CYNK-001-COVID-19

A PHASE I/II STUDY OF HUMAN PLACENTAL HEMATOPOIETIC STEM CELL DERIVED NATURAL KILLER CELLS (CYNK-001) FOR THE TREATMENT OF ADULTS WITH COVID-19

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CELULARITY CHIEF MEDICAL OFFICER SIGNATURE PAGE

[redacted]

Printed Name of Celularity Inc. Chief Medical Officer

By my signature, I indicate that I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator	
Institution Name	
Institution Site Number	

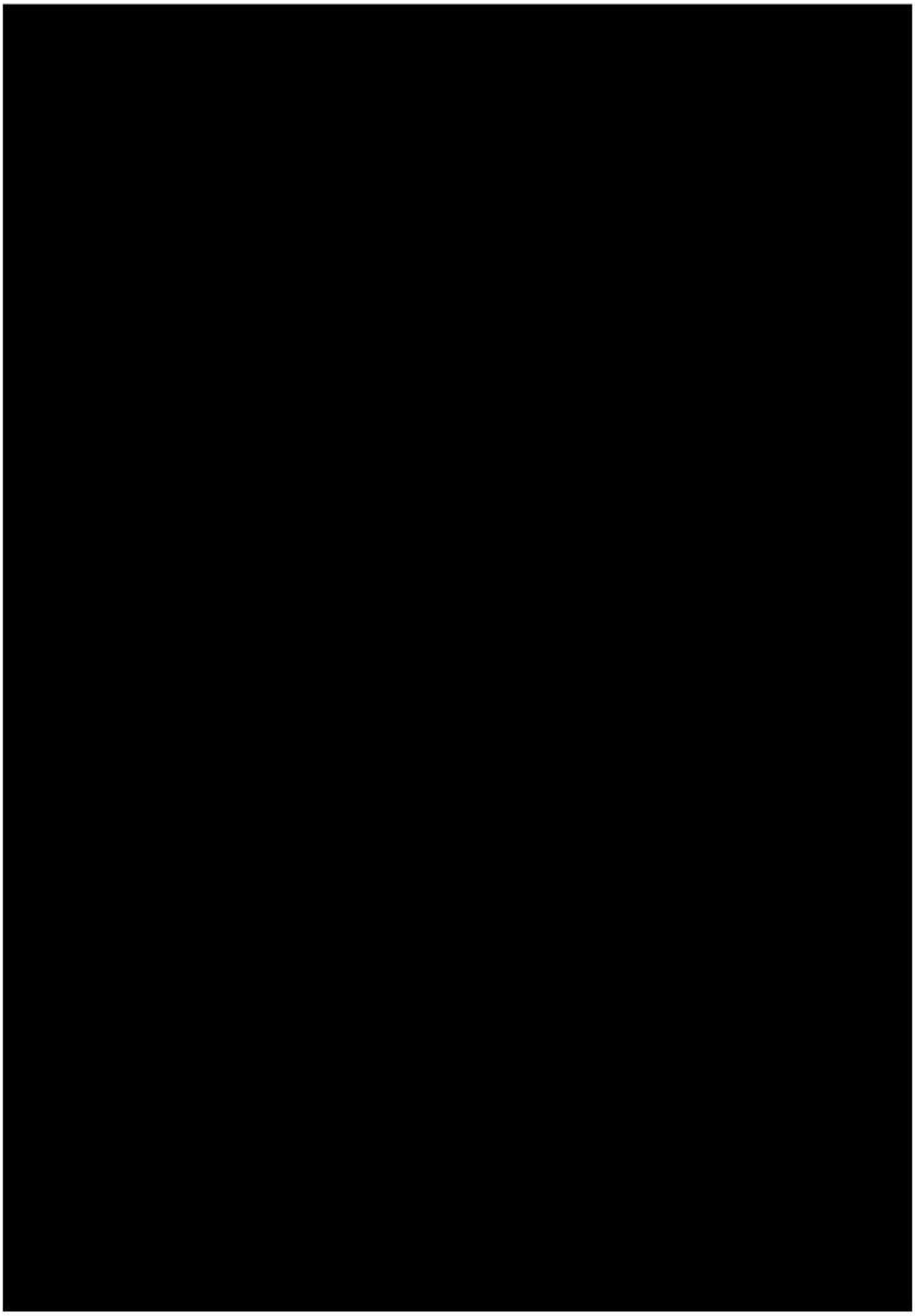
By my signature, I indicate that I have reviewed this protocol and find its content to be acceptable. I have received and read the Investigator's Brochure and understand the information provided including the potential risks and side effects of the investigational product.

I also agree to personally supervise the conduct of this study at my study site and agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations.

This study will be conducted in compliance with the protocol, informed consent, Ethics Committee (EC)/Institutional Review Board (IRB) procedures, instructions from Celularity Inc representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

I also agree to promptly report to the EC/IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. I will not make any changes in the research without EC/IRB or Celularity Inc approval, except where necessary to eliminate apparent immediate hazards to human subjects.

MEDICAL MONITOR OR EMERGENCY CONTACT INFORMATION



1. SYNOPSIS

Name of Sponsor/Company:
Celularity Inc. ("Celularity")

Name of Investigational Product:
CYNK-001

Title of Study:

A Phase I/II study of human placental hematopoietic stem cell derived natural killer cells (CYNK-001) for the treatment of adults with coronavirus disease (COVID-19)

Objectives:

Primary:

Phase I:

The primary objectives of the Phase I portion of the study is to evaluate the safety, tolerability, and efficacy of multiple CYNK-001 intravenous (IV) infusions administered with an initial dose of 150 x 10^6 cells on Day 1 followed by second and third doses each of 600 x 10^6 cells on Days 4 and 7 in subjects with COVID-19.

Overall, if the safety stopping rules are not met and if efficacy is demonstrated in at least 2 out of the 14 subjects by Day 15 of CYNK-001 infusion, the study will move forward to the Phase II portion of the study.

Phase II:

The primary objective of the Phase II portion is to evaluate the efficacy of CYNK-001 on subjects with COVID-19 by using the Ordinal Scale for Clinical Improvement (OSCI) defined by the World Health Organization (WHO).

Secondary:

The secondary objectives of the Phase II portion are:

A) To determine safety and tolerability of CYNK-001 as measured by the frequency and severity of adverse events (AEs) using CTCAE, version 5.0

B) To evaluate the overall clinical benefit of receiving CYNK-001 for COVID-19 as measured by rate of clinical improvement by OSCI, time to and rate of clinical improvement by NEWS2 Score, medical discharge, hospital utilization, and all-cause mortality rate, time to and rate of clearance of SARS-CoV-2, time to and rate of pulmonary clearance, duration of hospitalization, supplemental oxygen-free days, proportion of subjects requiring ventilation, SOFA score, and radiologic evaluation score.

