TITLE: Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Effect of Anti-CD14 Treatment in Hospitalized Patients with COVID-19 (DAIT-COVID -19-003)

SHORT TITLE: COVID-19 anti-CD14 Treatment Trial (CaTT)

VERSION 4.0 FEBRUARY 22, 2021

IND153196

SPONSOR: NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

NIAID Funding Mechanism: Grant #: 5 UM1 AI109565-07

Investigational Agent(s): IC14 (chimeric monoclonal antibody against human CD14)

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SITE INVESTIGATOR SIGNATURE PAGE	
Protocol Number: DAIT-COVID -19-003	**Version Number/Date:** Version 4.0/February 22, 2021
Protocol Title: Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Effect of Anti-CD14 Treatment in Hospitalized Patients with COVID-19	
IND/IDE Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	
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I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, 812 and in the International Conference for Harmonisation (ICH) document entitled *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)*. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.

By participating in this protocol, investigators and their designees also agree to:

i) Use IC14 and VEKLURY® (remdesivir) only in accordance with the Protocol and for no other Purpose.

ii) Not transfer IC14 or VEKLURY® (remdesivir) to any parties other than the Distributor identified by the NIAID.

iii) Not chemically modify, replicate, make derivatives of, or reverse engineer IC14 or VEKLURY® (remdesivir).

*[*The site Principal Investigator should print, sign, and date at the indicated location below. A written signature is acceptable, and an electronic signature is acceptable in a pdf version of the form.]*

_____

Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

National Institute of Allergy and Infectious Diseases

Protocol Synopsis

Title	**Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Effect of Anti-CD14 Treatment in Hospitalized Patients with COVID-19 (COVID-19-003)**
Short Title	**COVID-19 anti-CD14 Treatment Trial (CaTT)**
Clinical Phase	Phase 2
Number of Sites	Approximately 10-15 sites in the United States
IND Sponsor/Number	IND Sponsor: National Institute of Allergy and Infectious Diseases IND153196
Study Objectives	Primary objective: • Determine the efficacy of IC14, an anti-CD14 chimeric monoclonal antibody, in patients hospitalized with respiratory disease and hypoxemia due to SARS-CoV-2, in terms of improving the time to resolution of disease using the Eight-Point ordinal scale (Appendix C). Secondary objectives: • Determine the efficacy of IC14 in reducing the severity of respiratory disease in patients hospitalized with respiratory disease due to SARS-CoV-2. • Determine the safety of IC14 in patients hospitalized with respiratory disease due to SARS-CoV-2. Exploratory objectives: • Determine whether IC14 reduces markers of systemic inflammation in participants hospitalized with respiratory disease due to SARS-CoV-2. • Determine whether IC14 increases the proportion of participants experiencing clearance of detectable SARS-CoV-2 in nasopharyngeal specimens.
Study Design	Protocol DAIT COVID-19-003 is a double-blind, randomized placebo-controlled study. Participants will be randomized to IC14 or matching placebo and followed for 60 days after randomization. The study drug will be administered daily on Days 1-4 by intravenous infusion. All participants will receive standard of care antiviral therapy with remdesivir. Randomization will be stratified by baseline use of dexamethasone and groups of study sites.

Primary Endpoint(s)	The Primary Endpoint is time to clinical recovery, defined as the time from baseline to the first day that a participant is in categories 1, 2, or 3 on the Eight-Point Ordinal Scale through Day 28. The Eight-Point Ordinal Scale is an assessment of the clinical status on each study day. The Scale is defined as follows: 1) Not hospitalized, no limitations on activities 2) Not hospitalized, limitation on activities and/or requiring home oxygen 3) Hospitalized, not requiring supplemental oxygen—no longer requires ongoing medical care 4) Hospitalized, not requiring supplemental oxygen—requiring ongoing medical care (COVID-19-related or otherwise) 5) Hospitalized, requiring supplemental oxygen 6) Hospitalized, on non-invasive ventilation or high-flow oxygen devices 7) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) 8) Death
Secondary Endpoints	Efficacy: 1. Days-alive-and-free of any episodes of acute respiratory failure through Day 28 defined by need for any of the following oxygen delivery resources: a. High-flow nasal cannula (flow rates ≥30L/min with FiO_2 ≥0.4) b. Noninvasive positive-pressure ventilation through nasal or face mask, or nasal plugs c. Endotracheal intubation and mechanical ventilation d. Extracorporeal membrane oxygenation 2. Mean change in the ordinal scale from baseline to Days 14 and 28. 3. Ordinal scale value on Day 14. 4. All-cause mortality through Days 28 and 60. 5. Proportion of participants alive-and-free of any episode of acute respiratory failure through Day 28. 6. Days alive-and-free of invasive mechanical ventilation through Day 28. 7. Proportion of participants alive-and-free of invasive mechanical ventilation through Day 28. 8. Proportion of participants alive and discharged from the hospital through Day 28. 9. Proportion of participants who begin corticosteroid therapy for worsening COVID-19 illness after randomization. Safety: 1. Safety of IC14 as measured by change from baseline in liver (alanine transaminase, aspartate transaminase, total bilirubin),

	renal (creatinine), hematological (hemoglobin, white blood cell count with differential), and coagulation function (platelets, prothrombin time) through Day 28. 2. Cumulative incidence of Grade 3 and 4 clinical and/or laboratory adverse events through Day 28. 3. Cumulative incidence of serious adverse events through Day 60.
Exploratory Endpoints	1. Change from baseline in pro-inflammatory cytokines and other biomarkers in blood on Days 5, 7, 14 and 21. 2. Change in Sequential Organ Failure Assessment (SOFA) score from baseline to Days 5, 7, 14, 21 and 28. 3. Worst SOFA score from baseline to Day 28. 4. Time from baseline to improvement in one category using an ordinal scale through Day 28. 5. Time from baseline to improvement in two categories using an ordinal scale through Day 28. 6. Proportion of participants with negative nasal swab RT-PCR tests for SARS-CoV-2 on Days 7 and 14, or at discharge if prior to Day 14.
Accrual Objective	Approximately 300 participants, allocated 1:1 to IC14 or placebo
Study Duration	Approximately 6 months recruitment, 4 days treatment, 56 days follow up off treatment (8 months from first participant first visit to last participant, last visit)
Treatment Description	Intervention Arm: IC14 4 mg/kg intravenously (IV) on day 1, followed by IC14 2 mg/kg/day IV on days 2-4 (total 4 consecutive days). Placebo Arm: 0.9% w/v NaCl in a matching bag and volume administered IV daily on day 1-4 (total 4 consecutive days). All randomized participants will receive remdesivir 200 mg IV on day 1 followed by 100 mg IV/day on days 2-5 (total 5 consecutive days)

Inclusion Criteria	Patients included in the study must meet all the following criteria: 1. Patient or legally authorized representative able to provide informed consent 2. Age ≥18 years 3. Presence of SARS-CoV-2 infection documented by positive RT-PCR testing within 7 days of screening 4. Radiologic findings compatible with diagnosis of SARS-CoV-2 pulmonary infection with no alternative explanation for radiologic findings. 5. Hypoxemia as defined by any of the following: a. SpO_2 ≤94% on room air, or b. Requirement for ≥2L/m O_2 per standard nasal cannula to maintain SpO2>=94%, but not requiring high-flow nasal cannula (defined as ≥30 L/m) 6. Women of childbearing potential must have a negative pregnancy test and be willing to use birth control for the duration of the study.
Exclusion Criteria	An individual fulfilling **any** of the following criteria should be excluded from enrollment in the study: 1. Receiving non-invasive positive-pressure ventilation through nasal mask, face mask, or nasal plugs 2. Receiving invasive mechanical ventilation 3. Patient, surrogate, or physician not committed to full support (exception: a participant will not be excluded if he/she would receive all supportive care other than attempts at resuscitation from cardiac arrest) 4. Anticipated survival <48 hours 5. Underlying malignancy, or other condition, with estimated life expectancy of less than two months 6. Significant pre-existing organ dysfunction prior to randomization a. Lung: Currently receiving home oxygen therapy as documented in medical record b. Heart: Pre-existing congestive heart failure defined as an ejection fraction <20% as documented in the medical record c. Renal: End-stage renal disease requiring renal replacement therapy or eGFR <30 mL/min. d. Liver: Severe chronic liver disease defined as Child-Pugh Class C (Appendix D) or AST or ALT >5 times upper limit of normal e. Hematologic: Baseline platelet count ≤50,000/mm^3 7. Presence of co-existing infection, including, but not limited to: a. HIV infection not virally suppressed and with pre-hospitalization CD4 counts ≤ 500 cell/mm^3 b. Active tuberculosis or a history of inadequately treated tuberculosis c. Active hepatitis B or hepatitis C viral infection 8. Ongoing immunosuppression a. Solid organ transplant recipient

	b. High-dose corticosteroids (equivalent to >20 mg/prednisone/day) within the past 28 days, except for dexamethasone or equivalent treatment for COVID-19 illness. c. Oncolytic drug therapy within the past 14 days 9. Current treatment, or treatment within 30 days or five half-lives (whichever is longer) with etanercept (Enbrel®), infliximab (Remicade®), adalimumab (Humira®), certolizumab (Cimzia®), golimumab (Simponi®), anakinra (Kineret®), rilonacept (Arcalyst®), tocilizumab (Actemra®), sarilumab (Kevzara®), siltuximab (Sylvant®), or other potent immunosuppressant or immunomodulatory drugs or treatments 10. Current treatment with an anti-viral medication for COVID-19 (e.g. hydroxychloroquine, lopinavir/ritonavir) other than remdesivir 11. Current enrollment in an interventional trial for COVID-19 12. History of hypersensitivity or idiosyncratic reaction to IC14 13. Women who are currently breastfeeding 14. Received a live-attenuated vaccine within 30 days prior to enrollment. 15. Received five or more doses of remdesivir, including the loading dose, outside of the study as treatment for COVID-19 16. Any condition that in the opinion of the treating physician will increase the risk for the participant
Study Stopping Rules	Unblinded safety analyses will be conducted by the DSMB when 75 and 150 participants have completed the 28-day assessments. The DSMB may recommend stopping the study if there are safety concerns. When 150 participants complete the 28-day assessments, the DSMB will review an unblinded analysis of the primary endpoint for futility. The study may be stopped if the DSMB concludes that the predetermined futility rule has been met or if safety concerns preclude further enrollment (Section 13.5). An interim analysis for efficacy will not be conducted.

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Glossary of Abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALI	Acute Lung Injury
ALS	Amyotrophic Lateral Sclerosis
ALT	Alanine Aminotransferase
Anti-CD14	Anti-Cluster of Differentiation 14
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
BAL	Bronchoalveolar Lavage
CD14	Cluster of Differentiation 14
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DAMPS	Damage-Associated Molecular Patterns
DSMB	Data Safety Monitoring Board
ECMO	Extracorporeal Membrane Oxygenation
eGFR	Estimate Glomerular Filtration Rate
FDA	Food and Drug Administration
FiO2	The Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
IAV	H5N1 Avian Influenza A Virus
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Institutional Ethics Committee
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous

LDH	Lactate Dehydrogenase
LPS	Lipopolysaccharide
mAb	Monoclonal Antibody
MAP	Mean Arterial Pressure
mCD14	Membrane-CD14
MM	Medical Monitor
Mfg	Manufacturing
MOP	Manual of Procedures
NaCL	Sodium Chloride
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PAMPS	Pathogen-Associated Molecular Patterns
PI	Principal Investigator
PK	Pharmacokinetics
PO route	Oral administration
PT/INR	Prothrombin Time and International Normalized Ratio
RNA	Ribonucleic Acid
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
sHLH	Secondary Hemophagocytic Lymphohistiocytosis
sCD14	Soluble CD14
SOFA	Sequential Organ Failure Assessment score
SOP	Standard Operating Procedure
SpO2	Peripheral Oxygen Saturation
SUSAR	Serious Unexpected Suspected Adverse Reaction
TEAEs	Treatment Emergent Adverse Event
VCC	Vanderbilt Coordinating Center
V or vol	Volume
wt	weight
WHO	World Health Organization

1. Background and Rationale

Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2)

The SARS-CoV-2 virus is spreading rapidly and has been declared a global pandemic by WHO. Although most cases are thought to be mild or moderate in severity, many people have died, mostly with severe respiratory complications. In a review of 1099 people with COVID-19 in Wuhan, China (Guan et al. 2020), a primary composite endpoint consisting of ICU admission, mechanical ventilation or death, occurred in 6.1%. Of the total population, 5% were admitted to the ICU, 2.4% underwent mechanical ventilation and 1.4% died. Although exact figures are not available, the death rate in larger populations has ranged from 1-3% (WHO statistics). If the spread of disease continues, hospitals are likely to be overwhelmed and many more people are likely to die in the absence of effective treatments.

The pathogenesis of viral infections in the lungs involves several general steps: viral entry into target cells in the airways and alveolar surface via specific surface receptors (Hoffmann et al. 2020), an initial host immune response that recognizes and destroys infected cells, and subsequent recognition of liberated viral and host cell products (called pathogen-associated molecular patterns, PAMPs or damage-associated molecular patterns, DAMPs) by host immune cells. This causes an amplification of the inflammatory response, resulting in flooding of the gas exchange spaces in the lungs. In survivors there is a resolution phase that clears inflammatory debris and slowly restores homeostasis in the lungs. Of note, acute amplification of inflammation in the lungs is critical in the pathogenesis of hypoxemia, because increased alveolar flooding inactivates surfactant and promotes alveolar collapse.

The first phase begins as patients in the community are incubating the disease and a therapeutic that stops viral entry could be helpful (Hoffmann et al. 2020; Gurwitz et al. 2020), as in oral neuraminidase inhibitors for influenza infections. The second phase, amplification of lung inflammatory responses, occurs as patients are worsening clinically and seeking medical attention. The amplification phase is responsible for clinical deterioration with worsening hypoxemia and pulmonary infiltrates, the need for intensive care and ventilatory support and a greatly increased risk of death. Many of these patients will meet clinical criteria for the Acute Respiratory Distress Syndrome (ARDS), consisting of critical hypoxemia, bilateral pulmonary infiltrates consistent with edema and no evidence of primary cardiac dysfunction (ARDS Definition Task Force, 2012). At present, no treatments have blocked the amplification phase of any form of acute lung injury, in which pathogen-derived and host cell-derived cellular products trigger inflammatory cascades via stimulation of a series of pattern recognition receptors on the surface of monocytes, macrophages and other cells of the innate immune system. The third phase, the resolution phase, occurs if supportive care is successful.

Current management of COVID-19 respiratory complications is supportive, and respiratory failure from ARDS is the leading cause of mortality. Secondary hemophagocytic lymphohistiocytosis (sHLH) is an under-recognized, hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinemia with multiorgan failure (Mehta et al. 2020). In adults, sHLH is most commonly triggered by viral infections and occurs in 3.7–4.3% of sepsis cases (Karakike et al. 2019; Ramos-Casals et al. 2014). Cardinal features of sHLH include unremitting fever, cytopenias, and hyperferritinemia; pulmonary involvement (including ARDS) occurs in approximately 50% of patients (Seguin et al. 2016). A cytokine profile resembling sHLH is associated with COVID-19 disease severity, characterized by increased interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemo-attractant protein 1, macrophage inflammatory protein 1-α, interleukin 1β, and tumor necrosis factor-α (Huang et al. 2020). Predictors of fatality from a recent retrospective, multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin (mean 1297.6 ng/ml in non-survivors *vs* 614.0 ng/ml in survivors; p<0·001) and IL-6 (p<0·0001), suggesting that mortality might be due to virally driven hyperinflammation (Ruan et al. 2020).

