

Official Protocol Title:	A Randomized, Double-blind, Placebo-controlled, Multi-site, Phase III Study to Evaluate the Safety and Efficacy of CD24Fc in COVID-19 Treatment (SAC-COVID)
NCT number:	NCT04317040
Document Date:	16-Aug-2020

**A Randomized, Double-blind, Placebo-controlled, Multi-site, Phase III Study to Evaluate
the Safety and Efficacy of CD24Fc in COVID-19 Treatment**

Protocol Number: CD24Fc-007-US

Posted on ClinicalTrials.gov as NCT04317040.

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Protocol Version / Date: 1.9 / August 16, 2020

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STUDY SYNOPSIS

Title of the Study:	A Randomized, Double-blind, Placebo-controlled, Multi-site, Phase III Study to Evaluate the Safety and Efficacy of CD24Fc in COVID-19 Treatment (SAC-COVID)
Study Drug and Route:	CD24Fc, IV infusion.
Protocol Number:	CD24Fc-007-US
Principal Investigator:	Shyam Kottlilil, MD, PhD
Study Design:	<p>The study is designed as a randomized, placebo-controlled, double blind, multicenter, Phase III trial to compare two COVID-19 treatment regimens in hospitalized adult subjects who are diagnosed with severe COVID-19.</p> <p>Arm A: CD24Fc/Best Available Treatment Arm B: placebo/ Best Available Treatment</p> <p>CD24Fc will be administered as single dose of 480 mg via IV infusion on Day 1. Total of 270 subjects will be enrolled and randomized in 1:1 ratio to receive CD24Fc or placebo. All subjects will be treated with the best available treatment. The follow up period is 28 days.</p> <p>If the patient clinical status improves and is discharged to home care, the follow up visits can be carried out through telemedicine (phone or video interviews). The clinical investigators should make best effort to obtain the vital signs, clinical status evaluation, concomitant medicines and adverse events assessment. The laboratory tests, radiology study, ECG and research samples are optional.</p>
Primary Objective:	The primary objective of the Phase III study is to evaluate the safety and efficacy of adding CD24Fc to COVID-19 best available treatment by comparing COVID disease status improvement time between CD24Fc and placebo arms in 28 days.
Secondary Objectives:	Secondary objectives are to compare, for each treatment arm, the proportion of patients who died or had respiratory failure (defined as the need for mechanical ventilation, ECMO, non-invasive ventilation, or high flow oxygen devices), the time to disease progression, the rate of all-cause death, the proportion of death or respiratory failure, rates of hospital discharge time, rate of duration of mechanical ventilation, duration of mechanical ventilation, use of pressors, rate of duration of extracorporeal membrane oxygenation, rate of duration of supplemental oxygen, the length of hospital stay, and the changes in absolute lymphocyte count and markers of inflammation.
Exploratory objectives:	<p>To explore the effect of CD24Fc treatment of COVID-19 on systemic steroid dosage, inflammatory cytokine changes, D-dimer level changes, lymphocyte subtype distribution and T lymphocyte activation and exhaustion markers.</p> <p>To explore the effect of CD24Fc in pulmonary function, inflammatory markers, coagulation markers, cardiac function, liver enzymes and renal function.</p>

Study Endpoints:

Primary Endpoint:

Time to improvement in clinical status: the time (days) to the improvement of clinical status from “scale 2 to 4” to “scale 5 or above that is sustained without a drop to below 5” based on NIAID 8-point ordinal scales ([Appendix A](#)) within 28 days from randomization.

Secondary Endpoints:

- Proportion of patients who died or had respiratory failure, defined as the need for mechanical ventilation, ECMO, non-invasive ventilation, or high flow oxygen devices, at Day 29;
- Time to disease progression in clinical status: the time (days) for progression from scale 3 or 4 to scale 1 or 2, or 2 to 1, based on NIAID ordinal scale with 28 days from randomization;
- All-cause mortality at Day 15 and Day 29;
- Proportion of clinical relapse, as defined by rate of return to oxygen support for more than 1 day within 28 days from randomization after initial recovery;
- Conversion rate of clinical status on days 8 (proportion of subjects who changed from “scale 2 to 4” to “scale 5 or higher” on NIAID ordinal scale);
- Conversion rate of clinical status on days 15 (proportion of subjects who changed from “scale 2 to 4” to “scale 5 or higher” on NIAID ordinal scale);
- The discharge time
- Duration of mechanical ventilation (IMV, NIV) (days);
- Duration of pressors;
- Duration of extracorporeal membrane oxygenation (days);
- Duration of oxygen therapy (oxygen inhalation by nasal cannula or mask) (days);
- Length of hospital stay (days);
- Absolute lymphocyte count;
- D-dimer concentration in the plasma.

Exploratory endpoints:

- Effect of CD24Fc on systemic steroid usage;
- Effect of CD24Fc on cytokine levels;
- Effect of CD24Fc on lymphocyte subtype distribution.

Safety evaluation:

- Adverse events, vital signs, laboratory tests (blood routine, blood biochemistry, coagulation function, urine routine), ECG.

Study Population:

Hospitalized severe and critical COVID-19 adult patients.

Eligibility Criteria:

Inclusion criteria

- 1) Should be at least 18 years of age.

- 2) Male or female, female should have negative pregnancy test.
- 3) Diagnosed with COVID-19 and confirmed SARS-CoV-2 viral infection, prior positive viral results allowed.
- 4) Informed consent form signed by the patient or by the legally authorized representative.
- 5) Hospitalized and requiring oxygen support, NIAID 8-point ordinal score 2, 3 or 4, regardless of ARDS ([Appendix A](#)). The intubation for mechanical ventilation is within 7 days.
- 6) Women of childbearing potential, under the age of 54 years, who use adequate contraception and who agree to use adequate contraception for the duration of the study.

Exclusion criteria:

- 1) Patients who are pregnant, breastfeeding, or have a positive pregnancy test result before enrollment.
- 2) Patients who previously enrolled in CD24Fc clinical trial.
- 3) Intubation for invasive mechanical ventilation is over 7 days.
- 4) Documented acute renal or hepatic failure;
- 5) The investigator believes that participating in the trial is not in the best interests of the patient, or the investigator considers unsuitable for enrollment (such as unpredictable risks or subject compliance issues).

Treatment Description:

The Phase III study will be a randomized double-blind placebo controlled study in 270 subjects. Patients will be randomized 1:1 to receive one of the following treatments:

Arm A: CD24Fc, 480mg, diluted to 100ml with normal saline, IV infusion in 60 minutes.

Arm B: placebo, normal saline 100ml, IV infusion in 60 minutes.

The best available treatment and supportive care will be given to all subjects according to local institutional guideline. Those who uses immune modulators such as IL-6/IL-6R antagonists or experimental antiviral drugs such as remdesivir or convalescent plasma are allowed to participate the trial.

Accrual Objective:

The study will enroll 270 patients, or 135 per arm.

Accrual Period:

The estimated accrual period is 5 months.

Study Duration:

Patients will be followed for 28 days.

Interim Analysis:

The Phase III study will include one interim analysis:

Stopping Guidelines:

The interim analysis will be at the time when the required number of events is at 70% for the purpose of sample size re-estimation only.

Monitoring of the safety endpoint will be conducted by the CRO in a blinded fashion. The CRO will collect the data and share this with the DSMB at two safety reviews, respectively when 50% or 75% of enrolled patients reached D15. DSMB may call a meeting with the DSMB at other times if needed. DSMB may recommend early termination if it

find significantly higher SAE in the CD24Fc arm after considering the clinical benefit of the treatment. The final decision will be made by the sponsor.

Figure 1: Diagram of the study.

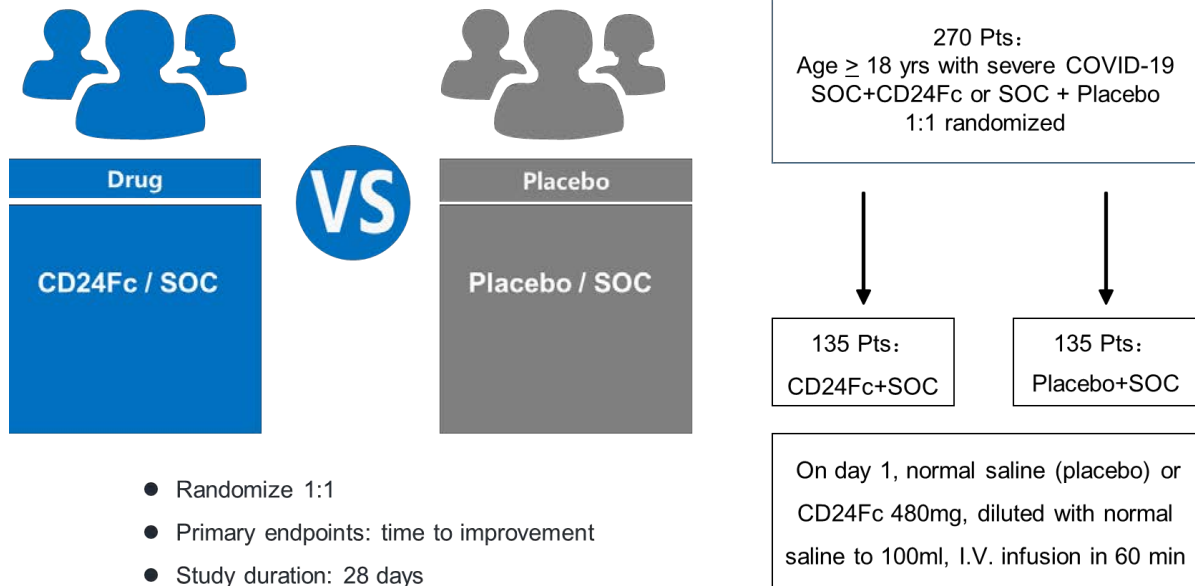


Table 1: Inclusion and Exclusion Criteria and NIAID 8-Point Scale for COVID-19.

Inclusion Criteria	Exclusion Criteria	NIAID 8-point scale for COVID-19
<ol style="list-style-type: none"> 1) Age ≥ 18 years 2) Male or Female, Female pregnancy test negative 3) Diagnosed with COVID-19 and confirmed SARS-CoV-2 infection. 4) Informed consent form signed by patient or by a legally authorized representative. 5) NIAID 8-point ordinal score 2 to 4 regardless of ARDS. The intubation for invasive mechanical ventilation should be within 7 days. 6) Women of childbearing potential who use adequate contraception and who agree to use adequate contraception for the duration of the study. 	<ol style="list-style-type: none"> 1) Patients who are pregnant, breastfeeding, or have a positive pregnancy test result before enrollment. 2) Patients who previously enrolled in CD24Fc study. 3) The intubation for invasive mechanical ventilation is over 7 days. 4) Documented acute renal or hepatic failure; 5) The investigator believes that participating in the trial is not in the best interests of the patient, or the investigator considers unsuitable for enrollment (such as unpredictable risks or subject compliance issues). 	<ol style="list-style-type: none"> 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home oxygen; 8) Not hospitalized, no limitations on activities.

Table 2: Phase III study schedule

Observations	Screening	Treatment/Follow up ⁷					
		D1	D4	D8	D15	D29	
Informed Consent	x						
Randomization		x					
Medical History	x						
Collect demographic data	x						
Confirm inclusion / exclusion criteria	x	x					
Vital Sign monitoring ¹	x	x ¹	x	x	x	x	
Physical Examination	x				x ²		
Laboratory Testing ³	x	x	x	x	x		
Digital oxygen saturation	x	As needed					
Arterial blood gas analysis	x ⁴	As needed					
Chest image study ⁴	x ⁴	As needed ⁴					
Pregnancy test (if applicable)	x						
ECG monitoring	x	x ¹		x	x		
COVID-19 test	x						
CD24Fc (Study Agent)		x					
Clinical status evaluation	x	x ^{5,7}					x ^{5,7}
IMV/NIV, ECMO, or supplement oxygen	x	x ⁵					x ⁷
Blood samples for cytokines and lymphocyte subtypes ⁶	x	x	x	x	x		
Concomitant Medications	x	x	x ⁷			x ⁷	
Adverse events assessment (NCI CTCAE V5.0)		x ⁷					x ⁷

1. Monitor vital signs before study drug infusion and at 60±10 minutes after drug infusion started. ECG before study drug infusion and at 2 hours ± 15 min after drug infusion. Body temperature should be recorded daily when in hospital.
2. The complete physical examination should be done during screening. The D15 visit should record any changes.
3. The tests that have been done 72 hr prior to screening are allowed in lieu of screening. See Section 7.1.5 for details.
4. Arterial Blood Gas (ABG) and Chest image study: Chest X-ray or CT scan frequency may be determined by local institutional guideline. The ABG and Chest Image Study at Screening is recommended but not required. The ABG and chest image studies that have been done 72 hr prior to Screening are allowed in lieu of screening.
5. The clinical status (NIAID ordinal scale) and respiratory treatment status should be evaluated and recorded daily while the patient is hospitalized. If the patient is discharged, these data should be captured for study visits through telemedicine.
6. For specified clinical sites only: Blood samples should be collected before and after study drug infusion, and on D4, D8, D15 to measure inflammatory cytokines (IL-1β, IL-6, TNF-α, MIPα, INF-γ, IP10, MCP, GCSF, IL-10) and DAMP molecules (HMGB-1, HSP70 / 90) in serum. The PBMC will be used to measure lymphocyte subtypes and lymphocyte activation and exhaustion markers (flow cytometry for: CD3 / CD4 / CD8 / PD1 / Tim3, etc.).
7. When enrolled patient is in the hospital for the treatment, the study schedule should be followed. If the patient is improved and discharged from the hospital, the follow up visits (D4±2, D8±2, D15±2, D29±3) can be conducted via telephone or video interview for clinical status evaluation, concomitant medications and adverse events assessment. The scheduled laboratory and radiology studies are recommended but not required.

CD24Fc-007-US PROTOCOL SIGNATURE PAGE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

This document may be signed and dated electronically through submission and approval by the Principal Investigator at institutional IRB Electronic Research Integrity and Compliance Administration (ERICA) system or be signed and dated with a hand-written signature on this signature page.

Instructions to multi-site Principal Investigators:

Return the electronically signed and dated or scanned hand-written signed and dated copy to OncoImmune Research Compliance Office at ^{PPD} [redacted]. Retain a copy in the regulatory binder.

Signature of Principal Investigator

Date

Principal Investigator Name (Print)

Name of Institution

Signature of Chief Medical Officer

Date

^{PPD} [redacted]
Name

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1. BACKGROUND AND SIGNIFICANCE

1.1. COVID-19

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly emergent coronavirus, SARS-CoV-2, that was first recognized in Wuhan, China, in December 2019, has now been detected in more than 100 locations internationally, including in the United States. On March 11, WHO characterized COVID-19 as a pandemic. As the unofficial data collected on April 8, 2020, there are approximate 1,530,000 confirmed cases and more than 89,000 deaths due to COVID-19 worldwide. Genetic sequencing of the virus suggests that it is a betacoronavirus closely linked to the SARS virus (1).

Although most people with COVID-19 have uncomplicated or mild illness (81%), some will develop severe illness requiring hospitalization and oxygen therapy (19%) and approximately 5% will require admission to an intensive care unit (ICU). Of those critically ill, most will require mechanical ventilation (2, 3). The most common diagnosis in severe COVID-19 patients is severe pneumonia. Older patients and those with comorbidities, such as cardiovascular disease and diabetes mellitus, have increased risk of severe disease and mortality. They may present with mild symptoms but have high risk of deterioration and should be admitted to a designated unit for close monitoring. In severe cases, COVID-19 can be complicated by the acute respiratory distress syndrome (ARDS), sepsis and septic shock, multiorgan failure, including acute kidney injury and cardiac injury (3). A recent multivariable analysis confirmed older age, higher Sequential Organ Failure Assessment (SOFA) score and d-dimer > 1 µg/L on admission were associated with higher mortality. This study also observed a median duration of viral RNA detection of 20.0 days (IQR 17.0–24.0) in survivors, but COVID-19 virus was detectable until death in non-survivors. The longest observed duration of viral shedding in survivors was 37 days (4, 5).

WHO issued a second edition (version 1.2) of “The Interim Guidance on Clinical Management of Severe Acute Respiratory Infection (SARI) When COVID-19 Disease Is Suspected” on Mar 13, 2020. This guidance will serve as a foundation for optimized supportive care to ensure the best possible chance for survival and to allow for reliable comparison of investigational therapeutic interventions as part of randomized controlled trials (6, 7). Table 3 listed the clinical syndromes associated with COVID-19 in adult patients. The appendix A has detailed description.

Table 3: Clinical syndromes associated with COVID-19

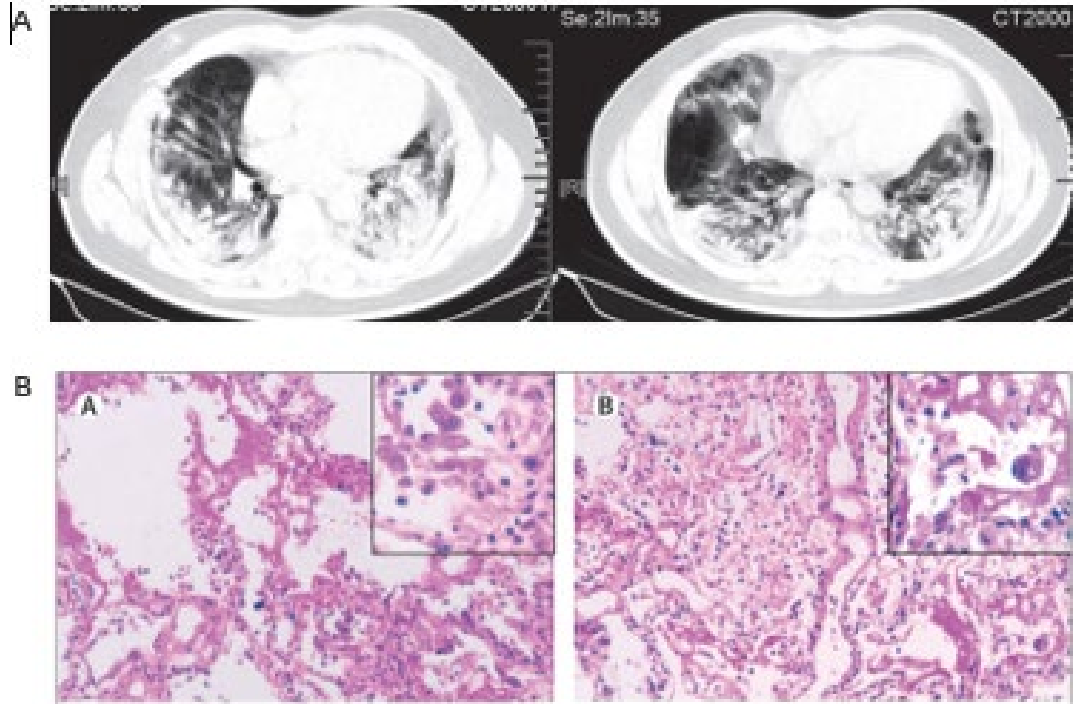
Mild illness	Patients may have non-specific symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhea, nausea, and vomiting (4, 8-10).
Moderate Pneumonia	Adult with pneumonia but no signs of severe pneumonia and no need for supplemental oxygen. Chest imaging may show increased bilateral interstitial changes.
Severe pneumonia	Adolescent or adult: fever or suspected respiratory infection, plus one of the following: respiratory rate ≥ 24 breaths/min; severe respiratory distress; or SpO ₂ $\leq 94\%$ on room air. Requires oxygen therapy. While the diagnosis is made on clinical grounds; chest imaging may identify or exclude some pulmonary complications.
Acute respiratory distress syndrome (ARDS) (11, 12) (Critical Condition)	Required admission to ICU and mechanical ventilation. Referred to Appendix A for detailed description

1.2. Rationale for Clinical Study of CD24Fc for COVID-19 Treatment

As the newest global medical emergency (9), COVID-19 exhibits features that are unlikely ameliorated solely by antiviral-based therapeutic approaches.

First, although the new coronavirus (SARS-CoV-2) viral load was reduced around day 9 after appearance of clinical symptoms in upper respiratory samples (13), radiology studies based on CT scan suggest that lung damage peaked after day 9 and lasted well beyond 14 days (3) (Figure 2a). The lung tissue in autopsy samples showed diffuse alveolar destruction and bronchiolar epithelial cell death. There are type II pneumocyte proliferation and interstitial infiltration of macrophages, some forming multi-nucleated giant cells similar to giant cell pneumonia. There are diffuse alveolar capillary congestion and alveolar disconnection and disintegration (14) (Figure 2b). This is reminiscent of findings in SARS-CoV infected patients where pneumonitis can peak after clearance of the virus (findings in SARS-CoV infected patients where pneumonitis can peak after clearance of the virus (15-17). Therefore, a successful countermeasure must include amelioration of lung inflammation by non-antivirals. In this context, it is of important to note that, since steroid, the anti-inflammatory drug widely used in addressing severe inflammation, was not recommended for COVID-19 or SARS (18, 19), new approach is urgently needed.

Figure 2: Radiological and histological presentation of COVID-19.



Second, patients with severe clinical symptoms show significant T cell lymphopenia that rivals human immunodeficiency virus (HIV) infection (Figure 3). In contrast, patients with mild clinical symptoms have largely normal lymphocyte counts (20). The reduction of lymphocytes is due to loss of CD4 and CD8 T lymphocyte as B cell numbers are unaffected (20). In addition, functional exhaustion of T cells is suggested by high expression of T-cell exhaustion markers (8). There were significant increase of several inflammatory cytokines in the serum (20) (Figure 4). The deletion and functional exhaustion of T cells prevent successful clearance of SARS-CoV2, therefore further delaying clinical recovery.

