A Phase 2 Randomized, Double-blinded Trial to Evaluate the Efficacy and Safety of Human Anti- SARS-CoV-2 Plasma for Early Treatment of COVID-19

Unique Protocol ID: **AAAT0052**
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Protocol (Population B)
Version 8June2021

PROTOCOL SUMMARY:

Long title: A Phase 2 Randomized, Double-blinded Trial to Evaluate the Efficacy and Safety of Human Anti- SARS-CoV-2 Plasma for Early Treatment of COVID-19

Short title: Convalescent Plasma for Early Treatment of COVID-19

Clinical Phase: 2

IND Sponsor: Andrew B. Eisenberger, MD

Principal Investigator: Jessica Justman, MD

Conducted by: Columbia University

Sample Size: SARS-CoV-2 positive nasal swab at baseline: 150 subjects

Study Population: High risk[1] for severe COVID-19 case who are 18 years of age or older and SARS-CoV-2 positive and asymptomatic or mildly to moderately symptomatic at baseline.

Study Duration: Accrual will take 4-6 months to complete and subjects will be followed for 90 days after enrollment.

Study Design: Double-blinded, randomized control trial to assess the efficacy and safety of anti-SARS-CoV-2 convalescent plasma as early treatment. Participants will be randomized 2:1 to receive either convalescent plasma qualitatively positive for SARS-CoV-2 antibody ("anti-SARS-CoV-2 plasma") or control (albumin 5%).

Study Locations: National Institute of Infectious Diseases Evandro Chagas (INI) at Oswaldo Cruz Foundation (Instituto Nacional de Infectologia Evandro Chagas-FIOCRUZ (INI-FIOCRUZ)(Avenida Brasil, 4365 – Manguinhos, Rio de Janeiro, Rio de Janeiro, Brazil, 21040-900); Laboratorio de Pesquisa em DST e AIDS do IPEC/FIOCRUZ (LAPCLIN/AIDS) (Avenida Brasil, 4365 – Manguinhos, Rio de Janeiro, Rio de Janeiro, Brazil, 21040-900); Laboratório Central do Instituto Nacional de Infectologia Evandro Chagas (Avenida Brasil, 4365 – Manguinhos, Rio de Janeiro, Rio de Janeiro, Brazil, 21040-900); Laboratório de Virus Respiratórios e Sarampo (IOC/FIOCRUZ) (Avenida Brasil, 4365 – Manguinhos, Rio de Janeiro, Rio de Janeiro, Brazil, 21040-900); Laboratório Richet de Pesquisa e Fisiopatologia Humana Ltda (Av. das Américas, 4801 - loja D - Barra da Tijuca, Rio de Janeiro, Rio de Janeiro, Brazil, 21040-900); Agência Transfusional - Laboratório Central INI (Avenida Brasil, 4365 – Manguinhos, Rio de Janeiro, Rio de Janeiro, Brazil, 21040-900);

[1] See Section 2.3.1 for definition of high risk

Center for Infection and Immunity (722 West 168th Street, 17th Floor, NY, NY 10032).

Study Agent:

- Anti-SARS-CoV-2 plasma: convalescent plasma (2 units of ~200-250 mL, total 400-500 mL) collected by apheresis from a volunteer who recovered from COVID-19 disease (collection and qualification covered by IRB protocol AAAS9845 [Convalescent plasma donors]))
- Control (albumin 5%): 2 units of 250mL, total 500 mL

Primary Efficacy Objective:

To evaluate the efficacy of early treatment with anti-SARS-CoV-2 plasma versus control (albumin 5%) at day 28

Primary Endpoint: The primary study endpoint will be a rating of disease severity on Day 28, or the last rating evaluated, using a seven-category severity scale:

1. Not hospitalized, negative PCR for SARS-CoV-2
2. Not hospitalized, positive PCR for SARS-CoV-2 without symptoms
3. Not hospitalized, positive PCR for SARS-CoV-2 with symptoms
4. Non-ICU hospitalization, not requiring supplemental oxygen
5. Non-ICU hospitalization, requiring supplemental oxygen
6. Requiring mechanical ventilation and/or in ICU
7. Death

Time to various dichotomizations on the severity scale.

Primary Safety Objective: To evaluate the safety of anti- SARS-CoV-2 plasma versus control (albumin 5%)

Primary Safety Endpoints:

1. Cumulative incidence of grade 3 and 4 adverse events during the study period
2. Cumulative incidence of serious adverse events during the study period

Secondary Objectives:

1. To compare the anti-SARS-CoV-2 titers between the recipients of anti-SARS-CoV-2 plasma versus control (albumin 5%) at days 3, 7, 14, 28 and 90.
2. To compare the proportion and duration of SARS-CoV-2 PCR positivity (RT PCR) between the recipients of the anti-SARS-CoV-2 plasma versus control (albumin 5%) at days 0, 3, 7, 14 and 28
3. To compare the levels of SARS-CoV-2 RNA between the recipients of anti-SARS-CoV-2 plasma and control (albumin 5%) at days 0, 3, 7, 14 and 28

Exploratory Objective:

1. To assess the correlation between SARS-CoV-2 PCR positivity from nasal swab specimens, based on RT PCR, and detection of viable SARS-CoV-2 from nasal swab specimens based on viral culture assays

LIST OF ABBREVIATIONS

ADR: Adverse Drug Reaction
ADE: Antibody-mediated enhancement of infection
AE: Adverse Event/Adverse Experience
CDC: United States Centers for Disease Control and Prevention
CFR: Code of Federal Regulations
CLIA: Clinical Laboratory Improvement Amendment of 1988
COI: Conflict of Interest
COVID-19: Coronavirus Disease
CRF: Case Report Form
DMC: Data Management Center
DSMB: Data and Safety Monitoring Board
EUA: Emergency Use Authorization
FDA: Food and Drug Administration
GCP: Good Clinical Practice
HBV: Hepatitis B virus
HCIP: Human Coronavirus Immune Plasma
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus
HTLV: Human T-cell lymphotropic virus
IB: Investigator's Brochure
ICF: Informed Consent (Informed Consent Form)
ICH: International Conference on Harmonization
ICU: Intensive Care Unit
IEC: Independent ethics committee
IND: Investigational New Drug Application
IRB: Institutional review board
ISBT: International Society of Blood Transfusion
IWRS: Interactive web response system
MERS: Middle East Respiratory Syndrome
OP: Oropharyngeal
RT-PCR: Reverse Transcriptase Polymerase chain reaction
PK: Pharmacokinetic
PPE: Personal Protective Equipment
PTID: Participant ID number
SAE: Serious adverse event
SARS: Severe Acute Respiratory Syndrome
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
TACO: Transfusion-associated circulatory overload
T. cruzi: *Trypanosoma cruzi*
TRALI: Transfusion-related acute lung injury
UP: Unanticipated Problem
UPnonAE: Unanticipated Problem that is not an Adverse Event
ZIKV: Zika virus

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1. BACKGROUND AND SCIENTIFIC RATIONALE

There are currently no proven treatments for mild coronavirus disease (COVID-19) nor are there prophylaxis options for those who have been exposed to the illness, which is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Human convalescent plasma has been successfully used for other infection prevention and treatment and thus may provide an option for prevention and treatment of COVID-19 and could be rapidly available from people who have recovered from disease and can donate plasma.

Passive antibody therapy involves the administration of antibodies against a given infectious agent to a susceptible or ill individual for the purpose of preventing or treating an infectious disease caused by that agent. In contrast, active vaccination requires the induction of an immune response that takes time to develop and varies depending on the vaccine recipient. Some immunocompromised patients fail to achieve an adequate immune response. Thus, passive antibody administration, in some instances, represents the only means of providing immediate immunity to susceptible persons and more predicable immunity for highly immunocompromised patients.

Passive antibody therapy has a storied history going back to the 1890s. It was the inaugural form of antimicrobial therapy and the only way to treat certain infectious diseases prior to the development of antimicrobial therapy in the 1940s (Casadevall, Dadachova, & Pirofski, 2004; Casadevall & Scharff, 1995). Experience from prior outbreaks with other coronaviruses, such as SARS-CoV-1 shows that convalescent plasma contains neutralizing antibodies to the relevant virus (Zhang et al., 2005). In the case of SARS-CoV-2, the anticipated mechanism of action by which passive antibody therapy would mediate protection is viral neutralization. However, other mechanisms may be possible, such as antibody dependent cellular cytotoxicity and/or phagocytosis. Convalescent serum was also used in the 2013 African Ebola epidemic. A small 73 non-randomized study in Sierra Leone revealed a significant increase in survival for those 74 treated with convalescent whole blood relative to those who received standard treatment (Sahr et al., 2017).

