2. Based on the ACTT-1 results and subsequent Emergency Use Authorization (EUA) from FDA, remdesivir is now considered the standard of care for hospitalized COVID-19 patients. Note, however, that while remdesivir has demonstrated efficacy in the treatment of COVID-19, the mortality rate is still high. Infection by pathogenic coronaviruses (e.g. SARS and SARS-CoV–2) often results in excessive cytokine and chemokine action with the development of acute respiratory distress syndrome (ARDS) (33-35). It is postulated that this dysregulated inflammatory immune response is contributing to the excessive mortality and targeting this response will further improve outcomes.

2.2.   Risk/Benefit Assessment

2.2.1.   *Known Potential Risks of Study Participation*

Potential risks of participating in this trial are those associated with having blood drawn, the IV catheterization, possible reactions to the study interventions (as noted in Section 2.2.2.1), and breach of confidentiality.

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 where blood will be drawn or at catheter site less likely.

2.2.1.1. *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 study records will be kept in a locked file cabinet or maintained in a locked room at the participating clinical site. 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 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 IRB, NCATS, and applicable regulatory agencies (e.g., FDA).

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2.2.2. *SoC - Remdesivir*

2.2.2.1. *Potential Risks of Remdesivir*

Remdesivir is an investigational therapeutic agent. 138 healthy adults have been dosed with remdesivir in four Phase 1 clinical trials. Few subjects to date experienced constipation, heartburn, itching, unusual feelings in the ear, dizziness, loss of appetite, nausea, vomiting, shaking of the leg and arm, headache, loose stool, or upset stomach. These AEs were temporary, lasting only a few days, and none were serious. In clinical studies, transient elevations in ALT and AST have been observed with single doses of remdesivir up to 225 mg and multiple once daily doses of remdesivir 150 mg for up to 14 days. Mild (Grade 1) reversible PT prolongation was also noted in some subjects but without any clinically significant change in INR or other evidence of hepatic effects. The mechanism of these elevations is currently unknown. Based on these clinical observations, patients with ALT or AST >5 times the upper limit of normal will not be eligible for study enrollment. Regular laboratory assessments will be performed in order to monitor hepatic function and PT. Any observed liver function-related laboratory abnormalities or possibly related AEs will be treated appropriately and followed to resolution.

In nonclinical animal studies, toxicity studies found dose-dependent and reversible kidney injury and dysfunction. In clinical studies, no evidence of nephrotoxicity has been observed with single doses of remdesivir up to 225 mg or multiple once daily doses of remdesivir 150 mg for up to 14 days. A 150-mg dose of the solution and lyophilized formulations of remdesivir contains 9 g and 4.5 g, respectively, of sulfobutylether-beta-cyclodextrin (SBECD), for which the maximum daily recommended daily dose (based on a European Medicines Agency (EMA) safety review) is approximately 250 mg/kg. Because SBECD is renally cleared, participants with moderate or severe renal impairment may have SBECD exposures greater than those with less severe renal impairment or normal renal function. Based on this information, patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min (including patients requiring hemodialysis or hemofiltration) will not be eligible for study enrollment.

Remdesivir is a substrate for CYP2C8, CYP2D6, and CYP3A4. However, coadministration with inhibitors of these CYP isoforms is unlikely to markedly increase remdesivir levels, as its metabolism is likely to be predominantly mediated by hydrolase activity. See IB for full discussion of clinical experience and risks.

There is the potential of the SARS-CoV-2 developing resistance to remdesivir, which could result in decreased efficacy. The clinical impact of the development of resistance is not clear at this time.

In vitro induction studies have demonstrated that a clinically relevant interaction with contraceptive steroids is considered to be of limited clinical significance. Therefore, the use of hormonal contraception with remdesivir is not recommended as the sole method for preventing pregnancy.

2.2.2.2. *Potential Benefits of Remdesivir*

A preliminary review of data from ACTT-1 occurring after 606 recoveries and 103 deaths (approximately 67% of the 1063 subjects enrolled) demonstrated that subjects that received remdesivir had a 31% faster time to recovery (11 vs 15 days, recovery rate ratio 1.312 (1.119, 1.541), p<0.001), and a decrease in mortality (8.0% vs 11.6%, p = 0.059). The DSMB asked that the sponsor be unblinded early given the public health implications of the results and implications for the design and conduct of ACTT-2. Based on the ACTT-1 results, remdesivir is now considered the standard of care for Covid-19 infected hospitalized patients. As a result, all subjects in ACTIV-1 IM will be given remdesivir as SoC, and the new therapeutic agents will be evaluated as add-on therapies to remdesivir.

This is a benefit to participation, though at some point, the new therapeutic agents evaluated under this master protocol may be available outside of clinical trials. In addition, society may benefit from their participation in this study resulting from insights gained about the efficacy of remdesivir combined with the new agents. Determining if additional clinical benefit can be realized by combining an antiviral with one of the new therapeutic agents being evaluated in ACTIV-1 IM for the treatment of COVID-19 may benefit society during this global COVID-19 pandemic.

2.2.2.3. *Assessment of Potential Risks and Benefits of Remdesivir*

Remdesivir is generally a well-tolerated medication. There are liver toxicities that have been observed in prior studies. These have been self-limited and resolved after cessation of the medication. There is the potential for renal

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toxicities as observed in pre-clinical data. By excluding those with elevated liver transaminases and decreased kidney function (eGFR <30 mL/min or requires hemodialysis or hemofiltration), and appropriate monitoring during the study, we can minimize the risk to participants. While there may not be benefits for an individual participant, there may be benefits to society if a safe, efficacious therapeutic agent can be identified during this global COVID-19 pandemic. The potential risks therefore are thought to be acceptable given the potential benefits.

2.2.3. *Therapeutic Agents*

For each of the therapeutic agents under investigation, findings from the preclinical and clinical studies are briefly described in the agent-specific appendices, including a summary of the findings described in the Investigator Brochures (IBs). The potential risks and benefits of the therapeutic agents are also summarized in the appendices.

3. OBJECTIVES AND ENDPOINTS

The overall objective of the study is to evaluate the clinical efficacy and safety of different investigational therapeutic agents relative to the control arm among hospitalized adults who have COVID-19.

Table 3-1. Trial objectives and measured endpoints

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
To evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in adults hospitalized with COVID-19 with respect to time to recovery by Day 29.	Day of recovery is defined as the first day on which the participant satisfies one of the following three categories from the ordinal scale: • Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical in-patient care; • Not hospitalized, limitation on activities and/or requiring home oxygen; • Not hospitalized, no limitations on activities. Recovery is evaluated up until Day 29.
Key Secondary	
• To evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in adults hospitalized with COVID-19 according to: • Clinical status (8-point ordinal scale) assessed on Day 15 and Day 29 for the previous day	1. Death; 2. Hospitalized, on invasive mechanical ventilation or ECMO; 3. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4. Hospitalized, requiring supplemental oxygen; 5. Hospitalized, not requiring supplemental oxygen – requiring ongoing in-patient medical care (COVID-19 related or otherwise); 6. Hospitalized, not requiring supplemental oxygen – no longer requires ongoing in-patient medical care (i.e., in hospital for social reasons, infection control, etc.); 7. Not hospitalized, limitation on activities and/or requiring home oxygen; 8. Not hospitalized, no limitations on activities.
• Mortality ○ 14-day mortality	• Date and cause of death (if applicable)

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OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
o 28-day mortality	
Additional Secondary	

To evaluate the clinical efficacy of different investigational therapeutics relative to the control arm as assessed by:
• **Clinical Severity**
  o Ordinal scale:
    ▪ Time to an improvement of one category and two categories from Day 1 (baseline) using an 8-point ordinal scale.
    ▪ Subject clinical status using 8-point ordinal scale at Days 3, 5, 8, 11, 15, 22, and 29.
    ▪ Mean change in the 8-point ordinal scale from Day 1 to Days 3, 5, 8, 11, 15, 22, and 29.
    ▪ Total severity score (TSS): 8-point ordinal scale summarized as a daily score (for days collected) averaged over time from Day 1 through Day 29
	• Clinical outcome assessed using ordinal scale daily while hospitalized and on Days 15, 22, and 29.

o Oxygenation:
    ▪ Oxygenation use up to Day 29.
    ▪ Incidence and duration of new oxygen use during the study.
	• Days alive and free of supplemental oxygen (if applicable) up to Day 29

o Non-invasive ventilation/high flow oxygen:
    ▪ Non-invasive ventilation/high flow oxygen use up to Day 29.
    ▪ Incidence and duration of new non-invasive ventilation or high flow oxygen use during the study.
	• Days alive and free of non-invasive ventilation/high flow oxygen (if applicable) up to Day 29

o Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO):
    ▪ Ventilator / ECMO use up to Day 29.
    ▪ Incidence and duration of new mechanical ventilation or ECMO use during the study.
	• Days alive and free of invasive mechanical ventilation/ECMO (if applicable) up to Day 29

• **Hospitalization** o Duration of hospitalization (days).	• Days alive and out of hospitalization up to Day 29
To evaluate clinical Status at Day 60	• 8-point Ordinal Scale
To evaluate the safety of different investigational therapeutics relative to the control arm as assessed by: • Cumulative incidence of SAEs through Day 29. • Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29. • Discontinuation or temporary suspension of study product administrations (for any reason)	• SAEs • Grade 3 and 4 AEs • WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, direct bilirubin, ALP, ALT, AST, CPK-MB, PT/INR, d-dimer,

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OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• Changes in white blood cell (WBC) count with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT reported as INR), d-dimer, and C-reactive protein (CRP) over time (analysis of lab values in addition to AEs noted above).	troponin, serum ferritin, and CRP on Day 1; Days 3, 5, 8, and 11 (while hospitalized); and Days 15 and 29 (if attends in-person visit or still hospitalized).
To evaluate the impact of different investigational therapeutics relative to the control arm of extrapulmonary manifestations of COVID-19.	Incidence of individual and "any" specified manifestations at Day 29.
Exploratory	
o National Early Warning Score (NEWS): ▪ Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first. ▪ Change from Day 1 to Days 3, 5, 8, 11, 15, and 29 in NEWS.	NEWS assessed daily while hospitalized and on Days 15 and 29, if feasible.
Collect blood samples for future research.	Blood draws on Days 1, 3, 8, 15, and 29.