Exploratory:

Exploratory objectives include the detection and clearance of SARS-CoV-2 via rRT-PCR in various specimen types including cytokine and chemokine measurement, immune monitoring, and alloreactivity measurement.

Methodology:

Study Population

SARS-CoV-2 positive subjects experiencing symptom(s) / clinical sign(s) of COVID-19 illness or having positive disease-related radiologic evaluation (chest x-ray/CT scan).

Duration of treatment:

Subject will receive up to 3 doses of CYNK-001 on Days 1, 4, and 7. A minimum of 2 doses is required for efficacy assessment. After the first dose, subsequent infusions on Days 4 and 7 will be provided only if no toxicity of Grade 3 and above (either related or unrelated to CYNK-001) is observed.

Study Design:

The study will include a Phase I portion wherein a total of 14 subjects will be enrolled to assess the safety and efficacy of CYNK-001. To evaluate the safety for potential dose limiting toxicities (DLTs), this phase will enroll 3 subjects initially treated with CYNK-001. The safety data for these 3 subjects will be evaluated 24 hours after the final dose was provided to the 3rd subject.

If deemed safe, the remaining 11 subjects will be enrolled and monitored per the safety stopping rule until Study Day 15 where the first CYNK-001 infusion occurs on Day 1. If any DLT is observed in the first three subjects, the DMC will be convened for a recommendation. For the remaining 11 subjects, DMC will be convened if the safety stopping rule is met. Overall, in case of 2 out of the 6 subjects had experienced DLTs in the Phase I portion of this study, the DMC will be convened for safety evaluation. Subjects treated in the Phase I portion of the study will be treated in the inpatient setting.

The starting dose of 150 x 10^6 cells was selected as a desensitizing dose on Day 1 followed by 600 x 10^6 cells on Days 4 and 7. The DLTs will be evaluated through Study Day 28 following the first dose of CYNK-001 infusion (Day 1). Once CYNK-001 is deemed safe per the stopping rules and if efficacy is established in at least 2 out of the 14 subjects by Study Day 15, Phase II portion of the study will be initiated.

The Phase II portion of the study is a randomized, open-label, multi-site study. Subjects will be randomized into either CYNK-001 or Control group with best supportive care alone as defined by the institutional practice by 1:1 ratio. All subjects in both Phase I and Phase II will receive the best supportive care. Subjects treated in the Phase II portion of the study may be treated in the outpatient setting, if deemed safe based on Phase I data review and recommendation by the DMC.

The study is divided into 3 study periods:

Screening Period

The Screening Period is defined as the period from signing the informed consent to just prior to the administration of CYNK-001. Due to the critical nature of this infection, this period may be less than a day. Upon giving written informed consent, all screening/baseline assessments will be completed. Some procedures that occur as part of standard of care in medical evaluation may be completed prior to the date of informed consent, according to institutional practices, and therefore do not need to be repeated. Chest x-rays, CT scans, rRT-PCR (or other approved test based on institutional

practices for baseline assessment) viral testing, and blood work should occur often as outlined in the Table of Events.

During the Screening period, after having signed an Informed Consent Form (ICF), subjects will be assessed for eligibility for the study. Eligibility must be confirmed prior to proceeding to the treatment period. This information will need to be gathered and entered into the Electronic Data Capture (EDC). Subject eligibility will be based on investigator assessment using the Inclusion/Exclusion criteria provided as part of the study. The Screening Period is followed by a Treatment Period.

Treatment Period (Day 1 – Day 28)

The treatment period begins with the administration of study drug on Study Day 1 (in the inpatient setting for subjects treated in Phase I). For those subjects who are allocated to treatment with CYNK-001, the initial dose will consist of 150 x 10^6 cells on Day 1 followed by second and third doses each of 600 x 10^6 cells administered intravenously (IV) on Days 4 and 7. Subjects will receive a minimum of two and up to three CYNK-001 infusions. CYNK-001 infusions will occur on Study Days 1, 4, and 7. After the first dose, subsequent infusions on Days 4 and 7 will be provided only if no toxicity of Grade 3 and above (either related or unrelated to CYNK-001) is observed for each subject. If any such ≥ Grade 3 toxicity is observed, the second and third doses will be delayed up to 48 hours until the noted event is resolved or reduced to Grade 1 toxicity level.

Subjects who were treated in the Phase 1 portion of the study may be discharged on the day following the final planned CYNK-001 infusion (i.e., discharged on Study Day 8, where infusions occur on Days 1, 4, and 7 or discharged on Study Day 5 if only two doses were received on Days 1 and 4.)

As part of discharge criteria, the study team should assess for further monitoring of subjects who may be experiencing toxicity of Grade 3 and above (either related or unrelated to CYNK-001) at the time of discharge and consult with the treating physician. The decision to discharge a subject should be in consultation with the treating physician and clinical site study team. Physicians should follow best clinical practice to determine appropriate timing of hospital discharge.

Upon discharge, plans should be made for appropriately delegated staff to have telephone contact with subjects every day between hospital discharge through at least Day 15 visit for safety/AE monitoring. The discharge plan should include follow-up visit schedule as well as planned telehealth visit schedule.

Upon discharge, subjects will be provided with a thermometer, pulse oximeter, and blood pressure monitor for at home collection of temperature, oxygen saturation, and blood pressure with written instructions on their use as well as expectations for self-monitoring. These daily measurements will be reported via telephone to the clinical staff during each daily telehealth visit. During these daily telehealth visits, subjects are to report any new symptoms or worsening of symptoms associated with previously identified adverse events and will also provide the study team with daily vital sign measurements. Any vital signs outside of normal range will be escalated to the clinical site study team and evaluated for appropriate management.

The subject will be asked during each call to report any new or worsening symptoms that could be consistent with adverse events since the previous visit or telephone call. The investigator (or appropriately delegated study staff) will determine if medical attention or an unscheduled clinic visit is required. Each telephone call should be carefully documented with date and time of the call in the source documents and reported as appropriate.

Consultation between the Medical Monitor and appropriately delegated site staff should occur every other day after hospital discharge up to Day 15 visit for ongoing review of the subject's clinical

status. This communication may occur via telephone contact or written message (i.e. email) and should be documented accordingly.

Subjects treated in the Phase II portion of the study will be treated either in the inpatient or outpatient setting, as determined after review of data from the Phase I portion of the study and based on DMC recommendation. The level of outpatient monitoring of subjects treated in the Phase II portion will be determined based on review of Phase I data and DMC recommendation.

A de-escalation dose (Dose -1) will be initiated based on the study safety stopping rules and dose-limiting toxicities. Dose de-escalation is defined as reducing the frequency of the doses (without reducing the total number of cells given per dose) by providing doses only on Days 1 and 7 due to any potential safety concerns per DMC recommendation.

On each day of CYNK-001 infusion, subjects will be pre-medicated and post-medicated with acetaminophen 650 mg orally (PO) and diphenhydramine 25 mg (PO/IV) at least 30 minutes prior to and approximately 4 hours following the end of the CYNK-001 infusion. Meperidine may also be administered to control rigors, if clinically indicated. Subjects must be monitored for at least 4 hours after completion of each CYNK-001 infusion.