CD14 Pattern Recognition Receptor in ARDS and COVID infection

The alveolar environment in ARDS is characterized by acute neutrophilic inflammation and an excess of pro-inflammatory cytokines, features consistent with an intense innate immune response. The primary pathway by which

the innate immune system is alerted to the presence of noxious stimuli is through Pattern Recognition Receptors (PRRs). PRRs are activated by exogenous PAMPs as well as DAMPs. This innate immune response driven by the recognition of PAMPs is critical for the host response to microbial pathogens such as viruses, bacteria, and fungi. PAMPs are recognized by a family of membrane toll-like receptors (TLRs) that activate macrophages and other innate immune cells. Multiple experimental studies have shown that both the membrane-bound and soluble forms of CD14 bind a diverse group of PAMPs and DAMPs. The membrane-bound form of CD14 is required for maximal innate immune responses through TLRs (Wright 1995; Aderem et al. 2000; Ulevitch 1999) and other intracellular pathways that comprise the innate immune system. Given that CD14 is a proximal component of the recognition of PAMPs and DAMPs by a variety of TLRs, it represents an attractive pharmacologic target. Blockade of CD14 may reduce recognition of viral and bacterial products and the initiation of events that lead to the production of pro-inflammatory cytokines and recruitment of inflammatory cells.

CD14 exists in membrane-bound and soluble forms and may be thought of as a master regulator of immune responses (Di Gioia et al. 2015). PAMPs and DAMPs drive and amplify innate immune responses that damage the lungs and other organs. CD14 may also play a role in inflammasome activation driven by NLRP3 and other closely related proteins. Membrane CD14 (mCD14) on the cell surface is critical to immune responses in the lung epithelium and is present on alveolar macrophages (Lin et al. 2004). Membrane CD14 and TLR4 mediate responses to respiratory syncytial virus (Kurt-Jones et al. 2000) and mCD14 is required for influenza A-driven cytokine production in murine macrophages (Pauligk et al. 2004). Activation of TLR3 by double-stranded RNA released by respiratory viruses is mediated by CD14 (Lee et al. 2006). Coronavirus lung pathology involves TLRs (Li et al. 2020) that require or utilize CD14 either as a co-receptor or for transport of immunogenic ligands to endosomes. CD14 mediates pathogenic oxidative stress in acute lung injury driven by oxidized phospholipids (Di Gioia et al. 2020) that are present in samples from patients with ARDS caused by infections with H5N1 avian influenza A virus (IAV) or SARS-CoV1 (Imai et al. 2008). In patients with COVID-19 infection, there is a clear increase in the number of circulating CD14+ monocytes, suggesting an enhanced inflammatory phenotype that is related to adverse clinical outcomes (Zhang et al. 2020). RNA profiling has shown that innate immunity pathways are activated in bronchoalveolar lavage cells of patients with COVID-19 (Zhou et al. 2020) and that the elevated $CD14^{hi}$ monocyte population expressing IL-1β persists into the recovery phase (Wen et al. 2020). Thus, CD14+ monocytes, macrophages, and dendritic cells central to innate immunity pathways have emerged as fundamental aspects of the immunopathogenesis of COVID-19 infection (Merad et al. 2020).

Soluble CD14 (sCD14) is produced in the liver and spleen and shed from the surface of inflammatory cells. Soluble CD14 is abundant in serum of sepsis patients and correlates with clinical severity (Landmann et al. 1995). In addition to conferring innate immune reactivity on cells that do not constitutively express mCD14 (e.g., endothelial cells) (Pugin et al. 1993), sCD14 may directly stimulate pathogenic pro-inflammatory cytokine/chemokine production in a manner independent of microbial products (Lévêque et al. 2017). We have found that soluble CD14 in the lungs is strongly associated with deleterious inflammatory responses in the lungs of patients with ARDS (Martin et al. 1997). Furthermore, a recent proteomics study showed high levels of sCD14 in plasma samples that increased dramatically with increasing severity of disease, leading the authors to suggest that CD14 could be an appropriate target for intervention in these patients (Messner et al. 2020).

In summary, these data suggest that CD14-dependent signaling is a key step in the initial pathways that amplify acute inflammatory reactions in the lungs and worsen the clinical severity of lung injury (Martin et al. 2020). Taken together, the available data provide strong support for CD14 as a key regulator of innate immune responses in the lungs and suggest that targeting both membrane-bound and soluble CD14 could be a highly effective strategy to limit the severity of inflammatory responses in the lungs and systemic circulation of patients with SARS-CoV-2 induced lung and organ injury. Clinical experience with an anti-CD14 antibody suggests that CD14 can be inhibited in humans without causing broad immunosuppression.

1.1. Rationale for Selection of IC14, Recombinant Chimeric Monoclonal Antibody against Human CD14

This study proposes to use IC14, a monoclonal antibody (mAb) recognizing human CD14, to block CD14-mediated cellular activation in patients early in the development of ARDS. The binding of IC14 to human CD14 prevents CD14 from participating in the recognition of PAMPs and DAMPs due to SARS-CoV-2 infection. The putative mechanism of action of IC14 in ARDS is to block PAMP and DAMP interactions with CD14, thus attenuating the inflammatory cascade that leads to increased endothelial and epithelial permeability and injury resulting in alveolar injury and fluid accumulation characteristic of ARDS.

IC14 is a murine/human chimeric IgG4 mAb that binds to both membrane-bound and soluble CD14 with high affinity, prevents ligand binding and thereby inhibits signaling. The IC14 mAb labels monocytes in human blood smears as well as intravascular monocytes and human tissue macrophages in multiple human tissues and does not cross react with other cells in human tissues. Blocking CD14 with IC14 treatment in normal volunteers strongly inhibits systemic inflammation in response to bacterial endotoxin (LPS) (Verbon et al. 2001). A small NIH-funded pilot trial suggested that IC14 treatment in 13 participants with ARDS, which suggested that IC14 treatment reduced alveolar inflammation. Currently, IC14 is being tested in neurodegenerative diseases, because the CD14 pathway has been shown to be important for several forms of chronic neurodegenerative injury. Chronic therapy with IC14 is being studied in patients with amyotrophic lateral sclerosis (ALS) at the Massachusetts General Hospital under IND 138610 (Merit Cudkowicz, MD) and has been selected for inclusion in the Healey Center platform phase 2b study in 54 sites across the USA in 2020. IC14 was also the subject of IND 105803 for a phase 2 study of ARDS from all causes which has been revised for the COVID-19 indication (IND 149641).

A dosing regimen for IC14 with favorable pharmacokinetics supporting once daily intravenous dosing has been defined, making this an acceptable treatment for hospitalized patients (Axtelle et al. 2003; Reinhart et al. 2004). . Two pharmacodynamic biomarkers can be used that are related to CD14: measurements of sCD14 (serum at baseline and follow up) as well as a CD14 fragment (sCD14-ST; presepsin) (Zou et al. 2014). In addition, an mCD14 target engagement assay is available and will be used to monitor IC14 blockade of the mCD14 target on circulating monocytes.

Therefore, because of the central role of CD14 in the amplification of lung inflammatory responses leading to severe lung injury and the safety record of IC14 in humans, we propose to conduct a clinical trial to test the safety and efficacy of IC14 treatment to prevent progression to severe respiratory disease in patients hospitalized with COVID-19 illness. Success with this study would provide a strong foundation for moving to a larger trial of the efficacy of IC14 in COVID-19 illness. The scientific rationale for CD14 as a therapeutic target, the urgent unmet medical need, the immediate availability of the IC14 antibody, and the clinical safety database all support the appropriateness and feasibility of this clinical trial.

1.2. Preclinical Experience with the IC14 Drug Product

IC14 is a murine/human chimeric anti-human CD14 monoclonal antibody (mAb) comprised of mouse variable and human IgG4 constant regions, produced in CHO $DHFR^-$/DG44 host cells. The chimeric antibody was developed from a mouse anti-CD14 antibody (designated 28C5) that recognizes both mCD14 and sCD14 and blocks PAMP and DAMP binding. The recombinant protein is secreted from CHO cells as an $L_2H_2\gamma_4$ immunoglobulin.

A safety database of 168 dosed participants across 8 clinical studies (in healthy volunteers [HV]; HV with LPS challenge; patients with severe sepsis; community-acquired pneumonia and sepsis; acute lung injury; and amyotrophic lateral sclerosis) supports the use of IC14 in patients. Because IC14 does not block a number of alternative pathways of inflammation that can be used by the host to respond to infection (e.g., complement), it is not broadly immunosuppressive and no increased risk of infection has been observed related to its use in clinical trials.

Preclinical Data

CD14 is a glycophosphatidylinositol-linked cell-surface protein that was originally described as a membrane-bound (mCD14) marker of macrophages, monocytes, and to a lesser extent, neutrophils. Subsequently it was found to be constitutively expressed in a soluble form (sCD14) that is present in peripheral blood plasma at microgram/mL concentration. It is well-documented that CD14 binds PAMPs such as LPS of Gram-negative bacteria; peptidoglycan, the major cell-wall component of Gram-positive bacteria; viral envelope epitopes; and lipoarabinomannan produced by mycobacteria; and acts as a co-receptor for TLRs to maximize innate immune responses (Kurt-Jones et al. 2000)(Lee et al. 2006). Notably, cells that do not express mCD14 can use sCD14 in combination with TLRs to induce production of pro-inflammatory cytokines and chemokines.

As noted above, CD14 can also bind endogenous DAMPs such as heat shock protein 60, heparin, HMGB1, hyaluronic acid fragments, and other endogenous ligands. CD14 presents these PAMPs and DAMPs to other receptors such as TLRs on cells of the innate immune system, leading to activation of signaling pathways including NF-κB and c-Jun N-terminal kinase resulting in the release of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-8.

The broad spectrum of PAMPs and DAMPs recognized by CD14 and its proximal position in the host recognition of these molecules makes it an attractive target to inhibit the pro-inflammatory responses induced by these factors. Blockade of both mCD14 and sCD14 should ensure that both CD14-expressing cells such as macrophages and dendritic cells, and non-CD14-expressing cells such as the vascular endothelium will have a dampened inflammatory response. Indeed, published studies by University of Washington researchers and others have shown that blocking CD14 with specific monoclonal antibodies (mAbs) reduces local and systemic inflammatory responses to LPS (Leturcq et al. 1996; Schimke et al. 1998; Verbon et al. 2001; Reinhart et al. 2004; Frevert et al. 2000).

The effect of anti-CD14 has been observed in experimental animal and human models. In non-human primates, LPS infusion causes a response that models septic shock. Treatment with two different anti-CD14 mAbs abrogated the systemic effects of LPS infusion with preservation of mean arterial pressure (MAP), reduced circulating cytokine levels, and a relatively preserved lung epithelial permeability barrier (Leturcq et al. 1996). In rabbits, treatment with an anti-CD14 mAb protected against the lethal effects of repeated LPS exposure (Schimke et al. 1998). In a model of Gram-negative pneumonia in rabbits, University of Washington investigators found that treatment with an anti-CD14 mAb protected animals from the systemic effects of localized infections (Frevert et al. 2000). Treated animals had improved MAP and required less intravenous fluid. The treated animals had slower clearance of the bacteria instilled in the lungs, which was not seen in a separate study of bacterial clearance in antibiotic treated rabbits (Axtelle et al. 2003; Verbon et al. 2001). These data show that anti-CD14 treatment can attenuate the adverse systemic effects of Gram-negative infections. More recently, studies in a porcine model of *E. coli* bacteremic sepsis have shown that pre-treatment with a different anti-CD14 monoclonal antibody reduced circulating levels of IL-1β, IL-6, and TNFα, as well as tissue levels of IL-6 in the lungs, liver, spleen, and kidneys (Thorgersen et al. 2010; 2013). Notably, anti-CD14 did not significantly alter the load of *E. coli* bacteria or LPS measured in lung tissue. LPS levels detected in liver and spleen were higher in the anti-CD14-treated animals suggesting augmented clearance of circulating LPS.

Taken together these preclinical data support using the CD14-blocking antibody, IC14, as a therapeutic intervention in lung injury. Dampening inflammation via transient blockade of CD14 can protect the host from the extreme pro-inflammatory environment present early in the development of lung injury, leading to less severe injury and better clinical outcomes.

1.3. Clinical Studies

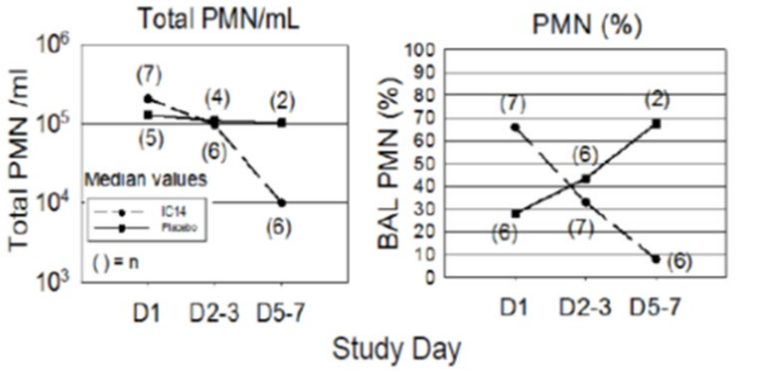
Human LPS-Challenge Study

In a human model of LPS infusion, researchers showed that pretreatment with IC14 (1 mg/kg i.v.) mitigated the inflammatory effects of intravenous LPS (4 ng/kg i.v.) (Verbon et al. 2001). This phase 1 study showed that IC14 is well tolerated and has anti-inflammatory effects in humans.

Clinical Data in Patients

In a randomized, double-blind, placebo-controlled, dose-ranging, multiple-center, phase 1 trial in patients with severe sepsis, IC14 was administered intravenously to four different groups (n=8/group): 1) single dose of 1 mg/kg, 2) single dose of 4 mg/kg, 3) 4 doses of 4 mg/kg/day, 4) 1 dose of 4 mg/kg on Day 0 followed by 3 doses of 2 mg/kg/day (Reinhart et al. 2004; Axtelle et al. 2003). A placebo arm was included for each group (n=2/group). Single and multiple doses of IC14 were generally well tolerated and did not induce anti-drug antibody formation or increase the incidence of secondary bacterial infections. Participants in the multi-day IC14 groups showed a trend towards reduced multi-organ dysfunction score (MODS) (p=0.06). No significant differences in mortality or inflammatory cytokine production were noted in this small study. One SAE occurred (hypotension and rash) in a treated participant, which resolved with ranitidine, dimetindine, and prednisolone.

An NIH-sponsored double-blind randomized placebo-controlled phase 2 study of 13 critically ill patients supports the use IC14 to treat lung injury resulting from increased epithelial and endothelial permeability. In this study, IC14 or placebo were administered to critically ill patients with ARDS at the University of Washington (Seattle, WA). Patients with ARDS were randomized to receive either IC14 4 mg/kg/day x 1 day and 2 mg/kg/day x 3 days (n = 7) or placebo for 4 days (n = 6). Bronchoalveolar lavage (BAL) was performed at baseline and again on Days 2-3 and 5-7 to measure leukocyte counts and differentials, total protein, and pro-inflammatory cytokines and chemokines in the BAL fluid. This trial was stopped early because patients were being enrolled in competing trials; nevertheless, the data showed trends for reductions in total and percentage of neutrophils in lung lavage fluid, as well as plasma IL-6 and IL-8, consistent with an improvement in lung and systemic inflammation (Figure 1 below). Notably, the pre-treatment BAL markers of lung inflammation were higher in the IC14-treated participants, suggesting worse lung inflammation at baseline. No IC14-related safety concerns were noted. Taken together, this trial suggests that administration of IC14 is feasible and safe in critically ill patients with ARDS and may reduce markers of inflammation indicative of breakdown of the endothelial and epithelial permeability barrier.