4. STUDY DESIGN

4.1. Overall Design

ACTIV-1 IM is a master protocol designed to evaluate multiple therapeutic agents for the treatment of moderately or severely ill hospitalized patients infected with COVID-19. Participants will be assessed daily while hospitalized. If the participants are discharged from the hospital, they will have a study visit at Days 8, 11, 15, 22, and 29. For discharged participants, it is preferred that the Day 8, 11, 15, and 29 visits are in person to obtain safety laboratory tests(Day 29) and blood (serum and plasma) samples for secondary research as well as clinical outcome data. However, infection control or other restrictions may limit the ability of the participant to return to the clinic. In this case, these visits may be conducted by phone, and only clinical data will be obtained. The Day 22 visit does not have laboratory tests or collection of samples and is conducted by phone. The Day 60 assessment will be conducted by phone. The primary outcome is time to recovery by Day 29 (see **Table 3-1** for definition of recovery based on the 8-point ordinal scale). Key secondary outcomes include treatment-related improvements in the 8-point ordinal scale at Day 15, evaluation of safety, and 14-day and 28-day mortality.

4.2. Scientific Rationale for Study Design

ACTIV-1 IM utilizes a master protocol to evaluate multiple therapeutic agents for the treatment of COVID-19 infection in hospitalized patients. Approximately 400 agents were identified and screened for clinical readiness by a panel of experts, and 170 agents were selected for further evaluation based on mechanism of action and need for further clinical testing (i.e., not previously studied or plan for study in other trials or trial networks). From this triaging exercise, three agents were initially selected for study in the ACTIV-1 IM master protocol. All three agents are immune modulators with substantial clinical experience available. Details about the initial set of selected agents are provided elsewhere (see Sections 2 and 4 and Appendices 1-3); additional agents may be entered into the ACTIV-1 IM master protocol after the study begins, depending on availability and network capacity. In that case, agent-specific information will be appended to the protocol for any new agents entering the study, and the randomization algorithm will be adjusted accordingly.

ACTIV-1 IM builds upon findings and the model used for ACTT-1 and -2. Including multiple therapeutic agents under a single protocol avoids duplication of effort in terms of infrastructure, trial governance, information systems

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(EDC, web-based randomization, etc.) and other aspects of study management. Implementation of the master protocol facilitates discontinuation of less promising agents and addition of possibly newly emergent agents that become available after the study begins, without stopping and starting the study itself for extended pauses.

All test agents are evaluated as add-on therapies to the local SoC at each clinic. The master protocol design allows for the efficacy and safety of each agent to be determined based on comparisons with a pooled control group, consisting of patients receiving SoC plus placebo. Sharing control patients across all test agents substantially reduces the sample size requirements for the study.

4.3. Justification for Dose

4.3.1. *Justification for Dose of Remdesivir*

The dose of remdesivir used in this study will be the same dose that was used in the ACTT-1 and ACTT-2 trials.

4.3.2. *Justification for Dose of Investigational Agents*

The dose of each investigational agent is provided in the agent-specific appendices to this master protocol.

5. STUDY POPULATION

Male and non-pregnant female adults ≥18 years of age or older with COVID-19 and who meet all eligibility criteria will be enrolled at up to approximately 60 clinical trial sites globally. The target population should reflect the community at large. The estimated time from screening (Day -1 or Day 1) to end of study for an individual participant is approximately 60 days.

Subject Inclusion and Exclusion Criteria must be confirmed by any clinician named on the delegation log. If there is any uncertainty, the PI should make the decision on whether a potential participant is eligible for study enrollment. There is no exclusion for receipt of SARS-CoV-2 vaccine (experimental or licensed).

Following are the inclusion and exclusion criteria for the master protocol population. These criteria apply to all patients enrolled, regardless of therapeutic agent to be assigned for treatment. Any agent-specific exclusion criteria that are required will be applied during recruitment in addition to these common criteria and are described in the appendices corresponding to each agent under study.

5.1. Inclusion Criteria

1. Admitted to a hospital or awaiting admission in the ED with symptoms suggestive of COVID-19.
2. Subject (or legally authorized representative) provides informed consent prior to initiation of any study procedures.
3. Subject (or legally authorized representative) understands and agrees to comply with planned study procedures.
4. Male or non-pregnant female adults ≥18 years of age at time of enrollment.
5. Has laboratory-confirmed (within 14 days prior to enrollment) SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen.
6. Ongoing illness of any duration, and at least one of the following:
    - Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
    - Blood oxygen saturation (SpO_2) ≤94% on room air, OR
    - Requiring supplemental oxygen, OR
    - Requiring mechanical ventilation or ECMO.
7. Women of childbearing potential must agree to either abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through Day 60.
8. Agrees to not participate in another intervention trial for the treatment of COVID-19 through Day 60.

5.2. Exclusion Criteria at Screening

1. ALT or AST >5 times the upper limit of normal.

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2. Estimated glomerular filtration rate (eGFR) <30 mL/min (including patients receiving hemodialysis or hemofiltration).
3. Neutropenia (absolute neutrophil count <1000 cells/μL) (<1.0 x 10^3/μL or <1.0 GI/L).
4. Lymphopenia (absolute lymphocyte count <200 cells/μL) (<0.20 x 10^3/μL or <0.20 GI/L)
5. Pregnancy or breast feeding.
6. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours.
7. Known Allergy to any study medication.
8. Received cytotoxic or biologic treatments (such as anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], IL-17, or T-cell or B-cell targeted therapies (e.g., rituximab), tyrosine kinase inhibitors including baricitinib, TNF inhibitors, or interferon within 4 weeks or 5 half-lives prior to screening. Steroid dependency defined as need for prednisone at a dose >10 mg (or equivalent) for >1 month within 2 weeks of screening is exclusionary. Note 1: Dexamethasone (at a dose of 6 mg per day for up to 10 days) is permitted for the treatment of COVID-19 in patients who are already mechanically ventilated and in patients who require supplemental oxygen at screening, but who are not mechanically ventilated in accordance with national guidelines. Note 2: Infusion of convalescent plasma is also allowed.
9. Based on medical history and concomitant therapies that would suggest infection, have suspected clinical diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening required).
10. Based on medical history and concomitant therapies that would suggest infection, suspected serious, active bacterial, fungal, viral (including, but not limited to, active HBV, HCV, or HIV/AIDS).
11. Have received any live vaccine (that is, live attenuated) within 3 months before screening, or intend to receive a live vaccine (or live attenuated) during the study. Note: Use of non-live (inactivated) vaccinations is allowed for all participants.
12. Severe hepatic impairment (defined as liver cirrhosis Child stage C).
13. Current severe heart failure (New York Heart Association [NYHA] III-IV).
14. In the Investigator's judgment, the patient has any advanced organ dysfunction that would not make participation appropriate.

5.3.   Exclusion of Specific Populations

Children and adolescents will not be included in this trial. The SoC, remdesivir, has only been used in a small number of pediatric patients. Initial information about the epidemiology of COVID-19 indicates that the overwhelming burden of severe disease occurs among older adults, especially those with comorbidities. Given significant gaps in knowledge in this population, and a low incidence of severe morbidity/ mortality in children, and that none of the agents initially selected for study or likely to be selected in the future have had or will have demonstrated efficacy in COVID-19, this research is not known to have the prospect of direct benefit to individual child participants, and the risk/benefits do not warrant inclusion of this population into this trial at this time.

In nonclinical reproductive toxicity studies, the SoC, remdesivir, demonstrated no adverse effect on embryo-fetal development when administered to pregnant animals. Embryonic toxicity was seen when remdesivir was initiated in female animals prior to mating and conception, but only at a systemically toxic dose. Remdesivir has not been studied in pregnant women. Information on nonclinical reproductive toxicity studies for the therapeutic agents selected for study is provided in the agent-specific appendices.

In animal studies, remdesivir metabolites have been detected in the nursing pups of mothers given remdesivir. It is not known whether remdesivir is secreted in human milk. Because the effects of the SoC, remdesivir, on the breastfeeding infant is not known, and because the effects of one or more therapeutic agents selected for evaluation in this study may also be unknown, women who are breast feeding are not be eligible for the trial.

5.4.   Inclusion of Vulnerable Subjects

Certain human subjects are categorized as vulnerable populations and require special treatment with respect to safeguards of their well-being. For this clinical trial, examples include cognitively impaired or mentally disabled persons and intubated individuals who are sedated. When it is determined that a potential research subject is cognitively impaired, federal and institutional regulations permit researchers to obtain consent from a legally

authorized representative (LAR). The study team will obtain consent from these vulnerable participants using an IRB-approved protocol- specific process for consent using a LAR.

For participants for whom a LAR gave consent, during the course of the study, if the subject regains the capacity to consent, informed consent must be obtained from the subject and the subject offered the ability to leave the study if desired.

5.5. Lifestyle Considerations

During this study, participants are asked to:
- Avoid getting pregnant during the study from Day 1 through Day 60.
- Agree not to participate in another interventional trial for the treatment of COVID-19 or SARS-CoV-2 through Day 60. This includes interventional trials that evaluate treatment of SARS-CoV-2 infection as well as the disease pathogenesis (e.g., treatment trials for the COVID-19-related thrombo-occlusive disease, respiratory complications, and dysregulated immune response to the virus). Co-enrollment for natural history studies of COVID-19 or SARS-CoV-2 infection is permitted; however, participation in both ACTIV-1 IM and natural history studies can only occur if the recommended blood collection volumes are not exceeded.

5.6. Screen Failures

Following consent, after the screening evaluations have been completed, the investigator or designee is to review the inclusion/exclusion criteria and determine the participant's eligibility for the study. If there is any uncertainty, the PI should make the decision on whether a potential participant is eligible for study enrollment.