Figure 3: The absolute lymphocyte numbers and subtype lymphocyte numbers in mild and severe COVID-19 patients.

Severe COVID-19 patients have lymphopenia and reduced T lymphocyte numbers similar to HIV infection.

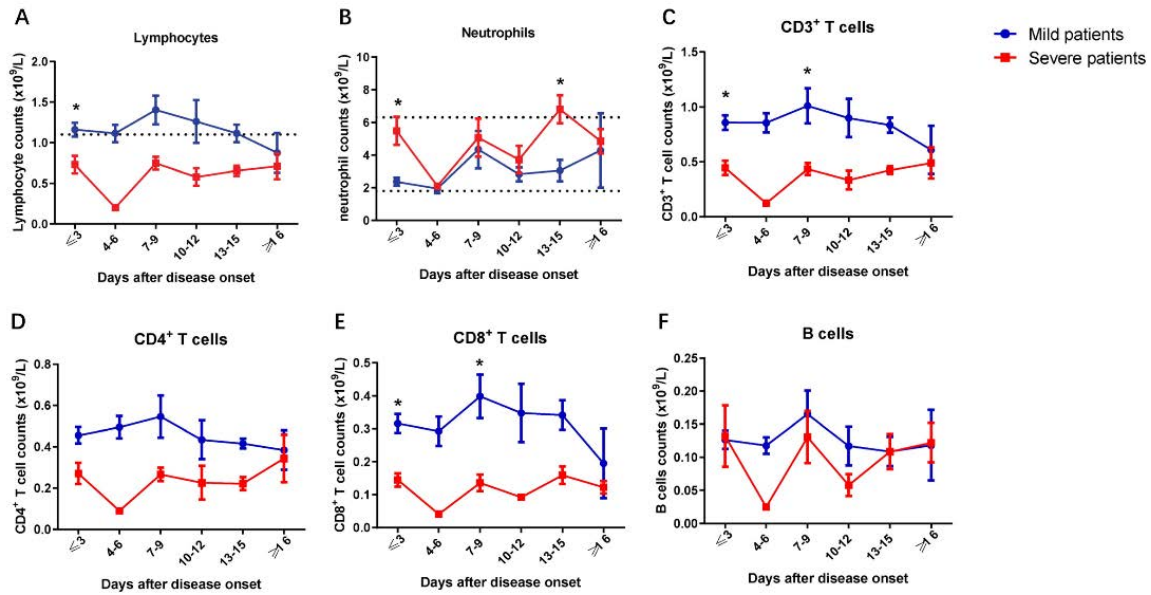
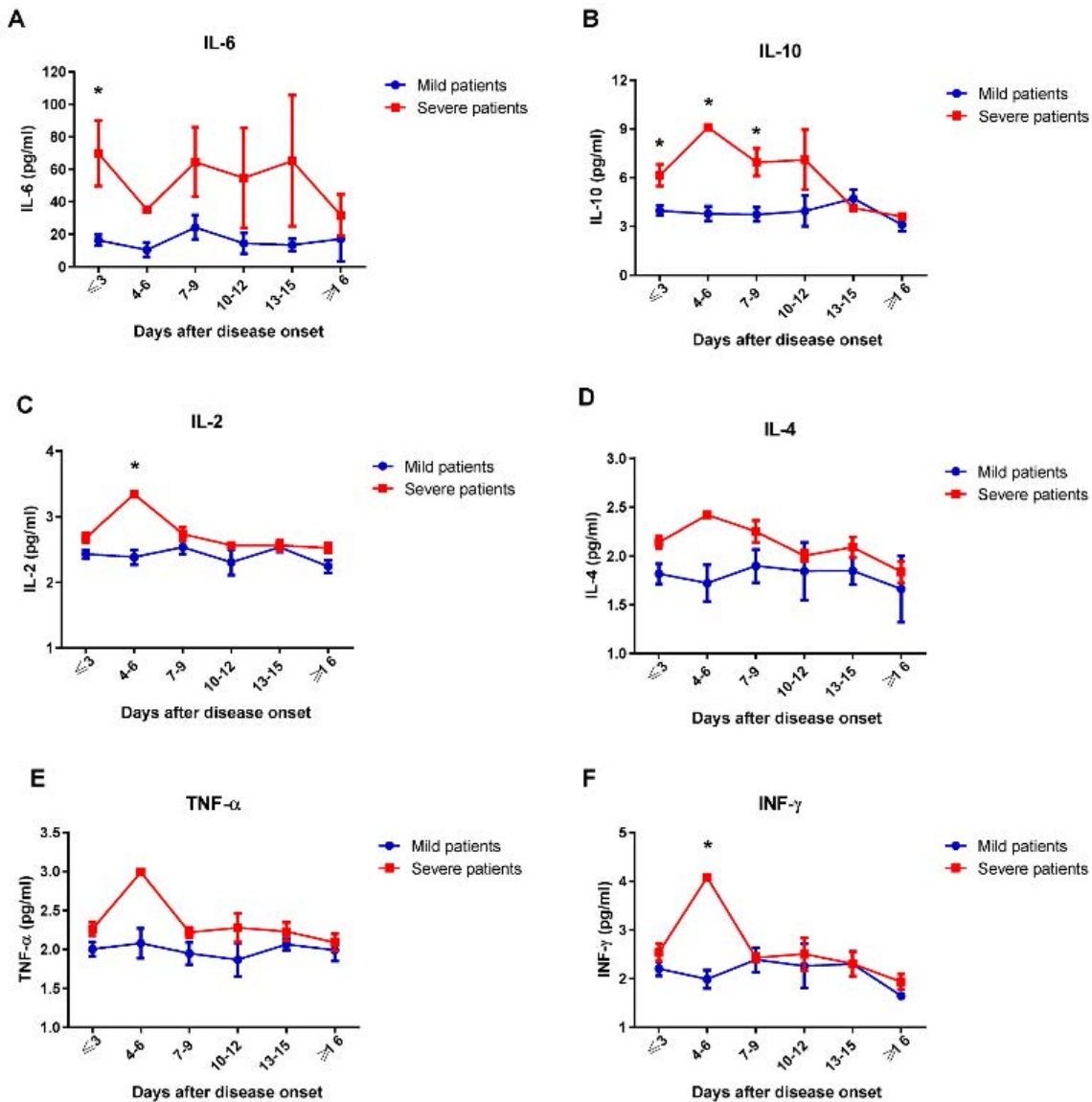


Figure 4: Serum inflammatory cytokine changes in mild and severe COVID-19 patients.



Taken together, in addition to viral damage of lung epithelial cells, the cause of COVID-19 may well involve inflammation in response to cellular injuries caused by the virus, which is mediated by inflammatory factors referred to as damage-associated molecular patterns, or DAMPs. The prototypical DAMPs such as HMGB1 and HSP70/90 are released when cells undergo either stress or necrosis, and trigger inflammation by interacting with TLR4 or RAGE. Over 10 years ago, we have revealed that the CD24-Siglec 10/G interaction selectively regulates inflammation to DAMPs (21) (22). Numerous studies have confirmed the role of DAMPs in the pathogenesis of HIV (23, 24) and coronavirus (25, 26) infections. Recent reports from our group in

collaboration with others have demonstrated a critical role for CD24 and Siglecs in inflammation associated with inflammation caused by human/simian immunodeficiency virus (HIV/SIV) (27).

Based on this new understanding, treatment of COVID-19 likely requires a combination of both antiviral and non-antiviral-based approaches. Antivirals can limit SARS-CoV2 replication; while immune modulators that ameliorate inflammation in the lung, preserve immune function by preventing T cell lymphopenia and functional T cell exhaustion, and prevent CRS. Given the biology of the CD24-Siglec pathway in limiting inflammation to DAMPs, it is of great interest to test if this innate immune checkpoint can be fortified to address these challenges. Our preliminary studies suggest that our product, currently at Readiness Level 7, may fulfill all these roles.

1.3. CD24Fc Overview

CD24Fc comprises the non-polymorphic extracellular regions of CD24, which we have shown to be an innate checkpoint against the inflammatory response to tissue injuries or DAMPs (danger-associated molecular patterns), attached to the Fc region of human IgG1. Preclinical and clinical studies have demonstrated that CD24Fc effectively addresses the major challenges associated with COVID-19. First, a Phase I clinical trial of healthy volunteers not only demonstrated safety of CD24Fc, but also demonstrated its biological activity in suppressing expression of multiple inflammatory cytokines (28, 29). Second, in a Phase II clinical trial in leukemia patients undergoing hematopoietic stem cell transplantation, three doses of CD24Fc effectively eliminated severe (Grade III-IV) acute graft vs host disease (NCT02663622), which is caused by transplanted T cells attacking recipient target tissues (30, 31).

As of this writing, OncoImmune has received Chinese Center for Drug Evaluation (CDE) approval for a Phase I/III clinical trial of CD24Fc for the treatment of severe COVID-19 patients in Wuhan, China. Here we propose an independent Phase III clinical trial in the US testing the clinical efficacy of CD24Fc for treating severe COVID-19 patients using a new clinical protocol adapted based on US clinical practice. The Phase III trial will involve 230 patients randomized into blinded placebo and CD24Fc arms, with time to clinical improvement from severe to mild symptoms as the primary endpoint. It is anticipated that by reducing inflammation in the lung, CD24Fc could be a new generation of immune modifier that will enable repair of lung damage resulting from SARS-CoV2 infection. At the same time, by rescuing T lymphocytes from deletion and functional exhaustion, CD24Fc will promote clearance of SARS-CoV2. Furthermore, by reducing cytokine storm, CD24Fc may further prevent multiple organ failures in COVID-19 patients.

1.4

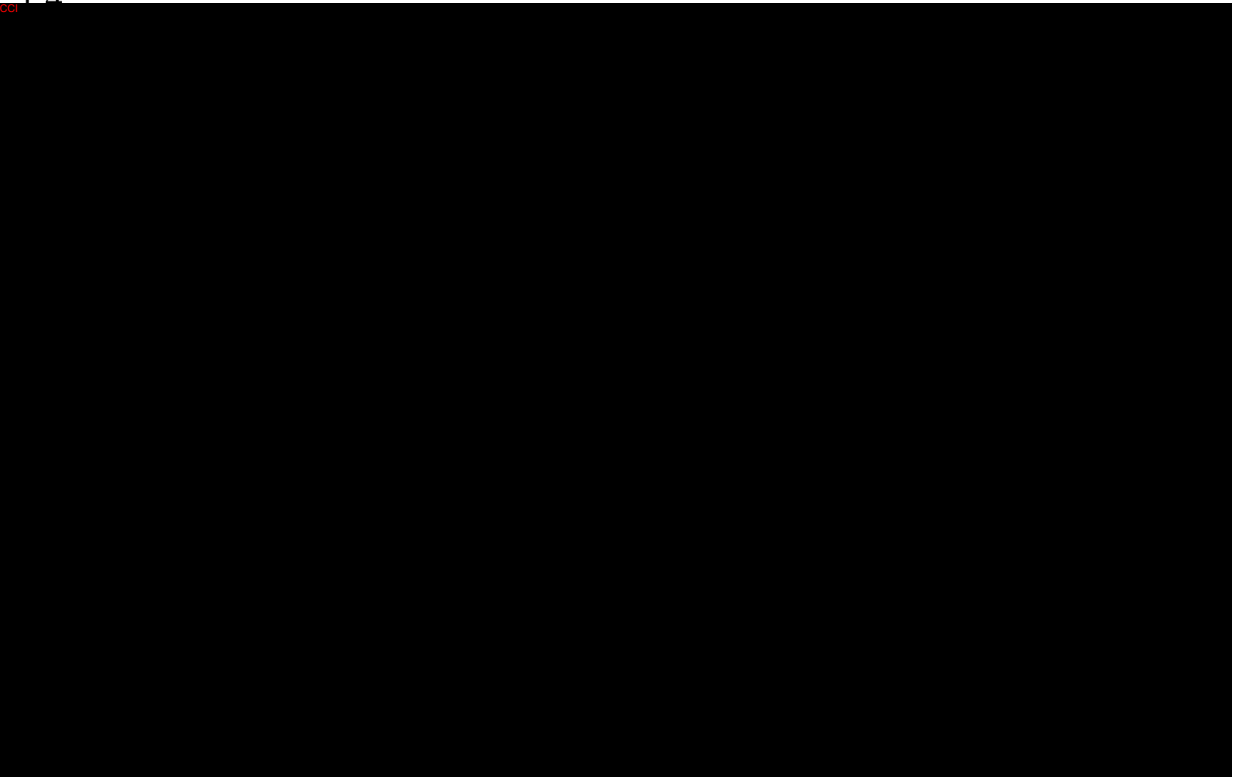


Figure 5: CD24Fc inhibits production of TNF- α and IFN- γ in activated human T cells.

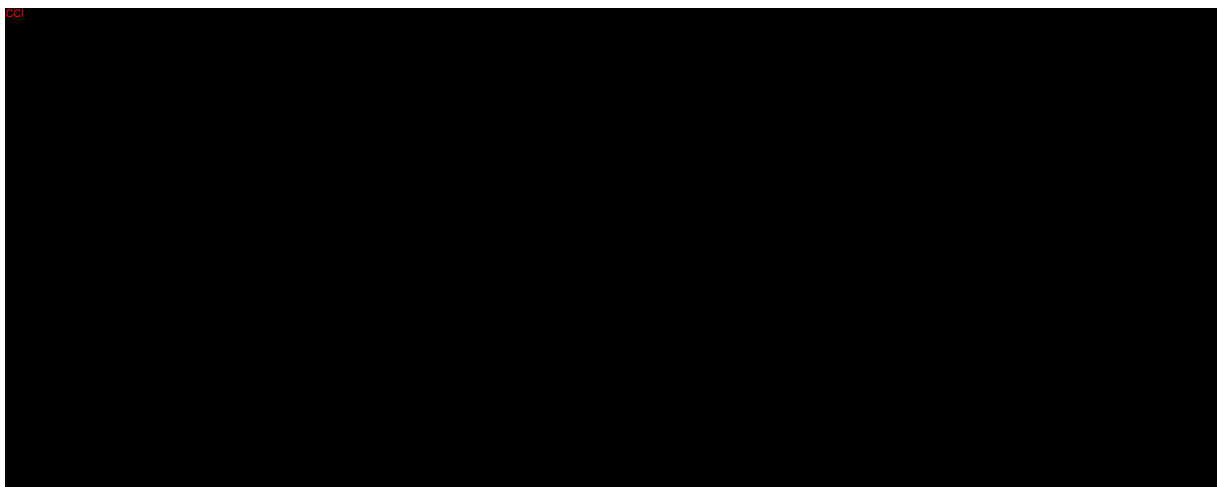


Figure 6: CD24 inhibits inflammatory cytokine production by human macrophages.



1.5. CD24Fc protects animals against virus-induced T cell lymphopenia and immunotherapy- or SIV-induced pneumonitis

Since T cell loss is associated with severe clinical symptoms in HIV patients, we established a mouse HIV model to study virally-induced T cell loss.

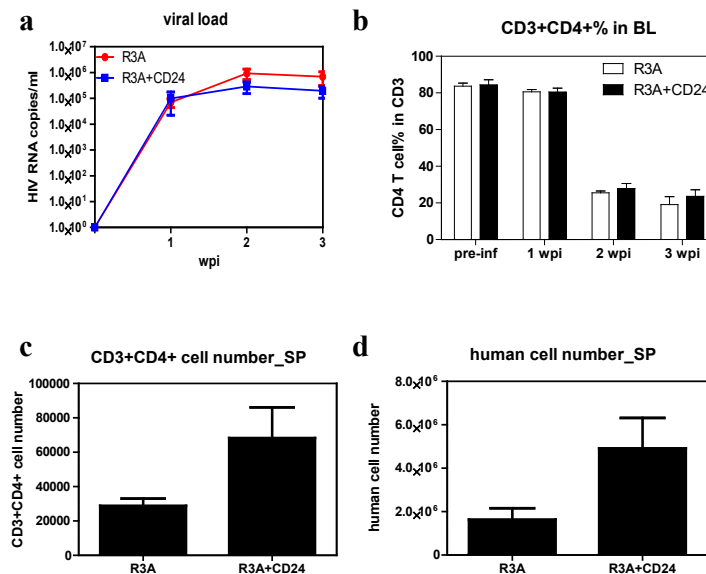
We first investigated whether CD24Fc treatment influences HIV-1 replication and immunopathogenesis in acute HIV-1 infection with humanized mice. As shown in [Figure 7a](#), in the vehicle-treated group, R3A replication rapidly increased to 1×10^6 copies/mL at 1 week post-infection (wpi) and then it gradually increased to 10^8 copies/mL at 2-3 wpi. In the CD24Fc treated group, R3A increase in the first week was unaffected. However, no further increase was observed at 2 and 3 wpi. Nevertheless, CD24Fc treatment affected both CD4 and CD8 T cells equally as it did not reduce CD4 T cell frequency among CD3⁺ T cells ([Figure 7b](#)). Notably,

CD24Fc treatment significantly increased the numbers of CD4⁺ T cells in the spleen at the termination of the mice at 3 wpi (Figure 7c). This increase of CD4⁺ T cell number corresponded with an increase of the total human lymphocytes in the spleen of humanized mice (Figure 7d). These data indicate that CD24Fc has the potential to reduce HIV-1 viral load and protect T cells from depletion in the spleen of humanized mice with acute HIV infection. Since the CD4 and CD8 ratio was not altered (Figure 7b), CD24Fc protected against loss of both CD4 and CD8 T cells.

Figure 7: CD24Fc treatment reduces HIV-1 viral load and protects CD4⁺ T cells from depletion in the spleen of humanized mice with acute HIV infection.

(a) The effect of CD24Fc treatment on plasma HIV-1 loads in of R3A infected mice with or without CD24Fc administered by i.p. at 5 mg/kg on days 1, 8 and 15 after infection. (b) Summary data of the percentages of CD4⁺ T cells in the peripheral blood of R3A infected mice with or without CD24Fc. (c and d) Summary data of the absolute number of CD4⁺ T cells (c) and total human lymphocytes (d) in the spleen of R3A infected mice with or without CD24Fc at termination. Data shown are mean and s.e.m. *P < 0.05, ** P < 0.01 (analysis of two-tailed unpaired Student's t-test). Similar protection of CD8 T cells are achieved as the CD4% in T cells was unaffected by CD24Fc.

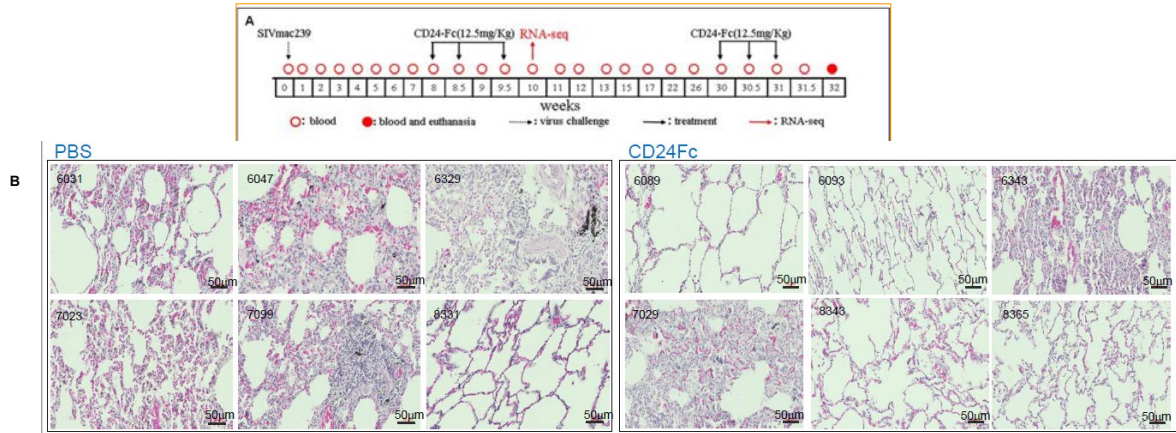
We have recently reported that CD24Fc protected Chinese rhesus monkey against SIV-induced AIDS and death, primarily by reducing organ damage caused by inflammation (18). To test



whether CD24Fc protects monkeys against SIV-induced pneumonitis, we analyzed the histology of the lung from SIV-infected monkey that were treated with either vehicle (PBS) or CD24Fc at 56 days after viral infection (Figure 8a). As shown in Figure 8b, 5 out of 6 monkeys receiving vehicle developed severe pneumonitis and two monkeys expired in week 13 and week 19. There are only 2 out of 6 monkeys that received CD24Fc had pneumonitis when examined after pre-specified euthanization. Thus, CD24Fc reduced the rate of viral pneumonitis from 83% to 33%.

Figure 8: CD24Fc protects SIV-infected monkeys from pneumonitis.