		Day 1 (baseline)	Day 3	Day 7
Plasma IL-6 pg/ml Median (IQR)	IC14	449.8 (42.4-4867.2)	109.5 (42.4-267.3)	90.2 (4.8-108.9)
	Placebo	180.8 (92.8-371.3)	75.3 (42.4-586.0)	319.1 (121.8-516.4)
BALF IL-6 pg/ml Median (IQR)	IC14	1047.6 (227.9-1396.2)	41.6 (25.6-738.3)	23.8 (4.8-45.2)
	Placebo	79.6 (7.0-979.7)	200.4 (13.3-4147.4)	173.6 (21.1-326.1)

Figure 1. IC14 Pilot Trial in ARDS

A phase 2, randomized double-blind study of IC14 in 180 patients with community-acquired pneumonia did not show a significant decrease in incidence of therapeutic failure, but the treatment was well tolerated with no significant increase in TEAEs, SAEs, or secondary infections (ICOS Abbreviated Clinical Study Report 2004).

Previous Phase 1-2 studies with IC14 have documented a favorable safety profile, and it has been generally well tolerated. Mild side effects reported in healthy participants included headaches, rashes and tingling lasting a few hours, runny nose, fever and chills, sleepiness, and light headedness. In patients with severe sepsis, one serious treatment-related adverse event was reported. That subject experienced hypotension and diffuse exanthema which resolved with administration of ranitidine, prednisolone and dimetindine. None of the 168 subject IC14 exposures has resulted in detectable anti-IC14 antibodies. IC14 has not been associated with an increase in ophthalmologic infiltrates or signs and symptoms of meningeal inflammation in humans. Signs of asymptomatic pleocytosis were noted in preclinical toxicology studies of nonhuman primates administered the antibody. In a phase 2 trial of IC14 for treatment of acute lung injury (ALI), there were no serious adverse events that were attributable to IC14 and no excess nosocomial infections.

2. Study Hypotheses/Objectives

The primary hypothesis is that inhibiting the CD14 pattern recognition receptor will reduce the intensity of deleterious host inflammatory responses to the SARS-CoV-2 virus and associated tissue damage and improve outcomes in patients with COVID-19 illness.

2.1. Primary Objective

Determine the efficacy of IC14, an anti-CD14 chimeric monoclonal antibody, in patients hospitalized with respiratory disease and hypoxemia due to SARS-CoV-2, in terms of improving the time to resolution of disease using the Eight-Point ordinal scale (Appendix C).

2.2. Secondary Objectives

1. Determine the efficacy of IC14 in reducing the severity of respiratory disease in patients hospitalized with respiratory disease due to SARS-CoV-2.

2. Determine the safety of IC14 in patients hospitalized with respiratory disease due to SARS-CoV-2.

2.3 Exploratory Objectives

1. Determine whether IC14 reduces markers of systemic inflammation in participants hospitalized with respiratory disease due to SARS-CoV-2.

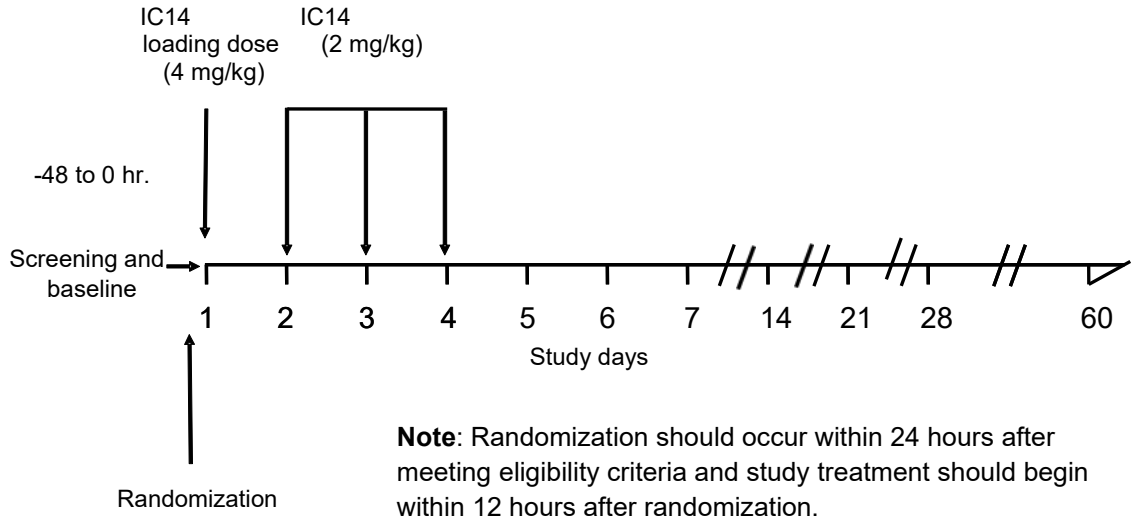
2. Determine whether IC14 increases the proportion of participants experiencing clearance of detectable SARS-CoV-2 in nasopharyngeal specimens.

3. Study Design

This is a randomized, double-blind, placebo-controlled study of IC14 (Figure 2 below). Patients hospitalized with pulmonary manifestations of SARS-CoV-2 infection will be randomized to treatment with intravenous IC14 at a dosage of 4 mg/kg on Day 1, then 2 mg/kg once daily on Days 2, 3, 4 or identical-appearing placebo. Study participation will be for a total of 60 days.

The screening window for eligibility will begin at the time of hospital admission. Once screening shows a patient may be eligible, they will be approached for consent. After consent is obtained, if necessary, a pregnancy test will be obtained to complete screening procedures and finalize eligibility. Baseline assessments, consenting and randomization should occur within 24 hours after meeting inclusion criteria and the first administration of study drug should occur as soon as possible within 12 hours after randomization. Study Days are defined as consecutive calendar days beginning from the start of the first study drug administration (Day 1). Study drug should be administered at approximately 24-hr intervals beginning from the start time of the first study drug administration (Day 1). Study participants will not be pretreated with antihistamines or steroids prior to infusion of study drug because of the rarity of infusion reactions in clinical studies with IC14 (e.g. one infusion reaction in 168 participants treated to date). However, if three or more infusion reactions occur during the study that are thought to be related to the study drug, consideration will be given to pretreating all subsequent participants with an antihistamine prior to infusion of the study drug.

Figure 2. Study Design



3.1. Primary Endpoint

The Primary Endpoint is time to clinical recovery, defined as time from baseline to the first day that a participant is in categories 1, 2, or 3 on the Eight-Point Ordinal Scale (below and Appendix C) through Day 28. The Eight-Point Ordinal Scale is an assessment of the clinical status on each study day. The Scale is defined as follows:

1) Not hospitalized, no limitations on activities
2) Not hospitalized, limitation on activities and/or requiring home oxygen
3) Hospitalized, not requiring supplemental oxygen—no longer requires ongoing medical care

4) Hospitalized, not requiring supplemental oxygen—requiring ongoing medical care (COVID-19-related or otherwise)

5) Hospitalized, requiring supplemental oxygen

6) Hospitalized, on non-invasive ventilation or high-flow oxygen devices

7) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)

8) Death

3.2. Secondary Endpoints

3.2.1. Secondary efficacy endpoints:

1. Days-alive-and-free of any episodes of acute respiratory failure through Day-28 defined by need for the following oxygen delivery resources:
    a. High-flow nasal cannula (flow rates ≥30L/min with FiO_2 ≥0.4)
    b. Noninvasive positive-pressure ventilation through nasal or face mask, or nasal plugs
    c. Endotracheal intubation and mechanical ventilation
    d. Extracorporeal membrane oxygenation
2. Mean change in the ordinal scale from baseline to Days 14 and 28.
3. Ordinal scale value on Day 14.
4. All-cause mortality through Days 28 and 60.
5. Proportion of participants alive-and-free of any episode of acute respiratory failure through Day 28.
6. Days-alive-and-free of invasive mechanical ventilation through Day 28.
7. Proportion of participants alive-and-free of invasive mechanical ventilation through Day 28.
8. Proportion of participants alive and discharged from the hospital through Day 28.
9. Proportion of participants who begin corticosteroid therapy for worsening COVID-19 illness after randomization.

3.2.2. Secondary safety endpoints:

1. Safety of IC14 as measured by change from baseline in liver (alanine transaminase, aspartate transaminase, total bilirubin), renal (creatinine), hematological (hemoglobin, white blood cell count with differential), and coagulation function (platelets, prothrombin time) through Day 28.
2. Cumulative incidence of Grade 3 and 4 clinical and/or laboratory adverse events through Day 28.
3. Cumulative incidence of serious adverse events through Day 60.

3.3. Exploratory Endpoints

1. Change from baseline in pro-inflammatory cytokines and other biomarkers in blood on Days 5, 7, 14 and 21.
2. Change in Sequential Organ Failure Assessment (SOFA) score from baseline to Days 5, 7, 14, 21 and 28.
3. Worst SOFA score from baseline to Day 28.
4. Time from baseline to improvement in one category using an ordinal scale through Day 28.
5. Time from baseline to improvement in two categories using an ordinal scale through Day 28.
6. Proportion of participants with negative nasal swabs for SARS CoV2 virus on Days 7 and 14, or at discharge if prior to Day 14.

3.4. Stratification, Randomization, and Blinding/Masking

Randomization will be stratified by groups of study sites to ensure treatment balance based on variation in standard of care, and by baseline use of corticosteroids for treatment of COVID-19. Block randomization with random block size will be used. The randomization schedule will be generated by the un-blinded study statistician. The participants and study staff will be blinded to the treatment.

3.4.1. Procedure for Unblinding/Unmasking

Unblinding must be approved by the study Vanderbilt Corordinating Center (VCC) Medical Monitor (MM) and the DAIT/NIAID Medical Officer unless an immediate life-threatening condition has developed and the VCC MM is not accessible, in which case the treating physician is authorized to unblind the treatment for an individual participant. The site investigator should send a blinded email to the protocol chair(s), the VCC study team, VCC Medical Monitor and DAIT/NIAID Medical Officer of the unblinding event within 24 hours. The emergency unblinding will also be reported to the Data and Safety Monitoring Board (DSMB).

A full account of the event will be recorded in the EDC either in AE Form or PD Form, whichever is applicable including the date and time of the unblinding, the reason for the decision to unblind, and the name of the individual who made the decision and the names of the VCC MM and others who were notified. The reasons for unblinding of a participant's treatment will be included in the final study report.

Unblinding the study due to an approved interim analysis, final analysis, or study termination will require written approval from DAIT/NIAID.

4. Selection of Participants

4.1. Rationale for Study Population

The goal of the study is to determine whether treatment with IC14 reduces the time to resolution of COVID-19 respiratory illness. The study population will consist of participants who are hospitalized with proven COVID-19 illness, defined by a positive RT-PCR test for SARS-CoV-2 virus, respiratory symptoms compatible with COVID-19 illness, hypoxemia and one or more pulmonary infiltrates, but who are not yet requiring monitoring or support in an intensive care unit.

4.2. Inclusion Criteria

Patients may be included in the study only if they meet **all** the following criteria:

1. Patient or a responsible family member or legal representative must be able to understand and give written informed consent.
2. Age greater than or equal to 18 years
3. Presence of SARS-CoV-2 infection documented by positive RT-PCR testing or history of positive RT-PCR test for SARS-CoV-2 within 7 days of screening
4. Radiologic findings compatible with diagnosis of SARS-CoV-2 pulmonary infection with no alternative explanation for the radiologic findings
5. Hypoxemia as defined by any of the following:
    a. $SpO_2 \leq 94\%$ on room air, or
    b. Requirement for ≥2L/m O_2 per standard nasal cannula to maintain SpO2≥94%, but not requiring high-flow nasal cannula (defined as ≥30 L/m)
6. Women of childbearing potential must have a negative pregnancy test and be willing to use birth control for the duration of the study.

4.3. Exclusion Criteria

An individual fulfilling **any** of the following criteria is to be excluded from enrollment in the study:

1. Receiving non-invasive positive-pressure ventilation through nasal mask, face mask, or nasal plugs
2. Receiving invasive mechanical ventilation
3. Patient, surrogate, or physician not committed to full support (exception: a participant will not be excluded if he/she would receive all supportive care other than attempts at resuscitation from cardiac arrest)
4. Anticipated survival <48 hours

5. Underlying malignancy, or other condition, with estimated life expectancy of less than two months
6. Significant pre-existing organ dysfunction prior to randomization
    a. Lung: Currently receiving home oxygen therapy as documented in medical record
    b. Heart: Pre-existing congestive heart failure defined as an ejection fraction <20% as documented in the medical record
    c. Renal: End-stage renal disease requiring renal replacement therapy or eGFR < 30 mL/min.
    d. Liver: Severe chronic liver disease defined as Child-Pugh Class C (Appendix D) or AST or ALT > 5 times the upper limit of normal
    e. Hematologic: Baseline platelet count $\leq$50,000/mm^3
7. Presence of coexisting infection, including, but not limited to:
    a. HIV infection not virally suppressed and with pre-hospitalization CD4 count ≤ 500 cell/mm^3
    b. Active tuberculosis or a history of inadequately treated tuberculosis
    c. Active hepatitis B or hepatitis C viral infection
8. Ongoing immunosuppression
    a. Solid organ transplant recipient
    b. High-dose corticosteroids (equivalent to >20 mg/prednisone/day) within the past 28 days, except for dexamethasone 6 mg daily or equivalent dose corticosteroid initiated for COVID-19 illness prior to randomization.
    c. Oncolytic drug therapy within the past 28 days
9. Current treatment, or treatment within 30 days or five half-lives (whichever is longer) with etanercept (Enbrel®), infliximab (Remicade®), adalimumab (Humira®), certolizumab (Cimzia®), golimumab (Simponi®), anakinra (Kineret®), rilonacept (Arcalyst®), tocilizumab (Actemra®), sarilumab (Kevzara®), siltuximab (Sylvant®), or other potent immunosuppressant or immunomodulatory drugs or treatments
10. Current treatment with an anti-viral medication for COVID-19 (e.g. hydroxychloroquine, lopinavir/ritonavir) other than remdesivir
11. Current enrollment in an interventional trial for COVID-19 illness.
12. History of hypersensitivity or idiosyncratic reaction to IC14 or any other monoclonal antibody.
13. Women who are currently breast feeding.
14. Received a live-attenuated vaccine within 30 days prior to enrollment.
15. Received five or more doses of remdesivir, including the loading dose, outside of the study as treatment for COVID-19
16. Any condition that in the opinion of the treating physician will increase the risk for the participant

5. Known and Potential Risks and Benefits to Participants

5.1. Risks of Investigational Product in Clinical Studies

To date, 168 healthy volunteers and patients have received IC14, across a range of clinical studies, LPS challenge (Verbon 2001), community-acquired pneumonia (Axtelle et al. 2003), sepsis (Reinhart et al. 2004;), acute lung injury, and amyotrophic lateral sclerosis. IC14 was generally well tolerated. Adverse events that were at least 5% more common in participants receiving IC14 compared to placebo (regardless of whether they were considered related to IC14 or were due to the underlying disease) are below:

Table 1. Adverse Events Observed with IC14

Side Effect	How often is it likely to occur?	How severe might it be?	How long might it last?
Low platelets (blood clotting cell)	*8.3% (2.7% in placebo)*	*mild-moderate*	*One week*

One SAE occurred (hypotension and rash) in a treated patient with sepsis, which resolved with ranitidine, dimetindine, and prednisolone.