Only basic demographic information and the reason(s) for ineligibility will be collected on screen failures. Prospective participants who are found to be ineligible will be told the reason(s) for ineligibility.

Individuals who do not meet the criteria for participation in this study (screen failure) because of an abnormal laboratory finding may be rescreened once.

5.7. Strategies for Recruitment and Retention

5.7.1. *Recruitment*

It is anticipated that patients with COVID-19 will present to participating hospitals, and that no external recruitment efforts towards potential participants are needed. Recruitment efforts may also include dissemination of information about this trial to other medical professionals / hospitals.

The hospitals that constitute the ACTIV-1 IM network span the United States and South America. As the pandemic migrates to different locations during the coming months, we anticipate being able to effectively follow the migration and focus recruitment efforts at hot spots through our network hospitals in different locales.

The IRB will approve the recruitment process and all materials provided prior to any recruitment to prospective participants directly.

Screening will begin with a brief discussion with study staff. Some will be excluded based on demographic data and medical history (i.e., pregnant, <18 years of age, renal failure, etc.). Information about the study will be presented to potential participants (or legally authorized representative) and questions will be asked to determine potential eligibility. Screening procedures can begin only after informed consent is obtained.

5.7.2. *Retention*

Retention of participants in this trial is very important for determining the primary endpoint of time to recovery by Day 29. As such, after hospital discharge, participants will be reminded of subsequent study visits and every effort will be made to accommodate the participant's schedule to facilitate follow-up within the specified visit window.

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Additionally, there are many circumstances that influence the ability to obtain outcome information after discharge. Follow-up visits may be conducted by phone if in-person visits are not feasible.

5.8.   Compensation Plan for Subjects

Compensation, if any, will be determined locally and in accordance with local IRB requirements, and subject to local IRB approval.

5.9.   Costs

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.

6.   STUDY PRODUCT

6.1.   Study Product(s) and Administration

Participants will first be randomized to one of the agents currently active in the study, and then to either the agent or its matching placebo. The dosing regimen and administration of each agent and matching placebo are described in the agent-specific appendices.

If there are supply limitations on any product, the arms containing that product will be temporarily closed to enrollment and the corresponding placebo is not needed. Currently, the trial team anticipates no difficulty in obtaining remdesivir for the SoC for this study; however, if remdesivir supply should become limited for the trial, the treating physician should enroll the patient without remdesivir using local SoC.

6.1.1.   *Study Product Description*

The SoC, remdesivir, is a single diastereomer monophosphoramidate prodrug designed for the intracellular delivery of a modified adenine nucleoside analog GS-441524. In addition to the active ingredient, the lyophilized formulation of remdesivir contains the following inactive ingredients: water for injection, SBECD, and hydrochloric acid and/or sodium hydroxide.

Descriptions of the therapeutic agents selected for evaluation in the study are provided in the agent-specific appendices.

6.1.2.   *Dosing and Administration*

For the SoC, remdesivir all participants will receive remdesivir as a 200 mg intravenous (IV) loading dose on Day 1, followed by a 100 mg once-daily IV maintenance dose for 5 days during hospitalization for patients not requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO). If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days. For patients requiring invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is 10 days.

Dosing of the SoC and investigational agents should not need to occur at the same time. In fact, no physical biochemical compatibility studies have been conducted to evaluate the co-administration of the remdesivir with other investigational agents. Therefore, it should not be infused concomitantly in the same intravenous line with other agents; therefore, if infused together, separate lines should be used to alleviate confounding of attribution of possible infusion reactions or hypersensitivity events.

Any dose that is delayed may be given later that calendar day. Any dose that is missed (not given that calendar day) is not made up. The treatment course continues as described above even if the participant becomes PCR negative.

Dosing and duration of therapy of the therapeutic agents selected for study are described in the agent-specific appendices.

6.1.3. *Dose Escalation*

Not Applicable.

6.1.4. *Dose Modifications*

SoC (remdesivir):
If the eGFR decreases to an eGFR <25 mL/min, the remdesivir infusion should not be given on that day. The infusion may be resumed on the next day if the eGFR returns to ≥30 mL/min. If the participant's renal function worsens to the point that they require hemodialysis or hemofiltration, SoC will be discontinued.

If the ALT and/or AST increases to >5 times upper limits of normal, the infusion should be held and not be restarted until the ALT and AST ≤5 times upper limits of normal.

If any of the therapeutic agents selected for study require dose modifications based on biomarkers or safety signals, these adjustments are described in the agent-specific appendices

6.1.5. *Overdosage*

There is no known antidote for the SoC, remdesivir. In the case of overdose, the participant should receive supportive therapy based on the participant´s signs and symptoms. Availability of antidotes for study agents is discussed in the agent-specific appendices.

6.1.6. *Preparation/Handling/Storage/Accountability*

6.1.6.1. *Acquisition and Accountability*

Investigational products (IP) will be shipped to the site either directly from participating companies, from the Sponsor, or from other regional or local drug repositories. SoC (remdesivir) will be provided to the sponsor's designated distributor through an understanding with the manufacturer, and the sponsor's distributor will provide the SoC agent to the sites. All other supplies should be provided by the site. Multiple lots of each IP may be supplied.

Study products received at the sites will be open label and not kit specific, unless specified in the protocol-specific Manual of Procedures (MOP) or pharmacy manual. For IV infusion agents, drug preparation will be performed by the participating site's unblinded research pharmacist on the same day of administration to the participant. For oral agents, the investigational agent and the placebo will be shipped to the site ready to administer. The participating site's unblinded research pharmacist will provide either the investigational agent or the placebo pill to the treating physician at the time of assignment to the sub-study and randomization to the appropriate arm. See the MOP Appendices for detailed information on the preparation, labeling, storage, and administration of investigational products.

Accountability:

The site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The site PI may delegate to the participating site's research pharmacist responsibility for study product accountability. The participating site's research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product(s). Time of study drug administration to the participant will be recorded on the appropriate data collection form (CRF). All study product(s), whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The Sponsor's monitoring staff will verify the participating site's study product accountability records and dispensing logs per the site monitoring plan. Refer to the protocol-specific MOP for details on storing study medications.

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Destruction:

After the study treatment period has ended or as appropriate over the course of the study after study product accountability has been performed, used active and placebo product can be destroyed on-site following applicable site procedures with a second staff member observing and verifying the destruction.

Unused product at the end of the study for any of the agents selected for study should be saved until instructed by sponsor.

6.1.6.2. *Formulation, Appearance, Packaging, and Labeling*

<u>SoC (remdesivir):</u>

The lyophilized formulation of remdesivir is a preservative-free, white to off-white or yellow, lyophilized solid containing 150 mg or 100 mg of remdesivir to be reconstituted with 29 mL or 19 mL (respectively) of sterile water for injection respectively and diluted into IV infusion fluids prior to IV infusion. Following reconstitution, each vial contains a 5 mg/mL remdesivir concentrated solution with sufficient volume to allow withdrawal of 30 mL (150 mg of remdesivir) or 20 mL (100 mg of remdesivir).

It is supplied as a sterile product in a single-use, Type 1 clear glass vial. In addition to the active ingredient, the lyophilized formulation of remdesivir contains the following inactive ingredients: water for injection, SBECD, hydrochloric acid, and/or sodium hydroxide. For more information, refer to the MOP.

Remdesivir will be labeled according to manufacturer specifications and include the statement "Caution: New Drug Limited by Federal (USA) Law to Investigational Use."

Interventional Agents:

Formulation, appearance, packaging, and labeling for each of the agents selected for study are described in the agent-specific appendices.

6.1.6.3. *Product Storage and Stability*

<u>SoC (remdesivir):</u>

Ambient vials of the lyophilized formulation of remdesivir should be stored below 30°C. The lyophilized formulation needs to be reconstituted and then diluted into IV infusion fluids before use. After reconstitution, the total storage time before completion of administration (including any time before or after dilution) should not exceed 4 hours at room temperature (20°C to 25°C) or 24 hours at refrigerated temperature (2°C to 8°C). See MOP for additional information.

<u>**Interventional Agents**</u>:

Product storage and stability for each of the agents selected for study are described in the agent-specific appendices.

6.1.6.4. *Preparation*

Refer to the protocol-specific MOP for details about preparation.

<u>SoC (remdesivir):</u>

Remdesivir does not meet the criteria for a hazardous compound as defined by NISOH and ASHP hazard classification systems. The SoC may be prepared in a clean room but do not need to be prepared or handled in a fume hood.

<u>**Interventional Agents**</u>:

Preparation of each of the agents selected for study are described in the agent-specific appendices.

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Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures as indicated in the IB.

6.2. Measures to Minimize Bias: Randomization and Blinding

Randomization will be stratified by:
- Geographic Region
- Severity of illness at enrollment (by ordinal scale)
  - Severe disease:
    - Hospitalized, on invasive mechanical ventilation or ECMO, or
    - Hospitalized, on non-invasive ventilation or high flow oxygen devices.
  - Moderate disease:
    - Hospitalized, requiring supplemental oxygen, or
    - Hospitalized, not requiring supplemental oxygen.

Randomization will proceed in two steps, with stratification at each step. At the first step, each participant will be assigned with equal probability to one of the agents available at the time the patient is enrolled and for which the patient is eligible to receive, after applying any agent-specific safety exclusions. At the second step, each participant will be assigned to either the test agent or its matching placebo in an n:1 ratio, where n = the number of agents currently active in the master protocol and for which the patient is eligible to receive. With SoC and three agents active simultaneously, and the participant meets the criteria to receive all three agents, this procedure results in the randomization ratio of 1:1:1:1. If 3 agents are available, but a patient is only eligible to receive 2 of them, the allocation ratio at the first step will be 1:1, and at the second step will be 2:1 (agent vs placebo).Inclusion of a matching placebo for each agent enables masking of study participants and clinical personnel to treatment assignment at the second stage. Data from patients receiving SoC plus placebo will be pooled across agents for comparative analyses and hypothesis testing. Comparative analyses of a particular agent will include the subset of pooled placebo patients who enrolled concurrently with the new agent. That is, patients enrolled to control arm prior to a new agent entering the trial will not be included in comparative analyses of that newly added investigation agent.