All subjects (even in control arm) should meet the inclusion/exclusion criteria.

The control arm subjects in the Phase II portion of the study will receive the best supportive care as defined by the institutional practice without CYNK-001. All subjects in both Phase I and Phase II will receive the best supportive care.

Additional testing including blood, nasopharyngeal and oropharyngeal (optional) swabs, and sputum (optional) may be collected for research purposes. In some cases, customary standard of care procedures may be conducted more frequently for the purpose of this clinical study.

Information will need to be gathered and entered in the EDC associated with the medical management of the subject.

Follow-up Period (Day 29 to 6 months):

The follow-up period is defined from Study Day 29 to 6 months. The Subjects will be followed at 3 months, and 6 months or until loss to follow-up, death, or withdrawal from study whichever occurs first.

The study will be conducted in compliance with ICH Good Clinical Practices (GCPs) and in concordance with local Health Authority regulations.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as specified in the protocol, whichever is the later date.

Dose Limiting Toxicity (DLT) Definition

Known pathologies associated with COVID-19 will be carefully considered and differentiated from potential CYNK-001-related effects in order to identify CYNK-001 related toxicities. Adverse events occurring up to Study Day 28 where the first dose of CYNK-001 infusion occurs on Study Day 1 will be included in the dose-limiting toxicity (DLT) determination.

A DLT is defined as the development of any new (not pre-existing) events:

- Grade 4 or 5 event in any organ system
- Grade 4 > 24 hours (Due to known organ damage associated with the COVID-19) in the following organ systems:
    - Cardiac
    - Pulmonary
    - Hepatic
    - Renal
    - Central Nervous System (CNS)
- Grade 3 or above allergic reaction that is suspected to be related to CYNK-001.
- Grade 3 or above Graft versus Host Disease (GvHD) event occurring within the first 28 days following CYNK-001 infusion (to Study Day 28).
- Grade 3 or above Cytokine Release Syndrome (CRS) event occurring within the 28 days following the first CYNK-001 infusion (to Study Day 28).

All above events to be identified in discussion with the clinical study Medical Monitor and reportable to Drug Safety team.

The events will be assessed for the first 3 subjects in Phase I and per the study stopping rule definition for the remaining subjects. Any such findings will be forwarded to the DMC for recommendation, review and confirmation as to whether or not the maximal tolerated dose (MTD) has been exceeded. If the MTD is confirmed by the DMC, no further CYNK-001 administration will occur within that dose level or at any higher dose level.

During Phase II portion of the study, DMC will be convened at midpoint (after 18 subjects have received CYNK-001 treatment) to evaluate safety for adverse event of interest such as shock, ARDS, and death in the treatment group versus the control group.

MTD is defined as the highest CYNK-001 dose level wherein it was deemed safe per the defined stopping rules or if the DMC recommends stopping the study due to DLTs suspected to be related to CYNK-001.

Number of subjects (planned):

This study will enroll up to 86 subjects in total, with 14 subjects in the Phase I portion and up to 72 subjects with a 1:1 randomization ratio to either CYNK-001 **or** the best supportive care control arm as defined by the institutional practice in the Phase II portion of the study.

Investigational product, dosage and mode of administration:

[redacted]

CYNK-001 dosage and mode of administration:

Dose Level 1: CYNK-001 with an initial Dose of 150 x 10^6 cells on Day 1 followed by 600 x 10^6 cells on Days 4 and 7 (second and third doses). After the first dose, subsequent infusions on Days 4 and 7 will be provided only if no toxicity of Grade 3 and above (either related or unrelated to CYNK-001) is observed for each subject. If any such ≥ Grade 3 toxicity is observed, the second and third doses will be delayed up to 48 hours until the noted event is resolved or reduced to Grade 1 toxicity level.

Dose de-escalation Level -1: Dose de-escalation is defined as reducing the frequency of the doses (without reducing the total number of cells given per dose) by providing doses only on Days 1 and 7 for any potential safety concerns per DMC recommendation. CYNK-001 with an initial dose of 150 x 106 cells on Day 1 followed by 600 x 106 cells on Day 7.

CYNK-001 is to be administered IV using a gravity IV administration set with a 16- to 22- gauge (or equivalent) needle or catheter with no filters. A central line may be used to infuse CYNK-001 after confirming that the catheter diameter is 16- to 22- gauge (or equivalent) needle. For substantial deviation from this catheter diameter consultation with the medical monitor is required. The recommended infusion rate is approximately 240 mL per hour.

Subjects will receive pre- and post- medication of acetaminophen (650mg PO) and diphenhydramine (25mg PO/IV) at least 30 minutes prior to and approximately 4 hours after each CYNK-001 infusion.

Vital signs will be taken prior to, approximately 30 minutes after the start, and approximately 4 hours after the completion of each infusion. Subjects must be monitored for at least 4 hours after completion of each CYNK-001 infusion.

Dose Modifications

Dose adjustments may occur if clinically indicated by the treating physician. In general, the following should be followed:

- Dose reductions are not permitted in this study. If DLTs safety concerns are observed, the dose de-escalation treatment with reducing frequency of doses will be implemented per DMC recommendation.
- Should dose delays for CYNK-001 be required:
    - Day 1 will be the date of initial dose
    - Day 4 dose may be delayed up to 48 hours
        - For non-safety reasons: If delayed longer than 48 hours, Day 4 dose will be skipped., and the subject will receive the Day 7 dose. If the Day 4 dose is given within 48 hours, the Day 7 dose will be delayed for three days from the actual day of when Day 4 dose was given (i.e., if Day 4 dose is given on Day 5, then Day 7 dose will be given on Day 8)
        - For safety reasons: Day 4 dose could be delayed if ≥ Grade 3 toxicity is observed after the first dose. In such cases, Day 4 dose is provided only if the event is resolved or reduced to Grade 1 toxicity level. If the toxicity did not resolve within 48 hours, the Day 4 dose will be skipped. If the Day 4 dose is given within 48 hours, the Day 7 dose will be delayed for three days from the actual day of when Day 4 dose given
        - If the subject has worsening of illness, study medication will be stopped.
    - Day 7 dose may be delayed up to 48 hours:
        - For non-safety reasons: If delayed longer than 48 hours, the subject will not receive additional therapy.
        - For safety reasons: If Day 4 dose was delayed but given within 48 hours of planned Day 4, then the Day 7 dose will be delayed for three days from the actual day of when Day 4 dose was given. If Day 4 dose was given as planned, Day 7 dose could be delayed if ≥ Grade 3 toxicity is observed after the second dose. If Day 4 dose was skipped, Day 7 dose could be delayed if ≥ Grade 3 toxicity is still observed after the first dose. In such cases, Day 7 dose is provided only if the event is resolved or reduced to Grade 1 toxicity level. If the toxicity did not resolve within 48 hours of the scheduled day, the Day 7 dose will not be administered.
        - If the subject has worsening of illness, study medication will be stopped.
    - All subjects who receive any amount of CYNK-001 will be followed to 6 months or until loss to follow-up, death, or withdrawal from study, whichever occurs first.