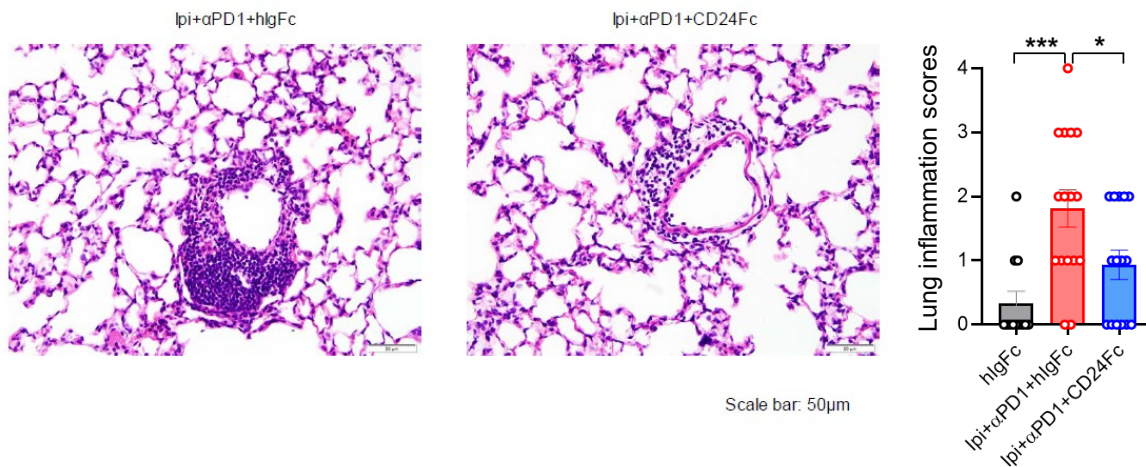
A. Diagram of experimental design. Note that monkeys received PBS or CD24Fc at 8 weeks after infection. All monkeys had established SIV infections and were randomized into treatment groups based on plasma viral titer, immune activation of CD8 T cells and CD4 T cell numbers. B. Histopathology of monkeys receiving PBS (left 6 panels) and CD24Fc (right panels). Pneumonitis were diagnosed based on histology in double blind fashion by 2 independent investigators.



To confirm if CD24Fc protects pneumonitis by virus-independent mechanisms, we tested its activity in mice that received combined immunotherapy of anti-PD-1 and anti-CTLA-4 antibodies, which can lead to immune-related adverse events (irAE) in the lung. As shown in Figure 9, CD24Fc significantly reduced inflammation in the lung.

Figure 9: CD24Fc reduces immunotherapy-induced pneumonitis.

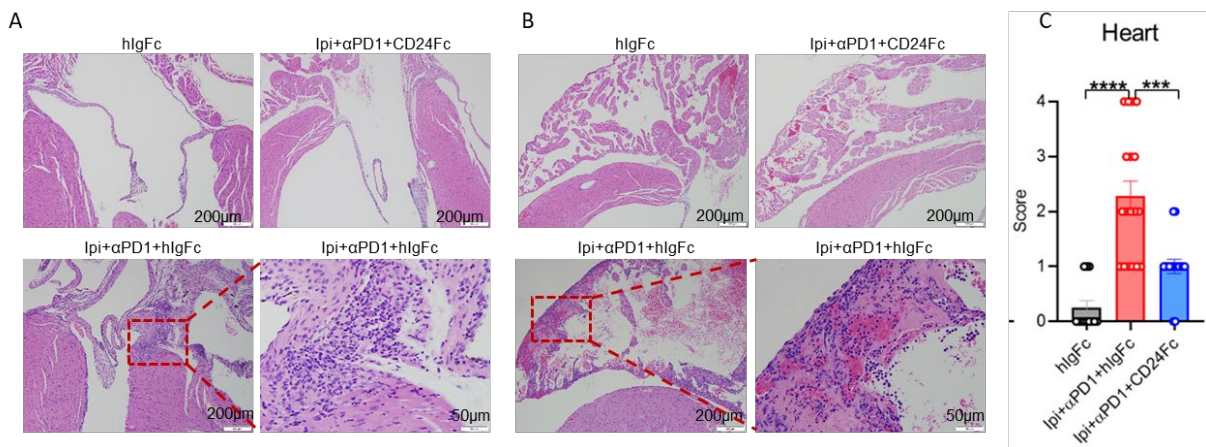
The left and middle panels show histopathology staining, while the right panel shows the summary of double blinded pathology scores.



Major cardiac complications have been reported to develop in a considerable number of patients with COVID-19 pneumonia, and people with underlying cardiovascular diseases are among the highest risk individuals for severe disease and death. Cardiac troponin I values are significantly increased in patients with severe SARS-CoV-2 infection compared to those with milder forms of disease (4, 10, 20, 35). To confirm if CD24Fc protects myocardial injuries by virus-independent mechanisms, we tested its activity in mice that received combined immunotherapy of anti-PD-1 and anti-CTLA-4 antibodies, which can lead to immune-related adverse events (irAE) in the heart. As shown in Figure 10, CD24Fc significantly reduced inflammation in the heart.

Figure 10: CD24Fc reduces immunotherapy induced myocardial inflammation and injuries.

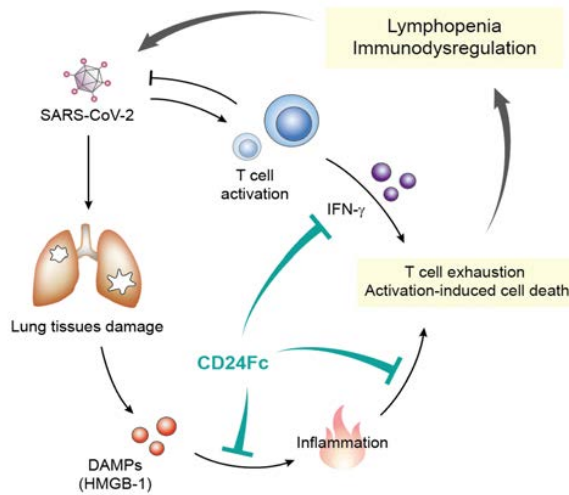
(A) The histopathology of the aorta base and left ventricle of the heart; (B) The histopathology of the right atrium of the heart; (C) The summary of double blinded pathology scores.



Taken together, our preclinical studies revealed that CD24Fc can effectively control inflammatory cytokines, rescue T cells from virus-induced depletion, and prevent lung inflammation. In addition, we also observed that CD24Fc significantly reduced exhaustion of human T cells in HIV-infected humanized mice (data not shown). Given the critical roles of these features in the pathogenesis of COVID-19, our data provided strong rationale for the clinical evaluation of CD24Fc as an immune modifier for COVID-19 (Figure 11).

Figure 11: The rationale for testing CD24Fc for the treatment of COVID-19.

SARS-CoV2 infected caused damage in the pneumocytes, resulting in release of DAMPs, which triggers production of inflammatory cytokines and a vicious cycle of tissue damage. Inflammation also cause T cell overdrive, resulting in functional T cell exhaustion and IFN γ -mediated activation-induced cell death (32-34), leading to T cell lymphopenia. CD24Fc blocks these key steps in COVID-19 pathogenesis, and thus represent a unique immune modifier that provides a new therapeutic approach for COVID.



CD24Fc abrogates multiple steps of COVID-19 pathogenesis

- 1. Inhibition of expression of multiple inflammatory cytokines**
- 2. Prevent expression of T lymphocyte exhaustion markers**
- 3. Prevention lymphopenia by inhibiting IFN γ production: an underlying cause of T cell death during viral infection.**

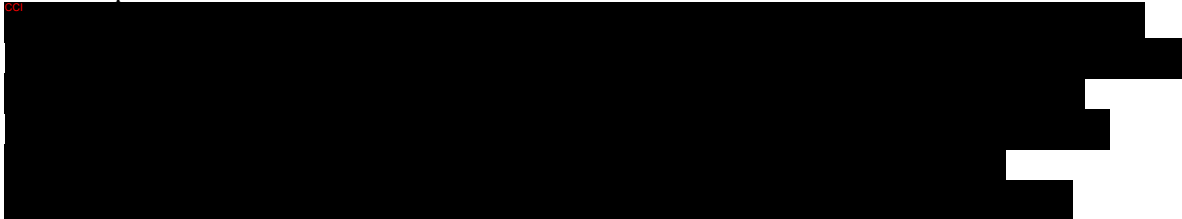
1.6. Pharmaceutical Information of Study Drug

1.6.1. CD24Fc or CD24IgG (OncoImmune, Inc.), Study Agent

CD24Fc (CD24 Ig) is a fusion protein consisting of the extracellular domain of mature human CD24 linked to the human immunoglobulin G1 (IgG1) Fc domain.

1.6.2. Molecular Formula and Formulation

The complete molecular formula of CD24Fc has not been determined at this time. The mature



CD24Fc has been formulated as single dose injection solution, at a concentration of 10 mg/mL in phosphate buffered saline at pH 7.2. Each 20 mL CD24Fc Drug Product vial 120 mg of CD24Fc in a volume that allows for extractable 12 ml. Each vial will be labeled according to Title 21 of the U.S. Code of Federal Regulations with “Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use. The label should have Product Name CD24Fc and Lot number: 0118-002.

1.6.3. Packaging, Ordering, and Inventory Management

CD24Fc Drug Product is supplied in clear borosilicate glass vials with chlorobutyl rubber stoppers and aluminum flip off seals. Vials of Lot 0118-002 are further packaged into 8 vial patient kit boxes comprising labeled paperboard boxes outfitted with cardstock box dividers and tamper evident seals. Drug product vials are stored at OncoImmune's clinical distribution site, Almac Clinical Services, at 25 Fretz Road, Souderton, PA. On site inventory will be managed by the CRO and additional drug will be ordered by OncoImmune or the CRO and shipped directly to the drug site from Almac.

1.6.4. Availability, Storage and Stability

CD24Fc is supplied as a sterile, clear, colorless, preservative-free aqueous solution for parenteral administration. CD24Fc is stored at -20° C until use. CD24Fc should be thawed and equilibrated to room temperature prior to administration. CD24Fc Drug Product used in the Phase I and Phase IIa trials (Lot 09MM-036) is stable for at least 66 months at -20°C, for 6 months at 5°C and 3 months at 25°C. New CD24Fc Drug Product has been manufactured as "Lot 0118-002". The new Drug Product has been administered 58 times in the Phase II expansion cohort study. Stability studies for Lot 0118-002 are ongoing and it has demonstrated to be stable for 24 months at the intended storage temperature, -20°C, for 6 months at 5°C and 1 month at 25°C.

1.6.5. Administration

CD24Fc at doses up to 480 mg will be prepared in a diluent comprising 0.9% Sodium Chloride in a volume of 100 ml and be administered by intravenous infusion over a minimum of 60 minutes.

1.7. Clinical Experience of CD24Fc in Humans

1.7.1. Phase I Summary:

OncoImmune Inc. has developed and manufactured clinical grade CD24Fc for use in humans. CD24Fc has been tested in a Phase I clinical trial in healthy human subjects, and this study showed preliminary safety of single dose CD24Fc by IV administration. A total of 40 subjects were randomized in 5 cohorts of 8 subjects, and 39 subjects completed the study. CD24Fc was administered via IV infusion over 1 hour at doses ranging from 10 to 240 mg, and the subjects were followed over a six-week period. A MTD was not encountered.

In general, adverse events were mild to moderate in severity. The most common AEs were headache (6 [15.0%] subjects), accidental burns second degree (3 [7.5%] subjects), non-sustained ventricular tachycardia (2 [5.0%] subjects), and upper respiratory tract infection (2 [5.0%] subjects). The rates of the AEs were similar in the placebo control group. The SAE of ventricular tachycardia was considered mild in severity by the investigator and did not lead to discontinuation of the subject from the study. This SAE was considered to be drug related due to its close temporal proximity to dosing, though similar short, isolated episodes of non-sustained ventricular tachycardia may be seen in up to 4% of normal, healthy populations. No deaths or adverse events leading to discontinuation occurred during the study.

1.7.2. Phase IIa Summary:

A Phase IIa prospective randomized double-blind clinical trial of CD24Fc for acute GVHD prophylaxis in myeloablative matched unrelated donor HCT was initiated in July 2016. The first patient was enrolled in Sept 2016. A total of 24 patients were enrolled in three cohorts, 240mg single dose given at day -1, 480mg single dose at day -1, 480-240-240mg multi-dose given on day -1, day 14 and day 28, with 6 patients receiving CD24Fc and 2 patients receiving placebo in each cohort. The last patient was enrolled in Dec 2017. The last patient reached one year post-HCT in December 2018. Data was locked and the final clinical study report (CSR) was submitted to FDA in April 2019. In total there are 18 patients in the CD24Fc group and 6 patients in the placebo group (3:1 randomization). All planned dosages were delivered on schedule.

1.7.2.1. Phase IIa Clinical Study Overview

The primary objectives of the Phase IIa are to assess the safety and tolerability of CD24Fc in combination with methotrexate and tacrolimus prophylaxis in subjects undergoing matched unrelated donor HCT following myeloablative conditioning, and to define the recommended Phase II dose (RP2D) or maximum tolerated dose (MTD). In addition, secondary efficacy objectives in the Phase IIa include:

- assessing grade II – IV aGVHD free survival (GFS) at day 180 after HCT,
- assessing the incidence of chronic GVHD (cGVHD) at one year following HCT
- assessing the incidence of relapse one year following HCT
- assessing the incidence of transplant-related mortality (TRM) one year following HCT
- assessing infection rates at day 100 following HCT
- evaluating overall survival (OS), absence of grade III-IV GVHD, and relapse-free survival one year following HCT
- evaluating conditioning toxicity including oral mucositis and organ failure

Other exploratory objectives include assessment of the pharmacokinetic (PK) profile of CD24Fc, examining the immune cell profile and functional responses of APCs and T cells after HCT in the CD24Fc and placebo groups, and assessing pharmacodynamics (PD) biomarkers such as the plasma concentrations of pro-inflammatory cytokines, DAMPs, lipids, and GVHD biomarkers in the CD24Fc and placebo groups.

Subjects between the ages of 18-70 years old undergoing matched unrelated donor allogeneic HCT for a malignant hematologic condition (AML, ALL, CML, CMML, MDS) with a Karnofsky performance score $\geq 70\%$ were eligible for the trial. An 8/8 HLA allelic match between the unrelated donor and the recipient at HLA-A, HLA-B, HLA-C, and HLA-DRB1 was required. All subjects received myeloablative conditioning and standard of care GVHD prophylaxis with methotrexate and tacrolimus per the Phase IIa protocol. Patients received a myeloablative conditioning regimen consisting of either fludarabine and busulfan (Flu/Bu) or

cyclophosphamide and total body irradiation (Cy/TBI), as decided by the treating physician, followed by an infusion of stem cells on day 0. The source of donor stem cells was either peripheral blood stem cells (PBSC) or bone marrow (BM). GVHD prophylaxis was administered to all subjects and consisted of tacrolimus (initiated Day -3 before transplant) and methotrexate (initiated Day +1 after transplant) in combination with CD24Fc in the treatment arms, and tacrolimus/methotrexate plus saline solution in the placebo arm. In the absence of GVHD, tacrolimus tapering started on day +100.

1.7.2.2. Phase IIa Clinical Study Summary

Overall, CD24Fc was well tolerated in the Phase IIa study. There were no infusion-related toxicities. There was one possible drug related treatment emergent adverse event (TEAE) of \geq grade III-IV hyperglycemia in the 480 mg CD24Fc group, which was managed with insulin. One dose-limiting toxicity (DLT) was observed in the placebo group, and no DLTs were observed in the CD24Fc group. There were no adverse events leading to death in subjects administered CD24Fc within the 180 days. There was one adverse event of pneumonia that led to the death of a subject at Day 48 in the placebo group. The development of anti-drug antibodies (ADA) were not detected in any of the 24 subjects at any point out to day 100 after HCT.

The most common TEAEs \geq grade III ($> 10\%$) included a decrease in platelet counts (83.3% placebo and 94.4% CD24Fc), decrease in WBC counts (66.7% placebo and 88.9% CD24Fc), decrease in neutrophil counts (50% placebo and 83.3% CD24Fc), decrease in lymphocyte counts (50% placebo and 77.8% CD24Fc), anemia (50% placebo and 66.7% CD24Fc), stomatitis (83.3% placebo and 50% CD24Fc), and nausea (0% placebo and 11.1% CD24Fc). These are expected SAEs were anticipated as they were hematologic in nature and were otherwise considered related to the myeloablative conditioning regimen of HCT.

In the Phase IIa study, compared to treatment with placebo, treatment with CD24Fc resulted in trends toward:

1. Higher Grade III to IV acute GFS rate at Day 180 (94.4% in CD24Fc treatment group, 50.0% in placebo) (hazard ratio = 0.1),
2. Higher DFS rate at 1 year (83.3% in CD24Fc treatment group, 50.0% in placebo) (hazard ratio = 0.2),
3. Higher OS rate at 1 year (83.3% in CD24Fc treatment group, 50.0% in placebo) (hazard ratio = 0.2),
4. Higher Grade III to IV acute GRFS rate at Day 180 (83.3% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 0.2),
5. Lower incidence of Grade III-IV acute GVHD by Day 180 (5.6% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 0.1),
6. Lower cumulative incidence of leukemia relapse at 1 year (11.1% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 0.3),
7. Lower incidence of non-relapse mortality at 1 year (5.6% in CD24Fc treatment group, 16.7% in placebo) (hazard ratio = 0.3),

8. Similar cumulative incidence of Grade II to IV acute GVHD by Day 180 (38.9% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 2.6),
9. Similar 1 year GRFS (Grade III-IV acute GVHD / chronic GVHD requiring systemic immunosuppressive treatment /relapse free survival) (32.4% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 0.7),
10. Higher cumulative incidence of all grade chronic GVHD at 1 year (63.3% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 2.1).

1.8. Safety in Humans

1.8.1. Phase I Safety Data

A Phase I, randomized, double-blind, placebo-controlled, single ascending dose study to assess the safety, tolerability, and PK of CD24Fc in healthy male and female adult subjects was conducted. Details are also provided in section 3.8 A total of 40 subjects were randomized in 5 cohorts of 8 subjects each, and 39 subjects completed the study. CD24Fc was administered via IV infusion over 1 hour. In total, 18 (45.0%) subjects had a treatment-emergent adverse event (TEAE) during the study: 6 (60.0%) subjects in the placebo group, 2 (33.3%) subjects in the CD24Fc 10 mg group, 3 (50.0%) subjects in the CD24Fc 30 mg group, 2 (33.3%) subjects in the CD24Fc 60 mg group, 3 (50.0%) subjects in the CD24Fc 120 mg group, and 2 (33.3%) subjects in the CD24Fc 240 mg group.

All TEAEs in the study were considered mild to moderate in severity by the Investigator except for 1 subject in the placebo group who experienced a severe headache. The most common TEAEs were headache (6 [15.0%] subjects), burns second degree (3 [7.5%] subjects), non-sustained ventricular tachycardia (2 [5.0%] subjects), and upper respiratory tract infection (2 [5.0%] subjects).

Overall, 5 (12.5%) subjects had a study drug-related TEAE: 1 (10.0%) subject in the placebo group, 2 (33.3%) subjects in the CD24Fc 10 mg group, 1 (16.7%) subject in the CD24Fc 30 mg group, and 1 (16.7%) subject in the CD24Fc 60 mg group. The study drug-related TEAEs during the study were headache (4 [10.0%] subjects) and ventricular tachycardia (1 [2.5%] subject). A drug-related SAE of ventricular tachycardia was experienced by 1 subject in the CD24Fc 60 mg group. This SAE occurred at a rate comparable with normal populations, was considered mild by the Investigator, and did not lead to discontinuation from the study. No subjects died during the study and no subjects discontinued from the study due to an adverse event. There were no clinically meaningful changes from baseline in laboratory parameters, vital signs, ECGs, or physical exams during the study.

1.8.2. Phase IIa Safety Data

The number of subjects with TEAEs from Day -1 to 30 or 60 days after the last dosing was the same between all treatment groups: 6 (100.0%) patients in the 240 mg CD24Fc single dose cohort, 6 (100.0%) patients in the 480 mg CD24Fc single dose cohort, 6 (100.0%) patients in the 480/240/240 mg multiple dose cohort, and 6 (100.0%) patients who received placebo experienced TEAEs.

The most common TEAEs were stomatitis (6 [100.0%] patients in the 240 mg CD24Fc single dose cohort, 6 [100.0%] patients in the 480 mg CD24Fc single dose cohort, 5 [83.3%] patients in the 480/240/240 mg CD24Fc multiple dose cohort, and 6 [100.0%] patients who received placebo); platelet count decreased (6 [100.0%] patients in the 240 mg CD24Fc single dose cohort, 6 [100.0%] patients in the 480 mg CD24Fc single dose cohort, 5 [83.3%] patients in the 480/240/240 mg CD24Fc multiple dose cohort, and 5 [83.3%] patients who received placebo); white blood cell count decreased (6 [100.0%] patients in the 240 mg CD24Fc single dose cohort, 6 [100.0%] patients in the 480 mg CD24Fc single dose cohort, 5 [83.3%] patients in the 480/240/240 mg CD24Fc multiple dose cohort, and 4 [66.7%] patients who received placebo). Severe stomatitis (\geq Grade 3) occurred in 3 (50.0%) patients in the 240 mg CD24Fc single dose cohort, 4 (66.7%) patients in the 480 mg CD24Fc single dose cohort, 2 (33.3%) patients in the 480/240/240 mg CD24Fc multiple dose cohort, and 5 (83.3%) patients who received placebo, with a clear inverse correlation between CD24Fc doses and duration of severe stomatitis.

One (16.7%) patient in the 480 mg CD24Fc single dose cohort and 2 (33.3%) patients who received placebo experienced a study drug-related TEAE. The most common study drug-related TEAE was diarrhea (1 [16.7%] patient in the 480 mg CD24Fc single dose cohort and 2 [33.3%] patients who received placebo). No patients in other cohorts experienced a study drug-related TEAE.

The incidence of Grade 3/4/5 TEAEs was the same between all treatments: 6 (100.0%) patients in the 240 mg CD24Fc single dose cohort, 6 (100.0%) patients in the 480 mg single dose cohort, 6 (100.0%) patients in the 480/240/240 mg multiple dose cohort, and 6 (100.0%) patients who received placebo. One (16.7%) patient in the 480 mg CD24Fc single dose cohort experienced hyperglycemia that was considered a study drug-related Grade 3/4/5 TEAE.