Additional details of the randomization procedure will be described in the MOP.

6.3. Study Intervention Compliance

Each dose of study product will be administered by a member of the clinical research team who is qualified and licensed to administer the study product OR trained and qualified hospital personnel under the direction of the site investigator. Administration, including date and time, will be entered into the case report form (CRF).

6.4. Concomitant Therapy

6.4.1. *Permitted Concomitant Therapy and Procedures*

Therapy prior to enrollment with any other experimental treatment or off-label use of marketed medications that are intended as specific treatment for COVID-19 or the SARS-CoV-2 infection (i.e., post-exposure prophylaxis [PEP]) are permitted (except as detailed in the inclusion/exclusion criteria) but must be discontinued on enrollment. Another example: hydroxychloroquine is allowed prior to screening but must be discontinued. There is no waiting period between discontinuation of these treatments and administration of study products. However, these prior treatments and their end date should be documented on the Concomitant Medication (CCM) form.

Participants who are taking another immunosuppressive drugs for other medical conditions except as noted below as prohibited medications, may continue with the treatment. Agent specific appendices should be referenced for further prohibitions on concomitant therapies.

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Local standard of care per written policies or guidelines for treatment for supportive care of COVID-19 or SARS-CoV-2 infection (i.e., not just an individual clinician decision) are permitted. This includes the evolving SoC with anticoagulant therapies. Dexamethasone (at a dose of 6 mg per day for up to 10 days) is permitted for the treatment of COVID-19 in patients who are mechanically ventilated and in patients who require supplemental oxygen but who are not mechanically ventilated in accordance with national guidelines. Infusion of convalescent plasma is also allowed if it is standard of care at the treating site.

VTE prophylaxis is recommended for all patients unless there is a major contraindication such as active bleeding events or history of heparin-induced thrombosis.

6.4.2.   *Prohibited Concomitant Therapy*

A participant cannot participate in another clinical trial for the treatment of COVID-19 until after Day 60 (see exclusion criteria).

If there are NO written policies or guidelines for local standard of care, concomitant use of any other experimental treatment or off-label use of marketed medications intended as specific treatment for COVID-19 or SARS-CoV-2 infection are prohibited. This includes medications that target the host immune response.

Any biologic therapies are prohibited. This includes, but is not limited to, TNF inhibitor, interleukin-1[IL-1], IL-6 [tocilizumab or sarilumab], IL-17, or T-cell or B-cell targeted therapies, JAK inhibitor(s), interferon, or plasma or immunoglobulin (IgG) for COVID-19.

Dexamethasone, at a dose of 6 mg per day for up to 10 days, or other steroids in equivalent doses are permitted for the treatment of COVID-19 in patients who are mechanically ventilated and in patients who require supplemental oxygen but who are not mechanically ventilated in accordance with national guidelines. The use of corticosteroids at doses >10 mg/day outside of this indication is prohibited.

The use of chloroquine or hydroxychloroquine is prohibited.

The use of any biologics will be assessed for 4 weeks prior to screening to determine eligibility. Concomitant medications will be assessed only from 7 days prior to enrollment to Day 15 or upon discharge, whichever comes first. Report all prescription medications taken during this time period. Record medications once regardless of the number of times it was given during the time period. For example, vasopressors or insulin should be recorded when first started (the start date) and end date if ended before Day 15 or discharge. Record all antipyretics and other medications given for symptomatic care, if they are administered while an inpatient. However, record these medications only once, even if given multiple times, as needed during hospital course. Do not report medications that the participant did not actually receive during study (e.g., prn medications that were never given).

Any medication or vaccine (including over the counter, prescription medicines, vitamins, herbal supplements, and/or cannabis or other specific categories of interest) that the participant is receiving at the time of screening, has received in the 30 days prior to screening, or is anticipated to receive during the study must be recorded along with:
   - Reason for use
   - Dates of administration including start and end dates
   - Dosage information including dose and frequency

The Sponsor's Medical Safety Physician or equivalent representative should be contacted if there are any questions regarding concomitant or prior therapy.

Due to potential interactions the additional medications maybe disallowed for specific agents on the trial as detailed in the sub-study appendices. If there is a medical need to utilize any of the medications disallowed, then the Investigator should discuss appropriate steps with the Sponsor.

6.4.3.   *Rescue Medicine*

Not Applicable.

6.4.4. *Non-Research Standard of Care*

Not Applicable.

7. STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Halting Criteria and Discontinuation of Study Intervention

7.1.1. *Individual Study Product Halting*

Study product administration for any given participant may be stopped for SAEs, clinically significant adverse events, severe laboratory abnormalities, or any other medical conditions that indicate to the Investigator that continued dosing is not in the best interest of the patient.

In addition, a participant in this clinical study may discontinue study drug at their request for any reason. Every effort should be made to encourage participants to remain in the study for the duration of their planned outcome assessments. Participants should be educated on the continued scientific importance of their data, even if they discontinue study drug.

Unless the participant withdraws consent, those who discontinue study drug early will remain in the study. The reason for participant discontinuation of study drug should be documented in the case report form.

See Section 6.1.4. for information about dosing modifications due to laboratory abnormalities.

7.1.2. *Study Halting*

There will be close oversight by the protocol team and frequent DSMB reviews of the safety data. The DSMB may recommend halting one or more of the therapeutic agents due to safety, futility, or efficacy issues observed during the study, or they may recommend halting the study as a whole, if a safety issue or issue relating to the COVID-19 pandemic that negatively impacts study continuation arises.

A sub-study will be paused for new enrollment/study drug administration and will be reviewed by the DSMB if the following rule is met:

- After a sub-study has enrolled at least 10% of its planned study population, the proportion of study participants who die within 14 days of study drug administration or first dose administration in the same sub-study exceeds 24% (based on the 11.9% death rate in the ACTT-1 placebo arm; Beigel et al. 2020).

7.2. Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request, without any consequence. Participants should be listed as having withdrawn consent only when they no longer wish to participate in the study and no longer authorize the Investigators to make efforts to continue to obtain their outcome data.

Participants who withdraw from this study or are lost to follow-up after signing the informed consent form (ICF) and administration of the study product, will not be replaced. The reason for participant withdrawal from the study will be recorded on the appropriate CRF.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to appear for all follow-up assessments. In lost to follow-up cases, attempts to contact the participant should be made and these efforts should be documented in the participant's records.

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7.4.   Readmission

If a participant is discharged from the hospital and then readmitted prior to Day 14, they may be given the remainder of the study product (i.e., remdesivir for up to a total of 10 days). If the participant did not withdrawal his/her consent to participate in the study, there is no need to reconsent upon readmission to the study hospital. However, the site will need to inform them that since he/she was readmitted, study product administration will resume and confirm that they still agree to receive study product. If the participant is re-admitted with diminished mental capacity, the site should discuss continued study participation with a LAR.

The site should not complete the Discontinuation of Treatment form since the participant came back to the study hospital to be readmitted. For all data collection procedures required for those readmitted, please see the MOP.

8.   STUDY ASSESSMENTS AND PROCEDURES

8.1.   Screening and Efficacy Assessments

8.1.1.   *Screening Procedures*

Screening procedures may be done over one to two calendar days (from Day -1 to Day 1). However, in many cases all the screening assessments can be done in less than 24 hours. If that is the case, Day 1 pre-study product administration baseline assessments, specimen collection and the initial study product administration can occur on the same calendar day as the screening procedures.

After the informed consent, the following assessments are performed to determine eligibility and obtain baseline data:

- Confirm the positive SARS-CoV-2 test result (per inclusion criteria).

- Take a focused medical history, including the following information:
  - Day of onset of COVID-19 signs and symptoms.
  - History of vaccinations within 4 weeks before screening and planned vaccinations.
    - Exclusionary vaccine history includes:
      - Has received any live vaccine (that is, live attenuated) within 4 weeks before screening, or intend to receive a live vaccine (or live attenuated) during the study. Note: Use of non-live (inactivated) vaccinations is allowed for all participants.
  - History of chronic medical conditions including chronic oxygen requirement prior to onset of COVID-19. See conditions included in exclusion criteria (Section 5.2) and on the Medical History (CMX) data collection form.
    - Exclusionary medical history includes:
      - Has diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening required).
      - Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking investigational product.
  - History of medication allergies.
  - Medications and therapies for this current illness taken in the 7 days prior to Day 1 and history of any medication listed in the exclusion criteria.
    - Exclusionary medication use includes:
      - Received cytotoxic or biologic treatments (such as anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], or T-cell or B-cell targeted therapies (e.g., rituximab), tyrosine kinase inhibitors including baricitinib, or interferon within 4 weeks or 5 half-lives prior to screening.
      - Received TNF inhibitors within 4 weeks prior to screening.

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- o Currently receiving corticosteroids at high doses (i.e., prednisone >10 mg per day or equivalent) for >1 month within 2 weeks of screening. Dexamethasone (at a dose of 6 mg per day for up to 10 days) is permitted for the treatment of COVID-19 in patients who are mechanically ventilated and in patients who require supplemental oxygen but who are not mechanically ventilated in accordance with national guidelines.
  - Ask if they are participating in another interventional trial or plan to enroll in another clinical trial in the next 60 days.
- – Women of childbearing potential should be counseled to either practice abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through Day 60. Women should be confirmed to not be breastfeeding.
  - Note: If a woman is either postmenopausal (i.e., has had ≥12 months of spontaneous amenorrhea) or surgically sterile (i.e., has had a hysterectomy, bilateral ovariectomy (oophorectomy), or bilateral tubal ligation), she is not considered to be of childbearing potential.