Statistical methods:

- **Statistical Overview**

The objectives of the Phase I portion are to evaluate the safety and efficacy (for lack of efficacy) of CYNK-001.

The overall clinical benefit in the Phase II portion of the study will be evaluated by comparing therapeutic effect of CYNK-001 versus the control group (best supportive care alone). Safety and tolerability by adverse events, labs, vital signs, etc. will also be evaluated.

A detailed Statistical Analysis Plan (SAP) will be provided in a separate document.

Efficacy Analysis

Phase I efficacy data will be summarized by descriptive analyses. The efficacy endpoint used in the lack of efficacy tests is the responses at Day 15 of the Ordinal Scale for Clinical Improvement (OSCI). The study may be terminated if less than 2 subjects have efficacy responses in Phase I.

Phase II efficacy data will be analyzed based on Intention to Treat (ITT) population which include all randomized subjects. The primary endpoints of the study is time to clinical improvement by OSCI. The secondary endpoints include clinical status by OSCI, time to and rate of clinical improvement by NEWS2 Score, medical discharge, hospital utilization, and all-cause mortality rate, time to and rate of clearance of SARS-CoV-2, time to and rate of pulmonary clearance, duration of hospitalization, supplemental oxygen-free days, proportion of subjects requiring ventilation, SOFA score, and radiologic evaluation score.

For time to event data, Kaplan-Meier estimates for medians and 2-sided 95% CIs will be calculated. Stratified log-rank test will be used to test the difference between treatment groups. Stratification is based on randomization factor (age). For event rate data, the point estimates and the 2-sided 95% CIs will be calculated. Fisher's exact test will be used to test the difference between groups. For ordinal data, the outcome will be analyzed by using Mann-Whitney-Wilcoxon-Test.

- **Safety Analysis**

Safety analysis will be based on the safety population which includes all subjects who are treated by any amount of CYNK-001 or who enroll into the control group. Descriptive statistics will be provided for AEs, vital sign measurements, physical examination findings, clinical laboratory test results, infusion site assessments, and concomitant medications and procedures.

- **Sample Size**

Phase I:

Fourteen (14) subjects will be treated by CYNK-001 in the Phase I portion. Based on clinical judgement, this sample size is appropriate to evaluate the safety of CYNK-001 and to evaluate the lack of efficacy. This number is not based on power calculation.

Phase II:

The primary efficacy endpoint is time to clinical improvement by OSCI.

As a preliminary proof of concept study without relevant data for the new coronavirus disease, 1-sided α of 0.05 will be used in the sample size consideration. With a sample size of 36 for each group (72 in total with 1:1 randomization ratio), a reduction of 50% for the time to event efficacy of CYNK-001 comparing with control can be detected with a power of at least 81% (assuming the time to

clinical improvement is 8 days or earlier for CYNK-001 group, and 16 days or earlier for the control group with the same reduction of 50%) by using Log-rank test. This estimation is based on the study design with a maximum follow up of 28 days for each subject for primary analysis.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
CAR	Chimeric antigen receptor
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CRS	Cytokine release syndrome
CYNK-001	Investigational product under study; allogeneic off the shelf cell therapy enriched for CD56+/CD3- NK cells expanded from human placental CD34+ cells
DMSO	Dimethyl sulfoxide
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EEG	Electroencephalography
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GvHD	Graft-versus-host disease
HC	Health Canada
HLA	Human leukocyte antigen

Abbreviation or Specialist Term	Explanation
HSA	Human serum albumin
IB	Investigator's Brochure
ICANS	Immune Effecter Cell Associated Neurotoxicity Syndrome
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenously
KIR	Killer-cell immunoglobulin-like receptor
KPS	Karnofsky Performance Status
KVO	Keep vein open
LN_2	Liquid Nitrogen
LRT	Lower respiratory tract
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome coronavirus
MHRA	Medicines and Healthcare products Regulatory Agency
MPV	Mean platelet volume
MRI	Magnetic resonance imaging
NaCl	Sodium chloride
NEWS2	National Early Warning Score 2
NK	Natural Killer cell
OAE	Other significant adverse event
OS	Overall survival
OSCI	Ordinal Scale for Clinical Improvement
PB	Peripheral blood
PD	Progressive disease
PI	Principal Investigator The investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
PO	Orally
PRA	Panel-reactive antibody
rRT-PCR	Real-time Reverse Transcriptase-Polymerase –Chain Reaction
SAP	Statistical analysis plan

Abbreviation or Specialist Term	Explanation
SAE	Serious adverse event
SARS-CoV	Severe acute respiratory syndrome coronavirus
sCRS	Severe Cytokine release syndrome
SGOT	Serum glutamic oxaloacetic transaminase
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse drug reaction
T cell	T lymphocyte cell
ULN	Upper limit of normal
US	United States of America
WHO	World Health Organization

4. INTRODUCTION

4.1. Disease Background

Among several coronaviruses that are pathogenic to humans, most cause mild clinical symptoms mainly represented as a respiratory tract infection, with two exceptions: the severe acute respiratory syndrome (SARS-CoV) and the Middle East respiratory syndrome (MERS-CoV) (Yin, 2018). A novel coronavirus emerged in the end of 2019 in Wuhan, China causing respiratory illness in people and has demonstrated rapid and effective person-to-person transmission, even from asymptomatic patients. The virus, initially called nCoV-2019, was identified by the Chinese Center for Disease Control and Prevention from a throat swab from a patient, and subsequently named SARS-CoV-2, that causes a coronavirus disease (COVID-19) (Chen, 2020).

Infection with SARS Coronavirus 2 (SARS-CoV-2) can lead to heterogeneous clinical manifestations, from asymptomatic infection to multi-organ system failure and need for intensive care support (Huang, 2020). Strategies to inhibit viral replication and reduce inflammation incited by SARS-CoV-2 (Xu 2020, Horby, 2020, Gritti, 2020, Guaraldi, 2020) are successful in selected cases. People with COVID-19 can seek medical care to help relieve symptoms, however even with appropriate early medical intervention, the illness can escalate to pneumonia, ARDS and in some cases requires intensive care. At the time of writing this protocol amendment, although most cases have presented in China, COVID-19 has been identified in over 217 countries and territories globally with more than 54 million cases and 1,280,860 fatalities (WHO, Nov 2020). In the US, more than 10 million confirmed cases have been identified in November 2020. The spread from carrier who may not show symptoms might be possible but people are more contagious when they are most symptomatic (CDC, 2020). A paper published on 21 February 2020 concluded that a familial cluster of 5 patients with COVID-19 pneumonia had contact before their symptom onset with an asymptomatic family member who had traveled from epidemic center of Wuhan with presumption that asymptomatic carrier transmission of COVID-19 (Bai 2020).