No patients receiving CD24Fc experienced a DLT during the study. One dose-limiting toxicity (DLT) was observed in the placebo group

In total, 1 (4.2%) patient died during the study. Patient ^{PPD} [REDACTED] received placebo and experienced Grade 4 pneumomediastinum and Grade 5 pneumonia TEAEs that resulted in death. Per the Investigator, it was considered unlikely that these TEAEs were related to study drug.

1.8.3. Treatment Emergent AEs (TEAEs)

In total, 9 (37.5%) patients experienced TESAEs from Day -1 to 30/60 days after the last dosing: 2 (33.3%) patients in the 240 mg CD24Fc single dose cohort (30 days), 1 (16.7%) patient in the 480 mg CD24Fc single dose cohort (30 days), 4 (66.7%) patients in the 480/240/240 mg CD24Fc multiple dose cohort (60 days), and 2 (33.3%) patients who received placebo (30, 30, 60 days). Treatment-emergent SAEs reported for patients who received CD24Fc (some patients had more than one condition) were nausea (2), stomatitis (1), abdominal pain (1), dehydration(1), decreased appetite (1), device related infection (1), pain (1), weight decreased (1), arthritis (1), cognitive disorder (1), and embolism (1).

In total, 1 patient experienced a TEAE that led to discontinuation of study drug: this patient received placebo. Patient ^{PPD} [REDACTED] experienced a Grade 4 pneumonia TEAE that led to discontinuation of study drug (ie, placebo). Per the Investigator, it was considered unlikely that this TEAE was related to study drug.

In Chemistry laboratory tests, the incidence of TEAEs of alanine aminotransferase increased or blood alkaline phosphatase increased were similar between patients who received CD24Fc and patients who received placebo (ALT: 44% vs 50%; ALP 22% vs 17%). The incidence of TEAEs of aspartate aminotransferase increased was higher for patients who received CD24Fc compared to patients who received placebo (28% vs 18%). Treatment-emergent adverse events of blood creatinine increased were only reported by patients who received placebo (33.3%). A TEAE of blood bilirubin increased was reported by 1 (16.7%) patient who received placebo. In general, TEAEs were consistent with toxicities normally associated with HCT conditioning and did not appear associated with investigational therapy or placebo.

Hematologic Effects:

In total, the incidence of TEAEs of white blood cell count decreased, lymphocyte count decreased, and neutrophil count decreased were higher in patients who received CD24Fc compared to patients who received placebo (white blood cells decrease 94% vs 67%, lymphocyte decrease 83% vs 50%, neutrophil decrease 89% vs 50%). The incidence of TEAEs of platelet count decreased was similar between patients who received CD24Fc and patients who received placebo (94% vs 83%).

No patient had a laboratory abnormality that was considered an SAE or resulted in discontinuation of study drug.

No patients who received either single or multiple dosing of CD24Fc had positive ADA results at any time point sampled pre- or post-infusion.

A TEAE of weight increased was reported by 1 (16.7%) patient who received placebo and A TEAE of weight decreased was reported by 3 (16.7%) patients who received CD24Fc. A TEAE of ECG QT prolonged was reported by 1 (16.7%) patient who received placebo.

Donor Cell Engraftment and Chimerism:

In total, 18 (100.0%) patients who received CD24Fc and 6 (100.0%) patients who received placebo experienced neutrophil engraftment. The median time to neutrophil engraftment was 13.5 days for patients in the 240 mg CD24Fc single dose cohort, 13.5 days for patients in the 480 mg CD24Fc single dose cohort, 13.0 days for patients in the 480/240/240 mg CD24Fc multi-dose cohort, and 15.5 days for patients who received placebo.

In total, 18 (100.0%) patients who received CD24Fc and 5 (83.3%) patients who received placebo experienced platelet engraftment. The median time to platelet engraftment was 15.5 days for patients in the 240 mg CD24Fc single dose cohort, 13.0 days for patients in the 480 mg CD24Fc single dose cohort, 12.0 days for patients in 480/240/240 mg CD24Fc multiple dose cohort, and 15.0 days for patients who received placebo. No patients experienced primary engraftment failure.

The mean CD3 cell chimerism on Day 28/Day 30 was 73.0% donor cells for patients who received CD24Fc and 77.4% donor cells for patients who received placebo. The mean CD3 cell chimerism on Day 100 was 80.9% donor cells for patients who received CD24Fc and 73.8% donor cells for patients who received placebo.

The mean CD33 cell chimerism on Day 28/Day 30 was 100.0% donor cells for patients who received CD24Fc and 100.0% donor cells for patients who received placebo. The mean CD33 cell chimerism on Day 100 was 99.4% donor cells for patients who received CD24Fc and 96.6% donor cells for patients who received placebo.

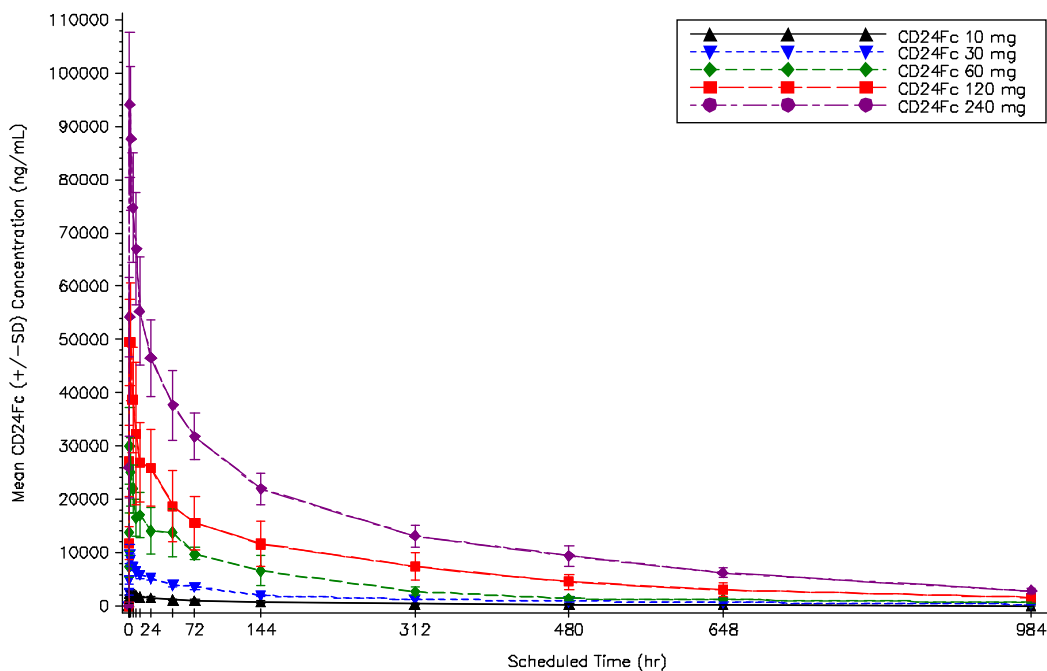
1.9. Pharmacokinetics in Humans

1.9.1. Phase I PK

The PK of CD24Fc in healthy human subjects was determined from the single dose Phase I study. The mean plasma concentration of CD24Fc increased proportionally to the dose of CD24Fc administered (Figure 12). For all dose groups except 120 mg, the maximum mean plasma concentration of CD24Fc was reached at 1 hour post-dose. The maximum mean plasma concentration of CD24Fc for the 120 mg group was reached at 2 hours post-dose. By Day 42 (984 hours), the mean plasma concentration of CD24Fc for all groups had decreased to between 2% and 4% of the maximum mean plasma concentration. CD24Fc reached T_{max} at 1.34 hours. The $t_{1/2}$ of plasma CD24Fc range was 280.83 to 327.10 hours.

Figure 12: Plot of Mean (\pm SD) Plasma CD24Fc Concentration by Treatment – PK Evaluable Population.

PK = pharmacokinetic; SD = standard deviation.
 Source: Investigators Brochure.



1.9.2. Phase IIa PK

The PK of CD24Fc in human subjects undergoing HCT has been determined from the Phase IIa study from the two single dose cohorts and one multi-dose cohort (Figure 13). With the 240 mg single dose, the mean plasma concentration of CD24Fc is similar to the 120 mg single dose in Phase I human volunteers. The 480 mg dose shows a proportional increase of CD24Fc at all time points. The 480/240/240 mg multi-dose maintains the CD24Fc plasma concentration over 10,000 ng/ml over the period of Day-1 to Day 42 post-HCT.

Following a single IV administration of CD24Fc (240 and 480 mg CD24Fc single dose cohorts), the geometric mean plasma exposure ($C_{max,-1d}$, AUC_{0-42d} , and AUC_{0-inf}) increased with increasing CD24Fc doses. The mean $t_{1/2}$ and λ_z were similar between the 240 and 480 mg doses of CD24Fc. The mean values of $t_{1/2}$ were 414.739 and 406.648 h and the mean values of λ_z were 0.0018 and 0.0017 h^{-1} for the 240 and 480 mg CD24Fc single dose cohorts, respectively. Additionally, there was an increase in the mean V_z and CL between the 240 and 480 mg doses of CD24Fc.

Following multiple IV administrations of CD24Fc (480/240/240 mg CD24Fc multi-dose cohort), the exposure of CD24Fc was sustained over time. Additionally, the mean plasma CD24Fc concentration on Day 100 was higher for the 480/240/240 mg CD24Fc multi-dose cohort (850.84 ng/mL) compared to the single dose cohorts (216.38 ng/mL and 330.96 ng/mL for the 240 and 480 mg CD24Fc single dose cohorts, respectively). Furthermore, the geometric mean $AUC_{0-last,overall}$ value was higher for the 480/240/240 mg CD24Fc multi-dose cohort (37,363,953.5 ng·h/mL) compared to the single dose cohorts (10,156,549.9 ng·h/mL and 15,522,686.2 ng·h/mL for the 240 and 480 mg CD24Fc single dose cohorts, respectively).

The median $t_{max,-1d}$ (2.10 h for both the 240 and 480 mg CD24Fc single dose cohorts and 2.13 h for the 480/240/240 mg CD24Fc multiple dose cohort) remained consistent across all of the CD24Fc doses. For the 480/240/240 mg CD24Fc cohort, the median $t_{max,-1d}$ and $t_{max,28d}$ were similar (2.13 and 2.52 h, respectively).

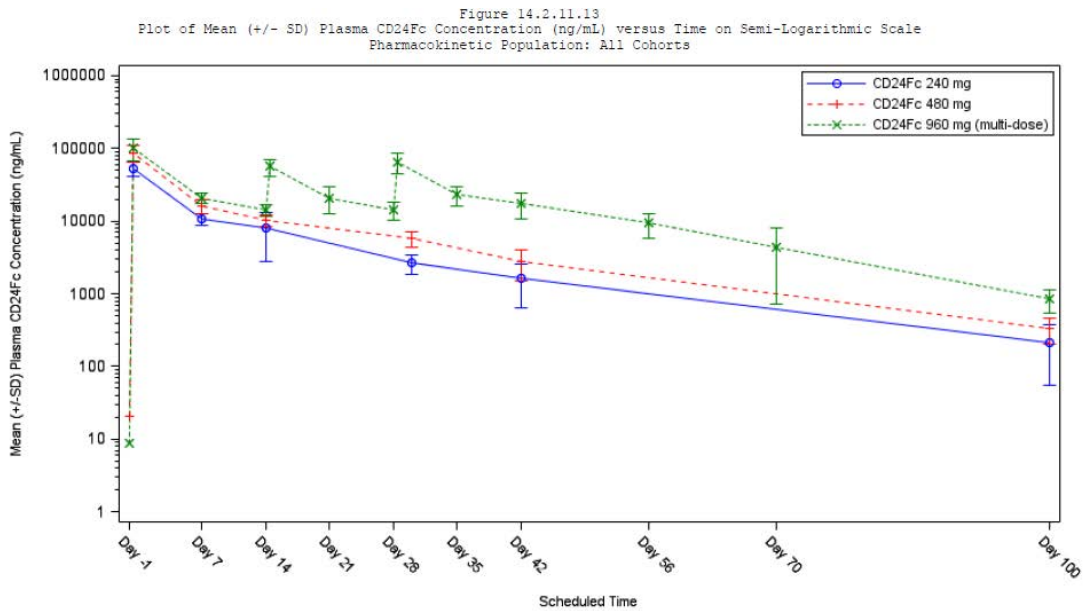
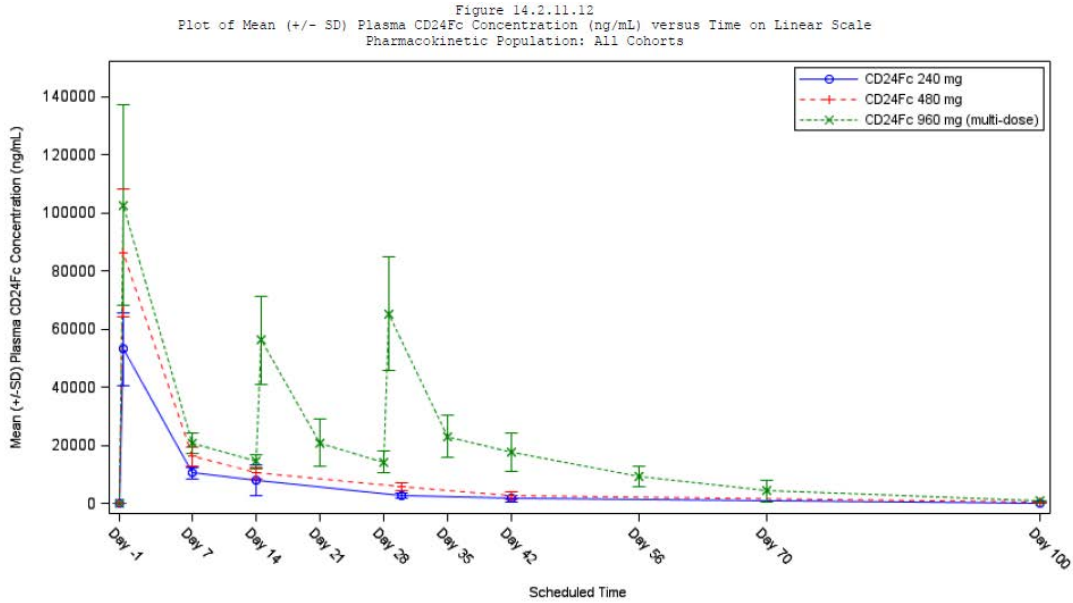
1.10. Immunogenicity in Humans

1.10.1. Phase I ADA

Serum samples in the Phase I study were screened for anti-drug antibodies. Anti-CD24Fc antibodies were detectable at Day 28 and Day 42 in 1 subject in each of the 5 dose cohorts; however, for the subject in the CD24Fc 120 mg group and the subject in the CD24Fc 240 mg group, anti-CD24Fc antibodies were also detectable pre-dose at levels higher than post-dose levels. Except for those subjects with significant pre-dose anti-CD24Fc antibody levels, all post-dose anti-CD24Fc antibody levels were modest. No deviations in PK were found in any subjects with detectable anti-CD24Fc antibody levels.

Figure 13: Plot of Mean (\pm SD) Plasma CD24Fc Concentration by Treatment – PK Evaluable Population.

Upper Panel: PK in linear scale. Lower Panel: PK in semi-log scale. Single dose cohorts, 240mg (n=6); 480mg (n=6); multi-dose cohort, 480-240-240mg (n=6).



1.10.2. Phase IIa ADA

In the Phase IIa allogeneic HCT context, given the immunoablation and immunosuppression of host immunity at time of CD24Fc administration, ADA responses were monitored but unlikely to be elicited.

For the two single dose cohorts, the samples were collected at 7 time points from Day-1 to Day 100. For the multi-dose cohort, the samples were collected at 13 time points from Day-1 to Day 100. As expected, all samples are negative for ADA in the Phase IIa study.

1.11. Rationale for CD24Fc in COVID-19 treatment

Early clinical trials of CD24Fc in the prevention of acute GVHD are based on the following principles: 1) Early tissue damage occurs during conditioning regimen before HCT. Early tissue damage leads to the release of DAMP inflammatory mediators, which triggers acute GVHD; 2) CD24Fc can significantly inhibit the DAMP inflammatory response that triggers acute GVHD by directly binding to DAMP molecules or by enhancing the interaction between CD24Fc and Siglec-10; and 3) studies from multiple pre-clinical models of acute GVHD demonstrate that early administration of exogenous human CD24Fc before infusion of donor cells can alleviate acute GVHD and improve survival after HCT. The results of the 2a clinical trial of CD24Fc provided the proof of concept in safety and efficacy in CD24Fc for the prevention of acute GVHD.

In non-human primates, CD24Fc effectively reduced the inflammatory response and AIDS caused by the monkey immunodeficiency virus (SIV). In a humanized mouse model, CD24Fc effectively inhibits the production of multiple inflammatory cytokines and prevents the HIV induced T cell depletion and T cell exhaustion.

Coronavirus SARS-CoV-2 infection involves lower respiratory tract and alveolar pneumocytes where the virus replicates. Early coronavirus infection triggers the body's innate immunity. Activated innate immune cells will release interferon type cytokines to limit the viral replication. A few days later, the adaptive immune system (adaptive immunity) joins the process of eliminating viral infected cells until the virus is cleared. However, the over-activated innate immunity and adaptive immunity may over reactive to cause damage to host tissues. ACE2, the receptor for SARS-CoV-2, is highly expressed on the epithelial cells of the lower respiratory tract and alveolar pneumocytes (36). Therefore, the host response induced by viral infection and specific inflammatory mediators may lead to bystander damage to lung tissues. This is considered to be the major mechanism for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) in COVID-19. Thus, the COVID-19 treatment should be the anti-viral drugs to inhibit viral replication in combination with non-anti-viral immunomodulators to protect lung tissue injury. Current clinical anti-inflammatory therapy consists of systemic corticosteroid and non-steroidal anti-inflammatory drugs. In this context, it is of important to note that, corticosteroid, the anti-inflammatory drug widely used in addressing severe inflammation, was not recommended for COVID-19 or SARS (18, 19).

CD24Fc plays a dual role in the innate immune response triggered by the release of DAMPs from necrotic cells. CD24Fc directly binds multiple DAMP molecules such as HMGB1 and HSP70 / 90 to neutralize DAMPs. CD24Fc also bind to Siglec 10 to activate the CD24-Siglec

signaling pathway on antigen presenting cells to suppress the NFkB activation and to reduce the biosynthesis of multiple inflammatory cytokines, including IL-6, IL-1 β , TNF- α and INF- γ . CD24Fc will be an important immunomodulator in COVID-19 treatment.

Here we provided the strong evidence from pre-clinical data from in vitro cell culture, humanized mouse HIV model, and nonhuman primate model of SIV viral pneumonitis, the safety and efficacy in clinical proof-of-concept studies, and the pathogenesis of COVID-19 to support the clinical study in testing the safety and efficacy of CD24Fc as an immunomodulator in COVID-19 treatment. Based on the clinical experience and pharmacokinetic data of CD24Fc, we plan to give a single dose of 480 mg CD24Fc to eligible patients with confirmed COVID-19 and severe pneumonia. This dose is deemed safe as 32 HCT patients have been exposed to this or higher doses. The only drug-related SAE is a transient hyperglycemia in 1 patient that responded well to insulin treatment. Furthermore, based on in vitro effect of IFN γ inhibition and PK in HCT patients, a single dose should be sufficient to provide adequate drug concentration during the study period of two weeks.

All patients should have best available treatment according to local institutional guideline in US. It is recommended to follow the WHO Interim Guidance on Clinical Management of Severe Acute Respiratory Infection (SARI) When COVID-19 is Suspected (version 1.2, Mar. 13, 2020).

1.12. **Rationale for a Randomized, double blind, placebo-controlled Phase III Trial**

The Phase 1, Phase IIa and Phase II expansion cohort studies suggest that CD24Fc is safe and well tolerized in healthy people and in patients with hematological malignancies heavily treated with chemotherapy and radiation.

This multicenter Phase III clinical trial will evaluate adding CD24Fc to best available treatment for the efficacy in increase the proportion of patients from severe COVID-19 to convert to mild or moderate COVID-19. The randomized, double blind and placebo-controlled study will provide the most rigorous analysis to assess the efficacy of the novel biological agent CD24Fc in COVID-19 treatment.

1.13. **Pharmacological study in dose selection**

Inflammatory response in COVID-2019 induces lymphopenia and T cell depletion in critically status patients. Increased levels of inflammatory cytokines can be detected in the severely pneumonia patients in early stage of disease. CD24Fc can block the viral infection associated activation induced cell death in T cells, reduce the T cell depletion, and reduce the inflammation caused by viral induced cell necrosis. IFN- γ is a valuable biomarker that can best reflect the effect of CD24Fc on inhibition of T cell activation and death.

In an in vitro pharmacodynamic experiment completed in March 2019, IFN- γ was used as an indicator to evaluate the in vitro inhibitory effect of different batches of CD24Fc products on human peripheral blood mononuclear leukocytes (PBML) activation. In the study, T cells in human PBML were activated with widely used T cell receptor agonist anti-CD3 antibodies and recombinant human IL-2. T cell activation was assessed by measuring IFN- γ production in cell

culture supernatants, and the biological activity of CD24Fc was determined by measuring the extent to which CD24Fc inhibited IFN- γ production. This study includes a batch of BF0222 CD24Fc preparations produced under GMP conditions (produced in February 2018 and has been applied to 20 subjects in Phase II expansion cohort clinical trial in GVHD prevention. The product is safe and well tolerated. This batch will be used in this COVID-19 study) and 09MM-036 (produced in December 2009, has been used in the US phase I and IIa GVHD prevention trials with good safety profile).