- – Height and weight (height can be self-reported; weight can be self-reported if not feasible to assess).
- – Results of recent radiographic imaging (x-ray or CT scan).
- – SpO_2.
- – Blood for screening laboratory evaluations if not done as part of routine clinical care in the preceding 48 hours:
  - CBC with differential
    - Evaluate if neutropenic (absolute neutrophil count <1000 cells/μL) (<1.0 x 10^3/μL or <1.0 GI/L) and/or lymphopenic (absolute lymphocyte count <200 cells/μL) (<0.20 x 10^3/μL or <0.20 GI/L)
  - ALT and AST.
    - Assess if ALT or AST >5 times the upper limit of normal.
  - Creatinine (and calculate eGFR).
    - Determine if eGFR <30 mL/min or receiving hemodialysis or hemofiltration.
    - Any automated calculation by the clinical laboratory or published formula for this calculation is acceptable. The site should select a formula to be used for all participants enrolled at the site for the duration of the study.
- – Urine or serum pregnancy test (in women of childbearing potential).

- – Clinical screening laboratory evaluations will be performed locally by the site laboratory. The volume of venous blood to be collected is presented in **Table 8-2**.

- – A targeted physical examination will be performed at screening (Day -1 or Day 1) prior to initial study product administration on Day 1. No routine physical exam is needed for study visits after Day 1.

  - o Study staff at some sites are not allowed into the participants' rooms due to a limited supply of PPE and the need for strict respiratory isolation measures for COVID-19 patients. Because of limited access to participants, physical exams can be performed by any licensed provider at the study hospital even if they are not study staff listed on the 1572. The study team can extract information from the hospital chart or EMR.

The overall eligibility of the participant to participate in the study will be assessed once all screening values are available. The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team.

8.1.2. *Efficacy Assessments*

For all baseline assessments and follow-up visits, refer to the Schedule of Assessments (SOA) for procedure to be done, and details below for each assessment.

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Measures of clinical support, limitations and infection control

The participant's clinical status will be captured on each study day while hospitalized through Day 29. If a participant is discharged prior to Day 15, clinical status is collected on Day 8, Day 11, Day 15, and Day 29 if the participant returns for an in-person clinic visit or by phone if an in-person visit is not possible. Clinical status will also be captured on Day 22 during a phone visit. Clinical status is largely measured by the 8-point ordinal scale and the NEWS. Unlike the NEWS, the ordinal scale can also be evaluated over the phone if the discharged participant is unable to return for visits on Day 8, 11, 15, or 29 as well as on Day 22.

Except for on Day 1, when the ordinal scale and the components of NEWS are is captured at the time of randomization, a site should try to complete the ordinal scale and the components of NEWS at approximately the same time each day. Ideally, complete the ordinal scale concurrently with components of NEWS just prior to study product administration, as time permits. The following measures are recorded for the ordinal scale:
- Hospitalization.
- Oxygen requirement.
- Non-invasive mechanical ventilation (via mask) requirement.
- High flow oxygen requirement.
- Invasive mechanical ventilation (via endotracheal tube or tracheostomy tube) requirement.
- ECMO requirement.
- Ongoing medical in-patient care preventing hospital discharge (COVID-19 related or other medical conditions).
- Limitations of physical activity (self-assessed).
- Isolated for infection control purposes.

Ordinal Scale

The ordinal scale is the basis for the primary and key secondary clinical outcomes in the study, namely, time to recovery, improvement in disease severity, and mortality.

The scale used in this study is as follows (from worst to best):
- Death;
- Hospitalized, on invasive mechanical ventilation or ECMO;
- Hospitalized, on non-invasive ventilation or high flow oxygen devices;
- Hospitalized, requiring supplemental oxygen;
- Hospitalized, not requiring supplemental oxygen – requiring ongoing medical in-patient care (COVID-19 related or otherwise);
- Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical in-patient care;
  - This would include those kept in hospital for quarantine/infection control/social reasons, awaiting bed in rehabilitation facility or homecare, etc.
- Not hospitalized, limitation on activities and/or requiring home oxygen;
- Not hospitalized, no limitations on activities

To determine a participant's clinical status using the ordinal scale: On Day 1, report their clinical status at randomization. After Day 1, collect the ordinal scale daily while hospitalized from Day 2 through Day 29 by providing the worst clinical assessment for the previous day (i.e., midnight to midnight; 00:00 – 23:59 [24-hr clock]). For those who are discharged prior to Day 15, collect ordinal scale on follow-up Days 8, 11, 15, 22, and 29 by providing the worst clinical assessment for the previous day (i.e., midnight to midnight; 00:00 – 23:59 [24-hr clock]). For example, on study Day 3 when completing the form, the worst clinical outcome measure of Day 2 is captured with the worst being death followed by ECMO, mechanical ventilation, etc. The Day 2 measurement is assessed as occurring anytime in that 24-hour period (00:00 to 23:59). For more information about the data collected for the ordinal scale, see the MOP.

Extrapulmonary manifestations

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The presence of the extrapulmonary manifestation of disease during the course of hospitalization will be assessed and reported at discharge. Specifically, clinical organ failure defined by development of any one or more of the following clinical events (see Protocol Information Manual) for criteria for what constitutes each of these conditions):

a. Respiratory dysfunction:
  1. Respiratory failure defined as receipt of high flow nasal oxygen, noninvasive 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. Hematological 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.

Longer term follow-up

Information on vital and clinical status and occurrence and duration of rehospitalization will be captured by phone on Day 60.

8.1.3. *Exploratory Assessments*

Blood for serum and plasma (for secondary research)
- If the samples can be processed and but not sent to the repository, the samples may be stored locally.

National Early Warning Score (NEWS)
Vital signs and other clinical assessments are collected for the calculation of the NEWS, and include temperature, systolic blood pressure, heart rate, respiratory rate, O_2 saturation and level of consciousness. Vital signs collected per standard of care can be used. NEWS has demonstrated an ability to discriminate subjects at risk of poor outcomes. (Smith, 2016). This score is based on 7 clinical parameters (see **Table 8-1**). The NEWS is being used as

an exploratory efficacy measure. The components of NEWS should be evaluated daily while hospitalized. It can be performed concurrently with the Ordinal Scale. This should be evaluated at a consistent time for each study day and prior to administration of study product. The 7 parameters can be obtained from the hospital chart or electronic medical record (EMR) using the last measurement prior to the time of assessment (including parameters collected prior to the time of consent) and a numeric score is given for each parameter (e.g., a RR of 9 breaths per minute is one point, oxygen saturation of 92% is two points). This is recorded for the day obtained (i.e., on Day 3, the vital signs and other parameters from Day 3 will be used to obtain NEWS for Day 3). ECMO and mechanically ventilated participants should be assigned a score of 3 for RR (RR ≤8 breaths per minute) regardless of the ventilator setting. Participants on ECMO should get a score of 3 for heart rate since they are on cardiopulmonary bypass.

Table 8-1. National Early Warning Score (NEWS)

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate (breaths per minute)	≤8 [a]		9 – 11	12 – 20		21 – 24	≥25
Oxygen Saturation (%)	≤91	92 – 93	94 – 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature (ºC)	≤35.0		35.1 – 36.0	36.1 – 38.0	38.1 – 39.0	≥39.1	
Systolic Blood Pressure (mm Hg)	≤90	91 – 100	101 – 110	111 – 219			≥220
Heart Rate (beats per minute)	≤40 [b]		41 – 50	51 – 90	91 – 110	111 – 130	≥131
Level of Consciousness				A			V, P, U

Level of consciousness = alert (A), and non-alert and arousable only to voice (V) or pain (P), and unresponsive (U).
[a] *If the participant is on ECMO or invasive mechanical ventilation, they will be given a score of 3 (≤8 breaths per minute) for respiratory rate regardless of ventilator setting.*
[b] *Participants on ECMO will also receive a score of 3 (≤40 beats per minute) for heart rate.*

8.2. Safety and Other Assessments

Study procedures are specified in the SOA. A study physician licensed to make medical diagnoses and listed on the 1572 will be responsible for all trial-related medical decisions.

Clinical laboratory evaluations:

- Fasting is not required before collection of laboratory samples.
- Blood will be collected at the time points indicated in the SOA.
  - Clinical safety laboratory tests include WBC, differential, Hgb, PLT, creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, ALP, PT/INR, d-dimer, CPK-MB, cardiac troponin, serum

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ferritin, and C-reactive protein. Sites that do not have access to a test for PT will be allowed to report an international normalized ratio (INR).

- Day 1 clinical laboratory evaluations are drawn prior to initial study product administration as a baseline and results do not need to be reviewed to determine if initial study product administration should be given. Note that Day 1 PK assessments need to be drawn after 1st dose of study drug, so will need to be drawn separately from Baseline lab assessments.

- Clinical laboratory testing will be performed at each clinical trial site in real time. PK samples will be analyzed at a central facility at a future date.

Table 8-2. Venipuncture Volumes[1]

	Screen	Baseline						
Day +/- Window	−1 to 1	1 ± 1	3 ± 1	5 ±1	8 ± 1	11 ± 1	15 ± 2	29 ± 3
Safety hematology, chemistry and liver tests	X 10mL[2]	X 10mL[2]	X 10mL[2]	X 10mL[2]	X 10mL[2]	X 10mL[2]	X[3] 10mL[2]	X[3] 10mL[2]
Blood for Serum and Plasma		X 18mL	X 18mL		X 18mL		X 18mL	X 18mL
PK Assessments [6]		X[4] 4mL			X[5] 4mL			X[5] 4mL
Total daily volume	10mL	32mL	28mL	10mL	32mL	10mL	28mL	32mL
Total all study days [7]								~182 mL[8]

PK = pharmacokinetic

1. See SOA in Section 1.1.8 for specific tests to be performed.

2. Total volume calculated assumes no further routine clinical laboratory done within 48 hours of screening that can be used for determining eligibility and no routine clinical laboratory tests were done within the window for that visit (±24 hours of Day 1, 3, 5, 8 and 11 and ±48 hours for Day 15 and ±72 hours for Day 29 if still hospitalized).