Three recent papers have provided some insight into the initial presenting symptoms and the progression of the illness to pneumonia, in some cases escalating to severe pulmonary and other organ distress, which could be fatal (Huang, 2020; Chen, 2020; Wang, 2020.). Chen et al presented 99 cases of patients infected with SARS-CoV-2, noting that the mean age was 55 and 68% were male. Of these cases 49% had been exposed to the Huanan Seafood Market, which is considered to be the source for the infection. Common symptoms (above 20% incidence) included shortness of breath, cough and fever, with 15% of patients exhibiting all three of these symptoms. However, it was noted that 90% of patients presented with more than one sign or symptom. ARDS was noted in 17% of these patients and with acute respiratory injury at 8%. Acute renal injury, septic shock or ventilator-associated pneumonia was rare (under 5%). Radiological findings noted unilateral pneumonia in 25% and bilateral pneumonia in 75% of the patients. Oxygen therapy was administered to 76% of these patients, and antibiotic, antifungal and antiviral therapy was used frequently. Intravenous immunoglobulin therapy was administered to 27% and glucocorticoids to 19%. At the time of data cut-off of this paper the mortality rate of the 99 patients infected by SARS-CoV-2 was 11%, with 58% remaining in hospital and 31% being discharged. Of these 99 patients, 23/99 (23%) were admitted to ICU,

oxygen therapy was administered to 76%, invasive mechanical intervention 4% (range 3-20 days), non-invasive mechanical intervention 13% (range 4-22 days), continuous renal replacement therapy 9%, extracorporeal membrane oxygenation 3%. Treatment with antibiotics, antifungal, and antiviral therapy received in 71%, 15% and 76% respectively. Glucocorticoids were administered in 19% and intravenous immunoglobulin therapy in 27% (Chen, 2020). Wang et al presented 138 cases of patients with confirmed SARS-CoV-2-infected pneumonia, noting the median age was 56 years and 75 % were men. Hospital-associated transmission was suspected as the presumed mechanism of infection for affected health care professionals (29%) and hospitalized patients (12.3%). Common symptoms included fever (98.6%), dry cough (59.4%), lymphopenia (70.3%), elevated lactate dehydrogenase (39.9%). Chest computed tomographic scans showed bilateral patchy shadows or ground glass opacity in the lungs of all patients. Most patients received antiviral therapy (89.9%) and many received antibacterial therapy (64.4%), and glucocorticoid therapy (44.9%). Thirty-six (26.1%) patients were transferred to ICU. The median time for first symptom to dyspnea was 5 days, to hospital admission was 7 days, and to ARDS was 8 days. Compared with patients not treated in the ICU (73.9%), patients treated in the ICU were older and more likely to have underlying comorbidities. Of the 36 patients in the ICU, 4 (11%) received high-flow oxygen therapy, 15 (41.7%) received noninvasive ventilation, and 17 (47.2%) received invasive ventilation (with 4 of them being switched to Extracorporeal membrane oxygenation). At the time of data cutoff of this paper, the article reports that 47 patients (34.1%) were discharged and 6 died (overall mortality, 4.3%), but the remaining patients are still hospitalized. Among those discharged alive (34.1%), the median hospital stay was 10 days (Wang, 2020).

The COVID-19 epidemic continues and is unlikely to wane anytime soon; clinical management and mortality rate warrants need for new therapeutic approaches to medically support the patients and prevent mortality.

The World Health Organization (WHO) has released an interim guidance dated 28 January 2020 on the clinical management of severe acute respiratory infection when SARS-CoV-2 infection is suspected (WHO, 2020). The Chinese government had released the diagnosis and treatment plan (provisional 6th edition) dated 19 February 2020 for Novel coronavirus pneumonia (https://www.chinalawtranslate.com/en/diagnostic-and-treatment-plan-6).

4.2. Testing for SARS-CoV-2 Infection

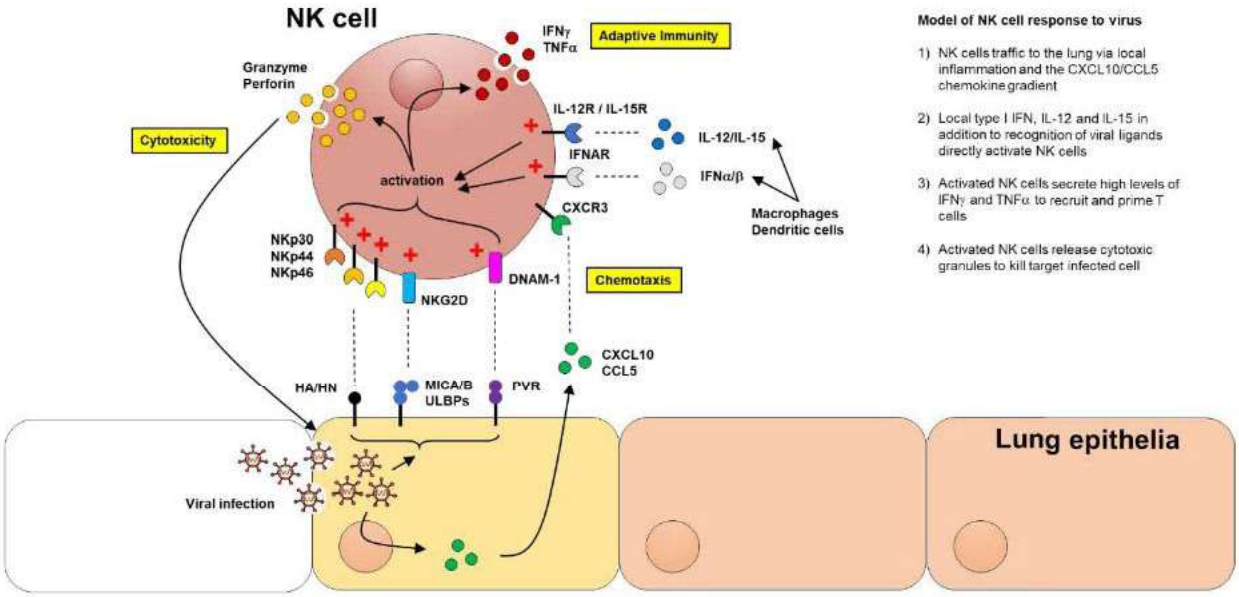
Real-time Reverse Transcriptase Polymerase-Chain-Reaction (rRT-PCR) assays for in vitro qualitative detection of SARS-CoV-2 in respiratory specimens and sera have been developed for identification of the COVID-19 infection. The CDC developed a new laboratory test kit for use in testing patient specimens called "Centers for Disease Control and Prevention (CDC) COVID-19 Real-Time Reverse Transcriptase (RT)-PCR Diagnostic Panel." The kits were shipped to qualified international laboratories internationally, however the US FDA issued the Emergency Use Authorization of this test on 04Feb2020 for use in the US.