The results showed that CD24Fc from 4 batches of production significantly reduced IFN- γ produced by human activated PBML in a dose-dependent manner. For IFN- γ inhibition, the concentration at which the test product produced 50% inhibition (IC₅₀) was used as the evaluation index. The IC₅₀ of batch 09MM-036 was 5.860 ug / mL, and the IC₅₀ of batch BF0222 was 9.455 ug / mL.

Based on the IC₅₀ data of the BF0222 batch, the blood concentration of CD24Fc in existing clinical trials is compared, and the Pharmacological Activity (PA) of CD24Fc at different blood concentrations is calculated using the Hill equation, as shown in [Table 4](#).

$$PA = \frac{C^\gamma}{IC_{50} + C^\gamma}$$

Note: PA represents the pharmacological activity level, IC₅₀ represents the half inhibitory concentration obtained in the in vitro experiment of this pharmacological activity, C represents the drug concentration at this pharmacological activity level, and the Hill coefficient γ used in the formula is set to 1.

Table 4: Summary of the Pharmacokinetics data from Phase I and Phase IIa studies

		CD24Fc 240mg	CD24Fc 480mg	CD24Fc 960mg ¹
D1	C _{max} average (ug/mL, PA%)	52.3 (84.7%)	86.3 (90.1%)	102.8 (91.6%)
D14	C _{min} average (ug/mL, PA%)	7.95 (45.7%)	10.4 (52.4%)	14.4 (60.4%)
D14	C _{min} (ug/mL, PA%)	4.95 (34.4%)	7.05 (42.7%)	11.4 (54.7%)
D14	C _{max} (ug/mL, PA%)	18.3 (65.9%)	12.5 (56.9%)	18.2 (65.8%)

1. Cumulative doses with first dose of 480mg.

The above data demonstrated that at a dose of 480 mg of CD24Fc, the concentration level of the drug can be maintained at more than 50% of the pharmacological activity of the drug after 14 days, and it should be expected to have a corresponding efficacy effect. The 480mg dose group also has good safety data. Additional dose escalation will be further explored in the Chinese population in the Phase I part of the study.

In addition, data from previous clinical trials have shown that with the increase in drug dose and exposure, the safety performance of CD24Fc observed in clinical trials has not changed significantly. Therefore, it is considered that the safety of CD24Fc is within the acceptable range even if the exposure is slightly increased in lower body-weight people.

Based on the above factors, we intend to apply a fixed dose of 480 mg in single administration on Day 1 for this COVID-19 study.

2. STUDY OBJECTIVES

2.1. Primary objective:

- To evaluate the safety and efficacy of adding CD24Fc to COVID-19 best available treatment by comparing COVID-19 disease status improvement time between CD24Fc and placebo arms within 28 days.

2.2. Secondary objectives:

- Secondary objectives are to compare, for each treatment arm, proportion of patients who died or had respiratory failure (defined as the need for mechanical ventilation, ECMO, non-invasive ventilation, or high flow oxygen devices), the time to disease progression, rate of all-cause death, proportion of death or respiratory failure, rates of hospital discharge time, rate of duration of mechanical ventilation, duration of mechanical ventilation, use of pressors, rate of duration of extracorporeal membrane oxygenation, rate of duration of supplemental oxygen, the length of hospital stay, and the changes in absolute lymphocyte count and markers of inflammation.

2.3. Exploratory objectives:

- To explore the effect of CD24Fc treatment of COVID-19 on systemic steroid dosage, inflammatory cytokine changes, D-dimer level changes, lymphocyte subtype distribution and T lymphocyte activation and exhaustion markers.
- To explore the effect of CD24Fc in pulmonary function, inflammatory markers, cardiac function, liver enzymes and renal function.

2.4. Primary Endpoints:

- Time to improvement in clinical status: the time (days) required for improvement from scale 2 - 4 to scale ≥ 5 or above that is sustained without a drop to below 5 based on NIAID ordinal scales ([Appendix A](#)) within 28 days from randomization.

2.5. Secondary Endpoints:

- Proportion of patients who died or had respiratory failure, defined as the need for mechanical ventilation, ECMO, non-invasive ventilation, or high flow oxygen devices, at Day 29
- Time to disease progression in clinical status: the time (days) for progression from scale 3 or 4 to scale 1 or 2 based on the NIAID ordinal scale within 28 days from randomization.
- All cause mortality at Day 15 and Day 29
- Proportion of clinical relapse, as defined by rate of return to oxygen support for more than 1 day within 28 days from randomization after initial recovery

- Conversion rate of clinical status on Day 8 (proportion of subjects who changed from “scale 2, 3 or 4” to “scale 5 or higher” in the NIAID ordinal scale)
- Conversion rate of clinical status on Day 15 (proportion of subjects who changed from “scale 2, 3 or 4” to “scale 5 or higher” in the NIAID ordinal scale)
- The discharge from hospital time
- Duration of mechanical ventilation (IMV, NIV) (days)
- Duration of pressors (days)
- Duration of extracorporeal membrane oxygenation (days)
- Duration of oxygen therapy (oxygen inhalation by nasal cannula or mask) (days)
- Length of hospital stay (days)
- Absolute lymphocyte count
- D-dimer concentration in the plasma

2.6. **Exploratory endpoints**

- Effect of CD24Fc on systemic steroid usage.
- Effect of CD24Fc on cytokine levels.
- Effect of CD24Fc on lymphocyte subtype distribution.

2.7. **Safety evaluation**

- Adverse events, vital signs, physical examination, laboratory tests (blood routine, blood biochemistry, coagulation function, urine routine), ECG.

3. STUDY DESIGN

3.1. Study Design Overview

This is a Phase III randomized double-blind placebo controlled multi-site study to compare two COVID-19 treatment regimens in hospitalized adult subjects who are diagnosed with severe COVID-19.

Arm A: CD24Fc/Best Available Treatment;

Arm B: placebo/Best Available Treatment.

CD24Fc will be administered as single dose of 480mg via IV infusion on Day 1. Total of 270 subjects will be enrolled and randomized in 1:1 ratio to receive CD24Fc or placebo. All subjects will be treated with the best available treatment. The follow up period is 28 days. Those who uses immune modulators such as IL-6/IL-6R antagonists or experimental antiviral drugs are allowed to participate the trial.

Phase III study consists of screening period and treatment/follow up period. Each subject should have 6 visits. Visit 1 (D-3 to D-1); Visit 2 (D1); Visit 3 (D4); Visit 4 (D8±1d); Visit 5 (D15±2d), Visit 6 (D29±4d).

If the patient's clinical status improves and is discharged to home care, the follow up visits can be carried out through telemedicine (phone or video interviews). The clinical investigators should make best efforts to obtain the vital signs, clinical status evaluation, concomitant medicines and adverse events assessment. The laboratory tests, radiology study, ECG and research samples are optional if the patient is discharged.

3.2. Sample size

In Phase III study, a total of 270 subjects will be enrolled in 1:1 ratio for study drug arm and placebo arm (135 subjects per arm). For the calculation method of sample size, please refer to Section 10.1.

4. ELIGIBILITY CRITERIA

4.1. Inclusion criteria

- 1) Should be at least 18 years of age,
- 2) Male or female, female should have negative pregnancy test,
- 3) Diagnosed with COVID-19 and confirmed SARS-CoV-2 viral infection, prior positive viral results allowed,
- 4) Informed consent form signed by patient or by a legally authorized representative,
- 5) Hospitalized and requiring oxygen support, NIAID 8-point ordinal score 2, 3, 4, regardless of ARDS (Appendix A), intubation for invasive mechanical ventilation should be within 7 days,
- 6) Women of childbearing potential, under the age of 54 years, who use adequate contraception and who agree to use adequate contraception for the duration of the study.

4.2. Exclusion criteria:

- 1) Patients who are pregnant, breastfeeding, or have a positive pregnancy test result before enrollment,
- 2) Patients previously enrolled in the CD24Fc study,
- 3) Intubation for invasive mechanical ventilation is over 7 days,
- 4) Documented acute renal or hepatic failure,
- 5) The investigator believes that participating in the trial is not in the best interests of the patient, or the investigator considers unsuitable for enrollment (such as unpredictable risks or subject compliance issues).

5. REMOVAL FROM STUDY

Patients have the right to withdraw from the study at any time for any reason. The clinical site PI also has the right to withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure, protocol violation, or other reasons. Should a patient (or a patient's legally authorized guardian or representative) decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation should be made at the time of the patient's withdrawal with an explanation of why the patient is withdrawing and every effort should be made to perform follow-up evaluations. Patients may be removed from the study treatment if one or more of the following events occur:

- Significant protocol violation or noncompliance, either on the part of the patient or the clinical site PI.
- Refusal of the patient to continue treatment and / or observations.
- Unacceptable or dose-limiting toxicity.
- Decision by the clinical site PI that removal from the study is in the patient's medical interest.
- Unrelated medical illness or complication.
- Lost to follow-up.

6. STUDY DRUG

6.1. Study drug CD24Fc

Name	CD24Fc for IV infusion.
Vial content	120mg/12mL
Formulation	Liquid formulation for IV infusion.
Route	IV Infusion
Storage	-20°C, avoid light.
Manufacturer	Catalent, Inc.
Provider	OncoImmune, Inc

6.2. Placebo

The placebo is 0.9% Sodium Chloride Solution for IV infusion.

6.3. Study drug administration

CD24Fc will be administered intravenously on day 1 in single dose.

Arm A: 480 mg CD24Fc diluted with normal saline to 100 ml, IV infusion in 60 min.

Arm B: Normal saline 100ml, IV infusion in 60 min.

6.4. Best available treatment

The best available treatment and supportive care will be given to all subjects according to local institutional guideline. Those who uses immune modulators such as IL-6/IL-6R antagonists or experimental antiviral drugs such as remdesivir are allowed to participate the trial.

7. STUDY PROCEDURES

7.1. Procedure and tests description

7.1.1. Informed consent

The researchers explain all the research procedures to the subjects before the screening, including information about the nature of the research, and obtain informed consent signed by the patient or by a legally authorized representative.

Before the process to obtain informed consent from the legal authorized representative, investigators should use the **EVALUATION TO SIGN A CONSENT FORM FOR RESEARCH** in [Appendix B](#) to assess the understanding of the consent process of person who may have cognitive impairments, or may elicit the information using clinical interview procedures.

7.1.2. Collect demographic data

Obtain the demographic data of the subjects during the screening period, including information such as date of birth, height, weight, gender, ethnicity, and race.

7.1.3. Allergy history / medical history, previous / combined medication collection

Obtain subjects' past medical history, especially chronic diseases (such as chronic obstructive pulmonary disease, angina pectoris, hypertension, cerebral thrombosis, diabetes, etc.) during the screening period and other major diseases and drug treatment history, surgery history, allergy history, and comorbidities judged by the investigator.

It is important to obtain the number of days of onset of the symptoms, the history of exposure to confirmed cases within 14 days before the onset of the symptoms, recent temperature, and the treatment status (antiviral drugs, antibacterial drugs, oxygen therapy, duration of treatment, etc.).

Concomitant medications: from the beginning of the screening period to the end of the treatment / follow-up observation period.

7.1.4. Vital signs and physical examination

Vital signs include body temperature (° C), blood pressure (mmHg), heart rate (beats / min), respiratory rate (beats / min), which need to be performed at each visit.

On the D1 for treatment, vital signs for body temperature, blood pressure, heart rate, respiratory rate should be recorded before (0 min) and after IV infusion (60 min). The data from monitor are allowed. During the IV infusion, the data from the remote monitoring can be recorded without entering the room at 60±10 min after the start of infusion.

Physical examination will be performed during the screening period. Any changes should be recorded at D15. Check the general body surface, skin, head and neck, chest (heart, lung, breast), abdomen (gastrointestinal and liver), musculoskeletal, nervous system including taste and smell changes, lymph nodes, etc.

If the patient clinical status improves and is discharged to home care, the follow up visits can be carried out through telemedicine (phone or video interviews). The clinical investigators should make best effort to obtain the vital signs, clinical status evaluation, concomitant medicines and adverse events assessment. The laboratory tests, radiology study and research samples are optional.

7.1.5. Laboratory tests

Blood tests: red blood cell count (RBC), hemoglobin concentration (HGB), white blood cell count (WBC), platelet count (PLT), neutrophil count (ANC), lymphocyte count (LY), monocyte count (MO), Eosinophil count (EO), basophil count (BA).

Blood biochemical tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ -glutamyl transpeptidase (γ -GT), albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), lactate dehydrogenase (LDH), urea nitrogen (BUN) / urea (Urea), creatinine (Cr), creatine kinase (CK), creatine kinase isoenzyme (CK -MB), fasting blood glucose and cardiac Troponin I.

C-reactive protein (CRP), ESR.

Urine routine examination: urine pH, urine red blood cells, urine white blood cells, urine protein, urine glucose, urine ketone body.

Examination of coagulation function: D-dimer, prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), plasma fibrinogen (Fbg).

Laboratory tests should include CBC, blood biochemistry, CRP, coagulation function and urine test during the screening period and the treatment / follow-up observation period (D1, D4, D8 and D15).

Laboratory tests done at Day 1 should be done prior to the infusion.

If the patient clinical status improves and is discharged to home care, the follow up visits can be carried out through telemedicine (phone or video interviews). The laboratory tests, radiology study, ECG and research samples are optional.

7.1.6. Analysis of oxygen saturation and arterial blood gas

It is recommended but not required to conduct arterial blood gas analysis at screening, and during the treatment / follow-up observation periods according to clinical needs.

7.1.7. Pregnancy test

Only for women of childbearing age, under 54 years old, during the screening period.

7.1.8. ECG

During the screening period (up to 72 hr prior to screening is allowed), treatment / follow-up observation period. On the drug administration day (Day 1), ECG should be done before drug infusion and 2 hrs after drug infusion. ECG should be done in visit D8 and D15, if patient is still in hospital.

7.1.9. Chest X-ray or CT scan

It is recommended but not required to have Chest X-ray or CT scan during the screening period. Imaging study that has been done up to 72 hr prior to screening is allowed in lieu of screening. During the treatment / follow-up observation period, the doctor can determine the number and time of chest image study.

7.1.10. SARS-CoV-2 Viral nucleic acid check

Positive viral tests that have been done prior to screening are allowed in lieu of screening. If the investigator conducts an unscheduled visit to the viral nucleic acid test, the data results must be recorded in the CRF. The follow up viral nucleic acid tests are optional.

7.1.11. Cytokine and lymphocyte subtype detection (For selected sites only)

If conditions permit, a 5 ml blood sample should be collected and separated into plasma and PBMC. The samples can be frozen and stored for research purposes. Plasma samples are for testing of inflammatory cytokines (IL-1 β , IL-6, TNF- α , MIP α , INF- γ , IP10, MCP, GCSF, IL-10). The PBMC are for testing lymphocyte subtypes and activation/exhaustion markers (flow cytometry detection analysis: CD3 / CD4 / CD8 / PD1 / Tim3, etc.) at D1 before IV infusion, D4, D8 and D15.

7.1.12. Evaluation of clinical status

Clinical status should be evaluated and recorded daily when the patient is hospitalized. The screening period must assess the clinical status and recorded as baseline.

If the patient clinical status improves and is discharged to home care, the follow up visits should follow the study schedule ([Table 2](#)), and the visits can be carried out through telemedicine (phone or video interviews). The clinical investigators should make best effort to obtain the vital signs, clinical status evaluation, concomitant medicines and adverse events assessment. The laboratory tests, radiology study, ECG and research samples are optional.

7.2. **REQUIRED OBSERVATIONS (STUDY CALENDAR as in Synopsis)**

7.2.1. **Screening period**

Visit 1

- Sign the informed consent by patient or by a legally authorized representative;
- Record the past medical history;
- Collect demographic data;
- Record vital signs and physical examination;
- Laboratory tests should be done according to Section 7.1.5. Tests done 72 hrs prior to screening are allowed;
- Record digital oxygen saturation;
- Arterial blood gas analysis (optional, tests done 72 hrs prior to screening are allowed);
- Pregnancy check (women only, under 54 years old);
- ECG. Tests done 72 hrs prior to screening are allowed;
- Chest CT scan or X-ray. Tests done 72 hrs prior to screening are allowed;
- Detection of SARS-CoV-2 viral nucleic acids. Prior positive viral results are allowed;
- Clinical status assessment;
- Collect blood samples for serum cytokines and lymphocyte subtypes (selected sites only);
- Confirm the inclusion / exclusion criteria;
- Record concomitant medications.

7.2.2. **Treatment / follow-up observation period (D1 ~ D29)**

Visit 2 (D1)

- Record vital signs before study drug infusion and at 60±10 minutes after the start of drug infusion;
- Confirm the inclusion / exclusion criteria;
- Subject is randomized;
- Chest CT examination (optional);
- Record digital oxygen saturation;
- Arterial blood gas analysis (optional);

- Laboratory tests according to Section 7.1.5;
- ECG before drug infusion, and at 2 hrs (120 ± 15 min) after drug infusion;
- Study drug administration;
- Clinical status assessment;
- Record IMV / NIV, ECMO, or oxygen therapy;
- Collect blood samples for serum cytokines and lymphocyte subtypes (selected sites only);
- Record adverse events and concomitant medications.

Visit 3 (D4 \pm 2d)

- Record vital signs;
- Clinical status assessment;
- Chest CT scan (optional);
- Record digital oxygen saturation;
- Arterial blood gas analysis (optional);
- Laboratory tests: CBC, blood biochemistry, C-reactive protein;
- Collect blood samples for serum cytokines and lymphocyte subtypes (selected sites only);
- Record adverse events and concomitant medications.

Visit 4 (D8 \pm 2d)

- Record vital signs;
- Laboratory tests: CBC, blood biochemistry, C-reactive protein, coagulation tests;
- Chest CT scan (optional);
- Record digital oxygen saturation;
- Arterial blood gas analysis (optional);
- ECG;
- Clinical status assessment;
- Record IMV / NIV, ECMO, or oxygen therapy;
- Collect blood samples for serum cytokines and lymphocyte subtypes (selected sites only);
- Record adverse events and concomitant medications.

Visit 5 (D15 ± 2d)

- Record vital signs;
- Laboratory tests: CBC, blood biochemistry, C-reactive protein; coagulation tests;
- Chest CT scan (optional);
- Record digital oxygen saturation;
- Arterial blood gas analysis (optional);
- ECG;
- Clinical status assessment;
- Record IMV / NIV, ECMO, or oxygen therapy;
- Collect blood samples for serum cytokines and lymphocyte subtypes (selected sites only);
- Record adverse events and concomitant medications.

Visit 6 (D29 ± 3d)

- Record vital signs;
- Detection of SARS-CoV-2 viral nucleic acids if the D15 test is positive;
- Clinical status assessment;
- Record IMV / NIV, ECMO, or oxygen therapy;
- Record adverse events and concomitant medications.

If the patient clinical status improves and is discharged to home care, the follow up visits can be carried out through telemedicine (phone or video interviews). The clinical investigators should make best effort to obtain the vital signs, clinical status evaluation, concomitant medicines and adverse events assessment. The laboratory tests, radiology study, ECG and research samples are optional.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.1. Adverse Events

8.1.1. Definition of Adverse Events

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related. Since the clinical study has the target population as hospitalized patients with COVID-19 diagnosis and requiring oxygen support, the Grade III to V adverse events will be collected and reported in this study.

8.1.2. Definition of Serious Adverse Events (SAE) in COVID-19

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor in this COVID-19 clinical trial, it results in any of the following outcomes: death, or a life-threatening adverse event other than COVID-19 progression that requires admission to the ICU, or organ failures in addition to COVID-19 respiratory failure.

8.1.3. Criteria for Determining the Severity of Adverse Events

AEs not listed in the CTCAE 5.0 version table can be classified into grades 1-5 with reference to the following table.

Grade	CTCAE
1	Asymptomatic or mild; only clinical or diagnostic observations; no intervention required
2	Moderate: Small, local, or non-invasive measures are required; age-related instrumental daily life activities (ADL) are limited *.
3	Serious or medically significant but not immediately life-threatening: hospitalization or lengthening of hospital stay required; disability, limited autonomic ADL **.
4	Life-threatening: urgent measures are needed. Intervention indicated to prevent permanent impairment, persistent disability or death.
5	deaths related to adverse events

8.1.4. Relationship to Study Drug

All Grade III-V adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and

cannot be explained by concurrent disease or other drugs or chemicals. The event must be pharmacologically or phenomenologically definitive.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.1.5. Expectedness

The PI will be responsible for determining whether a Grade III to V adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.1.6. Follow-up of Adverse Events

Grade III to V AEs including local and systemic reactions not meeting the criteria for SAEs will be captured in the study record. Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. Grade III to V AEs occurring while on study must be documented appropriately regardless of relationship. All Grade III to V AEs will be followed to adequate resolution. Grade III to V AEs and SAEs will be collected between Day 1 and Day 29 (completion of study).

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI or study coordinator will record all reportable Grade III or V events with start dates occurring after IP treatment is initiated until the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All enrolled subjects who have received CD24Fc or placebo will be evaluated for safety with the laboratory assays done at each visit as outlined in section 7.2. Safety will be assessed by vital signs, hematology, and chemistries. Vital signs will include pulse, blood pressure, respiratory rate, and oxygen saturation. The severity of signs, symptoms, and AEs will be determined by using CTCAE V5.0. The CD24Fc infusion will be administered over a minimum of 1 hour.