3. Safety laboratory tests will be collected on Days 8, 11, 15, and 29 if the participant is still hospitalized at these time points or if they return for an in-person outpatient visit and the site has the capacity to collect blood in the outpatient setting.

4. Single blood draw, separate from Day 1 Baseline labs, 3 hours post-dose (post-start of infusion or post-ingestion of oral drug), +/- 30 min. In patients that received an infusion, sample should be collected from the arm contralateral to that used for IV infusion.

5. a) If hospital discharge occurs prior to visit, then the PK blood sample should be collected at discharge; and, b) this sample may be drawn at the time of routine phlebotomy.

6. See specific footnotes for each blood draw in this row. Participants on ECMO may also have up to 4 additional PK samples (16 mL) taken from the ECMO circuit at each PK time point.

7. Total blood volumes may be lower if the participant is discharged early.

8. Participants on ECMO may provide a higher total volume over the course of the study (see footnote 6).

Additional PK blood collections from participants on ECMO:

ECMO has been repeatedly shown to substantially and unpredictably alter drug disposition (Wildschut et al. 2010; Watt et al. 2011). For ACTIV-1 IM participants supported with ECMO, the PK sampling scheme depicted in **Table 8-2** will be augmented with paired samples collected from the participant and the ECMO circuit at the same time.

If possible, and as clinically indicated, the following sections of the ECMO circuit would be sampled:

- Pre-oxygenator / pre-dialysis membrane or hemofilter
- Post-oxygenator / post-dialysis membrane or hemofilter
- Pre-oxygenator / post-dialysis membrane or hemofilter
- Post-oxygenator / pre-dialysis membrane or hemofilter

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8.2.1. *Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings*

If a physiologic parameter (e.g., vital signs, or laboratory value) is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition or was an error. A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

8.2.2. *Unscheduled Visits*

If clinical considerations require the participant to be contacted or seen prior to the next schedule assessment to assure the participant's well-being, it is permissible in this protocol. However, no research data is collected at this visit.

8.3.   Adverse Events and Serious Adverse Events

8.3.1. *Definition of Adverse Event (AE)*

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. If multiple abnormalities are part of the same clinical syndrome, they can be reported together as one AE under a unifying clinical diagnosis.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing (baseline) medical condition increases above baseline to severity grade 3 or 4, it should be recorded as an AE.

Given the nature of severity of the underlying illness, participants will have many symptoms and abnormalities in vital signs and laboratory values. All Grade 3 and 4 AEs will be reported in this trial. In addition, the following AEs will be reported:
- Any Grade 2 suspected drug-related hypersensitivity reactions associated with study product administration will be reported as an AE.
- Any infection (other than COVID-19) at any time during the study.
- Any AEs leading to dose modification
- Any AEs leading to discontinuation from the study.

Intermittent abnormal laboratory values or vital sign measurements common in the severely ill populations (such as electrolyte abnormalities, low blood pressure, hyperglycemia, etc.) that are part of the same clinical diagnosis (e.g., uncontrolled diabetic) can be recorded once with the worst grade for each adverse event (grade 3 and 4 only for this trial), with the start and stops dates of the intermittent syndrome. If there is clear resolution of the event, and then recurrence, it should be treated as a separate adverse event. Resolution is defined as return to baseline (either normal if was normal at Day 1, or baseline (Day 1) grade if already an abnormality on the toxicity table at Day 1) for > 48 hours.

8.3.2. *Definition of Serious Adverse Event (SAE)*

An AE or suspected adverse reaction is considered serious (i.e., is an SAE) if, in the view of either the investigator or the Sponsor, it results in any of the following outcomes:
- Death;
- A life-threatening AE;
- Inpatient hospitalization or prolongation of existing hospitalization;

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- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

Grade 4 AEs (potentially life-threatening events) are not always SAEs unless they are imminently life threatening.

Important medical events that may not meet the above criteria may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

"Life-threatening" refers to an AE that at occurrence represents an immediate risk of death to a participant. An event that may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered a SAE.

All SAEs, as with any AE, will be assessed for severity and relationship to study intervention.

All SAEs will be recorded on the AE CRF.

SAEs will only be reported to the designated pharmacovigilance group (see Section 8.3.6 for reporting procedure) if they are considered related to the study product (serious adverse reaction [SAR]).

All SAEs will be followed through resolution or stabilization by a licensed study physician (for IND studies, a physician listed on the Form FDA 1572 as the site PI or Sub-Investigator).

All SAEs will be reviewed and evaluated by the IND sponsor and will be sent to the DSMB (for periodic review), and the IRB/IEC. All secondary infections are regarded as adverse events of special interest (AESI) and will be reported to the DSMB.

8.3.3.   *Suspected Unexpected Serious Adverse Reactions (SUSAR)*

A SUSAR is any SAE where a causal relationship with the study product is at least reasonably possible but is not listed in the Investigator Brochure (IB), Package Insert, and/or Summary of Product Characteristics.

8.3.4.   *Classification of an Adverse Event*

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This includes but is not limited to physicians, physician assistants, and nurse practitioners.

Severity of Adverse Events

All AEs and SAEs will be assessed for severity using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

For AEs not included in the Table, the following guidelines will be used to describe severity. In addition, all deaths related to an AE are to be classified as grade 5 according to the DAIDS Table.

- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living and causes discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe (Grade 3): Events that interrupt usual activities of daily living, or significantly affect clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.
- Potentially life-threatening event (Grade 4): Events that are potentially life threatening.
- Deaths (Grade 5): All deaths related to an AE are classified as grade 5 (per DAIDS Table).

Relationship to Study Intervention

For each reported adverse reaction, the PI or designee must assess the relationship of the event to the study product using the following guideline:

- Related – There is a temporal relationship between the study intervention and event, and the AE is known to occur with the study intervention or there is a reasonable possibility that the study intervention caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related – There is not a reasonable possibility that the administration of 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.

8.3.5. *Time Period and Frequency for Event Assessment and Follow-Up*

For this study, all Grade 3 and 4 AEs and all SAEs occurring from the time the informed consent is signed through the Day 60 ± 5-day telehealth visit will be documented, recorded, and reported. In addition, patients will be contacted at the end of the safety follow-up period required for each study agent (see appendices for details) to assess AEs and SAEs occurring after drug withdrawal.

Investigator Reporting of AEs

Information on AEs will be recorded on the appropriate CRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. Secondary infections will be recorded on the appropriate CRF. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

8.3.6. *Serious Adverse Event Reporting*

Investigator Reporting of SAEs

Any AE that meets a protocol-defined criterion as a treatment related SAE (SAR) must be submitted within 24 hours of site awareness via an SAE form to the Technical Resources, International (TRI) Pharmacovigilance Group, at the following address: TRISafetyOffice@tech-res.com.

Other supporting documentation of the event may be requested by the TRI Pharmacovigilance Group and should be provided as soon as possible. The TRI Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study participant safety and protocol conduct.

At any time after completion of the study, if the site PI or appropriate sub-investigator becomes aware of an SAE that occurred during the participant's participation in the study, the site PI or appropriate sub-investigator will report the event to the TRI Pharmacovigilance Group.

Regulatory Reporting of SAEs

Any event that requires expedited reporting to Regulatory Authorities (i.e, Serious Unexpected Suspected Adverse Reactions [SUSARs]) based on applicable national regulations will be forwarded to the IND sponsor in time to meet reporting requirements (e.g. 7 days for fatal and life-threatening initial reports, with follow up reports within another 8 days, 15 days for all other SUSARs). The IND sponsor or its in-country representative as detailed in the Transfer of Regulatory Obligations (TORO) will submit safety reports (e.g. IND safety reports) to the regulatory agencies as necessary, and will inform the investigators of such regulatory reports. Site investigators must submit safety reports as required by their Institutional Review Board (IRB)/Research Ethics Board (REB). Documentation of the submission and receipt by the IRB/REB must be retained for each expedited safety report.

SAEs that are not SUSARs will be reported to the FDA at least annually in a summary format which includes all SAEs.

Sites may have additional local reporting requirements (to the IRB and/or national regulatory authority).

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8.3.7.   *Reporting of Pregnancy*

Pregnancy is not an AE. However, any pregnancy that occurs during study participation should be reported to the Sponsor on the appropriate CRF. Pregnancies should also be reported to the IRB. The Sponsor will report pregnancies to the DSMB. Pregnancy should be followed to outcome.

8.4.   **Unanticipated Problems**

8.4.1.   *Definition of Unanticipated Problems*

An Unanticipated Problem (UP) is any event, incident, experience, or outcome that meets the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- Related to participation in the research (meaning there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2.   *Unanticipated Problem Reporting*

To satisfy the requirement for prompt reporting, all UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the Statistical and Data Coordinating Center (SDCC)/study Sponsor within 24 hours of the investigator becoming aware of the event per the above described SAE reporting process.

- Any other UP will be reported to the IRB and to the SDCC/study Sponsor within 3 days of the investigator becoming aware of the problem.

9.   **STATISTICAL CONSIDERATIONS**

The ACTIV-1 IM master protocol utilizes an adaptive platform trial design that allows for four types of adaptations: (1) early stopping of agents for futility, to allow more speedy accrual to other agents remaining in the trial; (2) early stopping for strong evidence of efficacy of a particular agent; (3) substitution of one of the test agents as standard of care for the remainder of the trial, should early evidence of superiority over SoC support such a change, and (4) addition of newly emergent agents, if they become available after study start. A brief summary is provided here. Details will be described in the statistical analysis plan (SAP).

The total sample size for ACTIV-1 IM is based on the Kaplan-Meier estimate of the probability of recovery from ACTT-1. Preliminary data indicate this estimate is approximately 73% based on over 1,000 patients enrolled.

Sample size requirements are based on the number of agents being evaluated and the ability to pool control patients for analysis. Initial sample size estimates are derived assuming three agents are ready for testing at study start and will remain in the study for evaluation at the final analysis stage. If newly emergent therapies are entered into the master protocol after study start, sample size requirements will be adjusted accordingly.