No anti-drug antibodies have been detected in 168 participants treated with IC-14.

In separate randomized placebo-controlled studies of patients with community acquired pneumonia, sepsis or ARDS the number of patients thought to have new bacterial infections after beginning IC14 treatment was balanced across placebo and IC14 groups. In addition, hepatobiliary and renal failure serious adverse events occurred more often with IC14 than placebo (hepatobiliary events 3.8% in IC14 vs. 0% in placebo; renal failure events 5.3% in IC14 vs. 0.9% in placebo).

In studies of IC14 in non-human primates, small numbers of vitreous cells were noted in animals treated with IC14 daily for 14 days that resolved over the following 28 days. These changes were not associated with pathological findings in the eyes and were considered of minor toxicological significance. Eye findings have not been observed in 63 human participants treated with IC14 who had one or more ophthalmologic and/or slit lamp examinations and there were no pathological findings in the eyes of 20 non-human primates that were treated with weekly intravenous doses of either 20 mg/kg/week or 50 mg/kg/week for 26 weeks.

5.2. Risks of Investigational Product Cited in Medical Literature

There is a theoretical risk of immunosuppression with IC14 treatment, although this has not been reported in the medical literature. Medications that cause immunosuppression make patients more susceptible to certain kinds of infections, including bacterial infection. Because IC14 does not block a number of alternative pathways that can be used by the host to respond to infection (e.g., complement), it is not broadly immunosuppressive and the number of participants with secondary bacterial infections has not been increased in clinical trials of IC14. Nevertheless, treatment with IC14 could lead to secondary bacterial infections necessitating treatment with antibiotics, treatment in the ICU, or death. It is possible that IC14 might make COVID-19 worse, which could result in worsening respiratory failure, admission to the ICU, or death.

Monoclonal antibodies carry the risk of infusion reactions and in some cases have been reported to cause cytokine storm. In 168 healthy participants and participants with infections treated with IC14, one subject developed an infusion reaction (hypotension and rash), which was successfully treated with ranitidine, dimetindine, and prednisolone. IC14 does not cause cellular activation in vitro and no episodes resembling cytokine storm have been reported in the 168 treated participants treated with IC14.

5.3. Risks of Other Protocol Specified Medications

Participants in this study will be treated with remdesivir, an antiviral medication that has been shown to reduce the time to recovery in hospitalized patients with COVID-19 illness (Beigel et al. 2020). In a recent randomized placebo-controlled trial of remdesivir in hospitalized patients with COVID-19 illness, AEs and SAEs were numerically less frequent in the remdesivir vs. the placebo group. The most common AEs (>5%) in the remdesivir group were decreased hemoglobin (7.9%) and decreased GFR/increased creatinine (7.4%), but these were either more common or numerically similar in the placebo group (9.0% and 7.3%, respectively). In a randomized, open-label trial comparing 5 or 10 days of remdesivir

for moderate COVID-19 pneumonia (i.e. radiologic pulmonary opacities with SpO2 > 94%) against standard care (Spinner 2020: PMID: 32821939) serious adverse events were less common in the remdesivir groups (5% in both) than in the standard care group (9%). Adverse events were experienced by 51% of patients in the 5-day remdesivir group, 59% in the 10-day remdesivir group, and 47% in the standard care group. Adverse events that were more common in the remdesivir groups than in the standard care group included nausea, hypokalemia, and headache.

It is likely that many participants in this study may be treated with dexamethasone or an equivalent corticosteroid at baseline, or if they worsen during the study, because of the results of the RECOVERY trial (Recovery 2020). There is a theoretical rick that concomitant use of dexamethasone and IC14 could increase the risk of secondary infections, although there are no data to support this at the present time. This will be a common risk for all participants with COVID-19 who are treated with corticosteroids and a biological response modifier. At present there are no preclinical or clinical studies in which IC14 has been evaluated in the presence of dexamethasone or other corticosteroids.

5.4. Risks of Study Procedures

The only study-related procedures to be performed will be venipunctures for blood drawing and collection of nasal swabs. Venipuncture carries the risk of local pain, redness or swelling. Collection of nasal swabs may be associated with transient mild discomfort or epistaxis

5.5. Potential Benefits

Participants might benefit from participating in this trial if the IC14 antibody treatment improves the time to recovery from COVID-19 illness and/or if IC14 antibody treatment improves the number of days-alive-and-free of higher-level respiratory support in an intensive care unit, and they are randomized to the active treatment group. If the IC14 antibody treatment does not have benefits, then the participants will have no direct benefits from participating in this trial. Participants who participate in this trial will be helping other people in the future because this trial will help to determine what therapeutic agents in combination with remdesivir do or do not work for the treatment of COVID-19 illness.

6. Investigational Agent Intervention

6.1. Investigational Agent

6.1.1. Investigational Agent

The study drug/investigational agent, IC14, will be supplied to DAIT/NIAID by Implicit Bioscience Ltd. (Seattle, WA, USA). IC14 is a recombinant chimeric (murine/human) mAb against human CD14 in which the murine variable regions have been combined with IgG4 constant regions. The mAb binds surface and soluble human CD14 proteins with high affinity. IC14 is secreted from Chinese hamster ovary cells as an $L_2H_2\gamma_4$ immunoglobulin. IC14 bulk product is manufactured by AGC Biologics, Inc. (Bothell, WA, USA) under Good Manufacturing Practice guidelines.
IC14 drug product is manufactured by Althea Technologies, Inc. (now Ajinomoto Bio-Pharma Services, San Diego, CA, USA) under Good Manufacturing Practice guidelines.

6.1.1.1. Formulation, Packaging, Labeling and Shipping

The investigational drug product will be supplied as a sterile solution at a concentration of 5 mg/mL for intravenous administration totaling 125 mg in a volume of 25 mL in a 30-mL single-use glass vial. More than one vial may be required to prepare each dose.

IC14 drug product (Lot No. 1-FIN-0779) will be shipped from Implicit Bioscience's GMP storage facility maintained by Caligor Coghlan Pharma Services (Bastrop, TX) to the DAIT/ NIAID Distributor, Eminent Corporation (Frederick MD), who will add a label containing the study sponsor name and study ID. Glass vials (30 mL volume) of IC14 containing 125 mg of IC14 at

25 mg/mL are stored in tamper-resistant cardboard cartons that contain 10 vials per carton and are secured by a foam insert. IC14 must be stored and transported at 2-8ºC (36-46 F) in an upright position and protected from light. The temperature of all drug shipments is monitored and recorded by TempTale devices added to pre-conditioned and qualified shipping containers.

6.1.1.2. Dosage, Preparation, and Administration

The dosage regimen to be studied has been used safely in prior investigations of IC14 as a treatment for community-acquired pneumonia, severe sepsis and ARDS (Axtelle et al 2003; Reinhart et al 2004). In normal volunteers, a single intravenous dose of 4 mg/kg produced a Cmax = 72.85 mcg/mL with a $T_{1/2}$ = 15.79 hr. In participants with community-acquired pneumonia and sepsis treated with the proposed dosing regimen of 4 mg/kg on Day 1 followed by 2 mg/kg on Days 2, 3 4, the Cmax = 52.7 mcg/mL with a T1/2 = 23.6 hr. (Axtelle et al. 2003).

Participants will receive a dose of 4 mg/kg in a solution of 250 mL 0.9% w/v NaCl over 2 hours on Study Day 1, followed by 2 mg/kg in a solution of 250 mL 0.9% w/v NaCl over 2 hours once daily on Study Days 2-4. Premedication with antihistamines or corticosteroids is not necessary based on treatment of 168 normal volunteers and participants with infections (Section 5.1). Study drug will be administered as a single dose daily for four consecutive days at approximately 24-hr intervals. The dose of study drug will be calculated based on body weight of the participant. The maximum dose administered will be that for a 125-kg participant (i.e., if a participant weighs >125 kg, the dose of study drug will be calculated based on a weight of 125 kg – i.e. maximum dose is 500mg on study day 1 and 250 mg on study days 2-4). Preparation of the infusion bag may occur up to 12 hours before administration. Once prepared, the infusion bag must be kept refrigerated at 2-8°C until the time of administration. Placebo will consist of an identical-appearing infusion of 250 mL 0.9% w/v NaCl over 2 hours once daily.

Participants will not be pretreated with antihistamines or steroids prior to infusion of study drug because of the rarity of infusion reactions in clinical studies with IC14 (e.g. one infusion reaction in 168 participants treated to date)., and the likelihood that many participants will be receiving corticosteroids as part of standard of care However, if three or more infusion reactions occur during the study, consideration will be given to adding pretreatment prior to infusion of the study drug in subsequent participants.

The study drug or placebo should be administered via a volumetric infusion pump using standard tubing. Filtration of the study drug (IC14) is not needed prior to or during infusion. The infusion should be via a dedicated IV line or lumen of a multiple lumen catheter, preferably with no other medications, and flushed before and after with 10 mL normal saline. It should be infused over 2 hours at a rate of approximately 2 mL/min. Study drug start and stop times must be recorded in the participants' chart.

The Pharmacy will blind the study drug and the placebo for infusion using institutional standard operating procedures. All study personnel other than the study pharmacist will be blinded to study drug assignment.

Participants who improve rapidly and qualify for hospital discharge before completing all of the study drug infusions will not be held in the hospital to complete all infusions of the study drug; however they will remain in the intent-to-treat population provided that they have been randomized and have received one or more doses of the study drug.

6.1.1.3. Storage

Study drug must be refrigerated at 2-8°C. IC14 is a protein and should not be frozen, vigorously shaken, or transported via pneumatic tube delivery systems. To ensure appropriate storage conditions, refrigerator temperatures should be measured and recorded daily. The storage area should have access restricted to study personnel only.

6.2. Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of the investigational agent, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed.

All records regarding the disposition of the investigational product will be available for inspection.

At the end of the study all unused vials will be disposed of appropriately in accordance with study protocol and any institutional Standard Operating Procedures. Reconciliation of shipped, dispensed, and remaining drug will be performed. Any discrepancies noted will be investigated, resolved and documented.

6.3. Assessment of Participant Compliance with Investigational Agent

Participant compliance with the investigational agent will be monitored based on medication administration records in the participant's medical record and the study records.

6.4. Toxicity Prevention and Management

The study treatment (dose, timing, duration) should not be modified. The study medication should be stopped for suspected allergy or anaphylaxis as described below.

6.5. Premature Discontinuation of Investigational Agent

Participants may be discontinued from the study at any time for the following reasons:

a. Suspected allergy or anaphylaxis. The study drug infusion must be discontinued, and the participant must be discontinued from further study treatment if the participant develops signs and symptoms of anaphylaxis or hypersensitivity fulfilling the following criteria (Sampson et al. 2006):

   Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:

   i. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia); or

   ii. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

   Note: Collect a blood for serum tryptase measurement as soon as possible (within 60 minutes) after emergency treatment for suspected anaphylaxis. Collect another blood sample for tryptase levels between 60-120 minutes (but no later than 4 hours) after emergency treatment. If the first sample cannot be obtained within the first 60 minutes the second sample should still be obtained. In addition a baseline serum tryptase should be obtained 24 hours or more after the onset of symptoms. An elevated serum tryptase will support the diagnosis of anaphylaxis (NICE 2020). Respiratory compromise, reduced BP, or symptoms of end-organ dysfunction determined by the PI to be related to the underlying SARS-CoV-2 infection should not be considered as one of the clinical criteria for a severe allergic reaction listed above. The Site Principal Investigator should contact the VCC Medical Monitor to determine whether to discontinue study treatment for a given participant not meeting these criteria but for whom there is a clinical suspicion of a significant allergic reaction or possible anaphylaxis.

b. Eye symptoms. If a participant develops eye symptoms such as decreased visual acuity, significant redness (above baseline), pain, or light sensitivity, they should be discontinued from study drug and scheduled for a full ophthalmic examination with slit-lamp examination as soon as feasible.

c. New infections. If a participant develops a proven or suspected new infection during the 4 days of study drug treatment, the study drug should be discontinued, and the patient should be treated by participant's primary physicians as clinically appropriate.

d. Other safety concerns. The Site Principal Investigator is authorized to discontinue the study drug at any time if it is in the best interest of the safety of the participant. Treatment may also be discontinued at any time at the request of the study participant.

e. Investigator or treating physician choice. Study therapy may also be prematurely discontinued if the investigator believes that the study treatment is no longer in the best interests of the participant.

f. Patient choice. In addition, participants who are enrolled in this study may choose to terminate their participation in the study at any time.

6.5.1. Follow-up of participants who discontinue treatment

Participants who discontinue treatment for any reason will be asked if they agree to continue to be monitored by the Study Team through the final study Day (Day 60).

7. Other Medications

7.1. Concomitant Medications

7.1.1. Protocol-mandated medications

All participants in this study will receive remdesivir (antiviral) according to current approved dosing for COVID-19 illness. Remdesivir will be provided by Gilead Sciences, Inc., for the study and administered intravenously for 5 days beginning with a 200 mg loading dose on Day 1, followed by 100 mg/day on Days 2-5 (Beigel et al. 2020). Study participants may receive up to 10 doses of remdesivir if they have received up to 4 doses (including the loading dose) of this agent for the treatment of COVID-19 prior to enrolling in the study. If already on remdesivir prior to randomization, a second loading dose should not be administered.

7.1.2 Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of the VEKLURY® (remdesivir), including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed.

All records regarding the disposition of VEKLURY® (remdesivir) will be available for inspection.

At the end of the study all unused vials will be disposed of appropriately in accordance with study protocol and any institutional Standard Operating Procedures. Reconciliation of shipped, dispensed, and remaining drug will be performed. Any discrepancies noted will be investigated, resolved and documented.

7.1.3. Other permitted concomitant medications

Study participants may receive other approved medications at the discretion of the physician(s) caring for the participant, if they are not on the list of prohibited medications below.

Baseline use of dexamethasone at 6 mg/day by iv or po route, or the equivalent dose of another corticosteroid, is allowed at the discretion of the participant's physician. Randomization to study treatment will be stratified by baseline dexamethasone or equivalent dose of corticosteroid used for treatment of COVID-19 illness. For participants who are not on dexamethasone at baseline, dexamethasone may be added after randomization at a dose of 6 mg/day at the discretion of the participant's physician if the participant worsens by $\geq$1 category on the Eight-point ordinal scale.

Convalescent plasma may be added after randomization at the discretion of the participant's physician if the participant worsens by $\geq$1 category on the Eight-point ordinal scale.

The study investigators at each site are responsible for recording all non-study medications for each participant.