Subjects will be monitored after infusion is completed for 2 hours, and repeat vital signs and laboratory results will be ascertained as needed based on reported symptoms.

8.2. Adverse Event Reporting

Grade III to V AEs occurring from the time of treatment through the end of study will be documented, recorded, and reported. The Investigator will evaluate Grade III to V AEs with respect to **Severity** (intensity or grade) and **Causality** (relationship to study agent and relationship to research). The investigator will record nonserious adverse events and report them to the sponsor in a timely manner.

Grade III or V laboratory abnormalities that are gradable per the CTCAE v5.0 will be recorded as AEs or SAEs. All other laboratory abnormalities without clinical significance will not be recorded as AEs or SAEs. Grade III to V laboratory abnormalities that require medical or surgical intervention must be recorded as an AE or SAE if applicable. Laboratory assessments that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition. If a diagnosis is clinically evident, the diagnosis, rather than the individual signs and symptoms or lab abnormalities will be recorded as the AE.

Grade I or II adverse events that worsen to grade III or V during the study will be captured. Their start date will be the day the adverse events worsen to grade III or V.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any new or worsening adverse event that begins on or after the date of treatment until study completion. Summaries (number and percentage of subjects) of treatment-emergent adverse events will be provided at study completion.

At each contact with the subject as outlined above in the study activities table, information regarding Grade III or V AEs will be elicited by appropriate questioning and examinations and will be immediately documented in the subject's medical record. Medical records will be reviewed in a timely manner by the research team. The onset date, the end date, the severity of each reportable Grade III to V event, and the Investigator's judgment of the AEs relationship to CD24Fc will also be recorded.

8.3. Serious Adverse Event Reporting

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All Grade V event (death) should be reported as SAE to CRO and sponsor in a timely manner.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting

documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify the FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

The Medical Monitor will advise the Sponsor regarding the safety of the study participants as well as the continuing safety and scientific validity of the trial. The Medical Monitor may also review the results of any planned analysis, if applicable. If the data analysis shows significant findings with regards to safety, the Medical Monitor may recommend modification of the protocol, Informed Consent, and/or monitoring of the study. In these cases, the regulatory authorities and local review committees may be notified. The Medical Monitor may also stop the study for reasons of safety.

8.4. Reporting of Pregnancy

Pregnancy itself is not an AE. However, complications of pregnancies are AEs and may be SAEs. Pertinent obstetrical information of all pregnancies will be reported to the MM. The participant will be advised to notify her obstetrician of study agent exposure.

Pregnancy outcome data (e.g., delivery outcome, spontaneous, or elective termination of the pregnancy, presence of absence of birth defects, congenital abnormalities, or other complications) will be reported to the MM.

8.5. Infusion Reaction Management

No infusion reactions were observed in Phase I, Phase IIa, and Phase II expansion cohort clinical trials. However, administration of any recombinant protein may induce infusion reactions. CD24Fc includes the Fc portion of human IgG1. After targeted binding, CD24Fc can induce FcγR cross-linking, which is related to infusion reactions that may occur during some treatments.

Possible infusion reactions during or 2 hours after the infusion include, for example, changes in vital signs, fever, dyspnea, hypotension, systemic or facial edema, nausea, chills, changes in mental state, urticaria, or vomiting.

The following procedures are designed to closely monitor, manage and mitigate any possible infusion reactions:

- In this study, CD24Fc must be administered in hospital. During the administration of CD24Fc, the clinical condition of the subject must be closely monitored.
- The infusion time is at least 60 minutes. Researchers are allowed to reduce the IV rate and extend the infusion time based on the infusion response. If severe infusion

reactions occur, such as severe hypotension and hypoxemia, the infusion should be stopped.

- Provide supportive treatment based on clinical indications and the intensity of the infusion reaction, including oxygen supplementation, diphenhydramine, acetaminophen, ibuprofen, IV corticosteroids (ie, hydrocortisone), and intravenous fluid replacement.
- During CD24Fc administration, bedside first aid equipment, cardiopulmonary resuscitation life support equipment and drugs (eg, epinephrine) must be prepared in order to cope with possible hypersensitivity reactions, severe infusion reactions and / or cytokine release.

9. DATA MANAGEMENT

9.1. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data will be recorded in an electronic case report form (eCRF) using the secure electronic database. The data system includes password protection. The data entered will include but not be limited to clinical findings and observations, laboratory and test data, hospital medical records, physician or office charts, physician or nursing notes, recorded data from automated instruments, x-rays, etc.

9.2. Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

9.3. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Anticipated deviations in the conduct of the protocol will not be reported to the IRB unless they occur at a rate greater than anticipated by the study team, in accordance with findings from previous trials as outlined in the IB. If the rate of these events exceeds the rate expected by the study team, the events will be classified and reported as though they are unanticipated problems. Deaths related to the natural history of COVID-19 will be reported at the time of continuing review.

It is the responsibility of the site investigator to use continuous vigilance to identify and report unanticipated deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity.

9.4. Publication and Data Sharing Policy

The PI and study team share de-identified or identified data generated in this study with all collaborators and will have access to all data collected from all sites.

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This study will comply with the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting the study Sponsor.

At the conclusion of the study, the Sponsor will support the writing and publication of scientific reports, journal papers and oral presentations by the study principal investigator and others making scientific contribution to the research effort. Any reports, papers, and/or presentations must be reviewed and approved by prior to submitting for publication. All reports generated by this study will be in accordance with the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration of 1975, as revised in 1983.

All publications relating to the study will comply with the guidelines set forth by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals drawn up by the International Committee of Medical Journal Editors.

9.5. Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10. STATISTICAL ANALYSIS

10.1. Sample size

In the phase III trial, the patients will be randomized at 1: 1 ratio into CD24Fc or placebo arms. It was assumed that the time to improvement the clinical status of the patients obeyed the exponential distribution, and the improvement hazard ratio (HR) was 1.54. The median time to improvement in the control group is presumed 11 days, and the median time to improvement in the treatment group is projected as 7.14 days. An interim analysis for efficacy will be performed when 70% of the required events are reached. The O'Brien-Fleming type consumption function of the Lan-DeMets algorithm is used to control the overall class I error rate $\alpha = 0.025$ (one-sided), at least 80% of the degree of confidence. At least 208 events are required to achieve 80% power. Assuming 28 days of patient follow up, the estimated number of 208 events will be reached for the final analysis approximately 28 days after the last subject is enrolled. Assuming 78% recovery rate, 270 participants will be enrolled in this trial.

The sample size was calculated on SAS 9.4 PROC SEQDESIGN.

10.2. Analysis Set

10.2.1. Intended-to-treat Set (ITT)

Defined as all subjects who are enrolled in the randomized trial. The ITT population will be the main analysis population for the efficacy analysis of this study. Subjects will be analyzed based on the treatment group they are assigned.

10.2.2. Per Protocol Set (PPS)

PPS is a subset of the ITT. Refers to all randomized subjects who have received the protocol-specified single-dose treatment without significant protocol deviations that significantly affect the main efficacy. PPS-based analysis will complement ITT-based analysis as a supporting analysis. Subjects will be analyzed based on the treatment arm they plan to assign.

10.2.3. Safety Data Set (SS)

SS is defined as all subjects who received at least one test drug. The safety analysis population is the main analysis population for safety data. Subjects will be analyzed based on their actual assigned treatment arm.

10.3. Analysis methods

10.3.1. General principles

The statistical analysis uses SAS9.2 (or above) version of statistical analysis software, and the analysis process is all programmed. For continuous variables, the descriptive statistics will include the mean, median, standard deviation, maximal and minimal values (mean and median will be accurate to one more digit decimal point than the original data, and standard deviation will be accurate to two more digit decimal points than the original data, and the decimal points of

the maximum and minimum values will be the same as the original data, usually up to four decimal points are kept in the statistics table). Qualitative or grade indicators are summarized using descriptive statistics including the number of subjects, percentages, and / or number of events. The detailed statistical analysis plan and method will be described in detail in the statistical analysis plan.

10.3.2. Distribution of subjects

Descriptive statistics will be used to summarize the number of subjects screened, the number of screening failures, enrollment, entry into each analysis set (and reasons for excluding each analysis set), termination of treatment, withdrawal from the study, and follow-up. The number and percentage of subjects who entered each analysis set, discontinued treatment and study will be summarized by treatment arms.

10.3.3. Demographics, Medical History, and Baseline Characteristics

Demographic information and baseline characteristics, case history, and concomitant medications for all randomized subjects will be summarized using descriptive statistical methods based on randomization.

10.4. Efficacy Analysis

10.4.1. Primary efficacy endpoint

The primary endpoint “Time to Clinical Improvement” (TTCI) will be the time (days) from the randomization in which the patient's clinical status improved from baseline (scale 2-4, NIAID ordinal scale, [Appendix A](#)) to 5 or above that is sustained without a drop to below 5 within 28 days. Hospital discharge date (NIAID scale 7 or 8) is an important event time point. The date that clinical status evaluation ≥ 5 or the date of hospital discharge, whichever comes first will be used as the TTCI date.

The record of re-hospitalization with oxygen therapy is required to modify the TTCI date. The new TTCI date should be the time from randomization to the latest clinical status evaluation ≥ 5 or the date of the latest hospital discharge, whichever comes first.

Time to clinical improvement (days) is calculated as:

Time to Improvement = Date of (First Clinical Improvement/hospital discharge) – Date of Randomization

The discharge to home due to clinical improvement is scored as NIAID scale ≥ 7 . The date that clinical status evaluation ≥ 5 or the date of hospital discharge, whichever comes first will be used as the clinical improvement date. All subjects without clinical improvement within 28 days will be censored on the Day 29 visit.

The Log-Rank Test will be used to compare the following two sets of curves to test the following hypotheses:

$H_0: St(t) = Sp(t)$ vs. $H_1: St(t) > Sp(t)$ for improvement;

St(t) represents the improvement probability function of the experimental group, and Sp(t) represents the improvement probability function of the control group.

The probability function of clinical improvement will be estimated by Kaplan-Meier method. The median time and its 95% confidence interval for each group will be reported. The 95% confidence interval for the median time will be estimated using the Brookmeyer-Crowley method with log-log function conversion to achieve a normal approximation. The improvement rate will be estimated by the layered Cox-Model. Cumulative improvement rates estimated by the KM method for days 4, 8 and 15 and/or 29 their 95% confidence intervals will also be reported.

Time-event efficacy endpoints / censorship rules

For the primary endpoint, during the observation period, an improvement from NIAID scale 2, 3 or 4 to scale 5 or above, if sustained without a drop below 5, is considered as an event. The days from the randomization to the first time point of such improvement will be defined as time of improvement. Additional follow-up can be used to determine clinical improvement events.

Subjects who do not withdraw or do not experience improvement will be censored on the actual date of the D29 visit.

Subjects without improvement but lost to follow-up will be censored on the last date of follow-up.

Subjects with death within 28 days will be censored on D29.

Sensitivity analysis:

(1) Imbalances in age, baseline score, use of antiviral drugs such as remdesivir, or IL-6/IL-6R antagonist, or related factors that may affect the results will be investigated with sensitivity analyses and these factors will be evaluated separately in the Cox-Model to assess their potential impact on the primary efficacy endpoint.

(2) Use only data from planned visits to analyze time to improvement in the main analysis.

(3) The days from randomization to the first clinical improvement will be analyzed.

Since there are no available best supportive case (BSC) for this disease, controlling BSC use between two arms is difficult, and consequently there may be imbalance for some particular BSCs between two arms. To evaluate whether there may be some potential bias caused by such imbalance, we will evaluate the percentage of the largest and second largest BSC used in the trial if the difference of such BSC between two arms are significant. Further analyses will be performed to study whether the efficacy results are indeed caused by such differential BSC use between two arms.

10.4.2. Secondary efficacy endpoints

Proportion of death or respiratory failure, defined as the need for mechanical ventilation, ECMO, non-invasive ventilation, or high flow oxygen devices at D29. Cumulative number of subjects reaching the composite endpoint vs number of people in the ITT population. Chi-square test will be used to compare the difference between the two arms.

For the disease progression, during the observation period, a progression from scale 3 or 4 to scale 2 or 1, or from 2 to 1, is considered as an event. The days from the randomization to the first time point of progression will be defined as time of progression. The probability function of clinical progression will be estimated by Kaplan-Meier method. The median time and its 95% confidence interval for each group will be reported. The 95% confidence interval for the median time will be estimated using the Brookmeyer-Crowley method with log-log function conversion to achieve a normal approximation. The progression rate will be estimated by the layered Cox-Model. Cumulative progression rates estimated by the KM method for day 29 and the 95% confidence intervals will be reported.

All-cause mortality at Day 15 and Day 29: the Mantel-Haenszel stratum-weighted estimator of the risk difference will be used to compare the treatments.

Rate of clinical relapse, defined as proportion of patients who have initially reached score 5 (hospitalized, without oxygen therapy) for more than one day but subsequently become dependent on oxygen support. Since responders are not based on the randomization, a descriptive statistic will be reported and an exploratory analysis using a Chi-square test will be performed.

Improvement rate of clinical status on Days 8 and 15 (proportion of subjects with clinical improvement): percentage of subjects with clinical improvement on Day 8 or 15 in the ITT population. Chi-square test will be used to compare the difference between the two arms.

The discharge time starts from randomization to discharge. T-tests will be used to compare the differences between the two groups in completers.

Duration of each major treatment (days): Descriptive statistics will be analyzed for mechanical ventilation (IMV, NIV), extracorporeal membrane oxygenation, duration of oxygen therapy, and length of hospital stay.

Absolute Lymphocyte Count: patients' dynamic changes in absolute lymphocyte count during the treatment / observation period will be monitored to assess the possible correlation between lymphocyte levels and disease outcome and prognosis.

D-dimer levels: patients' dynamic changes in D-dimer levels during the treatment / observation period will be monitored to assess the possible correlation between lymphocyte levels and disease outcome and prognosis.

10.4.3. Exploratory Indicator Analysis

Effect of CD24Fc on systemic steroid dosage: The frequency and dosage of glucocorticoids in all treatment groups will be collected to evaluate the potential impact of CD24Fc on steroid dosage.

Effect of CD24Fc on cytokine levels: monitoring during the treatment / observation period including C-reactive protein, IL-6, IL-1 β , IFN- γ , TNF- α , IP10, MCP, GCSF, IL10 and other cytokines and their risks. The level of dynamic changes of related model molecules (HMGB-1, HSP70 / 90), to assess the possible correlation between the levels of various cytokines and disease outcome and prognosis.

Effect of CD24Fc on the distribution of lymphocyte subtypes: monitor the dynamic changes of the proportion of CD4 and CD8 T cell subtypes in lymphocytes during the treatment /

observation period and analyze the state of T cell depletion, and evaluate the lymphocyte level and disease outcome and prognosis may be relevant.

10.4.4. Safety Analysis

Adverse events will be summarized according to the system organ classification (SOC) and preferred term (PT) coded by the MedDra thesaurus. The number of AE, TEAE, SAE, and ADR cases, incidence and number of cases were summarized in each arm.

The results of specific laboratory tests, electrocardiograms, vital signs, and physical examinations will be summarized and their relative baseline changes will be reviewed. Where applicable, the baseline value and the value at each time point after the baseline are presented in the form of a crosstab.

10.5. Interim Analysis and Stopping Rules

This study will establish an independent Data and Safety Monitoring Board (DSMB) for interim analysis. The composition, task responsibilities and implementation details of DSMB will be specified in the DSMB charter.

Two blinded safety reviews will be performed, respectively, when 50% and 75% of the planned enrollment has occurred with follow-up time reaching D15 and mortality data are available.

The study will also include an interim analysis at 70% of the required 146 events. The final analysis will be carried out after all 270 subjects have been randomized, dosed and completed the study.

In the interim analysis, the DSMB will re-estimate the sample size to determine whether it supports increasing the number of clinical improvement event targets. Chen's method will be used to re-estimate the sample size (37).

Safety reviews and stopping rules

The study have two blinded safety reviews respectively, when 50% and 75% of the planned enrollment has occurred with follow-up time reaching Day 15 and SAE data are available. DSMB will be provided with list of SAE including mortality and may unblind the data at its discretion to evaluate the balance of SAE in the two study arms.

Stopping rules

If the DSMB found that SAE is significantly higher in the CD24Fc arm, it may recommend termination of the trial after review of potential benefit of the study drug by unblinding all study subjects. Sponsor will make final decision based on the recommendation of DSMB.

Sample Size Re-Estimation

The interim analysis for the primary endpoint only will be performed after reaching 146 events (70% of information). A sample size reassessment of efficacy will be performed.

There sample size re-estimation 146 events will be based on preliminary data that are not 100% source-verified. The method will be based on Chen et al as stated in the protocol. If the conditional power is < 50% or >85%, the trial will continue without a sample size increase; whereas if the conditional power is between 50% to 85%, the sample size will be re-calculated to

have 85%. To maintain trial integrity, the DSMB will pick a sample size in a nearest interval with 5 patients. For example, if the re-estimated sample size is 287, the DSMB could pick any number in the interval of 285 to 289. Also, the maximum increased sample size will not be more than 70 patients above what is needed to observe 208 events.

The final analysis will be performed when 270 randomized and dosed patients have completed 28 days of follow up, and the p-value cutoff is 0.05 (two-sided) based on the O'Brien-Fleming function of the Lan-DeMets algorithm.

10.6. Missing Data Convention

We will use the following rules to deal with missing data:

Participants who have not been lost to follow up or experienced the event will be censored at Day 29. Participants without an event but lost to follow-up will be censored at the last date of follow-up.

We will perform two more analyses on the following data sets for the purpose of sensitivity analysis:

First: Participants who have not dropped out or experienced an event are censored at Day 29. Participants not receiving study drug will be excluded from the analysis. Participants without an event but lost to follow-up will be censored at the last date of follow-up. When the event is documented, the time to the event is the length of time from the randomization to the event observed if at least one disease assessment before the event is documented.

Second: Participants who have not been lost to follow up or experienced an event and are followed at the end of the trial will be included. Participants not receiving study drug will be excluded. Participants who have documented the event and have at least one disease assessment(s) will be included.

We will compare the results of the primary analysis with the results from the analyses on the first and second sets, respectively. The impact of missing data and robustness of the primary analysis will be evaluated.

11. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1. Informed Consent Process

11.1.1. Consent/assent and Other Informational Documents Provided to participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

11.1.2. Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.1.3. Use of Legally Authorized Representative (Surrogate Consent)

Federal regulations permit investigators to obtain consent from a legally authorized representative. State laws define the categories of individuals who are allowed to provide surrogate consent for research. The following specific category applies to this study in end stage COVID-19 patient who is in ICU with mechanical ventilation.

“Individuals whose medical condition may render them temporarily unable to provide informed consent as a consequence of severe pain, confusion, or impaired consciousness due to events such as life-threatening illness or trauma.”

Definitions

1. Legally Authorized Representative (LAR): An individual or judicial, or other body authorized under applicable law to grant permission on behalf of a prospective participant for their participation in research activities.

2. **Surrogate Consent:** The use of a legally authorized representative with reasonable knowledge of the research participant.
3. **Advance Directive:** Documents written in advance of serious illness in which a person states their choices for healthcare or names someone to make those choices. When a person is selected to make the medical decisions, the document is called a Durable Power of Attorney and the designated person is called an Agent. The Agent can serve as a LAR to provide surrogate consent.
4. **Capacity to Consent:** The ability of the individual to understand the choices presented, to appreciate the implications of choosing one alternative or another, and to make and communicate a decision (e.g., whether or not to participate in a study).

Determining Capacity of Consent

Whenever possible, investigators should attempt to obtain informed consent directly from the research participant.

While there are no standardized measures for determining capacity to consent, participant should be assessed on the abilities to understand and to express a reasoned choice concerning the:

- Nature of the research and the information relevant to his/her participation;
- Consequences of participation for their own situation, especially concerning their health condition;
- Consequences of the alternatives to participation.

Investigators may use the **EVALUATION TO SIGN A CONSENT FORM FOR RESEARCH** ([Appendix B](#)) to assess the understanding of the consent process of person who may have cognitive impairments, or may elicit the information using clinical interview procedures.

Identifying an Appropriate Surrogate for End Stage COVID-19 Patient in ICU with Mechanical Ventilation

In an **emergency room setting or COVID-19 patient in ICU with mechanical ventilation**, the order of priority does not apply, not does the surrogate have to show reasonable knowledge of the research participant. Surrogate consent may be obtained from any of the following:

- The person's agent designated by an advance health care directive.
- He conservators or guardian of the person having the authority to make health care decisions for the person.
- The spouse of the person.
- The domestic partner of the person as defined in Section 297 of the California Family Code

- An adult son or daughter of the person.
- A custodial parent of the person.
- Any adult brother or sister of the person.

Important Note: In an emergency room or ICU environment, no surrogate may be utilized if there is a disagreement whether to consent among any available surrogates.

11.2. Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, the principal investigator, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

11.3. Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying

study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Institute of Human Virology and the Department of Epidemiology (University of Maryland School of Medicine). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. The PI and study team will have access to the password-protected database. At the end of the study, all study databases will be de-identified and archived at the University of Maryland School of Medicine.

11.4. Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the Institute of Human Virology (University of Maryland). After the study is completed, the de-identified, archived data will be retained at the Institute of Human Virology (IHV) for use by other researchers including those outside of the study. Permission to retain the data at the IHV will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the IHV. These samples could be used to research the causes of cardiovascular disease in HIV, its complications and other conditions for which individuals with HIV are at increased risk, and to improve treatment. IHV researchers will be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant. Genetic testing will not be performed.