The statistical analysis strategy calls for sharing of control patients across all agents available for study when enrollment begins. For agents added to the trial after study start, comparative analyses will be limited to those control patients enrolled concurrently with the new agent. That is, control patients enrolled prior to an agent entering the trial will not be included in comparative analyses of that agent. This approach was used in the recent PALM study in patients with Ebola virus disease (Mulangu et al. 2019). Although sharing of non-concurrently randomized control patients has been used successfully in studies of chronic diseases (DIAN-TU;

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https://clinicaltrials.gov/ct2/show/NCT01760005), it is not recommended here due to the evolving nature of the COVID-19 infection and treatment thereof. Exploratory analyses of the similarity between control patients enrolled early and late in the study, however, may be useful in informing the design of future master protocols in COVID-19.

If early evidence of superiority of any one of the test agents relative to SoC (plus placebo) is observed during the trial, consideration will be given to replacing the SoC with the test agent for the remainder of the trial. Such a change is dependent on the safety of combining the remaining test agents with this new SoC and will complicate the final data analyses somewhat. Comparative analyses will need to account for this change in SoC through stratification or other model-based methods. Details will be provided in the statistical analysis plan.

Preliminary reports of the completed RECOVERY Trial show that dexamethasone may reduce mortality in some hospitalized patients with COVID-19 (RECOVERY Collaborative Group, 2020). If dexamethasone or steroid, or other agents, become part of standard of care (SoC) or are used in a substantial number of patients, the observed potential benefit of immunomodulators may be altered. Nonetheless, ACTIV-1 IM is designed with high power to detect even a modest benefit of 25% for the primary outcome; attempting to detect smaller effects would cause a prohibitively large increase in sample size. Addition of dexamethasone or other agents to SoC may also affect the key secondary endpoint of mortality and alter the proportions of people in different cells of another key secondary endpoint, the 8-point ordinal scale. Accordingly, a blinded sample size re-estimation may be conducted at the 2nd interim analysis, after approximately one-half of the total number of expected recoveries has occurred. The purpose is to use the overall proportions of people in the different categories of the key secondary endpoint of the ordinal scale to recalculate power for that endpoint. If power for this key secondary endpoint is below 70%, the sample size might be increased, but by at most 25%. The sample size would not be reduced based on this potential re-estimation. More details will be provided in the SAP.

9.1.   Statistical Hypotheses

The primary null hypothesis being tested is that time-to-recovery does not differ between each test agent and the pooled control group, consisting of patients receiving SoC plus placebo. The alternative hypothesis is that the test agent and pooled control group differ in time-to-recovery. If Drug A, B, and C denote the initial set of agents to be tested in ACTIV-1 IM, and S denotes patients receiving SoC plus placebo, then the primary hypotheses are:

$H_{01}: TR_A = TR_S$ vs $H_{A1}: TR_A \neq TR_S$

$H_{02}: TR_B = TR_S$ vs $H_{A2}: TR_B \neq TR_S$

$H_{03}: TR_C = TR_S$ vs $H_{A3}: TR_C \neq TR_S$

There are two key secondary endpoints that will be evaluated as supportive evidence:

1.   The distribution of the 8-point ordinal scale at Day 15 and Day 29. For this, the parameter of interest is the "common odds ratio," which quantifies the shift in the severity distribution resulting from treatment. For an efficacious treatment, an odds ratio greater than 1 quantifies an improvement in disease severity; a value of 2 indicates a bigger improvement than a value of 1.25. The null hypothesis to be tested is that the odds of improvement on the ordinal scale is the same for the placebo and experimental treatment arms (i.e., the common odds ratio is 1). It is worth noting that, for large sample sizes, the test based on the proportional odds model is nearly the same as the Wilcoxon rank sum test.

2.   Mortality will be evaluated with standard survival analysis techniques. Kaplan Meier curves and associated log-rank statistics will be generated to compare mortality between each test agent and SoC. Mortality will also be evaluated at Days 15 and 29.

9.2.   Sample Size Determination

Primary endpoint: The Fine-Gray approach will be used to compare each test agent with SoC with respect to the cumulative incidence of recovery, accounting for the competing risk of mortality (Fine and Gray, 1999). The

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approach is similar to using a log-rank test on time to recovery, retaining in the risk set people who die. The two key determinants of power are the total number of events (i.e., recoveries) E and the treatment-to-control ratio of the rate of recovery, RRR. Without accounting for futility monitoring, the number of events required for power $1 - \beta$ to detect a recovery rate ratio of θ using a two-tailed test at alpha=0.05 is approximately

$$E = \frac{4(1.96 + z_\beta)^2}{\{\ln(RRR)\}^2},$$

where z_β is the $100(1 - \beta)$th percentile of the standard normal distribution. The number of events must be increased to account for futility monitoring. For 85% power, the $1.96 + z_\beta$ in the above equation is replaced by 3.1312.

Table 9-1 provides the numbers of recoveries and of patients required to provide 85% power for a single pairwise comparison of test drug versus control assuming a 73% recovery rate and various recovery rate ratios (RRRs). Note that the rate of recovery is the analogue of the hazard for each test agent or control treatment, and the RRR is the analogue of the hazard ratio for a test agent relative to control in this setting. As can be seen from the table, approximately 347 recoveries are required to detect a 40% increase in the rate of recovery ($\theta = 1.40$) from control. An RRR of 1.40 is similar to, but slightly higher than the figure of 1.31 reported in Cao et al. (2020) for a lopinavir/ritonavir trial that used time to improvement by 2 categories as primary endpoint. A total of 436 recoveries is needed for an RRR of 1.35 with 85% power. Sample size requirements for ACTT-1 assumed an RRR of 1.35, but the study was over-enrolled (1,063 patients were enrolled, compared to N=572 needed) due to more rapid than anticipated accrual. Preliminary results from ACTT-1 show an RRR of 1.32 ([CI = [1.12,1.55]) for remdesivir vs placebo.

Table 9-1. Number of recoveries and number of patients needed for 85% power assuming a type I error rate of 5% for various recovery ratios

Recovery rate ratio (θ)	Number of recoveries needed for 85% power	Sample Size assuming 73% recovery rate (1 test agent vs SoC)
1.25	**788**	**1,080**
1.30	570	781
1.35	436	598
1.40	347	476

The objective of ACTIV-1 IM is to provide evidence of efficacy and safety of selected agents that would support regulatory approval of their use in treating moderately to severely ill hospitalized Covid-19 patients. It was decided that a modest effect as low as a 25% improvement in recovery rate attributable to any one of the test agents in the study would be of interest to detect. Consequently, the sample size requirements are based on the ability to detect an RRR of 1.25 for each agent relative to SoC.

A total of 788 recoveries is required for each comparison to provide approximately 85% power to detect a recovery rate ratio of 1.25 for the therapeutic agent relative to control, accounting for the interim analyses. Assuming 73% of participants achieve recovery in 28 days, consistent with the ACTT-1 results, the total sample size to compare 1, 2, or 3 agents to control in ACTIV-1 IM is approximately 1,080, 1,620, and 2,160, respectively. Because each agent is being compared to SoC with no between-agent comparisons currently planned, no multiplicity adjustments will be made, provided the number of agents assessed in ACTIV-1 IM is three or fewer. If more than three agents are evaluated, a minor multiplicity adjustment will be considered to aid in interpreting the results of the study.

Key secondary endpoints: A sample size can be computed using an (assumed) ordinal scale distribution for the control and the odds ratio representing clinical improvement. The odds ratio represents the odds of improvement in the ordinal scale for treatment relative to control [Whitehead, 1993]. The sample size to detect a given odds ratio for 1:1 randomization using a 2-tailed test at level α is given by

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$$\frac{12\left(z_{\alpha/2} + z_\beta\right)^2}{\lambda^2(1 - \sum_{i=1}^{K} p_i^3)},$$

where λ is the log odds ratio, p_i is the overall probability (combined over both arms) of being in the ith category of the K ordinal outcomes, and $z_{\alpha/2}$ and z_β are the $1 - \alpha/2$ and $1 - \beta$ quantiles of the standard normal distribution.

A sample size of 1,080 for an (active, control) pair gives approximately 95% or 85% power to detect an odds ratio of 1.50 (the observed odds ratio in the ACTT-1 trial) or 1.40 using a 2-tailed test at level $\alpha = 0.05$.

The 28-day mortality probability in the remdesivir arm of ACTT-1 was approximately 12%. Power for comparing 28-day mortality is 90% only for a 50% relative reduction (from 12% to 6%).

9.3.   Populations for Analyses

The primary analysis will be based on an intention-to-treat population, including all participants randomized. Similarly, safety analyses will be based on a modified intention-to-treat population consisting of all participants who received at least one dose or injection of each drug administered in the randomization arm (e.g., test agent plus SoC). The primary analysis will be based on those participants enrolled in order to achieve 788 recoveries for each pairwise comparison as noted in section 9.1. Subsequent analysis will be performed on all enrolled participants.

9.4.   Statistical Analyses

9.4.1.   *General Approach*

This is a randomized, controlled, double-blinded trial testing a superiority hypothesis with respect to each therapeutic agent plus SoC versus SoC plus placebo with a two-sided Type I error probability of 5% for each agent. This is a randomized, controlled, double-blinded trial testing a superiority hypothesis with respect to each therapeutic agent plus SoC versus SoC plus placebo with a two-sided Type I error probability of 5% for each agent. Secondary hypotheses have been ordered according to relative importance, with key secondary hypotheses identified (corresponding to the odds ratio based on the 8-point clinical severity scale, and time to death). These will be described according to the appropriate summary statistics (e.g., proportions for categorical data, median for time-to-event data).

A statistical analysis plan will be developed and filed with the FDA prior to database lock and unblinding of treatment assignments.