7.2. Prophylactic Medications

(None)

7.3. Prohibited Medications

Participants in this trial may not receive any of the following concomitant medications:

Table 2. Prohibited Medications	
TNFα inhibitors	
a. Etanercept (Enbrel)	TNFα inhibitor (TNFR2 fusion protein)
b. Infliximab (Remicade)	TNFα inhibitor (anti- TNFα monoclonal antibody)
c. Adalimumab (Humira)	TNFα inhibitor (anti- TNFα monoclonal antibody)
d. Certolizumab (Cimzia)	TNFα inhibitor (anti- TNFα Fab' fragment)
e. Golimumab (Simponi)	TNFα inhibitor (anti- TNFα monoclonal antibody)
IL-1β inhibitors	
a. Anakinra (Kineret)	IL-1β receptor antagonist
b. Rilonacept (Arcalyst)	IL-1β inhibitor (IL-1β "trap")
IL-6 inhibitors	
a. Tocilizumab (Actemra)	IL-6 receptor inhibitor (anti-IL-6R monoclonal antibody)
b. Sarilumab (Kevzara)	IL-6 receptor inhibitor (anti-IL-6R monoclonal antibody)
Live-attenuated vaccines	
Other immunosuppressant/immunomodulatory drugs or treatments	
Other non-approved experimental drug therapies for COVID-19 including antiviral medications (e.g. hydroxychloroquine, lopinavir/ritonavir)	

7.4. Rescue Medications

Additional FDA approved medications can be added to the participant's treatment regimen during the study period at the discretion of the treating physician, except for the prohibited medications listed in Table 2 above. The study investigators at each site are responsible for recording all non-study medications for each participant.

8. Study Procedures

8.1. Enrollment

The research study will be explained in lay terms to each potential research participant. The potential participant or, in the instance that the patient is not able to sign for themselves, a Legally Authorized Representative (LAR) will sign an

electronic informed consent form before undergoing any study procedures. Once the electronic informed consent has been signed, the participant is considered to be enrolled in the study and will be assigned a unique participant number.

Participants will be enrolled at approximately 14 sites in the United States. Enrollment will occur over a period of 6 to 12 months until approximately 300 participants are enrolled, randomized and treated with the first dose of the study drug. If necessary, enrollment and treatment may continue for up to 350 participants. It is anticipated that enrollment will begin in Q1 2021.

8.2. Recruitment/Screening Period

The purpose of the recruitment and screening period is to confirm eligibility to enroll in the study. The screening period will begin when a patient is hospitalized. Patients admitted to acute care units at the clinical sites will be screened each day to identify patients meeting eligibility criteria. If determination of eligibility can be made based on review of data obtained as part of clinical care, the patient's attending physician will be approached for permission to enroll the patient in the study. If permission is given, the patient or their LAR will be approached to obtain informed consent. Once informed consent is given, the patient is considered to be enrolled in the study. (NOTE: Any of the procedures, assessments, and laboratory measures necessary for screening to assess eligibility that are not performed as part of standard clinical care at the clinical site's institution will require informed consent to complete screening. This includes obtaining a serum or urine pregnancy test for women of childbearing potential who did not have a pregnancy test as part of standard of care). Women of child bearing potential must be willing to use birth control for the duration of the study. After informed consent is obtained, any additional necessary screening procedures will be performed and final determination and documentation of inclusion and exclusion criteria will be completed. If, during recruitment and screening, the participant is determined to be SARS-CoV-2 positive but consent cannot be obtained or an eligibility criterion is not met, the participant will be considered to be "screened, not eligible". If a participant passes the screening phase they will be considered to be "screened, eligible" and the following will be completed:

a. Documentation of medical/surgical history.
b. Documentation of concomitant medications.
c. Documentation of SARS-CoV-2 RT-PCR test results.
d. Chest radiograph (posteroanterior and lateral views if possible)
e. Documentation of results of urine pregnancy test, if applicable .

Once a participant has been consented and screening has shown that a participant is eligible, the participant should be randomized within 24 hours and treatment should be started within 12 hours after randomization.

8.3. Study Visits or Study Assessments

8.3.1. Baseline – may be done on Study Day 1 Pre-Treatment

The following procedures must be performed, or samples must be collected, prior to study drug administration and within 24 hours of determining eligibility:

- Document reason for hospital admission.
- Document whether medical care is provided under conventional, contingency, or crisis standards of care.
- Physical examination.
- Record vital signs (height, weight, blood pressure, respiratory rate, heart rate and temperature).
- Record variables for Sequential Organ Failure Assessment score (SOFA; Appendix A).
- Determine and record Eight-Point Ordinal Scale (Appendix C).
- Draw the following clinical labs if not collected as part of clinical care: Complete blood count (hematocrit/hemoglobin, platelet count, white blood cell count with differential), PT/INR/PTT, Complete metabolic

panel (serum sodium, bicarbonate, potassium, blood urea nitrogen, creatinine, AST, ALT, alkaline phosphatase, total bilirubin), ferritin, CRP, LDH, D-dimer.

- Collect blood for study labs (15 ml blood)
  - Process and freeze (-80°C) serum for anti-drug antibodies.
  - Process and freeze (-80°C) serum for IC14 PK measurement (to be collected on 40 participants)
  - Process plasma specimens for prognostic biomarkers.
  - Collect nasal swab for viral detection.

8.3.2. Study Day 1 – Treatment and Post-Treatment

- Administer study drug over 2 hours. The participant should be monitored during infusion and for 1 hour following infusion. Document any interruption of study drug infusion during administration.
- Administer remdesivir 200 mg IV loading dose.
- Collect blood for study labs
  - Process and freeze (-80°C) serum for IC14 PK measurement approximately 1 hour after dosing is completed (to be collected on 40 participants)
- Record vital signs (blood pressure, respiratory rate, heart rate, and temperature) approximately 30 and 60 min after completion of study drug.
- Record variables for Sequential Organ Failure Assessment score (SOFA; Appendix A)
- Determine and record Eight-Point Ordinal Scale performed twice daily as close as possible to 8:00 a.m. and 8:00 p.m. (Appendix C)
- After completion of study infusion, complete the following evaluations in Section 8.3.3..

8.3.3. Daily Evaluations While Hospitalized

- Record vital signs (blood pressure, weight, respiratory rate, heart rate and temperature).
- Assessment for adverse events (medical record, bedside nurse, and patient if possible).
- Record concomitant medications
- Determine and record Eight-Point Ordinal Scale performed twice daily as close as possible to 8:00 a.m. and 8:00 p.m. (Appendix C).
- Record oxygenation (SpO2 and/or PaO2) and supplemental oxygen delivery (nasal cannula flow, high-flow nasal cannula – FiO2 and flow, non-invasive ventilation (CPAP level, FiO2), invasive ventilation (PEEP, FiO2) daily.
- Document presence or absence of eye symptoms, including decreased visual acuity, conjunctival redness, light sensitivity or pain in the eyes. If eye symptoms are present, discontinue dosing if still ongoing and schedule an eye examination as soon as feasible. If eye symptoms occur after dosing has been completed, schedule an eye examination as soon as feasible, but the participant may continue in the study and have all scheduled evaluations.
- Record date and time of participant death. Complete serious adverse event reporting requirements (see Section 12.4). Document whether death occurred after withdrawal of life support and/or comfort measures.
- Collect blood and process serum for tryptase between 60-120 minutes (but no later than 4 hours) after emergency treatment if participant has suspected allergic reaction/anaphylaxis post infusion (see section 6.5) .
- Unscheduled sampling of anti-drug antibodies should be performed if participant has a suspected immunologically related adverse event.
- Record complete blood count (hematocrit/hemoglobin, platelet count, white blood cell count with differential), PT/INR/PTT, Complete metabolic panel (serum sodium, bicarbonate, potassium, blood urea nitrogen, creatinine, AST, ALT, alkaline phosphatase, total bilirubin), ferritin, CRP, LDH, D-dimer , if collected as part of clinical care. Record value obtained closest to 8:00 AM on study day.

- Document whether medical care is provided under conventional, contingency, or crisis standards of care.

8.3.4. Study Day 2

- Conduct all study evaluations in Section 8.3.3, Daily Evaluations While Hospitalized.
- Determine and record Eight-Point Ordinal Scale performed twice daily as close as possible to 8:00 a.m. and 8:00 p.m. (Appendix C)
- Draw the following clinical labs if not collected as part of clinical care (values closest to 8:00 a.m. on study day): Complete blood count (hematocrit/hemoglobin, platelet count, white blood cell count with differential), PT/INR/PTT, Complete metabolic panel (serum sodium, bicarbonate, potassium, blood urea nitrogen, creatinine, AST, ALT, alkaline phosphatase, total bilirubin), ferritin, CRP, LDH, D-dimer.
- Collect blood for study labs
  - Process and freeze (-80°C) serum for PK prior to study drug infusion (to be collected on 40 participants).
  - Process and freeze (-80°C) plasma for prognostic biomarkers.
- Administer study drug over 2 hours. The participant should be monitored during infusion and for 1 hour following infusion. Document any interruption of study drug infusion during administration.
- Administer remdesivir 100 mg IV.

8.3.5. Study Day 3

- Conduct all study evaluations in Section 8.3.3, Daily Evaluations While Hospitalized.
- Determine and record Eight-Point Ordinal Scale performed twice daily as close as possible to 8:00 a.m. and 8:00 p.m. (Appendix C)
- Collect blood for study labs
  - Process and freeze (-80°C) serum for PK prior to study drug infusion (40 participants).
- Administer study drug over 2 hours. The participant should be monitored during infusion and for 1 hour following infusion. Document any interruption of study drug infusion during administration.
- Administer remdesivir 100 mg IV.

8.3.6. Study Day 4

- Conduct all study evaluations in Section 8.3.3, Daily Evaluations While Hospitalized.
- Determine and record Eight-Point Ordinal Scale performed twice daily as close as possible to 8:00 a.m and 8:00 p.m. (Appendix C)
- Record variables for Sequential Organ Failure Assessment score (SOFA; Appendix A).
- Draw the following labs if not collected as part of clinical care (values closest to 8:00 am on study day): Complete blood count (hematocrit/hemoglobin, platelet count, white blood cell count with differential), PT/INR/PTT, Complete metabolic panel (serum sodium, bicarbonate, potassium, blood urea nitrogen, creatinine, AST, ALT, alkaline phosphatase, total bilirubin), ferritin, CRP, LDH, D-dimer.
- Collect blood for study labs
  - Process and freeze (-80°C) serum for PK prior to study drug infusion (40 participants).
  - Process and freeze (-80°C) plasma for prognostic biomarkers.
  - Collect fresh whole blood for CD14 receptor occupancy determination (PD assessment) (to be collected from 30 participants at selected sites).
- Collect nasal swab for viral detection.
- Administer study drug over 2 hours. The participant should be monitored during infusion and for 1 hour following infusion. Document any interruption of study drug infusion during administration.

- Administer remdesivir 100 mg IV.

8.3.7. Study Day 5

- Conduct all study evaluations in Section 8.3.3, Daily Evaluations While Hospitalized.
- Determine and record Eight-Point Ordinal Scale performed twice daily as close as possible to 8:00 a.m and 8:00 p.m. (Appendix C)
- Record variables for Sequential Organ Failure Assessment score (SOFA; Appendix A).
- Collect blood for study labs
  - Process and freeze (-80°C) serum for PK at approximately 8:00 am (40 participants).
- Administer remdesivir 100 mg IV.

8.3.8. Study Day 7 **(if hospitalized) Conduct all study evaluations in Section 8.3.3, Daily Evaluations While Hospitalized.**

- Determine and record Eight-Point Ordinal Scale performed twice daily as close as possible to 8:00 a.m and 8:00 p.m. (Appendix C).
- Record variables for Sequential Organ Failure Assessment score (SOFA; Appendix A).
- Draw the following labs if not collected as part of clinical care (values closest to 8:00 a.m. on study day): Complete blood count (hematocrit/hemoglobin, platelet count, white blood cell count with differential), PT/INR/PTT, Complete metabolic panel (serum sodium, bicarbonate, potassium, blood urea nitrogen, creatinine, AST, ALT, alkaline phosphatase, total bilirubin), ferritin, CRP, LDH, D-dimer If not still hospitalized record the most recent lab values.
- Collect blood for study labs, if still hospitalized
  - Process and freeze (-80°C) serum for PK. (40 participants)
  - Process and freeze (-80°C) plasmafor prognostic biomarkers.
  - Collect fresh whole blood for CD14 receptor occupancy determination (PD assessment) (to be collected from 30 participants at selected sites).
- Collect nasal swab for viral detection.

8.3.9. Study Day 14 (if hospitalized or if patient has been discharged prior to this visit conduct a phone call to collect the Eight-Point Ordinal Scale and AE's) Conduct all study evaluations in Section 8.3.3, Daily Evaluations While Hospitalized.

- Determine and record Eight-Point Ordinal Scale performed twice daily as close as possible to 8:00 a.m and 8:00 p.m. (Appendix C).
- Record variables for Sequential Organ Failure Assessment score (SOFA; Appendix A).
- Draw the following labs if not collected as part of clinical care (values closest to 8:00 am on study day): Complete blood count (hematocrit/hemoglobin, platelet count, white blood cell count with differential), PT/INR/PTT, Complete metabolic panel (serum sodium, bicarbonate, potassium, blood urea nitrogen, creatinine, AST, ALT, alkaline phosphatase, total bilirubin), ferritin, CRP, LDH, D-dimer. If not still hospitalized record the most recent lab values.
- Collect blood for study labs, if still hospitalized
  - Process and freeze (-80°C) plasma for prognostic biomarkers.
  - Process and freeze (-80°C) serum for PK. (40 participants)
- Collect nasal swab for viral detection.

8.3.10. Study Day 21 (if hospitalized)Conduct all study evaluations in Section 8.3.3, Daily Evaluations While Hospitalized.

- Determine and record Eight-Point Ordinal Scale performed twice daily as close as possible to 8:00 a.m and 8:00 p.m. (Appendix C).
- Record variables for Sequential Organ Failure Assessment score (SOFA; Appendix A).
- Draw the following labs if not collected as part of clinical care (values closest to 8:00 am on study day): Complete blood count (hematocrit/hemoglobin, platelet count, white blood cell count with differential), PT/INR/PTT, Complete metabolic panel (serum sodium, bicarbonate, potassium, blood urea nitrogen, creatinine, AST, ALT, alkaline phosphatase, total bilirubin), ferritin, CRP, LDH, D-dimer. If not still hospitalized record the most recent lab values.
- Collect blood for study labs, if still hospitalized
  - Process and freeze (-80°C) plasma for prognostic biomarkers

8.3.11. Study Day 28

It is preferred that this visit is in person to obtain safety laboratory tests 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, the visit may be conducted by phone or virtually, and only clinical data will be obtained. All participants will undergo an ocular examination. This examination will be scheduled as a separate in-person visit, usually in the ophthalmology clinic. This visit should be competed at 28 +/-1 day to obtain the Eight-Point Ordinal Scale and survival. Chest x-ray and labs should be obtained at this visit or as soon as possible after the visit.