The only antibody type that is currently available for immediate use is that found in human convalescent plasma. As more individuals contract COVID-19 and recover, the number of potential donors will continue to increase.

A general principle of passive antibody therapy is that it is more effective when used for prophylaxis than for treatment of disease. When used for therapy, antibody is most effective when administered shortly after the onset of symptoms. The reason for temporal variation in efficacy is not well understood but could reflect that passive antibody works by neutralizing the initial inoculum, which is likely to be much smaller than that of established disease. Another explanation is that antibody works by modifying the inflammatory response, which is also easier during the initial immune response, which may be asymptomatic (Casadevall & Pirofski, 2003).

As an example, passive antibody therapy for pneumococcal pneumonia was most effective when administered shortly after the onset of symptoms and there was no benefit if antibody administration was delayed past the third day of disease (Casadevall & Scharff, 1994).

For passive antibody therapy to be effective, a sufficient amount of antibody must be administered. When given to a susceptible person, this antibody will circulate in the blood, reach tissues and provide protection against infection. Depending on the antibody amount and composition, the protection conferred by the transferred immunoglobulin can last from weeks to months.

1.1. Experience with the use of convalescent plasma against coronavirus diseases

In the 21st century, there were two other epidemics with coronaviruses that were associated with high mortality, SARS1 in 2003 and MERS in 2012. In both outbreaks, the high mortality and absence of effective therapies led to the use of convalescent plasma. The largest study involved the treatment of 80 patients in Hong Kong with SARS (Cheng et al., 2005). Patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective. In addition, those who were PCR positive and seronegative for coronavirus at the time of therapy had improved prognosis. There is also some anecdotal information on the use of convalescent plasma in seriously ill individuals. Three patients with SARS in Taiwan were treated with 500 ml of convalescent plasma, resulting in a reduction in plasma virus titer and each survived (Yeh et al., 2005). Three patients with MERS in South Korea were treated with convalescent plasma, but only two of the recipients had neutralizing antibody in their plasma (Ko et al., 2018). The latter study highlights a challenge in using convalescent plasma, namely, that some who recover from viral disease may not have high titers of neutralizing antibody (Arabi et al., 2016). Consistent with this point, an analysis of 99 samples of convalescent sera from patients with MERS showed that 87 had neutralizing antibody with a geometric mean titer of 1:61. This suggests that antibody declines with time and/or that few patients make high titer responses.

It is also possible that other types of non-neutralizing antibodies are made that contribute to protection and recovery as described for other viral diseases (Gunn et al., 2018; van Erp, Luytjes, Ferwerda, & van Kasteren, 2019). There are reports that convalescent plasma was used for therapy of patients with COVID-19 in China during the current outbreak (Xinhua, 2020). Although few details are available from the Chinese experience and published studies involved small numbers of patients, the available information suggests that convalescent plasma administration reduces viral load and was safe.

Convalescent plasma, compared to normal control plasma, was recently shown to confer lower mortality in New York City and Brazil among adults hospitalized with

severe COVID-19; overall clinical status based on an ordinal scale at Day 28, however, did not differ between the two arms (O'Donnell, 2021)

1.2. Overview of known potential risks

Historical and current anecdotal data on use of convalescent plasma suggest it is safe in coronavirus infection. Therefore, the large number of exposed healthcare workers, public servants and first responders, in combination with the high mortality of COVID-19, particularly in elderly and vulnerable persons, strongly argue that the benefits of convalescent serum outweigh its possible risks in high risk exposed individuals and/or those with early disease. However, for all cases where convalescent plasma administration is considered, a risk-benefit assessment must be conducted to assess individual variables.

The theoretical risk involves the phenomenon of antibody-mediated enhancement of infection (ADE). ADE can occur for several viral diseases and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms for ADE have been described and there is the theoretical concern that antibodies to one type of coronavirus could enhance infection to another viral strain (Wan et al., 2020). It may be possible to predict the risk of ADE of SARS-CoV-2 experimentally, as proposed for MERS. Since the proposed use of convalescent plasma in the COVID-19 epidemic would rely on preparations with high titers of neutralizing antibody against the same virus, SARS2-CoV-2, ADE may be unlikely. The available evidence from the use of convalescent plasma in patients with SARS1 and MERS (Mair-Jenkins et al., 2015), and anecdotal evidence of its use in patients with COVID-19 (Xinhua, 2020), suggest it is safe. Nevertheless, caution and vigilance will be required in for any evidence of enhanced infection.

Another theoretical risk is that antibody administration to those exposed to SARS-CoV-2 may avoid disease but modify the immune response such that those individuals mount attenuated immune responses, which would leave them vulnerable to subsequent re-infection. In this regard, passive antibody administration before vaccination with respiratory syncytial virus was reported to attenuate humoral but not cellular immunity (Crowe, Firestone, & Murphy, 2001). This concern will be investigated as part of this clinical trial by measuring immune responses in those exposed and treated with convalescent plasma to prevent disease. If the concern proved real these individuals could be vaccinated against COVID-19 when a vaccine becomes available.

Passive antibodies are derived from human serum. The antibodies used in this study will be derived from serum obtained from convalescent patients and will be subjected to testing protocols that are similar to those used by blood banks and transfusion services. However, as is the case with any biological product, there is a very small risk of allergy/anaphylaxis, transfusion related acute lung injury (TRALI), and transfusion associated circulatory overload (TACO) or passive transfer of potential unknown infectious agents or infections. Most adverse effects are mild and

transient including headaches, flushing, fever, chills, fatigue, nausea, diarrhea, blood pressure changes and tachycardia. Late adverse events are rare and include acute renal failure and thromboembolic events.

1.3. Known potential benefits

A benefit of convalescent plasma administration is that it can prevent infection and subsequent disease in those who are at high risk for disease following close contacts of patients with COVID-19. This is especially so for those with underlying medical conditions. Many who will qualify for prophylaxis are health care workers and first responders who are critical to maintenance of stability of the healthcare system. Passive antibody administration to prevent disease is already used in clinical practice. For example, patients exposed to hepatitis B and rabies viruses are treated with hepatitis B immune globulin (HBIG) and human rabies immune globulin (RIG), respectively. Botulism Immune Globulin Intravenous (Human) (BIG-IV) is an intravenous preparation for infant botulism. In addition, passive antibody is used for the prevention of severe respiratory syncytial virus (RSV) disease in high-risk infants. Until recently, polyclonal hyperimmune globulin (RSV-IG) prepared from donors selected for having high plasma titers of RSV neutralizing antibody, was used but these preparations have now been replaced by palivizumab, a humanized murine monoclonal antibody.

Another potential benefit is societal: If the frequency with which exposed persons become infected decreases, the risk of further transmission (R naught might be reduced and the epidemic slowed. Another avenue (not pursued in this protocol) is as a treatment for established infection. Convalescent plasma would be administered to those with clinical disease in an effort to reduce their symptoms and mortality. Based on the historical experience with antibody administration, it can be anticipated that antibody administration would be more effective in preventing disease than in the treatment of established disease.

Given that historical and current anecdotal data on use of convalescent plasma suggest it is safe in coronavirus infection, the high mortality of COVID-19, particularly in elderly and vulnerable persons, suggests that the benefits of its use in those at high risk for or with early disease outweigh the risks. However, for all cases where convalescent plasma administration is considered, a risk-benefit assessment must be conducted to assess individual variables.

1.4. Albumin (Human) 5% as Control Study Product

Participants randomized to the control arm will receive albumin (human) 5% infusion. The albumin will be prepared in bags that are as similar as possible to the bags used for plasma. The similar appearance of albumin and plasma will facilitate maintaining the blinded status of subjects and most of the study staff. Saline

solution or standard of care (no intervention at all) would not allow the subjects to remain blinded and if not blinded, subjects who receive convalescent plasma may alter their behavior, resulting in additional exposure to SARS-CoV-2 and risk of COVID-19.

While normal plasma is only very rarely associated with adverse reactions such as febrile, allergic, anaphylactic and hemolytic events, the risks of albumin infusions are even less frequent. Albumin infusions are rarely associated with rigors, hypotension/decreased BP, tachycardia/increased heart rate, pyrexia, feeling cold (chills), nausea, vomiting, dyspnea/bronchospasm, rash/pruritus as per the package insert. The risk of an anaphylactoid reaction to albumin is not described in the package insert but was observed with only 0.01% of over 60,000 units of infused albumin [Gales BJ and Erstadt BL, 1993]. Since then, the purification methods for albumin have improved even further. There is no risk of an ABO mismatch with albumin. The main risk of albumin infusion, as with plasma, is related to the risk of rapid volume expansion. The risk of volume overload will be mitigated by transfusing study product (CP plasma or albumin) over a 1- to 4-hour period, at the clinician's discretion, depending on the subject's medical history and clinical status.