The CDC recommends collecting and testing upper respiratory specimens (i.e., nasopharyngeal and oropharyngeal swabs), and lower respiratory tract (LRT) specimens (i.e., sputum). Sera testing is also an option as well as bronchoalveolar lavage (CDC, 2020). Note: as new testing has been developed to detect SARS-CoV-2, the use of alternate SARS-CoV-2 testing by other approved methods is permitted where institutional practice allows.

4.3. Natural Killer cells in the Treatment of Infection

NK cells are innate immune cells with an important role in early host response against various pathogens. Multiple NK cell receptors are involved in the recognition of infected cells, including NKG2D, DNAM-1 and the natural cytotoxicity receptors NKp30, NKp44 and NKp46, which bind common stress ligands or pathogen-associated molecules (see Figure 1) (Cook, 2014). NK cells kill their target cells by cytotoxic molecules perforin and granzymes, and via death receptor-mediated apoptosis (Loh, 2005). In addition to their cytotoxic functions, NK cells are important for priming adaptive immunity by the secretion of various chemokines and cytokines, including IFN-g. The important role of NK cells in virus control is illustrated by the diverse mechanisms human viruses have evolved to evade the NK cell recognition pathways, especially exemplified by CMV (Lanier, 2008).

Figure 1: Direct and indirect antiviral mechanism of NK cells



Studies in humans and mice have established that there is robust activation of NK cells during viral infection, regardless of the virus class (Ivanova, 2014), and that the depletion of NK cells aggravates viral pathogenesis (Littwitz, 2013; Gazit, 2006; Nogusa, 2008; Stein-Streilein, 1986. In murine and human CMV infection, NK cell-mediated anti-viral activity is dependent on IFN-g secretion and perforin-dependent lysis of infected cells (Loh, 2005; Wu, 2015). HIV-1 infection in pregnancy is inhibited by decidual NK cells (Quillay, 2016) and hepatitis C virus infection is controlled by NK cells in the liver (Guidotti, 2006). NK cells have a major role in the early control of lung infections with pathogenic organisms. Timely NK cell-mediated cytotoxicity and IFN-g production limit diverse respiratory bacterial, fungal and viral infections (Ivanova, 2014).

NK cells sense the environment using a broad repertoire of surface receptors that can differentiate between normal and malignant cells (cancerous or infected) by binding to stress

ligands and viral antigens. In particular, the stress ligand-induced NKG2D-MICA/B pathway has been shown to be important for NK cell activation and recognition of infected cells in multiple viral infections, including coronaviruses (Walsh, 2008; Lanier, 2008). Various viral glycoproteins expressed by enveloped viruses, including coronaviruses (Zeng, 2008), are specifically recognized by the natural cytotoxicity receptors NKp30, NKp44, and NKp46 (Cook, 2014). NK cell cytolytic activity against Influenza virus is triggered by the recognition of viral haemagglutinin by NKp46 receptor, but also induced by antibody-dependent cell-mediated cytotoxicity (ADCC) (Mandelboim, 2001). In infected tissue microenvironment, NK cell activation leads to increase activating receptor expression and their cytotoxic responses are strongly potentiated by type I IFNs produced by dendritic cells and infected epithelial cells, also enabling subsequent priming and T cell activation and memory (Lanier, 2008).

It was shown that coronavirus infection stimulates the recruitment of NK cells to control infection. Research following the SARS-CoV outbreak revealed that SARS-CoV infection in a mouse model resulted in acute expression of CCL5, CXCL10, and CCL3 chemokines in lung epithelial cells (Law, 2007). In a separate study, NK cells migrated to coronavirus-infected organs in a CXCL10 dependent manner and was associated with reduced coronavirus titers. Anti-viral activity accompanied NK cell homing to the tissue and IFN-g secretion (Trifilo, 2004).

A study of NK cells from peripheral blood of patients with SARS coronavirus (SARS-CoV) was evaluated for the number of NK cells, as it was previously noted that patients with lower NK cells in the HIV population were susceptible to retrovirus resistance. It was noted that patients with SARS coronavirus had significantly lower counts of NK cells in their peripheral blood compared to patients with mycoplasma pneumonia and healthy adults. It was unclear as to why the number was lower. It was hypothesized that either the NK cells had died as a direct attack from the virus or the NK cells were redistributed to targeted organs, such as the lungs (National Research Project of SARS, 2004). Hematological abnormalities such as thrombocytopenia and lymphopenia were common in both SARS-CoV and MERS-CoV patients. Thrombocytopenia and lymphopenia may be predictive of fatal outcome in MERS-CoV patients (Yin, 2018). Based on these observations, it is hypothesized that adoptive NK cell therapy may provide the antiviral activities in those with SARS-CoV-2 infection.

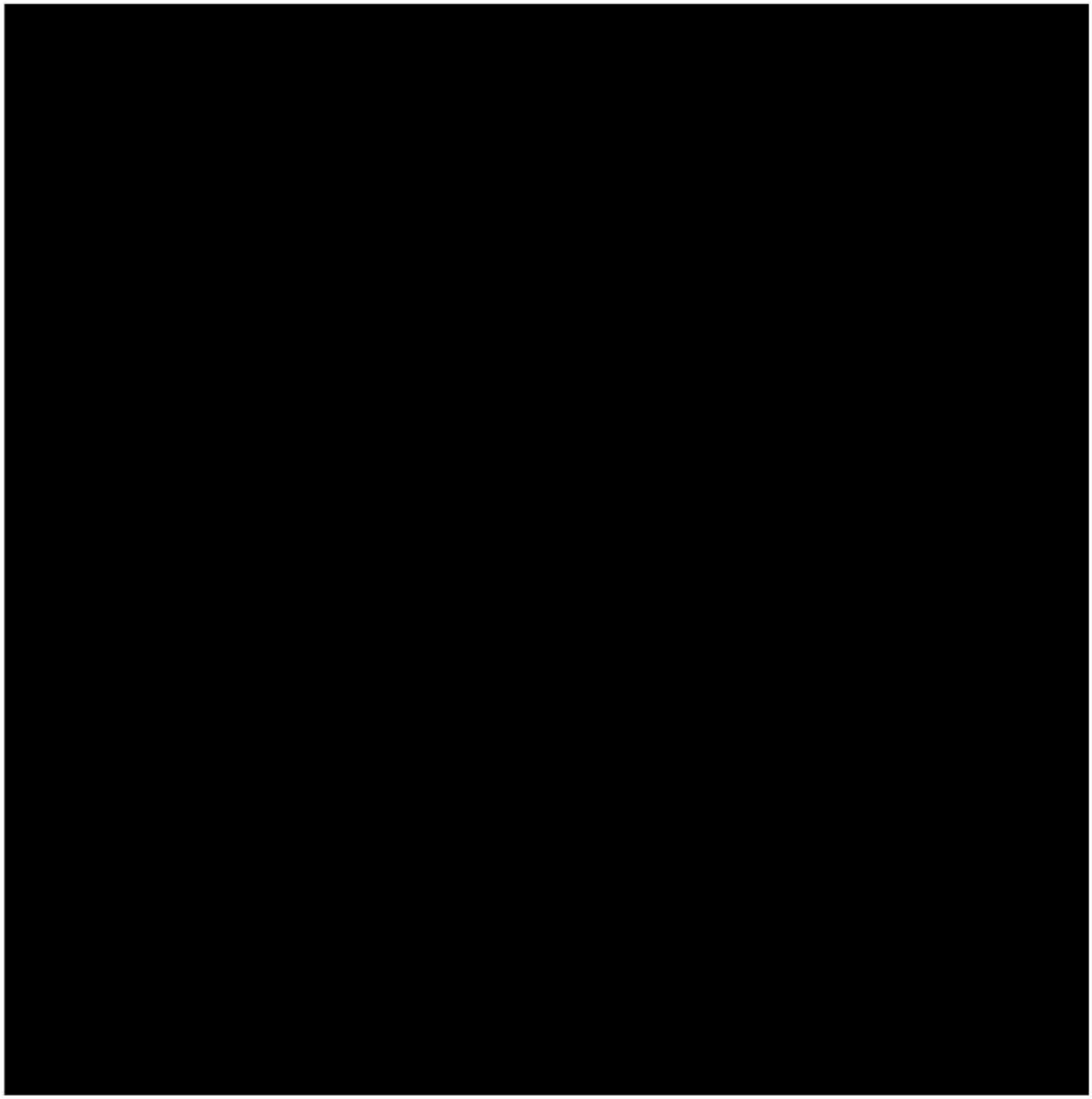
4.4. CYNK-001 in the treatment of COVID-19