Unblinding of study data for final analysis will occur for each test agent independently of other agents, consistent with the master protocol design. That is, once the planned number of recoveries required for a particular agent's comparative analysis are observed, study close-out procedures for that agent are applied for all study visits and data elements associated with the participants receiving the test agent as well as participants receiving SoC plus placebo during the randomization period for that agent (i.e., concurrently controlled participants). The study visits are monitored, data edits are completed, queries are resolved, database is locked, and treatment assignments are unmasked for that comparative analysis only. Note that, because control participant data are shared across agents, procedures for unmasking data for one agent's final analysis will be established to protect the ability to continue the ongoing study in a double-blinded manner for the remaining agents. It may be that recovery rates are similar enough across all agents in the study to enable a single study close-out with standard procedures. Any necessary modifications or updates to the statistical analysis should be made prior to the study unblinding.

9.4.2.   *Analysis of the Primary Efficacy Endpoint*

The primary efficacy analysis for the comparison of each test agent plus SoC versus SoC plus placebo is a stratified test based on the Fine-Gray proportional hazards approach, where stratification is according to region and baseline disease severity (i.e. protocol defined mild/moderate vs severe disease). The method provides an estimate of the cumulative incidence of recovery while accounting for the competing risk of death. The hazard ratio can also be computed. With no censoring, the hazard rate in each arm can be thought of as the hazard for recovery, treating deaths as never having recovered (see section 2 of Fine and Gray, 1999). Every attempt will be made to complete

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final clinic visits for patients dropping out of the study prematurely. For those unable to complete the final visit, data collection will be attempted via telephone interview. At a minimum, vital status will be obtained.

9.4.3. *Analysis of the Secondary Endpoint(s)*

1) The ordinal scale will be used to estimate a proportional odds model by disease strata. We will perform a stratified test to evaluate whether the common odds ratio for treatment is equal to one. The distribution of severity results will be summarized by treatment arm as percentages. Efforts to minimize loss-to-follow-up will be considerable. However, small amounts of missing data may occur. In such cases, participants without final outcome data will be excluded from the analysis. Sensitivity analyses will evaluate the impact of making different assumptions about missing observations. These analyses will be defined in the SAP.

2) When death is not a competing risk (for example, the endpoint includes death in the composite), differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves and 95% confidence bounds. When death is a competing risk (for example, time to at least a one-category improvement in ordinal scale, and time to at least a two-category improvement), the same competing risk approach will be used as for the primary analysis.

3) Change in ordinal scale at specific time points will be summarized by proportions (e.g., proportion who have a 1-, 2-, 3-, or 4-point improvement or 1-, 2-, 3-, 4-point worsening).

4) Differences in total severity score (TSS) over time will assessed by fitting a longitudinal mixed model to the 8-point clinical scale value on each day of assessment (in hospital plus Days 15, 22, 29). The average difference across days in study (analogous to the area under the severity curve) will be estimated with 95% confidence limits in the context of the longitudinal model.

5) Duration of event (e.g., duration of mechanical ventilation) will be summarized according to median days with quartiles.

6) Binary data (e.g., incidence of new oxygen use) will be summarized as a percent with 95% confidence intervals. Comparisons between arms will be presented as differences in proportions with 95% confidence intervals.

7) Categorical data (e.g., 28-day mortality or ordinal scale by day) may be summarized according to proportions by category and/or odds ratios with confidence intervals.

Procedures for handling missing data, including informative censoring (e.g., a missing duration of oxygen use endpoint due to a death), will be described in the statistical analysis plan.

9.4.4. *Safety Analyses*

Safety endpoints include death through Day 28 (as assessed at Day 29), SAEs, and Grade 3 and 4 AEs. These events will be analyzed univariately and as a composite endpoint. Time-to-event methods will be used for death and the composite endpoint. Each AE will be counted once for a given participant and graded by severity and relationship to COVID-19 or study intervention. AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by system organ class, duration (in days), start- and stop-date. Adverse events leading to premature discontinuation from the study intervention and serious AEs will be presented either in a table or a listing.

9.4.5. *Baseline Descriptive Statistics*

Baseline characteristics will be summarized by test agent versus control for each agent. For continuous measures the mean and standard deviation will be summarized. Categorical variables will be described by the proportion in each category (with the corresponding sample size numbers).

9.4.6. *Planned Early and Interim Analyses*

Data analyses will be conducted to monitor enrollment and follow-up rates and to summarize baseline characteristics throughout the course of the study. These early analyses will be conducted by the study team masked to treatment assignment. Summaries will be generated for each test agent separately. For agents entering the study at staggered

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times, data summaries (pooling test agent and control data in blinded fashion) will incorporate data from concurrently randomized control participants only.

Unblinded interim analyses are planned to (i) assess the futility of each agent, with the goal of discontinuing those with lower probabilities of success to more effectively utilize trial resources for the remaining agents and (iii) review comparative analyses for each test agent to assess early stopping for efficacy. Alpha spending functions will be used to appropriately control the probability of making an erroneous conclusion across interim and final analyses at $\alpha = 0.05$ (two-sided) for each agent.

A Data and Safety Monitoring Board (DSMB) will monitor ongoing results to ensure participant well-being and safety as well as study integrity. The DSMB will be asked to recommend early termination due to futility and early stopping for efficacy, only when stopping rules and conditions are clearly met. More details about the interim analyses are described in section 9.4.6.1 and 9.4.6.2 below as well as a separate guidance document for the DSMB.

Interim Safety Analyses

Safety analyses will evaluate Grade 3 and 4 AE and SAEs by treatment arm. Safety monitoring will be ongoing. The unblinded statistical team will prepare these reports for review by the DSMB.

Interim Analyses for Futility and Efficacy Review

Interim analyses for futility and efficacy are planned at three times during the study corresponding to the availability of approximately 25%, 50%, and 75% of total information. The planned randomization algorithm described above (Section 6.2) ensures equal allocation to each test agent or control (e.g., 1:1:1:1 for 3 test agents and control). It is anticipated that the interim analyses for each agent will occur at the same time, and the DSMB will make recommendations for all agents at their scheduled meetings. If recovery rates vary substantially by agent, however, it may be necessary to let the interim analysis times also vary by agent. Because Type I error probabilities are controlled for each, independently of the other agents, the need for additional DSMB reviews due to differential information accrual across agents should not pose any issues other than logistical ones.

The Lan-DeMets spending function analog of the O'Brien-Fleming boundaries will be used to monitor the primary endpoint as a guide for the DSMB. This spending function is conservative in that priority is given to preserving power for the final analysis with the use of stringent stopping rules early in the study.

In contrast, moderately aggressive stopping rules for futility will be implemented to promote early discontinuation of agents with low probabilities for success. The futility stopping rules will be considered non-binding by the DSMB in their review of interim data. The futility boundaries are computed based on the gamma family of spending functions $\alpha\{1-\exp(-\gamma t)\}/\{1-\exp(-\gamma)\}$ (Hwang et al. 1990). Figure 1 below illustrates the efficacy stopping boundaries based on the Lan-DeMets spending function (in blue shading) and the futility boundaries based on a Gamma (-2) spending function (in pink shading).

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Figure 1: **Stopping Boundaries for Efficacy (blue shading) and Futility (pink shading).**
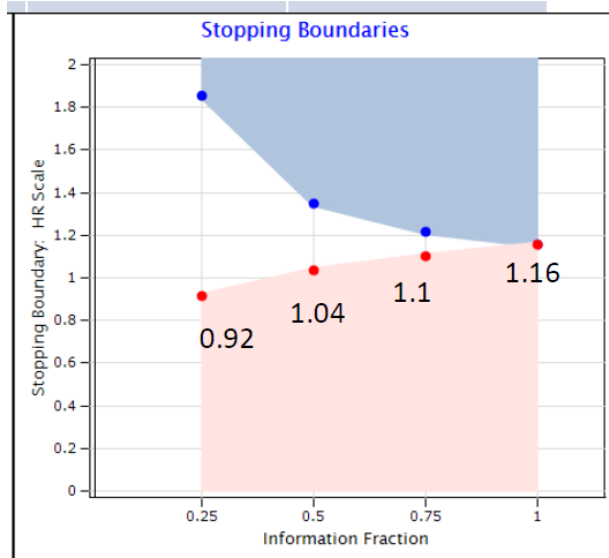
As can be seen from the figure, an RRR showing no more than a small amount of improvement in recovery time (RRR ≤ 1.04) will result in early discontinuation of the agent mid-way through information accrual in the study. When the null hypothesis is true (RRR = 1), the probability of discontinuing an agent at this point is 66%, but under the alternative, this probability is 4%. In simulations, the average number of recoveries under these efficacy and futility boundaries is 587, and the maximum sample size is approximately 1,080 participants.

The unblinded statistical team will prepare closed reports for each DSMB review meeting. Analyses will be presented with blinded codes for treatment arms to protect against the possibility that the DSMB report may fall into the wrong hands. Unblinding codes will be provided to DSMB members who wish to be unblinded. A DSMB charter will further describe procedures and membership. An additional document on statistical issues related to monitoring will be provided to the DSMB prior to the first interim analysis.

9.4.7.   *Sub-Group Analyses*

Subgroup analyses for the primary outcomes will evaluate treatment effects across the following subgroups: geographic region, duration of symptoms prior to enrollment, baseline disease severity (stratification variable of mild/moderate and severe, as well as ordinal scale of 4/5 vs 6/7) age, race, sex and comorbidities. A forest plot will display confidence intervals across subgroups. Interaction tests will be conducted to determine whether the effect of treatment varies by subgroup. These subgroup analyses will be carried out separately for each test agent.

9.4.8.   *Exploratory Analyses*

An exploratory analysis will compare treatment efficacy estimates for each agent according to the various scales outlined in section 8.1.3. Specifically, the probability of falling into category "i" or better will be compared between arms for each i. Exploratory analyses will also compare the difference between each test agent plus SoC and SoC plus placebo in TSS at each study day for which the clinical scale is administered (in-hospital and at Days 15, 22, and 29).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS – ALL STAGES

All supporting documentation and operational considerations are applicable to the entire platform trial and are not unique to the individual stages. These are therefore covered in the main protocol document.