1.5. SARS-CoV-2 testing

The Laboratorio de Pesquisa em DST e AIDS do IPEC/FIOCRUZ (LAPCLIN/AIDS), Laboratório de Virus Respiratórios e Sarampo (IOC/FIOCRUZ) or the Center for Infection and Immunity (CII) laboratory will conduct both a quantitative PCR assay and serologic assay. No clinical decisions will be made based on these results.

For asymptomatic individuals, PCR testing alone will be used for screening. For symptomatic individuals, two swabs will be collected from each potential participant, one for ID NOW (or comparable rapid antigen test) and one for a PCR-based test. The ID NOW test results are available in minutes and will make recruitment more efficient. In view of the high specificity of the ID NOW test (99.7%) (Dinnes, et al., 2021), if either the ID NOW and/or the PCR test results is positive, the individual will be confirmed as SARS-CoV-2 positive.

PCR testing will be conducted for all participants at screening, days 0, 3, 7, 14 and 28 and the viral load will be estimated. Results from the baseline ID NOW COVID-19 or PCR tests will be reported to subjects as SARS-CoV-2 positive or negative. Subsequent PCR results will not be shared with the subjects or the clinical research team in order to reduce bias.

ID NOW COVID-19 assay performed on the ID NOW Instrument is a rapid molecular in vitro diagnostic test utilizing an isothermal nucleic acid amplification technology intended for the qualitative detection of nucleic acid from the SARS-CoV-2 viral RNA in direct nasal, nasopharyngeal or throat swabs from individuals who are suspected

of COVID-19 by their healthcare provider within the first seven days of the onset of symptoms. ID NOW COVID-19 received Emergency Use Authorization from the US FDA in September 2020.

2. INVESTIGATIONAL PLAN

2.1. Study Objectives

2.1.1. Primary Efficacy Objective:

The primary study endpoint will be a rating of disease severity on Day 28, or last rating evaluated, using a seven-category severity scale:

1. Not hospitalized, negative PCR for SARS-CoV-2
2. Not hospitalized, positive PCR for SARS-CoV-2 without symptoms
3. Not hospitalized, positive PCR for SARS-CoV-2 with symptoms
4. Non-ICU hospitalization, not requiring supplemental oxygen
5. Non-ICU hospitalization, requiring supplemental oxygen
6. Requiring mechanical ventilation and/or in ICU
7. Death

Time to various dichotomizations on the severity scale will be assessed

2.1.2. Primary Safety Objective:

To evaluate the safety of anti- SARS-CoV-2 plasma versus control (albumin 5%)

2.1.3. Secondary Objectives:

1. To compare the anti-SARS-CoV-2 titers between the recipients of anti-SARS-CoV-2 plasma versus control (albumin 5%) at days 3, 7, 14, 28 and 90
2. To compare the proportion and duration of SARS-CoV-2 PCR positivity (RT-PCR) between the recipients of the anti-SARS-CoV-2 plasma versus control (albumin 5%) at days 0, 3, 7, 14 and 28
3. To compare the levels of SARS-CoV-2 RNA between the recipients of anti-SARS-CoV-2 plasma and control (albumin 5%) at days 0, 3, 7, 14 and 28

2.1.4 Exploratory Objectives:

To assess the correlation between SARS-CoV-2 PCR positivity from nasal swab[2] specimens, based on RT PCR, and detection of viable SARS-CoV-2 from nasal swab specimens based on viral culture assays.

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[2] A nasopharyngeal (NP) or nasal mid-turbinate (NMT) swab, also called a Deep Nasal Swab (may be self-collected by each research subject as per CDC guidance; https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html) are both acceptable

2.2 Definitions

I. Enrolled: from time consented to participate until designated as a screen failure or have been discontinued from the study or completed it.
II. Randomized: when a randomization PTID number has been assigned
III. Screen Failures: signed informed consent and received a screening PTID, but then determined to be ineligible or withdrew before being randomized
IV. Discontinued: randomized, but then withdrawn by investigator or withdrew consent
V. Completed: Subjects are considered completed when they are followed through to day 28 or if they die before day 28

2.3 Study population

2.3.1 Inclusion Criteria for Enrollment

1. Subjects must be 18 years of age or older
2. a. Recent close contact[3]* with a person with COVID-19, i.e. last close contact occurred within 7 days of anticipated infusion of study product. It is anticipated that most contacts will be household contacts with extensive interaction. All must meet the CDC criteria for close contacts. This includes healthcare workers at higher risk of developing severe disease.
   OR
   b. Recent self-reported or documented evidence of infection by nasal swab ID NOW or PCR that is positive for SARS-CoV-2, i.e., nasal sample was collected within 7 days or 10 days of anticipated infusion of study product for those who are asymptomatic or symptomatic, respectively. [4]
3. Evidence of infection by nasal swab ID NOW or PCR that is positive for SARS-CoV-2 at screening visit[5]

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[3] Close contact is defined by CDC as being within approximately 6 feet (2 meters) of a COVID-19 case for a prolonged period of time (without PPE); close contact can occur while caring for, living with, visiting, or sharing a healthcare waiting area or room with a COVID-19 case.
[4] 7 days (if asymptomatic at prescreening) or 10 days (if minimally to moderately symptomatic during prescreening) are based on the number of days from specimen collection date to anticipated infusion date
[5] A repeat ID NOW and PCR at screening is required for all participants. However, for participants with documented evidence of infection by nasal swab PCR that is positive for SARS-CoV-2 in the prior week, a positive swab is not required to enroll the participant since they were already positive in the past week and will be tested by PCR during the Infusion Visit. At screening, two swabs will be collected from each participant, one for ID NOW (or comparable rapid antigen test) and one for a PCR-based test. If ID NOW is positive, it will not be necessary to wait for the PCR based test result to confirm the positive. If the ID NOW is negative, it will be necessary to wait for the PCR test result: PCR negative will mean individual is not eligible and PCR positive will mean they are potentially eligible if all the other inclusion criteria are met.

4. May or may not be hospitalized
5. No symptoms or no more than 7 days of moderate symptoms at the time of screening.
   Moderate symptoms[6] may include:
   a. Moderate rhinorrhea
   b. Moderate sore throat or throat irritation
   c. Moderate cough
   d. Moderate fatigue (may interfere with ability to perform ADLs)
   e. Moderate chills, measured temperature and/or feeling feverish, muscle pain
6. Calculated Risk Score for severe COVID-19 [based on CDC description[7]] of 0 points if on supplemental oxygen at enrollment; otherwise Calculated Risk Score of ≥ 1.
   - Age 65-74: 1 point
   - Age ≥75: 2 points
   - Known cardiovascular disease (including hypertension): 1 point
   - Diabetes mellitus: 1 point
   - Pulmonary disease (COPD, moderate to severe asthma, current smoking or other): 1 point
   - Morbid obesity: 1 point
   - Immunocompromised state: 1 point
     Received a bone marrow or solid organ transplant at any time, received chemotherapy for a malignancy within the past 6 months, has an acquired or congenital immunodeficiency, currently receiving immunosuppressive or immune modulating medications, HIV with non-suppressed viral load and/or CD4+ T cell count <200 cells/mL).
7. Those who do not require more than 4 LPM of supplemental oxygen at enrollment.[8]

2.3.2 Exclusion Criteria for Enrollment

1. Receipt of any blood product in past 120 days.
2. Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigator, would affect subject safety and/or compliance.

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[6] Moderate symptoms are rated by the participant as moderate and may interfere with normal daily activities; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50
[7] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html
[8] Nasal cannula permitted for inclusion in study

3. Confirmed or self-reported presumed COVID-19, with symptoms that began more than 7 days prior to enrollment, and SARS-CoV-2 ID NOW or PCR positive sample that was collected more than 7 days prior to anticipated infusion for an asymptomatic participant or more than 10 days prior to anticipated infusion for a patient with mild to moderate symptoms at screening.
4. Symptoms consistent with COVID---19 infection that are more than moderate (as defined above) at time of screening.
5. Symptoms that have worsened in the period between screening and enrollment such that the subject is deemed to be medically unstable on the day of planned enrollment.
6. History of allergic reaction to transfusion blood products
7. Inability to complete infusion of the product within 48 hours after randomization.
8. Resident of a long term or skilled nursing facility
9. Known prior diagnosis of IgA deficiency
10. Participation in another clinical trial of anti-viral agent(s) for COVID-19

2.3.3 Recruitment Process:

Recruitment for this protocol will involve approaching two groups of subjects: 1) patients with confirmed COVID-19 (asymptomatic or mildly to moderately symptomatic) and 2) patients with suspected COVID-19 (asymptomatic or mildly to moderately symptomatic).