When the study is completed, access to study data and/or samples will be provided through the IHV.

11.5. Clinical Monitoring

Clinical studies must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices and in compliance with other applicable regulatory requirements. The following measures have been taken to ensure the safe conduct of this clinical trial:

Weekly teleconferences will be conducted among investigators from participating study sites, the principal investigator (PI), the Sponsor representatives and Medical Monitor from and other representatives from the CRO. At these meetings safety events, withdrawals, subjects' progress and other relevant events on trial will be reviewed and appropriate actions will be taken including amending or suspending the trial. Safety reports generated by the CRO will also be submitted to the DSMB. The Medical Monitor and the Sponsor will both be responsible for reviewing these reports monthly and if necessary taking appropriate steps to ensure the safety of subjects and compliance with this protocol (i.e. inquiries, suspension, or termination of trial).

Finally, whenever an unanticipated data, safety and monitoring board meeting takes place or when a new development occurs the Medical Monitor from the Sponsor and/or its designee (i.e. CRO) and IRB will be notified of the occurrence.

This study will be continuously monitored by a clinical monitor, and the Medical Monitor from the CRO. Monitoring visits will be made during the conduct of the study and at study close-out. Remote monitoring will be carried out to minimize the travel and in person contact.

Prior to subject recruitment, a site initiation meeting will be conducted by the Sponsor or the CRO. This meeting may take place by teleconference. The PI and the study staff should make every effort to attend the site initiation meeting. Study-related questions or issues identified during the site initiation meeting will be followed by the appropriate personnel until they have been answered and resolved.

The monitoring visits should be carried out through remote monitoring. The purpose is to verify:

- a. Adherence to the protocol
- b. Completeness and accuracy of study data and samples collected
- c. Proper storage, dispensing, and inventory of study medication
- d. Compliance with regulations

Monitoring may be in the form of a document review. During a monitoring visit, remote access to relevant hospital and clinical records must be given by the clinical site PI to the clinical monitor conducting the remote monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The clinical monitor expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated and are expected to be resolved in a time manner.

At close-out upon completion, termination, or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study will occur, and the clinical site PI will be informed of his / her ongoing responsibilities. In general, close-out is conducted during a formal remote site visit. However, a site close-out can occur without a site visit.

11.6. Quality Assurance and Quality Control

Data quality control (QC) checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The Medical Monitor 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)). To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

During the study, the Sponsor or designee will conduct periodic remote monitoring visits to ensure that the protocol and ICH GCP guidelines are being followed. The monitors may review source documents to confirm that the data recorded is accurate. The Investigator and institution will allow the Sponsor monitor or designee and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be participant to review by the IRB, and/or quality assurance audits performed by the Sponsor, or companies working with or on behalf of the Sponsor, and/or inspection by appropriate regulatory authorities.

11.7. Trained and Certified Personnel

All of the research protocol personnel who will work with study subjects, study subject data or subjects' research samples have completed training in the protection of human research participants per guidelines issued by the U. S. Department of Health and Human Services, Office of Human Research Protections. The documentation of completion of the certification is maintained by the CRO. The investigator and designated associates have attended an IRB sponsored HIPAA research presentation in accordance with the policy of the study site. Each participant in this research trial will be listed by study specific numbers, without initials or date of birth; however, the date of transplant may be included when corresponding with the IRB or outside agencies.

Designation of Responsibilities: The Clinical Principal Investigator(s) are solely responsible for the implementation, conduct and safety of human subjects enrolled in this trial. The Clinical Principal Investigator has however, designated associates to assist with the protocol implementation which includes but is not limited to the following:

1. Physicians – have been designated to assist with participant education, informed consent process, study implementation and compliance, recording of primary source documentation, AE assessment and reporting, adherence to all regulations.
2. Research Nurse(s) - have been designated to assist with participant education, informed consent process, study implementation and compliance, recording of primary source documentation and adherence to all regulations.

3. Data Manager(s) - have been designated to assist with patient enrollment/eligibility, verification of protocol compliance, all data collection and recording from primary source, AE reporting, DSM reports and adherence to all regulations.
4. Clinical Team - The members of the clinical team that have been designated to assist the investigator in any aspect of this protocol will be listed on the protocol specific designation log.

11.8. Independent Data and Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will be convened for the Phase II/III study. The purpose of the DSMB will be to safeguard the interests of study participants, assess the safety of the interventions, and monitor the overall conduct of the study. The DSMB will act as an advisory to the clinical study leadership team of OncoImmune. The clinical study leadership will have responsibility for overall conduct of the study including managing the communication of study data. The leadership team will be responsible for promptly reviewing the DSMB recommendations, for providing guidance regarding the continuation or termination of the trial, and for determining whether amendments to the protocol or changes to the study conduct are required.

11.9. Multi-center Coordination

The Phase III randomized, double blind, placebo controlled, multi-center study will be coordinated by the CRO.

11.9.1. Subject Screening and Registration Procedure

Patient registration for this trial will be centrally coordinated by the CRO as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on the Screening and Enrollment Log. It is the responsibility of the clinical site PI to determine patient eligibility prior to submitting patient registration request to site pharmacy.

Each subject will be given a randomization number. This number will be assigned in the order of the inclusion of subjects by onsite blind pharmacy. A computer-generated randomization list will be prepared by CRO statistician not directly involved in the conduct of the study and investigational study medication. It will be provided to the unblinded pharmacy team for study treatments preparation. All study personnel at the research site will be blinded to treatment identity during the conduct of the study until database lock. Subjects will be randomized such that both the investigators and the subjects will be blinded to the study medication they will receive on each visit. Identification code for randomized subjects has been prepared and validated according to the SOP. Only the unblinded statistician and the pharmacy staff have access to the unblinded randomization list.

11.9.2. Contact Information

Sponsor

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12. REFERENCES

1. NCPERC T. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) – China. *China CDC Weekly*. 2020;2(8):113-22.
2. Wu J, Wu B, Lai T. Compassionate Use of Remdesivir in Covid-19. *N Engl J Med*. 2020;382(25):e101. doi: 10.1056/NEJMc2015312. PubMed PMID: 32412708.
3. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020. doi: 10.1016/S2213-2600(20)30079-5. PubMed PMID: 32105632.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. Epub 2020/01/28. doi: 10.1016/S0140-6736(20)30183-5. PubMed PMID: 31986264.
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020. doi: 10.1016/S0140-6736(20)30566-3. PubMed PMID: 32171076.
6. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochweg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellingham GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med*. 2017;43(3):304-77. doi: 10.1007/s00134-017-4683-6. PubMed PMID: 28101605.
7. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, Nadel S, Schlapbach LJ, Tasker RC, Argente AC, Brierley J, Carcillo J, Carrol ED, Carroll CL, Cheifetz IM, Choong K, Cies JJ, Cruz AT, De Luca D, Deep A, Faust SN, De Oliveira CF, Hall MW, Ishimine P, Javouhey E, Joosten KFM, Joshi P, Karam O, Kneyber MCJ, Lemson J, MacLaren G, Mehta NM, Moller MH, Newth CJL, Nguyen TC, Nishisaki A, Nunnally ME, Parker MM, Paul RM, Randolph AG, Ranjit S, Romer LH, Scott HF, Tume LN, Verger JT, Williams EA, Wolf J, Wong HR, Zimmerman JJ, Kisson N, Tissieres P. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. *Pediatr Crit Care Med*. 2020;21(2):e52-e106. doi: 10.1097/PCC.0000000000002198. PubMed PMID: 32032273.

8. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-13. doi: 10.1016/S0140-6736(20)30211-7. PubMed PMID: 32007143.
9. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS, China Medical Treatment Expert Group for C. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020. doi: 10.1056/NEJMoa2002032. PubMed PMID: 32109013.
10. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020. doi: 10.1001/jama.2020.1585. PubMed PMID: 32031570; PMCID: PMC7042881.
11. Rivello ED, Kiviri W, Twagirumugabe T, Mueller A, Banner-Goodspeed VM, Officer L, Novack V, Mutumwinka M, Talmor DS, Fowler RA. Hospital Incidence and Outcomes of the Acute Respiratory Distress Syndrome Using the Kigali Modification of the Berlin Definition. *Am J Respir Crit Care Med*. 2016;193(1):52-9. doi: 10.1164/rccm.201503-0584OC. PubMed PMID: 26352116.
12. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526-33. doi: 10.1001/jama.2012.5669. PubMed PMID: 22797452.
13. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, Yu J, Kang M, Song Y, Xia J, Guo Q, Song T, He J, Yen HL, Peiris M, Wu J. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med*. 2020. doi: 10.1056/NEJMc2001737. PubMed PMID: 32074444.
14. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020. Epub 2020/02/23. doi: 10.1016/S2213-2600(20)30076-X. PubMed PMID: 32085846.
15. Chen J, Lau YF, Lamirande EW, Paddock CD, Bartlett JH, Zaki SR, Subbarao K. Cellular immune responses to severe acute respiratory syndrome coronavirus (SARS-CoV) infection in senescent BALB/c mice: CD4+ T cells are important in control of SARS-CoV infection. *J Virol*. 2010;84(3):1289-301. doi: 10.1128/JVI.01281-09. PubMed PMID: 19906920; PMCID: PMC2812346.
16. Beijing Group of National Research Project for S. Dynamic changes in blood cytokine levels as clinical indicators in severe acute respiratory syndrome. *Chin Med J (Engl)*. 2003;116(9):1283-7. Epub 2003/10/07. PubMed PMID: 14527349.
17. Nicholls J, Dong XP, Jiang G, Peiris M. SARS: clinical virology and pathogenesis. *Respirology*. 2003;8 Suppl:S6-8. Epub 2004/03/17. doi: 10.1046/j.1440-1843.2003.00517.x. PubMed PMID: 15018126.

18. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020;395(10223):473-5. doi: 10.1016/S0140-6736(20)30317-2. PubMed PMID: 32043983.
19. Lee FE, Walsh EE, Falsey AR. The effect of steroid use in hospitalized adults with respiratory syncytial virus-related illness. *Chest*. 2011;140(5):1155-61. doi: 10.1378/chest.11-0047. PubMed PMID: 21565965; PMCID: PMC3205848.
20. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, Li W, Tong Q, Yi J, Zhao L, Xiong L, Guo C, Tian J, Luo J, Yao J, Pang R, Shen H, Peng C, Liu T, Zhang Q, Wu J, Xu L, Lu S, Wang B, Weng Z, Han C, Zhu H, Zhou R, Zhou H, Chen X, Ye P, Zhu B, He S, He Y, Jie S, Wei P, Zhang J, Lu Y, Wang W, Zhang L, Li L, Zhou F, Wang J, Dittmer U, Lu M, Hu Y, Yang D, Zheng X. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *medRxiv*. 2020:2020.02.16.20023671. doi: 10.1101/2020.02.16.20023671.
21. Chen GY, Tang J, Zheng P, Liu Y. CD24 and Siglec-10 selectively repress tissue damage-induced immune responses. *Science*. 2009;323(5922):1722-5. Epub 2009/03/07. doi: 10.1126/science.1168988. PubMed PMID: 19264983; PMCID: PMC2765686.
22. Chen GY, Chen X, King S, Cavassani KA, Cheng J, Zheng X, Cao H, Yu H, Qu J, Fang D, Wu W, Bai XF, Liu JQ, Woodiga SA, Chen C, Sun L, Hogaboam CM, Kunkel SL, Zheng P, Liu Y. Amelioration of sepsis by inhibiting sialidase-mediated disruption of the CD24-SiglecG interaction. *Nat Biotechnol*. 2011;29(5):428-35. doi: 10.1038/nbt.1846. PubMed PMID: 21478876; PMCID: PMC4090080.
23. Saidi H, Bras M, Formaglio P, Melki MT, Charbit B, Herbeuval JP, Gougeon ML. HMGB1 Is Involved in IFN- α Production and TRAIL Expression by HIV-1-Exposed Plasmacytoid Dendritic Cells: Impact of the Crosstalk with NK Cells. *PLoS Pathog*. 2016;12(2):e1005407. Epub 2016/02/13. doi: 10.1371/journal.ppat.1005407. PubMed PMID: 26871575; PMCID: PMC4752468.
24. Melki MT, Saidi H, Dufour A, Olivo-Marin JC, Gougeon ML. Escape of HIV-1-infected dendritic cells from TRAIL-mediated NK cell cytotoxicity during NK-DC cross-talk--a pivotal role of HMGB1. *PLoS Pathog*. 2010;6(4):e1000862. Epub 2010/04/27. doi: 10.1371/journal.ppat.1000862. PubMed PMID: 20419158; PMCID: PMC2855334.
25. Huan CC, Wang HX, Sheng XX, Wang R, Wang X, Mao X. Glycyrrhizin inhibits porcine epidemic diarrhea virus infection and attenuates the proinflammatory responses by inhibition of high mobility group box-1 protein. *Arch Virol*. 2017;162(6):1467-76. Epub 2017/02/09. doi: 10.1007/s00705-017-3259-7. PubMed PMID: 28175983.
26. Duhalde-Vega M, Retegui LA. Uric acid and HMGB1 are involved in the induction of autoantibodies elicited in mice infected with mouse hepatitis virus A59. *Autoimmunity*. 2011;44(8):631-40. Epub 2011/05/25. doi: 10.3109/08916934.2011.579927. PubMed PMID: 21604970.
27. Tian RR, Zhang MX, Zhang LT, Zhang P, Ma JP, Liu M, Devenport M, Zheng P, Zhang XL, Lian XD, Ye M, Zheng HY, Pang W, Zhang GH, Zhang LG, Liu Y, Zheng YT. CD24 and Fc fusion protein protects SIVmac239-infected Chinese rhesus

- macaque against progression to AIDS. *Antiviral Res.* 2018;157:9-17. Epub 2018/07/10. doi: 10.1016/j.antiviral.2018.07.004. PubMed PMID: 29983395.
28. Zheng X, Wu W, Liu Y, Zheng P, inventors; OncoImmune, Inc, assignee. Methods of use of soluble cd24 for therapy of rheumatoid arthritis USA patent US20130231464A1. 2013.
29. Bai XF, Liu JQ, Liu X, Guo Y, Cox K, Wen J, Zheng P, Liu Y. The heat-stable antigen determines pathogenicity of self-reactive T cells in experimental autoimmune encephalomyelitis. *J Clin Invest.* 2000;105(9):1227-32. Epub 2000/05/03. doi: 10.1172/JCI9012. PubMed PMID: 10791997; PMCID: PMC315444.
30. Toubai T, Hou G, Mathewson N, Liu C, Wang Y, Oravec-Wilson K, Cummings E, Rossi C, Evers R, Sun Y, Wu J, Choi SW, Fang D, Zheng P, Liu Y, Reddy P. Siglec-G-CD24 axis controls the severity of graft-versus-host disease in mice. *Blood.* 2014;123(22):3512-23. doi: 10.1182/blood-2013-12-545335. PubMed PMID: 24695850; PMCID: PMC4041170.
31. Toubai T, Rossi C, Oravec-Wilson K, Zajac C, Liu C, Braun T, Fujiwara H, Wu J, Sun Y, Brabbs S, Tamaki H, Magenau J, Zheng P, Liu Y, Reddy P. Siglec-G represses DAMP-mediated effects on T cells. *JCI Insight.* 2017;2(14). Epub 2017/07/21. doi: 10.1172/jci.insight.92293. PubMed PMID: 28724800; PMCID: PMC5518560.
32. Liu Y, Janeway CA, Jr. Interferon gamma plays a critical role in induced cell death of effector T cell: a possible third mechanism of self-tolerance. *J Exp Med.* 1990;172(6):1735-9. Epub 1990/12/01. PubMed PMID: 2147950; PMCID: PMC2188763.
33. Groux H, Torpier G, Monte D, Mouton Y, Capron A, Ameisen JC. Activation-induced death by apoptosis in CD4+ T cells from human immunodeficiency virus-infected asymptomatic individuals. *J Exp Med.* 1992;175(2):331-40. doi: 10.1084/jem.175.2.331. PubMed PMID: 1346269; PMCID: PMC2119133.
34. Lohman BL, Welsh RM. Apoptotic regulation of T cells and absence of immune deficiency in virus-infected gamma interferon receptor knockout mice. *J Virol.* 1998;72(10):7815-21. PubMed PMID: 9733817; PMCID: PMC110096.
35. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. *Progress in cardiovascular diseases.* 2020. Epub 2020/03/15. doi: 10.1016/j.pcad.2020.03.001. PubMed PMID: 32169400.
36. Mehta P, McAuley, D.F., Brown, M. et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet.* 2020. doi: 10.1016/S0140-6736(20)30628-0.
37. Chen YH, DeMets DL, Lan KK. Increasing the sample size when the unblinded interim result is promising. *Statistics in medicine.* 2004;23(7):1023-38. Epub 2004/04/02. doi: 10.1002/sim.1688. PubMed PMID: 15057876.

13. APPENDIX A

NIAID 8-point Ordinal Scale for COVID-19 (NCT04280705)

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

14. APPENDIX B

EVALUATION TO SIGN A CONSENT

Protocol: CD24Fc-007-US

PI:

EVALUATION TO SIGN A CONSENT FORM FOR RESEARCH

Name: _____

Date of birth: _____

Directions:

Make a subjective judgment regarding item 1 below. Ask the patient questions 2 through 5. The evaluator may select the appropriate language to use in formulating the questions in order to assist the subject's understanding.

- 1) Is the patient alert and able to communicate with the examiner? ___ Yes ___ No

- 2) Ask the patient to name at least two (2) potential risks incurred as a result of participating in the study.

- 3) Ask the patient to name at least two things that will be expected of him/her in terms of patient cooperation during the study.

- 4) Ask the patient to explain what he/she would do if he/she decides that they no longer wish to participate.

- 5) Ask the patient to explain what he/she would do if he/she is experiencing distress, discomfort or pain.

6) Ask the patient if being in the study is voluntary or required.

I hereby certify that the above patient is alert, able to communicate and able to give acceptable answers to items 2, 3, 4, 5 and 6 above.

Evaluator

Date

Witness

Date

15. SUMMARY OF CHANGES

Substantive changes to the Protocol are outlined in the Table below. In cases where the change involves the insertion or deletion of one or a few words, the text may be underlined for ease of reviewing. Additional typographical corrections or edits may also be made throughout the Protocol but not detailed in the Table.

Section of the document	Revision and Justification
Title page and footer (all pages)	Protocol version number updated to 1.9, dated August 16, 2020
Study Synopsis: Study Design (Page 2)	<p>Study Design changed from:</p> <p>CD24Fc will be administered as single dose of 480 mg via IV infusion on Day 1. Total of 230 subjects will be enrolled and randomized in 1:1 ratio to receive CD24Fc or placebo. All subjects will be treated with the best available treatment. The follow up period is 28 days.</p> <p>To:</p> <p>CD24Fc will be administered as single dose of 480 mg via IV infusion on Day 1. Total of <u>270</u> subjects will be enrolled and randomized in 1:1 ratio to receive CD24Fc or placebo. All subjects will be treated with the best available treatment. The follow up period is 28 days.</p>
Study Synopsis: Study Endpoints: (Page 3) Section 2.4 Primary Endpoints: (Page 39)	<p>Primary Endpoint changed from:</p> <p>Time to improvement in clinical status: the time (days) to the improvement of clinical status from “scale 3 or 4” to “scale 5 or above that is sustained without a drop to below 5” based on NIAID 8-point ordinal scales (Appendix A) within 28 days from randomization.</p> <p>To:</p> <p>Time to improvement in clinical status: the time (days) to the improvement of clinical status from “scale <u>2 to 4</u>” to “scale 5 or above that is sustained without a drop to below 5” based on NIAID 8-point ordinal scales (Appendix A) within 28 days from randomization.</p>
Study Synopsis: Study Endpoints: (Page 3) Section 2.5 Secondary Endpoints: (Page 40)	<p>Secondary Endpoints changed from:</p> <p>Time to disease progression in clinical status: the time (days) for progression from scale 3 or 4 to scale 1 or 2 based on NIAID ordinal scale with 28 days from randomization;</p> <p>To:</p> <p>Time to disease progression in clinical status: the time (days) for progression from scale 3 or 4 to scale 1 or <u>2, or 2 to 1,</u> based on NIAID ordinal scale with 28 days from randomization;</p> <p>Secondary Endpoints changed from:</p> <p>Conversion rate of clinical status on days 8 (proportion of subjects who changed from “scale 3 or 4” to “scale 5 or higher” on NIAID ordinal scale);</p> <p>To:</p> <p>Conversion rate of clinical status on days 8 (proportion of subjects who changed from “scale <u>2 to 4</u>” to “scale 5 or higher” on NIAID ordinal scale);</p>