- Record adverse events.
- If hospitalized, conduct all study evaluations in Section 8.3.3, Daily Evaluations While Hospitalized.
- Determine and record Eight-Point Ordinal Scale performed twice daily as close as possible to 8:00 a.m and 8:00 p.m. (Appendix C).
- Draw or record labs, including Complete blood count (hematocrit/hemoglobin, platelet count, white blood cell count with differential), PT/INR/PTT, Complete metabolic panel (serum sodium, bicarbonate, potassium, blood urea nitrogen, creatinine, AST, ALT, alkaline phosphatase, total bilirubin), ferritin, CRP, LDH, D-dimer, if not collected as part of clinical care. Record value obtained closest to 8:00 AM on study day. If not still hospitalized and not seen in clinic, record the most recent lab values.
- Collect blood for study labs, if still hospitalized or if patient is seen in clinic
  - Process and freeze (-80°C) serum for anti-drug antibodies if the participant is still hospitalized or is seen in clinic.
- Chest radiograph (PA and lateral views)
- A full ocular examination should be scheduled when the participant is clinically stable, free of COVID-19 symptoms, beyond the quarantine period, and able to comply with the exam (typically between Day 28 and before Day 60).

8.3.12. Study Day 60 End-of-Study Evaluation

It is preferred that this visit is in person. However, infection control or other restrictions may limit the ability of the participant to return to the clinic. In this case, the visit may be conducted by phone or virtually and the chest radiograph scheduled as soon as feasible. This visit should be at 60+/-3 days.

- Record serious adverse events
- Patient-Reported Outcomes assessment using the EQ-5D-5L instrument (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/)
- Chest radiograph (PA and lateral views)
- A full ocular examination should be scheduled when the participant is clinically stable, free of COVID-19 symptoms, beyond the quarantine period, and able to comply with the exam (between Day 28 and on or before Day 60).

Table 3. Schedule of Assessments

	Screening	Baseline before study drug	D1	D2	D3	D4	D5	Daily While Hospitalized	D7[12]	D14[12]	D21[12, 13]	D28[13]	D60 (End of Study)
Visit Windows												+/- 1 day	+/- 3 days
Informed consent	X												
Inclusion/Exclusion	X												
Med/surg history	X												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
SARS-CoV-2 RT-PCR[1]	X												
Chest x-ray	X											X	X
PRO: EQ-5D-5L													X
Pregnancy test[2]	X												
Physical exam		X											
Vital signs (including weight)		X	X	X	X	X	X	X	X	X	X	X	
Full Ocular examination [3]												X	X
Record oxygen/ventilatory support		X	X	X	X	X	X	X	X	X	X	X	
Eight-Point ordinal scale (Appendix C) twice daily		X	X	X	X	X	X	X	X	X	X	X	
SOFA score (Appendix A)		X	X			X	X		X	X	X		
Potential Telephone Calls										X		X	X
Draw or record Clinical Lab Values[4]		X		X	X*	X	X*	X*	X	X	X	X	
Whole blood for CD14 receptor binding (PD)[5]						X			X				
Serum for IC14 PK[6]		X	X	X	X	X	X		X	X			
Serum anti-drug antibodies[7]		X										X	
Plasma for prognostic biomakers[8]		X		X		X			X	X	X		
Nasal swab for viral detection		X				X			X	X			
Administer study drug[9]			X	X	X	X							
Administer remdesivir[10]			X	X	X	X	X						
Assess for AEs[11]			X	X	X	X	X	X	X	X	X	X	
Assess for SAEs and death			X	X	X	X	X	X	X	X	X	X	X

1. Positive RT-PCR for SARS-CoV-2 within 1 week before enrollment is sufficient to meet inclusion criteria but repeat test should be obtained.
2. Serum beta-hCG or urine pregnancy test must be collected in women of childbearing potential.
3. A full ocular examination should be scheduled when the participant is clinically stable, free of COVID-19 symptoms, beyond the quarantine period, and able to comply with the exam (typically between Day 28 and before Day 60)..
4. Draw or record labs per section 8.3 at baseline and Days 2, 3, 4, 7, 14, 21, 28 if hospitalized and if not collected as part of clinical care (values closest to 8:00 am on study day. * Record Daily and Days 3 and 5 clinical lab values only if drawn as part of clinical care.
5. Whole blood samples to be drawn at selected sites on a total of 30 participants enrolled.
6. Serum PK on Days 2-4 should be drawn before study drug infusion on 40 participants.
7. Additional unscheduled sampling of anti-drug antibodies should be performed if participant has a suspected immunologically related AE.
8. Collect plasma for prognostic biomarkers.
9. Study drug will be given as a 120-min IV infusion as a single dose once daily for four consecutive days (at 24-hr intervals).
10. Remdesivir will be given as loading dose 200 mg IV on day 1 then 100 mg IV on day 2-5
11. To be assessed through examination of daily progress notes and through communication with bedside nurse and, if possible, participant
12. If still hospitalized.
13. Preferred that this visit is in person to obtain safety laboratory tests and clinical outcome data. However, if participant is unable to return to the study site clinic the visit may be conducted by phone or virtually and the chest radiograph and labs scheduled as soon as possible. If not still hospitalized and not seen in clinic, record the most recent lab values.

8.4. Unscheduled Visits

If a study participant develops eye signs or symptoms [decreased visual acuity, redness (above baseline), pain] after completion of the study drug administration (i.e. Day 5 and onward) they should be scheduled for a full ophthalmic examination after discharge or at the end of Day 28+/-7 days. The study team will schedule this examination and the study will pay for this visit.

8.5. Visit Windows

Study monitoring should take place daily through Day 28 or as long as the participant is hospitalized. For participants who are discharged prior to day 28, the Day 28 visit should be completed remotely within +/- 1-day window if the participant is unable to return to the clinic. Likewise, if the participant has been discharged, the Day 14 and 21 visits should be completed remotely if the participant is unable to return to the clinic. The Day 60 visit should occur in person if possible, within a +/- 3-day window. If unable to return to the clinic this visit can occur remotely.

8.6. Telephone visits

If a study participant has been discharged prior to one of the scheduled Study Day visits, then that study visit should be conducted by telephone to ascertain the participant's clinical status. Determine and record Eight-Point Ordinal Scale and record adverse events.

8.7. Reimbursement for Study Visits

Study participants will not be reimbursed for time during hospital monitoring. Study participants who are outpatients will be reimbursed for their time for telephone interviews and in-person outpatient visits.

9. Mechanistic Assays

Mechanistic assays will be performed on stored blood samples collected during the study. These assays include serum measurements of soluble CD14 (sCD14), inflammatory biomarkers (CRP, ferritin, LDH), and cytokines (TNFα, IL-1β, IL-6, IL-8, IL-10, GM-CSF and others). We expect that sCD14 will rise in serum, reflecting complexing with the IC14 anti-CD14 monoclonal antibody. We expect that inflammatory biomarkers and cytokines will fall in participants treated with the IC14 monoclonal antibody.

10. Biospecimen Storage

Aliquots of serum and plasma will be stored frozen in the University of Washington Central Research Laboratory and analyzed in batches after the final participant has completed the study. Left over aliquots of serum and plasma will be stored frozen (-80C) in a biorepository of participant samples at a location approved by DAIT/NIAID. The biorepository samples will be coded and will be permanently unlinked from the patient's clinical information collected during the study and the hospitalization for COVID-19 illness.

11. Criteria for Participant and Study Completion and Premature Study Termination

11.1. Participant Completion

The study will be complete for each participant at the end of the Day 60 visit.

11.2. Participant Stopping Rules and Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.

2. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
3. The participant dies.
4. The Investigator no longer believes participation is in the best interest of the participant.
5. Individual safety stopping rules:
    a. Suspected allergy or anaphylaxis. The study drug infusion must be discontinued, and the participant must be discontinued from further study treatment if the participant develops signs and symptoms of anaphylaxis or hypersensitivity fulfilling the following criteria (Sampson et al. 2006):

    Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:

        i. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia); or
        ii. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

        Note: Collect a blood sample for serum tryptase measurement as soon as possible (within 60 minutes) after emergency treatment for suspected anaphylaxis. Collect another blood sample for tryptase levels between 60-120 minutes (but no later than 4 hours) after emergency treatment. If the first sample cannot be obtained within the first 60 minutes the second sample should still be obtained. In addition a baseline serum tryptase should be obtained 24 hours or more after the onset of symptoms. An elevated serum tryptase will support the diagnosis of anaphylaxis (NICE 2020). Respiratory compromise, reduced BP, or symptoms of end-organ dysfunction determined by the PI to be related to the underlying SARS-CoV-2 infection should not be considered as one of the clinical criteria for a severe allergic reaction listed above. The Site Principal Investigator should contact the study monitor to determine whether to discontinue study treatment for a given participant not meeting these criteria but for whom there is a clinical suspicion of a significant allergic reaction or possible anaphylaxis.

    b. Eye symptoms or signs. If a participant develops eye symptoms such as decreased visual acuity, significant redness (above baseline), pain, or light sensitivity, they should be discontinued from study drug and scheduled for a full ophthalmic examination with slit-lamp examination as soon as feasible.

    c. New infections. If a participant develops a proven or suspected new infection during the 4 days of study drug treatment, the study drug should be discontinued, and the patient should be treated by participant's primary physicians as clinically appropriate.

    d. Other safety concerns. The Site Principal Investigator is authorized to discontinue the study drug at any time if it is in the best interest of the safety of the participant. Treatment may also be discontinued at any time at the request of the study participant.

11.3. Participant Replacement

Randomized participants will not be replaced for any reason.

11.4. Follow-up after Early Study Withdrawal

If a participant receives one or more doses of the study drug and withdraws from the study for any reason, the study team should ask the participant if they would be willing to be followed by the study team for the duration of the study,

i.e. through Day 60 in order to determine the participant's clinical status and to assess for any adverse events that might be attributable to the study drug.

11.5. Study Stopping Rules

The study may be stopped prematurely for reasons of feasibility (e.g. inability to recruit) or based on DSMB recommendations related to safety or futility after an interim analysis.

12. Safety Monitoring and Reporting

12.1. Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 12.5, *Reporting of Serious Adverse Events and Adverse Events*) to the sponsor (DAIT/NIAID). Appropriate notifications will also be made to site principal investigators, Institutional Review Boards (IRBs), and health authorities.
Information in this section complies with *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice*, 21CFR Parts 312 and 320).

12.2. Definitions

12.2.1. Adverse Event (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)

12.2.1.1. Suspected Adverse Reaction (SAR)

Any adverse event for which there is a reasonable possibility that the investigational drug [or investigational study therapy regimen] caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

12.2.2. Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity, severity, or rate of occurrence that has been observed; or, *if an Investigator Brochure is not required or available*, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended (21 CFR 312.32(a)).

"Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a)

12.2.3. Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor (DAIT/NIAID), it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or Sponsor (DAIT/NIAID) its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.

3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization 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 above.

12.2.4. Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the specific to the sponsor's program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

12.3. Grading and Attribution of Adverse Events

12.3.1. Grading Criteria

The study site will grade the severity of adverse events experienced by the study participants according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE) except for anaphylaxis which will use Table 4 listed below. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the Study Principal Investigators and has been deemed appropriate for the participant population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild
Grade 2 = moderate
Grade 3 = severe
Grade 4 = life-threatening or urgent intervention required.
Grade 5 = death.

All adverse events regardless of grade are considered recordable for this study. For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from the time that consent is given to baseline will also be recorded as adverse events but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

Table 4. Grading System of Severity of Anaphylaxis (Brown, 2004)

Grade	Defined by
1. Mild (skin and subcutaneous tissues, gastrointestinal, and/or mild respiratory)	Flushing urticaria, periorbital or facial angioedema; mild dyspnea, wheeze, or upper respiratory symptoms; mild abdominal pain and/or emesis
2. Moderate (mild symptoms and features	Marked dysphagia, hoarseness, and/or stridor; shortness of breath, wheezing, and retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness
3. Severe (hypoxia), hypotension, or neurological compromise	Cyanosis or SPO2 $\leq$92% at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence

12.3.2. Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE electronic case report form (AE/SAE eCRF). Final determination of attribution and expectedness based on the 21CFR312 for safety reporting will be determined by the DAIT/NIAID (Sponsor) in consultation with the VCC Medical Monitor. The relationship of an adverse event to study therapy regimen or procedures will be determined using the descriptors and definitions provided in Table 5.

Table 5. Attribution of Adverse Events

Code	Descriptor	Relationship to primary investigational product and/or other concurrent mandated study therapy or study procedure
UNRELATED CATEGORY		
1	Not Related	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possibly Related	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Related	The adverse event is clearly related.

12.4. Collection and Recording of Adverse Events

12.4.1. Collection Period

Adverse events will be collected from the time of consent until a participant completes study participation; every attempt will be made to collect adverse events through Study Day 60 if a participant withdraws prematurely (without withdrawing consent) or is withdrawn from the study.

12.4.2. Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the participant.
- Interviewing the participant [e.g., using a checklist, structured questioning, diary, etc.].
- Receiving an unsolicited complaint from the participant.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 12.3, *Grading and Attribution of Adverse Events.*

12.4.3. Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 12.2, *Definitions)* on the appropriate eCRF regardless of the relationship to study therapy regimen or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or through Study Day 60 after the participant prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

12.4.3.1. Adverse Events of Special Interest

AESIs for the IC14 study drug are listed below and will be collected and reported in this trial:

- eye abnormalities (new redness, pain, light sensitivity, photophobia)
- new infections
- new thrombocytopenia/serious bleeding
- infusion reactions/anaphylaxis
- hepatobiliary disorders
- acute renal failure

12.5. Reporting of Serious Adverse Events and Adverse Events

12.5.1. Reporting of Serious Adverse Events to Sponsor (DAIT/NIAID)

This section describes the responsibilities of the site investigator to report serious adverse events to the sponsor via VCC using the eCRF. Timely reporting of adverse events is required by 21 CFR 312.32 and ICH E6 (R2) guidelines.

Site investigators will report to the VCC all serious adverse events (see Section 12.2.3, Serious Adverse Event), regardless of relationship or expectedness to the investigational product within 24 hours of discovering the event. The VCC will report all SAEs to DAIT/NIAID (sponsor) as per section 12.7.

For serious adverse events, all requested information on the AE/SAE eCRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE eCRF will be updated and submitted.

12.5.1.1 Reporting AESIs to the IND Sponsor

All AESI will be summarized in a monthly aggregated report that will be reviewed by the VCC MM and DAIT/NIAID MO. If an AESI (Section 12.4.3.1) meets the definition of an SAE (Section 12.2.3*)* the investigator or designee is responsible for reporting the AESI via eCRF within 24 hours of becoming aware of the event. As additional details become available, the eCRF should be updated and submitted. Every time the eCRF is submitted, it should be electronically signed by the investigator or sub-investigator.

12.5.2. Reporting to Health Authority

After an adverse event requiring 24 hour reporting to the sponsor (per Section 12.5.1, Reporting of Serious Adverse Events to Sponsor) is submitted by the site investigator and assessed by the VCC MM and DAIT/NIAID Medical Officer, as per section 12.7, there are two options for DAIT/NIAID to report the adverse event to the appropriate health authorities.

12.5.2.1. Annual Reporting

DAIT/NIAID will include in the annual study report to health authorities all adverse events classified as:

Serious, expected, suspected adverse reactions (see Section 12.2.1.1, Suspected Adverse Reaction, and Section 12.2.2, Unexpected Adverse Event).

Serious and not a suspected adverse reaction (see Section 12.2.2, Suspected Adverse Reaction).

Pregnancies (see section 12.6, Pregnancy Reporting).

Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the Annual Report.