2.3.3.1 Recruitment Process for Confirmed & Suspected COVID-19 Patients

Patients (including healthcare workers) who are asymptomatic or have mild to moderate symptoms (see Section 2.3.1.5) and have confirmed OR suspected COVID-19 will be approached by study staff, in-person, to introduce the study and see if they are interested in participating. Study staff may opt to phone potential participants after the ID NOW or PCR result becomes available to complete the assessment of eligibility and schedule the screening visits.

2.3.3.2 Pre-Screening Potential Participants

Potential participants will be approached by study staff and introduced to the study. The study staff will ascertain whether:

1. the potential subject has interest in the study and is willing to be screened, AND

2. the potential subject has had recent close contact with a COVID-19 case (see Section 2.3.1.2) or has recent self-reported or documented evidence of infection by nasal swab ID NOW or PCR that is positive for SARS-CoV-2, AND
3. the potential subject is at risk for severe COVID-19 disease based on age and/or their medical co-morbidities (see Section 2.3.1.6), AND
4. the potential subject is currently asymptomatic or minimally or moderately symptomatic of COVID-19 disease

Potential subjects who meet the above criteria and have a risk score for COVID-19 [0 risk if on supplemental oxygen at enrollment; otherwise $\geq$ 1 risk] will be invited to attend a screening visit at the site within the next 1-2 business days.

After the study is explained in detail, written consent will be obtained, and screening questionnaires, locator forms and required lab work will be completed. Those who provide consent will be eligible to enroll in the study when their screening nasal swab is positive for SARS CoV-2.

Table: Schedule of Events

Study period	Screen	Baseline	Infusion	Follow up						
Day	-1 to 0	0	0	1	3±2	7±1	14±3	28±7	60±7	90±7
Eligibility										
Informed consent	x									
Demographic and Medical history	x									
COVID-19 symptom screen	x		x							
SARS-CoV-2 ID NOW and RT-PCR obtained for eligibility	x[9]									
Pregnancy test [10]	x									
ABO[11]	x									
Study Drug Administration										
Randomization		x								
Drug infusion			x							
Study Procedures										
COVID-19 Symptom screen	x		x	x	x	x	x	x	x	
Other symptoms screen	x		x	x	x	x	x	x	x	
Concomitant medications	x		x	x	x	x	x			
Vital signs	x		x[12]		x	x	x			
Targeted physical examination	x		x			x	x			

[9] A repeat ID NOW and PCR at screening is required for all participants. However, for participants with documented evidence of infection by nasal swab PCR that is positive for SARS-CoV-2 in the prior week, a positive swab is not required to enroll the participant since they were already positive in the past week and will be tested by PCR during the Infusion Visit. At screening, two swabs will be collected from each participant, one for ID NOW (or comparable rapid antigen test) and one for a PCR-based test. If ID NOW is positive, it will not be necessary to wait for the PCR based test result to confirm the positive. If the ID NOW is negative, it will be necessary to wait for the PCR test result: PCR negative will mean individual is not eligible and PCR positive will mean they are potentially eligible if all the other inclusion criteria are met.

[10] Urine pregnancy test for women of childbearing potential

[11] Assessment of ABO type on file; requires two tubes of blood drawn 5 minutes apart, as per NYP Blood Bank procedures

[12] Vital sign testing: Immediately prior to infusion, 10-20 minutes after start of infusion, at completion of infusion and 15-60 minutes after the end of the infusion

Study period	Screen	Baseline	Infusion	Follow up						
Day	-1 to 0	0	0	1	3±2	7±1	14±3	28±7	60±7	90±7
Assessment of composite outcome of disease severity[13]			x	x	x	x	x	x	x	
Adverse event monitoring			x	x	x	x	x	x	x	
Laboratory testing										
CBC and CMP[14]	x					x	x			
SARS-CoV-2 RT-PCR[15,16]	x		x		x	x	x	x		
SARS-CoV-2 antibody	x				x	x	x	x		x
Blood for future testing	x				x	x	x	x		
Viral culture[17]	x					x				
Blood for PBMC for future testing	x									

2.3.4 Subject Withdrawal

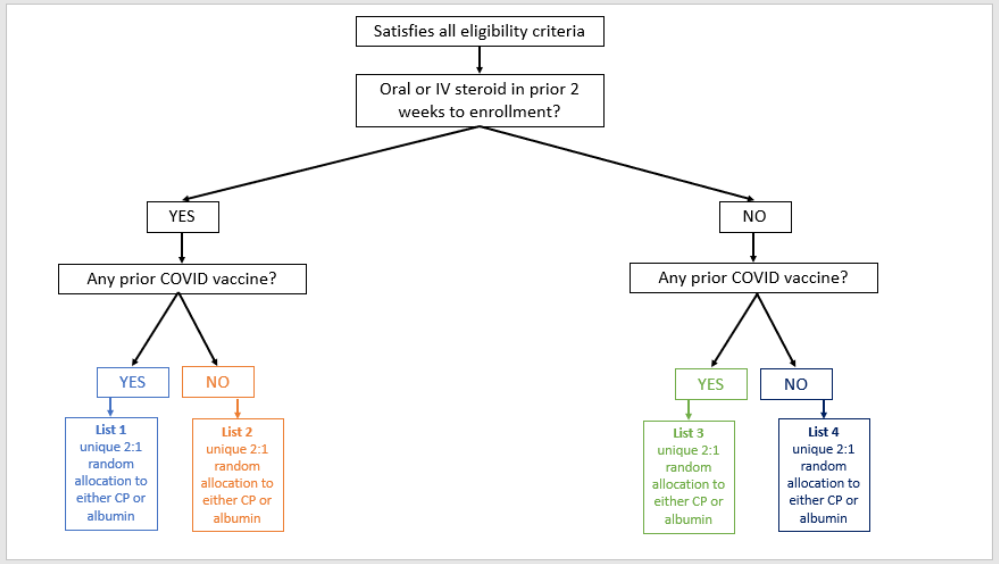
1. Subjects can terminate study participation and/or withdraw consent at any time without prejudice.
2. Randomized subjects who withdraw from the study will not be replaced.
3. The investigator may withdraw subjects if they are non-compliant with study procedures or if the investigator determines that continued participation in the study would be harmful to the subject or the integrity of the study data
4. Discontinuation of the study: The study sponsor, FDA and IRB all have the right to terminate this study at any time

2.3.5 Stratified Randomization

1. Subjects enrolled in the study will be stratified and randomized using an interactive web- based system

[13] Assessment evaluates whether subject has shifted from "no clinical or laboratory evidence of COVID-19 infection to any of the composite outcomes of disease severity
[14] Comprehensive metabolic panel
[15] Nasal swab
[16] Includes sequencing for viral variants
[17] 10 % sample of the nasal swabs

2. Subjects will be stratified by steroid administration (prior oral or IV steroids within prior 2 weeks at time of enrollment or prior inhaled steroids within prior 24 hours at time of enrollment) and by vaccination status (prior COVID-19 vaccine at time of enrollment) and then randomized in a 2:1 ratio to either CP or albumin 5%



2.3.6 Intervention

I. Subjects will be randomized within each population in a 2:1 ratio to receive anti-SARS-CoV-2 plasma versus control (albumin 5%).
II. Study drug: The investigational product is anti-SARS-CoV-2 plasma. Patients identified as having recovered from COVID-19 will serve as potential donors. Testing will confirm presence of anti-SARS-CoV-2 antibody prior to donation. Plasma donors will be screened for transfusion-transmitted infections (e.g. HIV, HBV, HCV, WNV, HTLV-I/II, *T. cruzi*, ZIKV) and plasma will be collected using apheresis technology. This is similar to standard blood bank protocols.
III. Active arm will receive 2 units (200 – 250 mL each, 400-500 mL total) of anti-SARS-CoV-2 plasma from the same donor. These units have been verified to have a neutralizing titer of 1:320 each.
IV. Control arm will receive 2 units of 250mL (500 mL total) of albumin 5%
V. Both active and control drugs will be in standard plasma unit bags, with a study-specific ISBT label with the statement, "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

2.4 Study Product Considerations

The preparation of the anti-SARS plasma will take place at the New York Blood Center and the CUIMC-NYPH Blood Bank will dispense the plasma products to Brazil sites. The plasma collection procedures are not part of this research protocol and are described in separate protocols, which has separate IRB approval (AAAS9845). The description below provides a summary of study product considerations as context.