CYNK-001 is the only cryopreserved allogeneic, off-the-shelf NK cell therapy being developed from placental hematopoietic stem cells as a potential treatment option for various hematologic cancers and solid tumors. NK cells are a unique class of immune cells, innately capable of targeting cancer cells and virus infecting cells and interacting with adaptive immunity. CYNK-

[redacted]

This study is the first study that will evaluate the safety and potential efficacy of CYNK-001 in subjects with SARS-CoV2. The study will be comprised of Screening Period, Treatment Period, and Follow-up Period. The Treatment Period will include CYNK-001 cells along with clinical care. For the Phase II control arm, treatment period will include Best Supportive Care.

4.4.1. CYNK-001 and Cell Dosing



5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

Phase I:

The primary objectives of the Phase I portion of the study is to evaluate the safety, tolerability, and efficacy of multiple CYNK-001 intravenous (IV) infusions administered at an initial dose of 150 x 10^6 cells dose on Day 1 followed by 600 x 10^6 cells doses on Days 4 and 7 in subjects with COVID-19.

Overall, if the safety stopping rules are not met and if efficacy is demonstrated in at least 2 out of the 14 subjects by Day 15 of CYNK-001 infusion (as defined by at least one "Patient State" category of improvement on the Ordinal Scale for Clinical Improvement (OSCI) (Appendix D), the study will move forward to the Phase II portion of the study.

Phase II:

The primary objective of the Phase II portion is to evaluate the efficacy of CYNK-001 on subjects with COVID-19 by using the OSCI defined by the World Health Organization (WHO) (Appendix D).

5.2. Secondary Objectives

The secondary objectives of the Phase II portion are:

A) To determine safety and tolerability of CYNK-001 as measured by the frequency and severity of AEs using CTCAE, version 5.0

B) To evaluate the overall clinical benefit of receiving CYNK-001 for COVID-19 as measured by rate of clinical improvement by OSCI, time to and rate of clinical improvement by NEWS2 Score, medical discharge, hospital utilization, and all-cause mortality rate, time to and rate of clearance of SARS-CoV-2, time to and rate of pulmonary clearance, duration of hospitalization, supplemental oxygen-free days, proportion of subjects requiring ventilation, SOFA score, and radiologic evaluation score.

5.3. Exploratory Objectives

Exploratory objectives include detection of SARS-CoV-2 via rRT-PCR in various specimen types, cytokine and chemokine measurement, and immune monitoring, alloreactivity measurement.

5.4. Study Endpoint Descriptions

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
		Phase 1	
Phase 1 Primary	Safety	Frequency and severity of adverse events, changes in vital signs, laboratory assessments, Performance Status assessment, and immunological and inflammation assessments.	DLTs assessed from Study Day 1 through Day 28
Futility Check for go/no go decision to move to Phase 2:		Efficacy as measured by clinical improvement by OSCI. At least 2 out of 14 subjects must achieve at least 1 "Patient State" category improvement in Ordinal Score (OSCI)	Study Day 15
		Phase 2	
Phase 2 Primary	Time to clinical improvement by OSCI	Time to clinical improvement measured by OSCI	Study Day 28
Phase 2 Secondary	Clinical status by OSCI	Ordinal scale by OSCI	Study Day 28
	Rate of clinical improvement by OSCI	Proportion of subjects who achieved clinical improvements by OSCI	Study Day 28
	Time to clinical improvement by NEWS2	Time to clinical improvement measured by NEWS2 Score	Study Day 28
	Rate of clinical improvement by NEWS2	Proportion of subjects who achieved clinical symptom improvement by NEWS2 Score	Study Day 28
	Rate of clearance of SARS-CoV-2	Proportion of subjects with clearance of SARS-CoV-2 from mucosal specimens (nasopharyngeal swab, oropharyngeal swab if available)	Study Day 28
	Time to clearance of SARS-CoV-2	Clearance of SARS-CoV-2 by rRT-PCR testing of mucosal samples (nasopharyngeal swab, oropharyngeal swab if available); negative results should be confirmed by same sample type at least 24 hours after the first negative result	Study Day 28

	Time to pulmonary clearance	Time to disappearance of virus from LRT specimen where it has previously been found (induced sputum if available, endotracheal aspirate if available)	Study Day 28
	Rate to pulmonary clearance	Proportion of subjects who had disappearance of virus from LRT specimens where it has previously been found.	Study Day 28
	Duration of hospitalization	Duration of hospitalization from time from hospitalization to medical discharge	Study Day 28
	Supplemental oxygen-free days	For subjects requiring supplemental oxygen, days with supplemental oxygen-free days	Study Day 28
	Proportion of subjects requiring ventilation	Proportion of subjects who need invasive or non-invasive ventilation	Study Day 28
	SOFA Score	Sequential Organ Failure Assessment (SOFA) score	Study Day 28
	Radiologic Evaluation Score	Chest x-ray and/or CT scan results will be evaluated and scored	Study Day 28
	All-cause Mortality rate	Proportion of subjects who died	up to Study Day 28 and Month 6
	Safety	Frequency and severity of adverse events, changes in vital signs, laboratory assessments, Performance Status assessment, and immunological and inflammation assessments.	Month 6
[redacted]			

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

The proposed study will evaluate the safety and the clinical efficacy of CYNK-001 in SARS-CoV-2 positive subjects as measured by clearance of the SARS-CoV-2 and improvement in clinical symptoms as measured by OSCI and NEWS2 scores.