	<p>Secondary Endpoints changed from:</p> <p>Conversion rate of clinical status on days 15 (proportion of subjects who changed from “scale 3 or 4” to “scale 5 or higher” on NIAID ordinal scale);</p> <p>To:</p> <p>Conversion rate of clinical status on days 15 (proportion of subjects who changed from “scale <u>2 to 4</u>” to “scale 5 or higher” on NIAID ordinal scale);</p>
<p>Study Synopsis: Study Endpoints: (Page 3) Section 2.7 Safety evaluation (Page 40)</p>	<p>Safety evaluation changed from:</p> <p>Adverse events, vital signs, laboratory tests (blood routine, blood biochemistry, coagulation function, urine routine), <u>12 lead</u> ECG.</p> <p>To:</p> <p>Adverse events, vital signs, laboratory tests (blood routine, blood biochemistry, coagulation function, urine routine), ECG.</p>
<p>Study Synopsis: Study Population: (Page 3)</p>	<p>Language changed from:</p> <p>Hospitalized severe COVID-19 adult patients.</p> <p>To:</p> <p>Hospitalized severe <u>and critical</u> COVID-19 adult patients.</p>
<p>Study Synopsis: Eligibility Criteria: (Page 3-4) Table 1 (Page 6) Section 4.1 Inclusion criteria (Page 42)</p>	<p>Inclusion criteria changed from:</p> <ol style="list-style-type: none"> 1) Should be at least 18 years of age. 2) Male or female, female should have negative pregnancy test. 3) Diagnosed with COVID-19 and confirmed SARS-CoV-2 viral infection, prior positive viral results allowed. 4) <u>Able to sign the consent form.</u> 5) Hospitalized and requiring oxygen support, NIAID 8-point ordinal score 3 to 4, regardless of ARDS (Appendix A). 6) Women of childbearing potential, under the age of 54 years, who use adequate contraception and who agree to use adequate contraception for the duration of the study. <p>To:</p> <ol style="list-style-type: none"> 1) Should be at least 18 years of age. 2) Male or female, female should have negative pregnancy test. 3) Diagnosed with COVID-19 and confirmed SARS-CoV-2 viral infection, prior positive viral results allowed. 4) <u>Informed consent form signed by the patient or by the legally authorized representative.</u> 5) Hospitalized and requiring oxygen support, NIAID 8-point ordinal <u>score 2, 3 or 4</u>, regardless of ARDS (Appendix A). <u>The intubation for mechanical ventilation is within 7 days.</u> 6) Women of childbearing potential, under the age of 54 years, who use adequate contraception and who agree to use adequate contraception for the duration of the study.
<p>Study Synopsis: Eligibility Criteria: (Page 4) Table 1 (Page 6) Section 4.1 Exclusion criteria (Page 42)</p>	<p>Exclusion criteria changed from:</p> <ol style="list-style-type: none"> 1) <u>Patients with COVID-19 in critical condition (Appendix A) or NIAID 8-point ordinal score 2 (Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)).</u> 2) <u>Patients with documented bacterial / fungal infections.</u> 3) <u>Patients with sepsis or septic shock.</u>

	<p>4) Patients who are pregnant, breastfeeding, or have a positive pregnancy test result before enrollment.</p> <p>5) <u>Severe liver damage (Child-Pugh score \geq C, AST > 5 times the upper limit), the tests can be done 72 hr prior to screening.</u></p> <p>6) <u>Patients with known severe renal impairment (creatinine clearance \leq 30 mL / min) or patients receiving continuous renal replacement therapy, hemodialysis, or peritoneal dialysis, the tests can be done 72 hr prior to screening.</u></p> <p>7) The investigator believes that participating in the trial is not in the best interests of the patient, or the investigator considers unsuitable for enrollment (such as unpredictable risks or subject compliance issues).</p> <p>To:</p> <p>1) Patients who are pregnant, breastfeeding, or have a positive pregnancy test result before enrollment.</p> <p>2) <u>Patients who previously enrolled in CD24Fc clinical trial.</u></p> <p>3) <u>Intubation for invasive mechanical ventilation is over 7 days.</u></p> <p>4) <u>Documented acute renal or hepatic failure;</u></p> <p>5) The investigator believes that participating in the trial is not in the best interests of the patient, or the investigator considers unsuitable for enrollment (such as unpredictable risks or subject compliance issues).</p>
<p>Study Synopsis: Treatment Description: (Page 4)</p>	<p>Language changed from:</p> <p>The Phase III study will be a randomized double-blind placebo controlled study in 230 subjects. Patients will be randomized 1:1 to receive one of the following treatments:</p> <p>Arm A: CD24Fc, 480mg, diluted to 100ml with normal saline, IV infusion in 60 minutes.</p> <p>Arm B: placebo, normal saline 100ml, IV infusion in 60 minutes.</p> <p>The best available treatment and supportive care will be given to all subjects according to local institutional guideline. Those who uses immune modulators such as IL-6/IL-6R antagonists or experimental antiviral drugs such as remdesivir are allowed to participate the trial.</p> <p>To:</p> <p>The Phase III study will be a randomized double-blind placebo controlled study in <u>270</u> subjects. Patients will be randomized 1:1 to receive one of the following treatments:</p> <p>Arm A: CD24Fc, 480mg, diluted to 100ml with normal saline, IV infusion in 60 minutes.</p> <p>Arm B: placebo, normal saline 100ml, IV infusion in 60 minutes.</p> <p>The best available treatment and supportive care will be given to all subjects according to local institutional guideline. Those who uses immune modulators such as IL-6/IL-6R antagonists or experimental antiviral drugs such as remdesivir <u>or convalescent plasma</u> are allowed to participate the trial.</p>
<p>Study Synopsis: Interim Analysis: (Page 5)</p>	<p>Language changed from:</p> <p>The Phase III study will include <u>two interim analyses:</u></p> <p><u>-The first interim analysis will occur after 70 subjects are enrolled without a pause in enrollment. This will be a futility study with a requirement for positive</u></p>

	<p><u>therapeutic activity of CD24Fc (HR\geq1.14 based on TTCI; or HR\leq0.88 based on the proportion of patients who died or had respiratory failure.</u></p> <p>-The <u>second</u> interim analysis will be <u>for efficacy analysis for the primary endpoint</u>, at the time when the required number of events is at 70%. A sample size re-estimation will be conducted on these two interim analyses.</p> <p>To:</p> <p>The Phase III study will include <u>one interim analysis</u>:</p> <p>-The interim analysis will be at the time when the required number of events is at 70% <u>for the purpose of sample size re-estimation only</u>.</p>
<p>Study Synopsis: Stopping Guidelines: (Page 4)</p>	<p>Language changed from:</p> <p>Monitoring of the safety endpoint will be conducted by the CRO in a blinded fashion. The CRO will collect the data and share this with the DSMB at the planned two interim analyses or call a meeting with the DSMB at other times if needed.</p> <p>To:</p> <p>Monitoring of the safety endpoint will be conducted by the CRO in a blinded fashion. The CRO will collect the data and share this with the DSMB <u>at two safety reviews, respectively when 50% or 75% of enrolled patients reached D15. DSMB may call a meeting with the DSMB at other times if needed. DSMB may recommend early termination if it find significantly higher SAE in the CD24Fc arm after considering the clinical benefit of the treatment. The final decision will be made by the sponsor.</u></p>
<p>Section 3.1 Study Design Overview (Page 41)</p>	<p>Language changed from:</p> <p>CD24Fc will be administered as single dose of 480mg via IV infusion on Day 1. Total of <u>230</u> subjects will be enrolled and randomized in 1:1 ratio to receive CD24Fc or placebo. All subjects will be treated with the best available treatment. The follow up period is 28 days. Those who uses immune modulators such as IL-6/IL-6R antagonists or experimental antiviral drugs are allowed to participate the trial.</p> <p>To:</p> <p>CD24Fc will be administered as single dose of 480mg via IV infusion on Day 1. Total of <u>270</u> subjects will be enrolled and randomized in 1:1 ratio to receive CD24Fc or placebo. All subjects will be treated with the best available treatment. The follow up period is 28 days. Those who uses immune modulators such as IL-6/IL-6R antagonists or experimental antiviral drugs are allowed to participate the trial.</p>
<p>Section 6.4 Dose modification based on laboratory values Section 6.4.1 Renal Function Section 6.4.2 Hepatic Function</p>	<p>Dose modification sections deleted to reflect that there will be no dose modifications based on laboratory values.</p>

<p>Section 7.1.1. Informed consent (Page 45)</p>	<p>Language changed from:</p> <p>The researchers explain all the research procedures to the subjects before the screening, including information about the nature of the research, and obtain informed consent signed by the subject themselves.</p> <p>To:</p> <p>The researchers explain all the research procedures to the subjects before the screening, including information about the nature of the research, and obtain informed consent signed by <u>the patient or by a legally authorized representative</u>.</p> <p><u>Before the process to obtain informed consent from the legal authorized representative, investigators should use the EVALUATION TO SIGN A CONSENT FORM FOR RESEARCH in Appendix B to assess the understanding of the consent process of person who may have cognitive impairments, or may elicit the information using clinical interview procedures.</u></p>
<p>Section 7.2.1. Screen period Visit 1 (Page 48)</p>	<p>Language changed from:</p> <ul style="list-style-type: none"> • Sign the informed consent; <p>To:</p> <ul style="list-style-type: none"> • Sign the informed <u>consent by patient or by a legally authorized representative</u>;
<p>Section 8.1.6 Follow up of Adverse Events (Page 52)</p>	<p>Language changed to indicate that Grade III-V AEs will be captured, rather than Grade III-IV AEs.</p>
<p>Section 8.2 Adverse Event Reporting (Page 53)</p>	<p>Language changed to indicate that Grade III-V AEs will be recorded, rather than Grade III-IV AEs.</p>
<p>Section 10.2.2. Per Protocol Set (PPS) (Page 58)</p>	<p>Language changed from:</p> <p>PPS is a subset of the ITT. Refers to all subjects who <u>are randomized to receive</u> the protocol-specified treatment without significant protocol deviations that significantly affect the main efficacy. PPS-based analysis will complement ITT-based analysis as a supporting analysis. Subjects will be analyzed based on the treatment arm they plan to assign.</p> <p>To:</p> <p>PPS is a subset of the ITT. Refers to all <u>randomized</u> subjects who <u>have received</u> the protocol-specified <u>single-dose</u> treatment without significant protocol deviations that significantly affect the main efficacy. PPS-based analysis will complement ITT-based analysis as a supporting analysis. Subjects will be analyzed based on the treatment arm they plan to assign.</p>
<p>Section 10.4.1 Primary efficacy</p>	<p>Language changed from:</p>

<p>endpoint (Page 59)</p>	<p>The primary endpoint will be the time (days) from the randomization in which the patient's clinical diagnosis improved from baseline (scale 3 or 4, NIAID ordinal scale) to 5 or above that is sustained without a drop to below 5 within 28 days.</p> <p>To: The primary endpoint "<u>Time to Clinical Improvement:</u>" (TTCI) will be the time (days) from the randomization in which the patient's clinical status improved from baseline (scale <u>2-4</u>, NIAID ordinal scale, <u>Appendix A</u>) to 5 or above that is sustained without a drop to below 5 within 28 days. <u>Hospital discharge date (NIAID scale 7 or 8) is an important event time point. The date that clinical status evaluation ≥ 5 or the date of hospital discharge, whichever comes first will be used as the TTCI date.</u> <u>The record of re-hospitalization with oxygen therapy is required to modify the TTCI date. The new TTCI date should be the time from randomization to the latest clinical status evaluation ≥ 5 or the date of the latest hospital discharge, whichever comes first.</u> <u>Time to clinical improvement (days) is calculated as:</u> <u>Time to Improvement = Date of (First Clinical Improvement/hospital discharge) – Date of Randomization</u></p> <p><u>The discharge to home due to clinical improvement is scored as NIAID scale ≥ 7. The date that clinical status evaluation ≥ 5 or the date of hospital discharge, whichever comes first will be used as the clinical improvement date. All subjects without clinical improvement within 28 days will be censored on the Day 29 visit.</u></p> <p>Time-event efficacy endpoints / censorship rules changed from:</p> <p>For the primary endpoint, during the observation period, an improvement from NIAID scale 3 or 4 to scale 5 or above, if sustained without a drop below 5, is considered as an event. The days from the randomization to the first time point of such improvement will be defined as time of improvement. Additional follow-up can be used to determine clinical improvement events.</p> <p>To: For the primary endpoint, during the observation period, an improvement from NIAID scale <u>2,3</u> or 4 to scale 5 or above, if sustained without a drop below 5, is considered as an event. The days from the randomization to the first time point of such improvement will be defined as time of improvement. Additional follow-up can be used to determine clinical improvement events.</p>
<p>Section 10.4.2 Secondary efficacy endpoint (Page 59)</p>	<p>Language changed from:</p> <p>For the disease progression, during the observation period, a progression from scale 3 or 4 to scale 2 or 1, is considered as an event. The days from the randomization to the first time point of progression will be defined as time of progression. The probability function of clinical progression will be estimated by Kaplan-Meier method. The median time and its 95% confidence interval for each</p>

	<p>group will be reported. The 95% confidence interval for the median time will be estimated using the Brookmeyer-Crowley method with log-log function conversion to achieve a normal approximation. The progression rate will be estimated by the layered Cox-Model. Cumulative progression rates estimated by the KM method for day 29 and the 95% confidence intervals will be reported.</p> <p>To:</p> <p>For the disease progression, during the observation period, a progression from scale 3 or 4 to scale 2 or 1, <u>or from 2 to 1</u>, is considered as an event. The days from the randomization to the first time point of progression will be defined as time of progression. The probability function of clinical progression will be estimated by Kaplan-Meier method. The median time and its 95% confidence interval for each group will be reported. The 95% confidence interval for the median time will be estimated using the Brookmeyer-Crowley method with log-log function conversion to achieve a normal approximation. The progression rate will be estimated by the layered Cox-Model. Cumulative progression rates estimated by the KM method for day 29 and the 95% confidence intervals will be reported.</p>
<p>Section 10.5 Interim Analysis and Stopping Rules (Page 62)</p>	<p>Language changed from:</p> <p>The study will also include an interim efficacy analysis at 70% events, which is 146 events. The final analysis will be carried out after all 270 subjects have been randomized, dosed and completed the study.</p> <p>In the interim analysis, the DSMB will determine whether the trial demonstrates the efficacy and also re-estimate the sample size to determine whether it supports increasing the number of clinical improvement event targets. Chen's method will be used to re-estimate the sample size.</p> <p>To:</p> <p>The study will also include an interim analysis at 70% <u>of the required 146</u> events. The final analysis will be carried out after all 270 subjects have been randomized, dosed and completed the study.</p> <p>In the interim analysis, the DSMB will re-estimate the sample size to determine whether it supports increasing the number of clinical improvement event targets. Chen's method will be used to re-estimate the sample size.</p>

<p>Section 10.5 Interim Analysis and Stopping Rules (Page 62)</p>	<p>Safety reviews and stopping rules language deleted and replaced with:</p> <p><u>The study have two blinded safety reviews respectively, when 50% and 75% of the planned enrollment has occurred with follow-up time reaching Day 15 and SAE data are available. DSMB will be provided with list of SAE including mortality and may unblind the data at its discretion to evaluate the balance of SAE in the two study arms.</u></p> <p><u>Stopping rules</u></p> <p><u>If the DSMB found that SAE is significantly higher in the CD24Fc arm, it may recommend termination of the trial after review of potential benefit of the study drug by unblinding all study subjects. Sponsor will make final decision based on the recommendation of DSMB.</u></p>
<p>Section 10.5 Interim Analysis and Stopping Rules (Page 63)</p>	<p>Interim Efficacy Analysis section deleted</p>
<p>Section 10.5 Interim Analysis and Stopping Rules (Pages 63 and 64)</p>	<p>Sample Size Re-estimation changed form:</p> <p>The sample size re-estimation (at 70% of patients completing 28 days follow-up) will be based on Chen et al (37). If the conditional power is < 50% or >85%, the trial will continue without a sample size increase; whereas if the conditional power is between 50% and 85%, the sample size will be re-calculated to have 85%. To maintain trial integrity, the DSMB will pick a sample size in a nearest interval with 5 patients. For example, if the re-estimated sample size is 287, the DSMB could pick any number in the interval of 285 to 289. Also, the maximum increased sample size will not be more than 70 patients above what is needed to observe 208 events.</p> <p>The final analysis will be performed when 270 randomized and dosed patients have completed 28 days of follow up, and the p-value cutoff is 0.0455 (two-sided) based on the O'Brien-Fleming function of the Lan-DeMets algorithm.</p> <p>To:</p> <p><u>The interim analysis for the primary endpoint only will be performed after reaching 146 events (70% of information). A sample size reassessment of efficacy will be performed.</u></p> <p><u>There sample size re-estimation 146 events will be based on preliminary data that are not 100% source-verified. The method will be based on Chen et al as stated in the protocol. If the conditional power is < 50% or >85%, the trial will continue without a sample size increase; whereas if the conditional power is between 50% to 85%, the sample size will be re-calculated to have 85%. To maintain trial integrity, the DSMB will pick a sample size in a nearest interval with 5 patients. For example, if the re-estimated sample size is 287, the DSMB could pick any number in the interval of 285 to 289. Also, the maximum increased sample size will not be more than 70 patients above what is needed to observe 208 events.</u></p> <p><u>The final analysis will be performed when 270 randomized and dosed patients have completed 28 days of follow up, and the p-value cutoff is 0.05 (two-sided) based on the O'Brien-Fleming function of the Lan-DeMets algorithm.</u></p>

<p>Section 10.6. Missing Data Convention (Page 64)</p>	<p>Language changed from:</p> <p>Participants who have not been lost to follow up or experienced the event will be censored at Day 29. <u>Participants who received no CD24Fc or placebo will be excluded from analysis.</u> Participants without an event but lost to follow-up will be censored at the last date of follow-up.</p> <p>We will perform two more analyses on the following data sets for the purpose of sensitivity analysis:</p> <p>First: Participants who have not dropped out or experienced an event are censored at Day 29. Participants not receiving study drug will be excluded from the analysis. Participants without an event but lost to follow-up will be censored at the last date of follow-up. When the event is documented, the time to the event is the length of time from the randomization to the event observed if at <u>most one missed</u> disease assessment before the event is documented. <u>If more than one clinical status assessment is missing before the event is documented, it censors at the last disease assessment without the event.</u></p> <p>Second: Participants who have not been lost to follow up or experienced an event and are followed at the end of the trial will be included. Participants not receiving study drug will be excluded. Participants who have documented the event and <u>no missing</u> disease assessment(s) will be included.</p> <p>To:</p> <p>Participants who have not been lost to follow up or experienced the event will be censored at Day 29. Participants without an event but lost to follow-up will be censored at the last date of follow-up.</p> <p>We will perform two more analyses on the following data sets for the purpose of sensitivity analysis:</p> <p>First: Participants who have not dropped out or experienced an event are censored at Day 29. Participants not receiving study drug will be excluded from the analysis. Participants without an event but lost to follow-up will be censored at the last date of follow-up. When the event is documented, the time to the event is the length of time from the randomization to the event observed <u>if at least one</u> disease assessment before the event is documented.</p> <p>Second: Participants who have not been lost to follow up or experienced an event and are followed at the end of the trial will be included. Participants not receiving study drug will be excluded. Participants who have documented the event and <u>have at least one</u> disease assessment(s) will be included.</p>
<p>11.1.3 Use of Legally Authorized Representative (Surrogate Consent) (Page 64-66)</p>	<p>Section added:</p> <p><u>Federal regulations permit investigators to obtain consent from a legally authorized representative. State laws define the categories of individuals who are allowed to provide surrogate consent for research. The following specific category applies to this study in end stage COVID-19 patient who is in ICU with mechanical ventilation.</u></p> <p><u>“Individuals whose medical condition may render them temporarily unable to provide informed consent as a consequence of severe pain, confusion, or impaired consciousness due to events such as life-threatening illness or trauma.”</u></p> <p><u>Definitions</u></p>

	<p>a. <u>Legally Authorized Representative (LAR): An individual or judicial, or other body authorized under applicable law to grant permission on behalf of a prospective participant for their participation in research activities.</u></p> <p>b. <u>Surrogate Consent: The use of a legally authorized representative with reasonable knowledge of the research participant.</u></p> <p>c. <u>Advance Directive: Documents written in advance of serious illness in which a person states their choices for healthcare or names someone to make those choices. When a person is selected to make the medical decisions, the document is called a Durable Power of Attorney and the designated person is called an Agent. The Agent can serve as a LAR to provide surrogate consent.</u></p> <p>d. <u>Capacity to Consent: The ability of the individual to understand the choices presented, to appreciate the implications of choosing one alternative or another, and to make and communicate a decision (e.g., whether or not to participate in a study).</u></p> <p><u>Determining Capacity of Consent</u></p> <p><u>Whenever possible, investigators should attempt to obtain informed consent directly from the research participant.</u></p> <p><u>While there are no standardized measures for determining capacity to consent, participant should be assessed on the abilities to understand and to express a reasoned choice concerning the:</u></p> <ul style="list-style-type: none">• <u>Nature of the research and the information relevant to his/her participation;</u>• <u>Consequences of participation for their own situation, especially concerning their health condition;</u>• <u>Consequences of the alternatives to participation.</u> <p><u>Investigators may use the EVALUATION TO SIGN A CONSENT FORM FOR RESEARCH (Appendix B) to assess the understanding of the consent process of person who may have cognitive impairments, or may elicit the information using clinical interview procedures.</u></p> <p><u>Identifying an Appropriate Surrogate for End Stage COVID-19 Patient in ICU with Mechanical Ventilation</u></p> <p><u>In an emergency room setting or COVID-19 patient in ICU with mechanical ventilation, the order of priority does not apply, not does the surrogate have to show reasonable knowledge of the research participant. Surrogate consent may be obtained from any of the following:</u></p> <ul style="list-style-type: none">• <u>The person's agent designated by an advance health care directive.</u>• <u>He conservators or guardian of the person having the authority to make health care decisions for the person.</u>• <u>The spouse of the person.</u>• <u>The domestic partner of the person as defined in Section 297 of the California Family Code</u>
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	<ul style="list-style-type: none">• <u>An adult son or daughter of the person.</u>• <u>A custodial parent of the person.</u>• <u>Any adult brother or sister of the person.</u> <p>Important Note: <u>In an emergency room or ICU environment, no surrogate may be utilized if there is a disagreement whether to consent among any available surrogates.</u></p>
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