2.4.1 Collection

Donors will be pre-qualified for blood donation via study procedures described in IRB protocol AAAS9845. This will ensure that all convalescent plasma units in the CUIMC-NYPH Blood Bank will have high titers of IgG. All activities pertaining to the collection and processing of plasma will take place at [New York Blood Center/NYBC]. NYBC is one of the largest independent, community-based, nonprofit blood centers in the United States. It is operational in multiple states i.e. it is not confined to New York. NYBC has a longstanding research program and is well versed in the regulatory and ethical aspects of research, including clinical trials. The organization is FDA-licensed to produce convalescent plasma and AABB (American Association of Blood Banks) accredited, attesting to robust quality oversight of all operations.

2.4.2 Collection and processing

- Standard apheresis plasma collection will be performed per routine standard operating procedure at the collection facility (NYBC).
- As per routine practice, samples will be collected at time of donation for testing for transfusion-transmissible infections (all donors), ABO and red cell antibodies (all donors) and HLA antibodies (female donors with prior pregnancies).
- Target collection volume: ~450-600mL; this will allow for later splitting (separation) into 200-250mL daughter units.
- The plasma will be processed per routine practice; it will be frozen within 24 hrs of collection per AABB standards.
- The plasma will be maintained in quarantine at the blood center pending laboratory test results (i.e. infectious screening, ABO and RhD status, Red cell and HLA antibodies).
- If laboratory testing is acceptable (i.e. negative infectious and antibody screening), the products will be distributed to hospital blood bank for storage.
- In the event of an abnormal test result, the product will be discarded and the donor will be notified by the blood center as is standard practice.

2.4.3 Control arm

The control (albumin 5%) will be prepared by the Brazil Research Pharmacy in bags that are identical to the bags used for plasma.

2.4.4 Rationale for dosing

We will infuse 2 units (200-250 mL each, 400-500 mL total) of plasma with an anti-SARS-CoV-2 antibody ≥1:320 and 2 units of 250mL of albumin 5%, 500 mL total. Assuming a plasma volume of 3,500 ml, 500 ml of plasma with an antiviral titer of 1:320 would yield a final antiviral titer of 1:45. Dosing is based on a previous report wherein convalescent plasma therapy showed efficacy in COVID-19 patients following infusion of 200ml of convalescent plasma with a titer of 1:640 (Duan et al., 2020). We have not been able to identify sufficient numbers of plasma units with this titer to conduct this trial. Hence, we will employ two units with neutralizing titers of ≥1:320.

2.5 Study drug administration

- Drug will be administered within 48 hours (24 hours if possible) of randomization
- Infusion rate ≤ 250 mL/hour at physician discretion
- Pretreatment to minimize transfusion reactions (e.g. acetaminophen, diphenhydramine) will not be given, but will be available as needed to treat fever or allergic reactions. For severe allergic reactions corticosteroids (e.g., 125 mg methylprednisolone IV or comparable) may be used. For rare severe anaphylaxis, epinephrine will be available.
- If an AE develops during infusion, the infusion may be slowed or stopped as per investigator's decision.
    - Most reactions to plasma are relatively minor and the infusion can generally be continued. Infusion site burning and non-allergic systemic effects can generally be managed with slowing of the infusion. Infusion is generally stopped in cases of itching; participant is treated and then infusion cautiously re-started.
    - Severe allergic reactions generally require discontinuation of the infusion. These include:
        - Respiratory compromise: dyspnea, wheezing, stridor, hypoxemia

        - A decrease in systolic blood pressure to < 90 mmHg or >30% decrease from baseline or a diastolic drop of >30% from baseline.
        - Tachycardia with an increase in resting heart rate to > 130 bpm; or bradycardia <40 that is associated with dizziness, nausea or feeling faint.
        - Syncope
        - Confusion
        - Any other symptom or sign which in the good clinical judgment of the study clinician or supervising physician warrants halting the infusion. For example, the rapid onset of gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and cramps, for instance, may be manifestations of anaphylaxis and may warrant an immediate halt prior to meeting full SAE criteria
    - Concomitant medications used during the infusion will be documented on the CRF

3 STATISTICAL CONSIDERATIONS

3.1 Design Overview

This is a double-blinded, randomized phase 2 trial to evaluate the efficacy and safety of human SARS-CoV-2 immune plasma in individuals who are close contacts to person with COVID-19 within 7 days according to the CDC definition. This will also serve as an internal pilot in the seamless phase 2/3 study.

Eligible participants will be randomized to receive high-titer anti-SARS-CoV-2 immune plasma or control (albumin 5%) in a 2:1 ratio. We plan to enroll a total of 150 participants, with a maximum of 100 receiving the plasma and 50 receiving the control.

Each participant will be followed for 28 days after randomization and treatment, and will tested and evaluated at baseline and on Days 3, 7, 14, 28 using a seven-category severity scale:

1. Not hospitalized, negative PCR for SARS-CoV-2
2. Not hospitalized, positive PCR for SAR-CoV-2 without symptom
3. Not hospitalized, positive PCR for SAR-CoV-2 with symptoms
4. Non-ICU hospitalization, not requiring supplemental oxygen
5. Non-ICU hospitalization, requiring supplemental oxygen
6. Requiring mechanical ventilation and/or in ICU
7. Death

The primary study endpoint is the rating on Day 28, or last rating evaluated. We will also consider time to various dichotomizations on this scale as secondary

outcomes, including time to death, time to requiring critical care, and time to requiring hospitalization

Other endpoints include:

- Anti-SAR-CoV-2 titers (Days 3, 7, 14, 28, 90 in addition to baseline)
- SAR-CoV-2 PCR positivity (Days 0, 3, 7, 14, 28 in addition to baseline)
- SAR-CoV-2 RNA (Days 0, 3, 7, 14, 28 in addition to baseline)

Exploratory objective:

- To assess the correlation between SARS-CoV-2 PCR positivity from nasal swab specimens, based on RT PCR, and detection of viable SARS-CoV-2 from nasal swab specimens based on viral culture assays

Serious adverse events, and grades ≥3 adverse events will be monitored during the study period.

3.2 Statistical Analysis

Primary Analysis and go/no-go decision: The severity scale of the two groups will be compared using stratified, Mann Whitney test. Specifically, a one-sided $P<0.15$ favoring the immune plasma arm will constitute a "go decision" in this phase 2 trial, suggesting evidence of promise for further investigation in an expanded Phase 3 study. The results in this trial will then be used to plan the Phase 3 sample size, with possibility that the data in this Phase 2 trial will be included in the final analysis using adjusted P values. Details of sample size re-estimation and adjusted analysis, as well as the final statistical analysis plan, will be determined before unblinding the study data.

This analysis will be intent-to-treat. Given the short study duration and the nature of the treatment, however, we anticipate minimal non-compliance and loss to follow-up.

Subgroup Analysis: If the stratified analysis reaches the go decision, with $P<0.15$, we will explore the treatment effect within each stratum using Mann Whitney test.

Secondary Analyses: All secondary efficacy analyses will be intent-to-treat. Time-to-event variables (e.g. time to death) will be analyzed using Cox proportional hazard model. Longitudinal data collected over multiple days (e.g., PCR positivity) will be analyzed explored using generalized linear mixed models. Treatment effects on these variables will be estimated with 95% confidence intervals.

Safety Analyses: Serious adverse events will be summarized by grades and types using proportions and 95% confidence intervals for the two study arms, and the two arms will be compared using Fisher's exact test.

3.3 Power Consideration

Assuming a shift odds ratio of 2 under a proportional odds model on the severity rating scale, with a sample size of 150, the study will have 74% to 80% power of reaching the go decision in the scenarios we considered. The actual power will depend the distribution of the severity scale in the control arm. Table 2 gives the power of the two extreme scenarios: Scenario 1 describes scenario with higher rates for more severe outcomes, and Scenario 2 with majority of participants remaining or becoming PCR negative; the outcome distributions are identical between the two strata in these scenarios. We have evaluated the power for in-between scenarios and scenarios where non-infected and infected strata are different; the power is within the range 74% and 80% in all scenarios we have considered.