12.5.2.2. Expedited Safety Reporting

This option, with 2 possible categories, applies if the adverse event is classified as one of the following:
Category 1: Serious and unexpected suspected adverse reaction [SUSAR] (see Section 12.2.1.1, *Suspected Adverse Reaction* and Section 12.2, *Unexpected Adverse Event* and 21 CFR 312.32(c)(1)i).
The sponsor shall report to the health authority any suspected adverse reaction that is both serious and unexpected. The sponsor shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, or Stevens-Johnson Syndrome)
2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Certain SAEs occur commonly in this study population and will not be considered as a SUSAR unless there is evidence to suggest a causal relationship to the study intervention (IC14 monoclonal antibody).

Category 2: Any findings from studies that suggest a significant human risk

The sponsor shall report to the Health Authority any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or *in vitro* testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure or package insert or other aspects of the overall conduct of the study.

DAIT/NIAID shall notify the FDA and all participating investigators of expedited Safety Reports within 15 calendar days. Unexpected fatal or immediately life-threatening suspected adverse reaction(s) shall be reported as soon as possible or within 7 calendar days.

12.5.3. Reporting of Adverse Events to IRBs/IECs

All investigators shall report adverse events, including expedited reports, in a timely fashion to their respective IRBs/IECs in accordance with applicable regulations and guidelines. All Safety Reports to the FDA shall be distributed by DAIT/NIAID or designee to all participating investigators for site IRB/IEC submission.

- Pregnancy Reporting. New pregnancies should be reported if pregnancy occurs on or before final study visit at Day 60.

While pregnancy itself is not considered to be an AE or SAE, the investigator shall be informed immediately of any pregnancy in a study participant. A pregnant participant will not receive further study medication and will be withdrawn from active participation in the study, but AEs and SAEs will continue to be monitored. The investigator shall counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy.

The investigator shall report to the VCC all pregnancies within 1 business day of becoming aware of the event using the Pregnancy eCRF. All pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy eCRF shall be updated and submitted to the VCC, VCC MM, and DAIT/NIAID when details about the outcome are available.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities

Any pregnancy complication such as miscarriage or elective termination of a pregnancy for medical reasons must be reported as an SAE to the sponsor as described in Section 12.5.1 Reporting of Serious Adverse Events to Sponsor (DAIT/NIAID). In addition, if the pregnancy results in a congenital abnormality or birth defect, a separate SAE report must be submitted to the VCC, VCC MM, and the Sponsor (DAIT/NIAID), using the SAE reporting procedures described above.

12.6. Reporting of Other Safety Information

An investigator shall promptly notify the VCC when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an adverse event. The VCC, VCC MM and the DAIT/NIAID Medical Officer will review. The VCC MM will report to the IRB of record if applicable.

12.7. Review of Safety Information

12.7.1. Vanderbilt Coordinating Center Medical Monitor Review

The VCC MM will be notified by the site PI of all SAEs within 24 hours of the site becoming aware of the incident. The VCC MM shall review and make initial decisions on the disposition of the SAE and pregnancy reports received by the VCC (See Sections 12.5.1, Reporting of Serious Adverse Events to Sponsor, and 12.6, Pregnancy Reporting).

The VCC MM shall receive weekly line listing from the VCC containing cumulative information on AEs, SAEs, and pregnancies recorded by the study site(s) on appropriate eCRFs.

The VCC MM shall be available to discuss AEs and SAEs with investigators, review safety data to be delivered to DSMB, weekly safety line listing, attend DSMB meetings to participate in discussions on safety and AEs, and participate in discussions related to unblinding.

The VCC MM shall inform the DAIT/NIAID Medical Officer of all SAEs and pregnancies reported within 24 hours of notification of the event.

12.7.2. DAIT/NIAID Medical Officer

The DAIT/NIAID Medical Officer shall review and make final decisions on the disposition of the SAE and pregnancy reports received by the VCC and reviewed by the VCC MM (See Sections 12.5.1, Reporting of Serious Adverse Events to Sponsor, and 12.6, Pregnancy Reporting).

The DAIT/NIAID Medical Officer shall receive weekly reports line listing from the VCC containing cumulative information on AEs, SAEs, and pregnancies recorded by the study site(s) on appropriate eCRFs.

12.7.3. DSMB Review

12.7.3.1. Planned DSMB Reviews

To ensure participant safety and data integrity, a DSMB will be formed with members described in the DSMB Charter. The DSMB will approve the DSMB charter that will guide DSMB operations.
The DSMB will review blinded study safety data on a monthly basis. The first DSMB review of blinded safety data will occur within 30 days of the first participant treatment or when 30 participants have been enrolled, whichever comes sooner.

Two unblinded DSMB reviews are planned: first, when 75 participants have completed the 28-day portion of the study and second when 150 participants have completed the 28-day portion of the study. At each time, an unblinded safety analysis report will be prepared by the study statistician at the Study Coordinating Center and submitted to the DSMB for review. The DSMB safety reports will be based on the SAP with additional specifications as outlined in the DSMB charter. The second DSMB review at 150 participants also will be used for the interim analysis, described below (Section 13.5).

12.7.3.2. *Ad hoc* DSMB Reviews

Given the potential severity of COVID-19, there are no pre-specified study stopping rules other than the interim analysis for futility (see below). Instead there will be close oversight by the sponsor (DAIT/NIAID), the VCC Medical Monitor, the protocol chair, and monthly DSMB reviews of study safety data.

The DSMB will review any data that potentially affects safety at the request of the protocol chair or DAIT/NIAID.

After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

12.7.3.2.1. Temporary Suspension of enrollment/drug dosing or bo*th* for *ad hoc* DSMB Safety Review

At the recommendation of the DSMB Chair, the Protocol Chair or DAIT/NIAID, a temporary halt in enrollment and drug dosing may be implemented if an *ad hoc* DSMB safety review is required. If a halt in enrollments is implemented while the DSMB ad hoc safety review is in progress, potential new participants will continue to be screened, consented, but not enrolled. All participants who are currently enrolled in the study will complete dosing and will continue the study monitoring and sample collection procedures, unless DSMB recommendations preclude further dosing.

13. Statistical Considerations and Analytical Plan

13.1. Overview

This is a double-blind, placebo-controlled randomized study to assess the efficacy and safety of IC14 in COVID-19 participants admitted to an acute care hospital with signs and symptoms consistent with level 5 on the 8-category ordinal scale (OS). Participants will be randomized to IC14 or placebo with 1:1 ratio and followed for 60 days after randomization. The study drug will be administered daily on Days 1-4. The randomization will be stratified by groups of study sites and concomitant use of dexamethasone or equivalent corticosteroid at baseline. All participants will receive baseline antiviral therapy with remdesivir.

13.2. Endpoints

13.2.1. Primary Endpoints

The Primary Endpoint is time to clinical recovery, defined as the time from the first dose of study drug to the first day that a participant is in categories 1, 2, or 3 on the Eight-Point Ordinal Scale through Day 28 or censored at day 28. The Eight-Point Ordinal Scale is an assessment of the clinical status on each study day. The Scale is defined as follows:

1) Not hospitalized, no limitations on activities

2) Not hospitalized, limitation on activities and/or requiring home oxygen

3) Hospitalized, not requiring supplemental oxygen—no longer requires ongoing medical care

4) Hospitalized, not requiring supplemental oxygen—requiring ongoing medical care (COVID-19-related or otherwise)

5) Hospitalized, requiring supplemental oxygen

6) Hospitalized, on non-invasive ventilation or high-flow oxygen devices

7) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)

8) Death

13.2.2. Secondary efficacy endpoints:

1. Days alive and free of any episodes of acute respiratory failure through Day 28 defined by need for the following oxygen delivery resource:
   a. High-flow nasal cannula (flow rates ≥30L/min with FiO_2 ≥0.4)
   b. Noninvasive positive-pressure ventilation
   c. Endotracheal intubation and mechanical ventilation
   d. Extracorporeal membrane oxygenation
2. Mean change in the ordinal scale from baseline to Days 14 and 28.
3. Ordinal scale value on Day 14.
4. All-cause mortality through Days 28 and 60.
5. Proportion of participants alive and free of any episode of acute respiratory failure through Day 28.
6. Days alive and free of invasive mechanical ventilation through Day 28.
7. Proportion of participants alive and free of invasive mechanical ventilation through Day 28.
8. Proportion of participants alive and discharged from the hospital through Day 28.
9. Proportion of participants who begin corticosteroid therapy for worsening COVID-19 illness after randomization.

13.2.3. Secondary safety endpoints:

1. Safety of IC14 as measured by change from baseline in liver (alanine transaminase, aspartate transaminase, total bilirubin), renal (creatinine), hematological (hemoglobin, white blood cell count with differential), and coagulation function (platelets, prothrombin time) through Day 28.
2. Cumulative incidence of all clinical and/or laboratory adverse events through Day 28.
3. Cumulative incidence of serious adverse events through Day 60.

13.2.4. Exploratory endpoints:

1. Change from baseline in pro-inflammatory cytokines and other biomarkers in blood on Days 4, 7, 14 and 21.
2. Change in Sequential Organ Failure Assessment (SOFA) score from baseline to Days 5, 7, 14, 21 and 28.
3. Worst SOFA score from baseline to Day 28.
4. Time from baseline to improvement in one category using an ordinal scale through Day 28.
5. Time from baseline to improvement in two categories using an ordinal scale through Day 28.
6. Proportion of participants with negative nasal swabs for SARS CoV2 virus on Days 7 and 14 or at discharge if prior to Day 14.

13.3. Other Safety/Tolerability Endpoints

The safety and tolerability of IC14 will be determined by examining the toxicities and adverse events that are attributable to treatment. The safety parameters will include an evaluation of the clinical signs and symptoms from the history and physical exam, vital signs, adverse events, and safety laboratory findings (chemistries, complete blood count, platelet count). New infections will be recorded as adverse events and should include the site of infection and source of culture. Each study participant should have a complete opthalmological examination, including slit lamp examination, when the participant is clinically stable, free of COVID-19 symptoms , beyond the COVID-19 quarantine period and able to comply with the examination.

13.4. Prognostic Biomarkers

Baseline serum prognostic biomarkers to be measured include presepsin (fragment of sCD14), sCD14, D-dimer, ferritin, C-reactive protein (CRP), and lactate dehydrogenase (LDH).

13.5. Inflammatory Biomarkers

In addition, a biomarker bank of serum and/or plasma samples will be established and stored frozen. It may be used to measure additional biomarkers, for example, but not necessarily including, procalcitonin, TNFα, IL-1β, IL-2, IL-6, IL-7, IL-8, G-CSF, sTNFR1, sRAGE, GM-CSF, C-reactive protein, interferon-gamma inducible protein 10 (CXCL10), monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, soluble CD163, fibrinogen, triglycerides, or others.

13.6. Pharmacokinetic/Pharmacodynamic Markers

Pharmacokinetic measurements will be made of serum IC14 before infusion with measures on Days 2, 3, 4, 7 and 14. Pharmacodynamic markers will consist of a mCD14 receptor occupancy assay.

13.7. Measures to Minimize Bias

Randomization will be stratified by study site and concomitant use of dexamethasone at baseline to ensure treatment balance within each clinical center and users of dexamethasone. Block randomization with random block size will be used. The randomization schedule will be generated by the unblinded study statistician. Study participants and attending physicians will be blinded to the treatment the participants receive.

13.8. Analysis Plan

13.8.1. Analysis Populations.

The Intent-to-Treat population (ITT) is defined as all study participants who were randomized. The modified-ITT population (m-ITT) is defined as all study participants who were randomized and received at least one dose of the investigational agent. The per-protocol population (PP) is defined as all study participants in the ITT population with with no major protocol deviations. Before data unblinding, the protocol chairs, the DAIT/NIAID Medical Officer and the study statistician will review all protocol deviations and produce a list of participants with major protocol deviations who will be removed from the m-ITT population for the per-protocol analysis.

Participants meeting criteria for hospital discharge will not remain hospitalized to complete a full course of study drug, but will remain in the m-ITT population, providing they were randomized and received the start of the first dose of the study drug.

The modified intention-to-treat (m-ITT) analysis will be primary and the per-protocol analysis will be secondary.

13.8.2. Analysis of Primary Endpoint

The primary endpoint is time to event (recovery defined above). Study participants who die before day 28 will be assigned the worst time to recovery (28 days); if data are analyzed while some participants are still in follow-up, the Fine-Gray approach to censoring deaths will be used (that is, participants who die will be censored based on time since randomization, with a maximum of 28 days). (Fine and Gray, 1999)

13.8.2.1. Primary Analysis of Primary Endpoint

This time to event endpoint will be tested for treatment effect (IC14+SOC vs placebo+SOC) using the stratified log-rank test, as the study will be stratified by groups of study sites and dexamethasone use at baseline.

13.8.2.2. Secondary Analysis of Primary Endpoint

The treatment effect represented as the recovery rate ratio will be estimated using Cox proportional hazard regression. The Kaplan-Meier estimates of the recovery proportions over time will be provided to graphically present the data. Covariates to be used in the secondary analysis of the primary endpoint will be specified in the Statistical Analysis Plan and will include age and co-existing diseases, such as hypertension and diabetes mellitus.

13.8.3. Analyses of Secondary and Other Endpoints

Secondary endpoints can be divided into 4 groups: continuous endpoints such as days alive and free of acute respiratory failure through Days 14 and 28, binary endpoints such as participants alive and free of any episode of acute respiratory failure (yes or no), and time to event data such as all-cause mortality and ordinal categorical data such as Ordinal Score at Day 14. These endpoints will be analyzed accordingly based on these categories. Briefly, continuous endpoints will be tested between treatment groups using the Wilcoxon rank sum test. Categorical variables will be compared between groups using Chi-squared test or Fisher exact test based on the number of events. Time to event data will be analyzed using the same methods as for the primary endpoints described above. Ordinal categorical data will be analyzed by the proportional odds logistic model. Covariates for the secondary model-based analyses such as GLM, logistic regression, Cox regression, and proportional odds logistic regression will be described in the Statistical Analysis Plan.

13.8.4. Analyses of Safety Endpoints

Safety endpoints include continuous endpoints such as change from baseline in liver, renal, hematological, and coagulation function and binary endpoint such as adverse events. The continuous endpoints will be summarized for the treatment groups using mean±SD, median and interquartile range and tested using the Wilcoxon rank sum test between groups. The binary adverse event endpoints will be summarized for the treatment groups using count and proportion tested using Chi-squared test or Fisher exact test based on the number of events. The safety data analysis will be conducted at each interim analysis and reported to the DSMB.

13.8.5. Descriptive Analyses

Standard graphing and screening techniques will be used to detect outliers and to ensure data accuracy. Summary statistics for both numerical and categorical variables will be reported by study arms to describe the study sample. Comparability between the randomization groups will be assessed on demographic characteristics, baseline medications, and baseline clinical status using the ordinal scale.

13.8.6. Missing Data

The study is an in-hospital study, so missing data will be unusual. Every effort will be made to minimize missing follow-up data. For patients who do not return for Day 28 and Day 60 visits, vital status on Day 60 will be ascertained by telephone calls to the subject or relatives, or via death records, or by other available means. A sensitivity analyses with missing

endpoints imputed under conservative assumptions will be conducted to assess their effect. These sensitivity analyses will be specified in the SAP.