Table 2: Power Calculation & Distribution of severity rating scale in the study

Category	Scenario 1			Scenario 2	
	Control (albumin 5%)	Immune plasma		Control (albumin 5%)	Immune plasma
PCR negative	0%	0%		60%	75%
PCR positive, asymptomatic	0%	0%		0%	0%
PCR positive with symptom	70%	82%		28%	19%
Hospitalization	10%	7%		4%	2%
Hospitalization requiring oxygen	10%	6%		4%	2%
ICU/ventilation	5%	3%		2%	1%
Death	5%	2%		2%	1%
Study power	74%			80%	

4 STUDY PROCEDURES

4.1 Day -1 to 0 (Recruitment Pre Screen)

1. Script information about study protocol
2. Verification that the potential subject has interest in the study and is willing to attend a screening visit at the site on the next day
3. Verification that the potential subject had significant close contact with the COVID-19 case within the prior seven days OR has self-reported or documented recent evidence of infection by nasal swab (ID NOW or PCR) that is positive for SARS-CoV-2

4. Medical eligibility questionnaire
    - Ascertainment that the potential subject has risks for severe COVID-19 disease based on CDC risk criteria-age of the potential subject and their medical co-morbidities (hypertension, cardiovascular disease, pulmonary disease [including COPD or moderate to severe asthma], other immune suppressing condition)
    - Verification that the potential subject is currently asymptomatic or minimally or moderately symptomatic of COVID-19 disease for $\leq$ 7 days

4.2 Day -1 to 0 (Screening Visit+)

1. Informed consent (obtained before performing study related activities) and assignment of screening PTID
2. New York Presbyterian Hospital (NYPH) blood transfusion consent (this is the standard procedure for all transfusions of blood products at NYPH)
3. Verification of eligibility (inclusion/exclusion)
4. Locator form
5. Demographics (age, sex ethnicity, race)
6. Medical history (timing of exposure to COVID---19 source patient, acute and chronic medical condition, medications, allergies. Any medical condition arising after randomization and infusion of study product should be recorded as AE
7. COVID---19 symptom screen (fevers, cough, rhinorrhea, sore throat, diarrhea, shortness of breath, ADLs)
8. Vital signs (pulse, blood pressure, weight, height, temperature, oxygen saturation)
9. Targeted physical examination
10. ID NOW COVID-19 and PCR test to confirm positivity for SARS-CoV-2[18]
11. Laboratory Evaluation
    - SARS-CoV-2 testing (RT-PCR) from nasal swab (10% of the swabs will also be submitted for viral culture).
    - ABO Blood typing (two tubes), CBC, comprehensive metabolic panel
    - Serological testing: anti-SARS CoV-2 titers
    - Blood samples for future studies, including sample for peripheral blood mononuclear cells
    - Urine or serum pregnancy test for females of childbearing potential.

[18] At screening, two swabs will be collected from each participant, one for ID NOW (or comparable rapid antigen test) and one for a PCR-based test. If ID NOW is positive, it will not be necessary to wait for the PCR based test result to confirm the positive. If the ID NOW is negative, it will be necessary to wait for the PCR test result: PCR negative will mean individual is not eligible and PCR positive will mean they are potentially eligible if all the other inclusion criteria are met.

Results from laboratory tests obtained up to 7 days before enrollment may be used for the pregnancy test.

- Volume overload
    - Volume status will be assessed via (1) medical history: history of congestive heart failure and use of heart failure medications; and (2) physical exam: vital signs, lung exam, assessment for peripheral edema.
    - Enrollment will be deferred for patients who have active volume overload in order to avoid cardiovascular decompensation from the receipt of additional volume. Once the patient's volume status has improved, enrollment may then proceed. [note this is not an exclusion]
    - For these patients, the potential risk of a recurrence of volume overload will be mitigated by infusing the plasma or albumin (a total of 400-500 mL) more slowly, i.e., over 2 - 4 hours.

4.3 Day 0 + Baseline

1. Subjects will be contacted and scheduled for an infusion window
2. Randomization will then be done using an interactive web-based system to receive study convalescent plasma (CP) versus control (albumin 5%) at a 2:1 ratio
3. Study Product Administration: Two units of immune plasma or control (albumin 5%) will be transfused. Time at start and end of infusion will be recorded and vital signs will be measured immediately prior to infusion, 10-20 minutes after start of infusion, at completion of infusion and between 15-60 minutes after the end of the infusion.
4. COVID-19 symptom screen (fevers, cough, shortness of breath)
5. Assessment of clinical status (composite outcome of disease severity)
6. New medical conditions, concomitant medication, AE evaluation
7. Physical examination
8. SARS-CoV-2 testing (RT-PCR) from nasal samples

For follow-up visits, home visits by qualified phlebotomists and/or visiting nurses will be permitted.

4.4 Day 1

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (composite outcome of disease severity)
3. New medical conditions, AE evaluation

4.5 Day 3 ± 2

1. Vital signs

2. COVID-19 symptom screen (fevers, cough, shortness of breath)
3. Assessment of clinical status (composite outcome of disease severity)
4. New medical conditions, AE evaluation
5. SARS-CoV-2 testing (RT-PCR) from nasal samples
6. Serological testing: anti-SARS-CoV-2 titers
7. Stored samples for future studies

4.6 Day 7 ± 1

1. Vital signs
2. COVID-19 symptom screen (fevers, cough, shortness of breath)
3. Assessment of clinical status (composite outcome of disease severity)
4. New medical conditions, AE evaluation
5. Targeted physical examination
6. SARS-CoV-2 testing (RT-PCR) from nasal samples
7. Serological testing: anti-SARS-CoV-2 titers
8. Comprehensive metabolic panel and CBC
9. Stored samples for future studies

4.7 Day 14 ± 3

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (composite outcome of disease severity)
3. New medical conditions, AE evaluation
4. Targeted physical examination
5. CBC, comprehensive metabolic panel
6. SARS-CoV-2 testing (RT-PCR) from nasal samples
7. Serological testing: anti-SARS-CoV-2 titers
8. Stored samples for future studies

4.8 Day 28 ± 7

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (composite outcome of disease severity)
3. New medical conditions, AE evaluation
4. SARS-CoV-2 testing (RT-PCR) from nasal samples
5. Serological testing: anti-SARS-CoV-2 titers
6. Stored samples for future studies

4.9 Day 60 ± 7

1. COVID-19 symptom screen (fevers, cough, shortness of breath)
2. Assessment of clinical status (composite outcome of disease severity)

3. New medical conditions, AE evaluation

4.10 Day 90 ± 7

1. Serological testing: anti-SARS-CoV-2 titers

+ In order to minimize exposure to SARS-Cov-2 virus, at the clinician's discretion, face to face interactions may be minimized by collecting information by phone or by telemedicine (Zoom HIPAA compliant conferencing)

5 EFFICACY, VIROLOGIC AND PK MEASURES

5.1 Clinical Efficacy (composite outcome of disease severity)

1. Not hospitalized, negative PCR for SARS-CoV-2
2. Not hospitalized, positive PCR for SARS-CoV-2 without symptom
3. Not hospitalized, positive PCR for SARS-CoV-2 with symptoms
4. Non-ICU hospitalization, not requiring supplemental oxygen
5. Non-ICU hospitalization, requiring supplemental oxygen
6. Requiring mechanical ventilation and/or in ICU
7. Deceased

5.2 Virologic measures

- Rates and duration of SARS-CoV-2 PCR positivity (RT PCR) at days 0, 3, 7, 14 and 28
- Peak quantity levels of SARS-CoV-2 RNA at days 0, 3, 7,14 and 28
- Culture positivity at baseline and at day 7 in a subset of specimens
- Correlation between viral culture positivity and PCR positivity for SARS-CoV-2

5.3 Serologic titers

- Serologic measures: Anti-SARS-CoV-2 titers at days 3, 7, 14, 28 and 90 days after infusion.

6 RISKS AND BENEFITS

6.1 Potential benefits of treatment

The potential benefits of antiviral treatment with anti-SARS CoV-2 plasma in patients at high risk for developing COVID-19 due to a close contact with another individual with COVID-19 are unknown. However, it is anticipated that treatment will decrease the risk of developing symptomatic disease and decrease the severity of illness should it develop.

6.2 Potential risks of study procedures

1. Risks of plasma: Fever, chills, rash, headache, serious allergic reactions, TRALI, TACO, transmission of infectious agents
2. Risk of albumin: chills, fever, low blood pressure, fast heart rate, urticaria, skin rash, nausea, TACO
3. Risks of phlebotomy: local discomfort, bruising, hematoma, bleeding, fainting
4. Total blood draws will not exceed 125 mL over the 90-day follow up period
5. Risks of nasal swab: local discomfort, vomiting
6. Risks of IV placement: bleeding, infection, thrombosis

6.3 Potential risks of genetic testing

Samples obtained for future research may include a search for genetic correlates of COVID-19 susceptibility or severity. Specimens will be labeled by study IDs, rather than names. This information will not be released to participants and will not become part of their medical records. Risks related to discrimination or other problems are deemed highly unlikely.