13.8.7. Subgroup Analyses

We have pre-specified the grouping variables as age (< 65 versus ≥ 65), hypertension, diabetes mellitus, baseline viral load, and sCD14. To determine whether there is heterogeneity of treatment effect to warrant reporting of findings within subgroups, the interaction between the subgroup variable and treatment effect will be tested in the Cox model. Only if it is significant will we conduct a separate analysis within the subgroups. If warranted the subgroup analysis will be conducted using the same Cox model as for the primary efficacy endpoint, but with the subgroup variable removed from the model. In this case, we will be liberal when considering whether a subgroup has an interaction with the treatment. We will use the alpha level of 0.1 instead of the usual 0.05 for testing the interaction effect. The subgroup analysis will only be conducted for the primary endpoint. Details of the subgroup analyses will be included in the Statistical Analysis Plan.

13.9. Interim Analyses

13.9.1. Interim Analyses

The DSMB will perform unblinded analyses when 75 and 150 participants have competed the 28-day study period. The first DSMB analysis will be for safety and the second will be for safety and review of primary efficacy data for futility.

a. First Interim Analysis: When 75 participants have completed the 28-day study period a safety analysis report will be prepared by the unblinded study statistician and submitted to the DSMB for review. The DSMB will evaluate potential safety imbalances between the two study groups and consider whether or not safety concerns preclude continuation of the study, or whether some study modification is needed.

b. Second Interim Analysis: When 150 study participants have completed the 28-day study period the Study and Data Coordinating Center will perform an unblinded summary of safety data and the primary endpoint for the DSMB to review. The safety data will be reviewed for imbalances between the two study groups, as at the first interim analysis. The primary endpoint data will be reviewed to evaluate the rate ratio between the study groups. No matter what the estimated rate ratio is, the study will not be stopped early to declare efficacy.

c. The biostatisticians at the Study and Data Coordinating Center have conducted extensive simulations to assess this rule under various scenarios. In the simulations, we assume the placebo+SOC arm would have similar recovery experience as shown for the remdesivir arm in Panel C of Figure 2 in the ACTT-1 study (Beigel, et al. 2020). The time to recovery was modeled using the Weibull distribution to describe this experience. The Weibull distribution assumes the hazard decreases over time and we found this distribution with shape parameter 0.73 and median survival of 7 days fit the recovery curve well. For the ic14+SOC arm, the shape parameter is the same as that of the placebo+SOC arm, and the scale parameter is determined by pre-specified recovery rate ratio (RR). Participants are randomized to the placebo+SOC and ic14+SOC arms at a 1:1 ratio. After 150 participants complete 28 days of follow-up, the Cox PH regression will be used to estimate the RR. If the estimated RR is less than a pre-specified threshold, then the DSMB would recommend stopping the trial. Table 6 summarizes the probability of stopping the trial for different values of the threshold and the true underlying RR. In order to achieve a balance between: 1) the need to terminate the trial in the event that the

intervention is actually harmful, and 2) premature termination of the trial if the intervention is actually beneficial. We have selected the stopping rule threshold of 1.0 to have a high probability (>50%) of stopping the trial if the intervention is harmful (i.e. true RR is <1.0) and a low probability (<10%) of stopping the trial if the intervention is beneficial (i.e. true RR is >1.3)(see highlighted row in Table 6).

Table 6. Evaluation of Stopping Rules

	True Recovery Rate Ratio (RR)							
Stopping Threshold	**0.8**	**0.9**	**1.0**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**
0.96	0.84	0.64	0.41	0.22	0.10	0.040	0.014	0.0054
1.00	0.89	0.71	0.50	0.29	0.15	0.064	0.024	0.0086
1.02	0.91	0.75	0.54	0.33	0.17	0.078	0.032	0.011
1.04	0.92	0.79	0.58	0.37	0.20	0.097	0.041	0.015
1.06	0.94	0.81	0.62	0.42	0.23	0.12	0.052	0.021
1.08	0.95	0.84	0.66	0.46	0.27	0.14	0.065	0.027
1.10	0.96	0.86	0.70	0.50	0.31	0.17	0.080	0.034
1.14	0.98	0.91	0.76	0.58	0.38	0.22	0.12	0.054

The values in the table show the probabilities for stopping the trial at given stopping thresholds for different underlying true recovery rate ratios (RR>1 is beneficial).

13.9.2. Interim Analysis of Safety Data

13.9.3. Futility Analysis

13.10. Statistical Hypotheses

The primary hypothesis is that IC14 will be efficacious in treating COVID 19 participants. To test this hypothesis, we will use time to recovery as the primary endpoint. The treatment effect will be presented as the recovery rate ratio. A ratio greater than 1 indicates beneficial effect of IC14. A ratio of 1 corresponds to the null hypothesis that IC14 has no treatment effect compared to placebo.

13.11. Sample Size Calculations

It is assumed that the placebo arm will have a similar recovery experience as shown for the remdesivir arm in Panel C of Figure 2 in the ACTT-1 study (Beigel et al. 2020). The time to recovery can be modeled using the exponential or the Weibull distribution to describe this experience. The exponential distribution assumes constant hazard and the Weibull distribution assumes the hazard decreases with time. The Weibull distribution with shape parameter 0.73 and median time to recovery of 7 days appears to fit the recovery curve better than the exponential for the remdesivir group in ACTT-1. The first column in Table 7 below assumes the Placebo arm in this study will have almost identical recovery experience as the remdesivir arm in ACTT-1. The second and the third column (median time to recovery of 6 and 5 days, respectively) assume improved recovery rate in our Placebo arm (0.882 and 0.913 versus 0.851) when factoring in corticosteroid use and evolving SOC in general. The sample size required for risk ratios ranging from 1.35-1.5, is shown in Table 7. and suggests a sample size of approximately 350 participants will have 80% power to detect a risk ratio of 1.37.

Table 7 shows the sample size needed to have 80% power with type I error rate of 0.05 to detect various RR for differing values of median days to recovery in the SOC+placebo arm. The entries in the cells show the sample size needed along with expected 28-day recovery rates in the placebo vs. IC14 arms.

Table 7. Sample Size Calculations

	Standard of Care Group: Median Days to Recovery		
Effect (RR)	**7**	**6**	**5**
1.35	392[a] 0.851 / 0.924[b]	382 0.882 / 0.944	372 0.913 / 0.963
1.40	312 0.851 / 0.931	302 0.882 / 0.950	296 0.913 / 0.967
1.45	254 0.851 / 0.937	248 0.882 / 0.955	242 0.913 / 0.971
1.50	212 0.851 / 0.943	208 0.882 / 0.959	202 0.913 / 0.974

a. Sample size (n) b. Recovery rate (placebo arm / IC14 arm)

Based on available data regarding current standard of care with remdesivir and/or dexamethasone, sample size calculations for this study are based on a median time to recovery of 6 days in the Placebo arm and a RR ratio of 1.4. Under this scenario, enrollment of 302 study participants would be expected in order to observe 278 recoveries. Because the recovery rate in the placebo arm and the RR may vary, anticipated enrollment will be between 302-350 participants to observe at least 278 recoveries. If at least 278 recoveries are observed after 302 participants have completed the study, enrollment will stop. Otherwise enrollment will continue until 278 recoveries are observed or the maximum enrollment of 350 participants is reached. Because this study will be conducted in hospitalized patients, the dropout rate is not expected to affect these sample size assumptions in a significant manner.

14. Identification and Access to Source Data

14.1. Source Data

Source documents and source data are considered to be the original documentation where patient information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial. The Source Documents for this study will consist of the records collected by the study team (e.g. eCRFs, etc.). Some of this information may be collected from the participant's medical record.

14.2. Access to Source Data

The site investigators and site staff will make all source data available to the DAIT/NIAID, as well as to relevant health authorities noted above and to the staff of Implicit Biosciences, Ltd. if requested, all of whom are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

15. Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. Study personnel at the Vanderbilt Clinical Coordinating Center and the PPD research organization will review and monitor participant data for quality control purposes.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

16. Protocol Deviations

16.1. Protocol Deviation Definitions

Protocol Deviation – The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

16.1.1. Major Protocol Deviation (Protocol Violation)

A Protocol Violation is a deviation from the IRB approved protocol that may affect the study participant's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

16.1.2. Non-Major Protocol Deviation

A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major effect on the study participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

16.2. Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

Upon determination that a protocol deviation (major or minor) has occurred, the study staff will; a) notify the site Principal Investigator, and b) will complete an eCRF Protocol Deviation form. The Protocol Deviation form will document, at a minimum, the date the protocol deviation (PD) occurred, the date PD identified, a description of event, whether the deviation resulted in SAE/AE, the signature of PI, a report to the sIRB, and documentation of a corrective action plan. The VCC, the VCC MM and the IND sponsor (DAIT/NIAID) may request a discussion with the PI to determine the effect of the protocol deviation on the study participant and his/her further study participation, the effect of the protocol deviation on the overall study, and corrective actions. The PI will review and verify the Protocol Deviation form and the VCC will submit to the sIRB, per sIRB regulations. Major protocol deviations will be reviewed by the DSMB. The decision as to whether the Deviation is major or not will be determined by the VCC MM and the IND sponsor (DAIT/ NIAID)

17. Ethical Considerations and Compliance with Good Clinical Practice

17.1. Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the University of Washington Central IRB and the local institutional IRB at each Study Site. Any amendments to the protocol or to the consent materials will also be approved by the University of Washington Central IRB before they are implemented.

17.2. Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the FDA 1572 will review the consent and answer questions. The consent designee must be listed on the delegation log and have knowledge of the study. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. Informed consent may be obtained using paper or electronic procedures, and must comply with relevant regulations and guidance for obtaining consent for COVID-19 studies and the approved use of electronic consent: https://www.fda.gov/media/116850/download

The consent process will be ongoing. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

17.3. Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

18. Publication Policy

The study has a publication policy on file with the VCC that will apply to use of study results for this trial.

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Appendix A: Sequential Organ Failure Assessment (SOFA)

Record the worst value in the previous 24 hours:

PaO_2 _____ mm Hg

FiO_2* _____ %

Respiratory system

PaO2/FiO2 [mmHg (kPa)]	SOFA Score
Greater than or equal to 400 (53.3)	0
Less than 400 (53.3)	+1
Less than 300 (40.0)	+2
Less than 200 (26.7) **and** mechanically ventilated	+3
Less than 100 (13.3) **and** mechanically ventilated	+4

Nervous system (See appendix D)

Glasgow coma scale	SOFA Score
15	0
13-14	+1
10-12	+2
6-9	+3
Less than 6	+4

Cardiovascular system

Mean arterial pressure OR administration of vasoactive agents required (Listed doses are in units of mcg/kg/min)	SOFA Score
No hypotension	0
MAP less than 70 mmHg	+1
DOPamine less than or equal to 5 or DOBUTamine (any dose)	+2
DOPamine greater than 5, EPINEPHrine less than or equal to 0.1, or norEPINEPHrine less than or equal to 0.1	+3
DOPamine greater than 15, EPINEPHrine greater than 0.1, or norEPINEPHrine greater than 0.1	+4

Liver

Bilirubin, mg/dL (µmol/L)	SOFA Score
1.2 - 1.9 (20-32)	+1
2.0 - 5.9 (33-101)	+2
6.0 – 11.9 (102-204)	+3
Greater than or equal to 12.0	+4

Coagulation

Platelets, $\times 10^3/\mu L$	SOFA Score
Greater than or equal to150	0
100-149	+1
50-99	+2
20-49	+3
Less than 20	+4

Kidneys

Creatinine, mg/dL (µmol/L) (or urine output, UOP)	SOFA Score
Less than 1.2 (less than 110)	0
1.2 - 1.9 (110-170)	+1

2.0 - 3.4 (171-299)	+2
3.5 - 4.9 (300-440) or UOP less than 500 mL per day	+3
Greater than or equal to 5.0 (greater than 440) or UOP less than 200 mL per day	+4

*Estimating FiO_2 from oxygen flow/delivery rates:

Type of O_2 delivery	**Flow rates, L/min**	**FiO_2**
Nasal Cannula		~4% FiO_2 added above room air** per 1 L/min
	Room Air	21%
	1 liter per minute	25%
	2 liters per minute	29%
	3 liters per minute	33%
	4 liters per minute	37%
	5 liters per minute	41%
	6 liters per minute	45%
Simple face mask	~6-12 liters per minute	35-60%**
Non-rebreather mask	10-15 liters per minute	~70-90%
High-flow nasal cannula	Up to 60 liters per minute	30-100%

**Varies based on respiratory rate and minute ventilation.

Even though it is calculated sequentially based on the worst values in the past 24 hours, the SOFA Score is not meant to indicate the success or failure of interventions or to influence medical management.

Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the third International Consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315 (8):762-774.

Appendix B: Glasgow Coma Scale (Used to Calculate SOFA Score)

The Glasgow Coma Scale (GCS) is scored between 3 and 15, 3 being the worst and 15 the best. It is composed of three parameters: best eye response (E), best verbal response (V), and best motor response (M). The components of the GCS should be recorded individually; for example, E2V3M4 results in a GCS score of 9. A score of 13 or higher correlates with mild brain injury; a score of 9 to 12 correlates with moderate injury; and a score of 8 or less represent severe brain injury.

Glasgow Coma Scale

Best eye response (E)	Spontaneous – open with blinking at baseline	4
	Opens to verbal command, speech, or shout	3
	Opens to pain, not applied to face	2
	None	1
Best verbal response (V)	Oriented	5
	Confused conversation, but able to answer questions	4
	Inappropriate responses, words discernible	3
	Incomprehensible speech	2
	None	1
Best motor response (M)	Obeys commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws from pain	4
	Abnormal (spastic) flexion, decorticate posture	3
	Extensor (rigid) response, decerebrate posture	2
	None	1

Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1972; 2 (7872): 81-4.

Appendix C: Eight-Point Ordinal Scale

The ordinal scale is an assessment of the clinical status at the first assessment of a given study day.

The scale is as follows:

1) Not hospitalized, no limitations on activities
2) Not hospitalized, limitation on activities and/or requiring home oxygen
3) Hospitalized, not requiring supplemental oxygen -- no longer requires ongoing medical care
4) Hospitalized, not requiring supplemental oxygen -- requiring ongoing medical care (COVID-19-related or otherwise)
5) Hospitalized, requiring supplemental oxygen
6) Hospitalized, on non-invasive ventilation or high-flow oxygen devices
7) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
8) Death

From Beigel et al. 2020_Adaptive COVID-19 Treatment Trial (ACTT)

Appendix D: EQ-5D-5L Instrument (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/)

Sample_UK-English-E
Q-5D-5L-Paper-Self-C

Appendix E: Child-Pugh Score

Clinical and Laboratory Criteria	Points		
	1	2	3
Encephalopathy	None	Grade 1: Altered mood/confusion or Grade 2: Inappropriate behavior, impending stupor, somnolence	Grade 3: Markedly confused, stuporous but arousable Or Grade 4: Comatose/unresponsive
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	Less than 2	2 to 3	Greater than 3
Albumin (g/dL)	Greater than 3.5	2.8 to 3.5	Less than 2.8
Prothrombin time Seconds prolonged International normalized ratio			
	Less than 4	4 to 6	Greater than 6
	Less than 1.7	1.7 to 2.3	Greater than 2.3
Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points) Class A: 5 to 6 points (least severe liver disease) Class B: 7 to 9 points (moderate severe liver disease) Class C: 10 to 15 points (most severe liver disease)			

References

1. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973; 60:646. PubMed ID: 4541913
2. Child CG, Turcotte JG. *The Liver and Portal Hypertension*. Philadelphia, WB Saunders Co. 1964. NLMN ID: 46218
3. Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. *NEJM*. 1966; 274:473. PubMed ID: 5904286