6.4 Alternatives

The alternative to participation in this study is routine care and monitoring following close contact with an individual with COVID-19 or enrollment in a different clinical trial.

6.5 Infection prevention and control measures

Care will be taken throughout the study to minimize the risk of transmission of the SARs-CoV-2 virus during study visits.

1. Participants will be provided with a surgical mask upon entry to the medical center and asked to wear a mask during their visit (other than during nasal swabbing) and during transit to and from the study site.
2. Participants will be asked not to use public transportation during the first two weeks of the study and will be provided with transportation reimbursement to study visits in a single occupancy vehicle.
3. Study staff will wear surgical masks, eye protection, gown and gloves during visits with study participants during visits -1 to 30 and at any time that community transmission of SARS-Cov-2 is reported by the

NYS Department of Health.

4. Scheduling of visits will be done with the goal of minimizing wait times at the study site.
5. Participants will be immediately placed in single exam rooms upon arrival.
6. All areas of participant contact will be wiped down with an approved viricidal agent after each visit. Doorknobs and other high touch areas will be cleaned at regular intervals as per medical center IPC guidelines.
7. At the clinician's discretion, face to face interactions may be minimized by collection of data from participants by phone or by telemedicine (using Zoom HIPAA compliant conferencing)
8. All clinical specimens will be transported according to hospital policy in biohazard bags using clinical carriers.

6.6 Safety monitoring

1. Safety evaluations will assess for the safety of anti-SARS-CoV-2 plasma and determine if risks are higher, lower or the same as control (albumin 5%)
2. Clinical evaluations: Vital signs and symptom screen on days -1, 0,3,7,14 and symptom screens on days 1, 28 and 60. Parameters requiring referral for urgent medical care are included in each evaluation
3. Safety laboratory tests, including ABO blood type (day -1) pregnancy testing (day -1), CBC and comprehensive metabolic panel (days -1, 7 and 14), will be performed at the local CLIA-certified clinical laboratory

6.7 Adverse Event Reporting

An **Adverse Event (AE)** is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.
Serious Adverse Event (SAE): any adverse event temporarily associated with the subject's participation in research that meets any of the following criteria:

- Results in death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect; or
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subjects' health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An **Unanticipated Problem (UP)** is any incident, experience or outcome involving risk to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (i.e., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized

A **Suspected Adverse Reaction (SAR)** is any AE for which there is a reasonable possibility that it was caused by the drug.

Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE. Examples of reasonable possibility are:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure.
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug.
- An aggregate analysis of specific events observed in a clinical trial that indicates that those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

The S-I must report the following SARs:

- To the FDA, as soon as possible, but no later than 7 calendar days after the S-I's initial receipt of the information, any **unexpected fatal or life-threatening SAR.**
- To the FDA and all participating investigators, as soon as possible but no later than 15 calendar days after the S-I determines that information qualifies for reporting, in an IND safety report, **any SAR that is both serious and unexpected.**
- To the FDA and all participating investigators, as soon as possible but no later than 15 calendar days after the S-I determines that the information qualifies for reporting, **any findings from epidemiological studies, pooled analysis of multiple studies or clinical studies, whether or not conducted under an IND or by the S-I, that suggest a significant risk in humans exposed to the drug**.
- To the FDA and all participating investigators, as soon as possible, but no later than 15 calendar days after the S-I determines that the information

qualifies for reporting, **any findings from animal or *in vitro* testing, whether or not conducted by the S-I, that suggest a significant risk in humans exposed to the drug**.

- To the FDA and all participating investigators, as soon as possible, but no later than 15 calendar days after the S-I determines that the information qualifies for reporting, **any clinically important increase in the rate of a Serious SAR over that listed in the protocol or Investigator Brochure.**
- Expected SAEs and AEs should be included in the IND Annual Reports.

Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable are so reportable, the sponsor must report such experience as soon as possible, but no later than 15 calendar days after the determination is made.

To IRB:

1. Unanticipated Problems (UPs) must be reported promptly, but not later than 7 calendar days following the occurrence of the UP or the Principal's Investigator's acquiring knowledge of the UP.
2. Expected AEs must be reported at the time of continuing review of a protocol.

Reporting Interval:

All AEs and SAEs will be documented from the first administration of study product All AEs and SAEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an adverse event is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

At any time after completion of the study, if the investigator becomes aware of a SAE that is suspected to be related to study product.

Investigator's Assessment of Adverse Events:

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

Laboratory abnormalities will be reported as AEs if they generate medical intervention (treatment and/or procedures) or are considered clinically

significant and are not linked to a reported clinical AE. If a laboratory abnormality is related to a clinical AE, grading will be related to clinical AE. The grading of the laboratory AEs will be based on the toxicity tables in the Common Terminology Criteria for Adverse Events (CTCAE) version 5, Nov 27, 2017.

Assessment of Seriousness:

I. Event seriousness will be determined according to the protocol definition of an SAE
II. Assessment of Severity

Event severity will be assigned according to the Toxicity Tables. For parameters not included in the Toxicity Table the following definitions will be used:

1 = Mild: Transient or mild discomfort (<48 hours); no medical intervention/therapy required.)
2 = Moderate: Mild to moderate limitation in activity-some assistance may be needed; no or minimal medical intervention/therapy required)
3 = Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
4 = Life-threatening: Extreme limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization or hospice care probable
5= Death

Assessment of Association:

The association assessment categories that will be used for this study are:

- Associated – The event is temporally related to the administration of the study product and no other etiology explains the event.
- Not Associated – The event is temporally independent of the study product and/or the event appears to be explained by another etiology.

The investigator must provide an assessment of association or relationship of AEs to the study product based on:

- Temporal relationship of the event to the administration of study product;
- Whether an alternative etiology has been identified;
- Biological plausibility;
- Existing therapy and/or concomitant medications.

7 SAFETY OVERSIGHT

7.1 Monitoring Plan

1. All AEs and SAEs will be reviewed by the study team in real time.
2. A data safety monitoring board (DSMB) composed of independent experts without conflict of interests will be established. The Board will review the

study before initiation and quarterly thereafter. The Board will review study data to evaluate the safety, efficacy, study progress, and conduct of the study

7.2 Study monitoring

As per ICH-GCP 5.18 and FDA 21 CFR 312.50, clinical protocols are required to be adequately monitored by the study sponsor. Monitors will verify that:

(1) There is documentation of the informed consent process and signed informed consent documents for each subject
(2) There is compliance with recording requirements for data points
(3) All SAEs are reported as required
(4) Individual subjects' study records and source documents align
(5) Investigators are in compliance with the protocol.
(6) Regulatory requirements as per Office for Human Research Protections-OHRP), FDA, and applicable guidelines (ICH-GCP) are being followed.

7.3 Halting Criteria for the Study

The study enrollment and dosing will be stopped and an ad hoc review will be performed if any of the specific following events occur or, if in the judgment of the study physician, subject safety is at risk of being compromised:

1. Unexpected death of a dosed subject in relation to infusion
2. Occurrence of a life-threatening allergic/hypersensitivity reaction (anaphylaxis), manifested by bronchospasm with or without urticaria or angioedema requiring hemodynamic support with pressor medications or mechanical ventilation.
3. One subject with an unexpected SAE associated with study product.
4. Two subjects with a Grade 3 or higher toxicity for the same parameter associated with study product.
5. An overall pattern of symptomatic, clinical, or laboratory events that the DSMB consider associated with study product and that may appear minor in terms of individual events but that collectively may represent a serious potential concern for safety.
6. Any other event(s) which is considered to be a serious adverse event in the good clinical judgment of the responsible physician. This will be appropriately documented.

Furthermore, given that ADE may be an issue with convalescent antibody treatment, out of an abundance of caution we will monitor the number of subjects in each trial arm that progresses to an indication for need of mechanical ventilation. In monitoring the number of subjects that progresses to this stage, we will present these data to the DSMB masked so that they may objectively evaluate and determine whether they would like to be unmasked. After at least 50% of trial participants have accumulated follow-up, the number of subjects that progress to this stage will be presented to the masked DSMB and formally asked whether they (1) see a clinically meaningful difference between trial arms that trigger an unmasking of the

DSMB and (2) if so do they require a formal interim analysis. At any point should the DSMB asked to be unmasked and require a formal interim analysis, we will examine the difference in treatment arms for need for mechanical ventilation. This interim analysis will adjust for factors related to need for mechanical ventilation including age and presence of cardiopulmonary comorbidities.

Upon completion of this review, DSMB will determine if study entry or study dosing should be interrupted or if study entry and study dosing may continue according to the protocol. Should the trial not be stopped at this time point, the final analysis would need to account the number of interim analyses that were conducted. Therefore, we would penalize any final analysis dividing our 0.05 alpha in half for each interim analysis.

Halting Criteria/Rules for Subject Infusion

Infusion of study drug will be halted if any of the following manifestations of anaphylaxis develop and will not be restarted:

- Skin or mucous membrane manifestations: hives, pruritus, flushing, swollen lips, tongue or uvula
- Respiratory compromise: dyspnea, wheezing, stridor, hypoxemia
- A decrease in systolic blood pressure to < 90 mmHg or >30% decrease from baseline or a diastolic drop of >30% from baseline.
- Tachycardia with an increase in resting heart rate to > 130bpm; or bradycardia <40 that is associated with dizziness, nausea or feeling faint.
- Syncope
- Confusion
- Any other symptom or sign which in the good clinical judgment of the study clinician or supervising physician warrants halting the infusion. For example, the rapid onset of gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and cramps, for instance, may be manifestations of anaphylaxis and may warrant an immediate halt prior to meeting full SAE criteria

8 ETHICS/PROTECTION OF HUMAN SUBJECTS

8.1 Ethical standard

The investigators are committed to the integrity and quality of the clinical studies it coordinates and implements. The investigators will ensure that the legal and ethical obligations associated with the conduct of clinical research involving human subjects are met. The information provided in this section relates to all sites participating in this research study.

As the Department of Health and Human Services continues to strengthen procedures for human subjects' protections via new regulations, the investigators will review these evolving standards in relation to the proposed activities and will advise the investigators on those that may apply.

In addition, The Trustees of Columbia University in the City of New York, has a Federalwide Assurance (FWA) number on file with the Office for Human Research Protections (OHRP). The FWA number for CU is FWA00002636.

This assurance commits a research facility to conduct all human subjects' research in accordance with the ethical principles in The Belmont Report and any other ethical standards recognized by OHRP. Finally, per OHRP regulations, the research facility will ensure that the mandatory renewal of this assurance occurs at the times specified in the regulations.

8.2 Institutional Review Board

The Columbia University Irving Medical Center (CUIMC) IRB will review this protocol and all protocol-related documents and procedures as required by OHRP and local requirements before subject enrollment. The CUIMC IRB currently holds and will maintain a US FWA issued by OHRP for the entirety of this study.

8.3 Informed consent process

The subject will be formally consented and will sign the informed consent document at the screening visit, before any procedures are undertaken for the study. A copy of the signed informed consent document will be given to the subject for their records. The consent will explain that subjects may withdraw consent at any time throughout the course of the trial.

Extensive explanation and discussion of risks and possible benefits of this investigation will be provided to the subjects in understandable language. Adequate time will be provided to ensure that the subject has time to consider and discuss participation in the protocol.

The consent will describe in detail the study interventions/products/procedures and risks/benefits associated with participation in the study. The rights and welfare of the subjects will be protected by emphasizing that their access to and the quality of medical care will not be adversely affected if they decline to participate in this study.

8.4 Subject confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsors and their agents. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. The results of the research study may be published, but subjects' names or identifiers will not be revealed. Records will

remain confidential. To maintain confidentiality, the PI will be responsible for keeping records in a locked area and results of tests coded to prevent association with subjects' names.

Data entered into computerized files will be accessible only by authorized personnel directly involved with the study and will be coded. Subjects' records will be available to the FDA, the NIH, the manufacturer of the study product and their representatives, investigators at the site involved with the study, and the IRB.

8.5 Future use of stored specimens

Subjects will be asked for consent to use their samples for future testing before the sample is obtained. The confidentiality of the subject will be maintained. They will be no plans to re-contact them for consent or to inform them of results. The risk of collection of the sample will be the small risk of bruising or fainting associated with phlebotomy however these samples will be taken at the same time as other protocol required samples.

Other use of stored specimens may include genetic testing with the goal of understanding why some individuals are resistant to SARS-CoV-2 and others develop severe or even fatal disease. In the future, we plan to conduct genetic testing that consists of RNA sequencing of whole blood (PAXgene tubes) and genetic and epigenetic studies of DNA in peripheral blood mononuclear cells from subjects. We hope these studies will identify biomarkers that differentiate treatment response and will further our understanding of pathogenesis. We anticipate that other Columbia investigators will want to search for host factors in treatment response as well. Whole genome sequencing will not be conducted.

These studies have the potential to lead to treatments that reduce COVID morbidity and mortality. This research is done only to the extent authorized in the study informed consent form, or as otherwise authorized under applicable law.

Additional research on specimens will occur only after review and approval by the protocol team and the IRB/EC of the researcher requesting the specimens. The informed consent form is written so that the participant either explicitly allows or does not allow their samples to be used in other research when they sign the form. Participants who initially agree to other use of their samples may rescind their approval once they enter the study; such participants will remain in this study and their samples will only be used for the studies described in this protocol. If a participant decides against allowing other research using his or her samples, or at any time rescinds prior approval for such other use, the study PI must notify the CII in writing not to use samples from these participants for other purposes.

Blood samples will be collected at 6 time points (Day 0 (screen), 1, 3±2, 7±2,14±2 and 28±3) (See Schedule of Events). Plasma will be frozen in 1-ml aliquots. These samples will be used to answer questions that may arise while the study is underway or after it is completed. If for instance, there were unanticipated AEs, serum could be used to run tests that might help determine the reason for the AEs. Cytokines could be measured, for example.

Samples would not be shared with investigators other than investigators at CUIMC unless outside investigators had relevant assays or expertise not available to the study investigators. The specimens would remain linked and at CUIMC for 5 years. Any use of these specimens not specified in the current protocol will be reviewed by the CUIMC IRB.

8.6 Data management and monitoring

8.6.1 Source Documents

Source documents may include research records documenting study procedures, laboratory test reports, and any medical records that may be generated during the study period (e.g. hospitalization due to adverse events or disease progression). These will be considered the source documents for the purposes of auditing the study. The investigator will retain a copy of source documents. The investigator will permit monitoring and auditing of these data, and will allow the sponsor, IRB and regulatory authorities access to the original source documents. The investigator is responsible for ensuring that the data collected are complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) will support the data collected and entered into the study database/case report form and will be signed and dated by the person recording and/or reviewing the data. Data entered into the study database will be collected directly from subjects during study visits or will be abstracted from subjects' study records including laboratory test reports.

8.6.2 Data Management Plan

All paper documents will be maintained under double-locked conditions and will be stored separately from all other study records. Similarly, any electronically captured data will be stored in a unique database on a secure server separate from study databases. Only authorized study staff will have access to forms and databases containing study data.

The study database will be programmed using REDCap, which is 21 CFR Part 11 and HIPAA compliant, and hosted in an Amazon Web Services (AWS). AWS has a Business Associates Agreement (BAA) with Columbia University.

Study data will be collected at the study site(s) and entered into the study database. Data entry is to be completed on an ongoing basis during the study. All study data will be collected during study visits using encrypted and password-protected tablets, laptops or computers.

The database will include automated quality checks that flag outliers, suspicious distributions and means, values that violate frequency or numeric thresholds, and error-prone submissions.

User permissions will be adjusted according to staff role and responsibility. Only designated study staff will access study data from the encrypted server to conduct data cleaning and quality checks and generate reports to monitor study progress. Only authorized staff will access data for the purpose of conducting study operations. Study data will be collected at the study site and entered into the study database or case report forms. Data entry is to be completed on an ongoing basis during the study.

8.6.3 Study Record Retention

The site investigator is responsible for retaining all essential documents listed in the ICH GCP Guidelines. The FDA requires study records to be retained for up to 2 years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records are also to be maintained in compliance with IRB, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent provided by federal, state, and local law. It is the site investigator's responsibility to retain copies of source documents until receipt of written notification to the sponsor.

No study document should be destroyed without prior written agreement between the sponsor and the Principal Investigator. Should the investigator wish to assign the study records to another party and/or move them to another location, the site investigator must provide written notification of such intent to sponsor with the name of the person who will accept responsibility for the transferred records and/or their new location. The sponsor must be notified in writing and written permission must be received by the site prior to destruction or relocation of research records.

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