The study will include a Phase I portion wherein a total of 14 subjects will be enrolled to assess the safety and efficacy of CYNK-001. To evaluate the safety for potential DLTs, this phase will enroll 3 subjects initially treated with CYNK-001. The safety data for these 3 subjects will be evaluated 24 hours after the final dose was provided to the 3rd subject. If deemed safe, the remaining 11 subjects will be enrolled and monitored per the safety stopping rule until Day15 after the first CYNK-001 infusion. If any DLT is observed in the first three subjects, the DMC will be convened for recommendation. For the remaining 11 subjects, DMC will be convened if the safety stopping rule is met. Overall, in case of 2 out of the 6 subjects had experienced DLTs in the Phase I portion of this study, the DMC will be convened for safety evaluation.

The Phase II portion of the study is a randomized, open-label, multi-site study. Subjects will be randomized to either CYNK-001 group or Control group (best supportive care) with 1:1 ratio stratified by age (< 45 vs. ≥ 45 years old). All subjects in both Phase I and Phase II will receive the best supportive care. Best supportive care will be inclusive of biologic immunomodulatory therapy aimed at reducing morbidity from cytokine release syndrome, such as IL-6 (tocilizumab or siltuximab) or GM-CSF inhibitors.

During Phase II portion of the study, DMC will be convened at midpoint (after 18 subjects have received treatment) to evaluate safety for adverse event of interest such as shock, ARDS, and death in the treatment group versus the control group.

The study is divided into 3 study periods: Screening Period, Treatment Period, and Follow-up Period, each with associated evaluations and procedures that must be performed at specific timepoints.

Subject participation is dependent on slot availability based on time of entry into the study.

6.1.1. Screening Period

The Screening Period is defined as the period from signing the informed consent to just prior to the administration of CYNK-001. Due to the critical nature of this infection, this period may be less than a day. Upon giving written informed consent, all screening / baseline assessments will be completed. Some procedures that occur as part of standard of care in medical evaluation may be completed prior to the date of informed consent, according to institutional practices, and therefore do not need to be repeated. Chest x-rays and blood work should occur often as outlined in the Table of Events.

During the Screening period, after having signed an ICF, subjects will be assessed for eligibility for the study. Eligibility must be confirmed prior to proceeding to the treatment period. This information will need to be gathered and entered into the EDC. Subject eligibility will be based on investigator assessment using the Inclusion/Exclusion criteria provided as part of the study. The Screening Period is followed by a Treatment Period.

6.1.2. Treatment Period (Day 1 to Day 28)

The treatment period begins with the administration of study drug on Study Day 1. For those subjects who are allocated treatment to CYNK-001, the initial dose will consist of 150 x 10^6 cells followed by the second and third doses each of 600 x 10^6 cells administered intravenously (IV). Subjects will receive a minimum of two and up to three CYNK-001 infusions. CYNK-001 infusions will occur on Study Days 1, 4, and 7. After the first dose, subsequent infusions on Days 4 and 7 will be provided only if no toxicity of Grade 3 and above (either related or unrelated to CYNK-001) is observed for each subject. If any such ≥ Grade 3 toxicity is observed, the second and third doses will be delayed up to 48 hours until the noted event is resolved or reduced to Grade 1 toxicity level.

Subjects treated in Phase I will receive all planned CYNK-001 infusions in the inpatient setting and may be discharged one day following the final planned CYNK-001 infusion (i.e., discharged on Study Day 8, where infusions occur on Days 1, 4, and 7). If any dose is delayed, subjects will remain inpatient until one day following the final CYNK-001 infusion.

As part of discharge criteria, the study team should assess for further monitoring of subjects who may be experiencing toxicity of Grade 3 and above (either related or unrelated to CYNK-001) at the time of discharge and consult with the treating physician. The decision to discharge a subject should be in consultation with the treating physician. Physicians should follow best clinical practice to determine appropriate timing of hospital discharge.

Upon discharge, plans should be made for appropriately delegated staff to have telephone contact with subjects every day between hospital discharge through at least Day 15 visit for safety/AE monitoring.

Subjects will be provided with a thermometer, pulse oximeter, and blood pressure monitor for at home collection of temperature, oxygen saturation, and blood pressure with written instructions on their use as well as expectations for self-monitoring. These daily measurements will be reported via telephone to the clinical staff during each daily telehealth visit. During these daily telehealth visits, subjects are to report any new symptoms or worsening of symptoms associated with previously identified adverse events.

The subject will be asked during each call to report any new or worsening symptoms that could be consistent with adverse events since the previous visit or telephone call. The investigator (or appropriately delegated study staff) will determine if medical attention or an unscheduled clinic visit is required. Each telephone call should be carefully documented with date and time of the call in the source documents and reported as appropriate.

Consultation between the Medical Monitor and appropriately delegated site staff should occur every other day after hospital discharge up to Day 15 visit for ongoing review of the subject's clinical status. This communication may occur via telephone contact or written message (i.e., email) and should be documented accordingly.

Subjects treated in the Phase II portion of the study will be treated either in the inpatient or outpatient setting, as determined after review of data from the Phase I portion of the study and based on DMC recommendation. The level of outpatient monitoring of subjects treated in the Phase II portion will be determined based on review of Phase I data and DMC recommendation.

A de-escalation Dose level -1 will be initiated based on the study stopping rules and dose-limiting toxicities. Dose de-escalation is defined as reducing the frequency of the doses (without reducing the total number of cells given per dose) by providing doses only on Days 1 and 7 due to potential safety concerns per the DMC recommendation.

Meperidine may also be administered to control rigors, if clinically indicated. Subjects must be monitored for at least 4 hours after completion of each CYNK-001 infusion.

If subject has been found to be SARS-CoV-2 negative by rRT-PCR or the third dose is skipped per protocol allowances, and has received two doses of CYNK-001, the third dose is not mandatory. If the subject does not receive the third dose, the subject may be discharged one day following the final planned dose at the discretion of the treating physician based on clinical status.

All subjects (even in control arm) should meet the inclusion/exclusion criteria.

The control arm subjects in the Phase II portion of the study will receive the best supportive care as defined by the institutional practice without CYNK-001. All subjects in both Phase I and Phase II will receive the best supportive care.

Additional testing including blood, nasopharyngeal and oropharyngeal (optional) swabs, and sputum (optional) may be collected for research purposes. In some cases, customary standard of care procedures may be conducted more frequently for the purposes of this clinical study.

Information will need to be gathered and entered into the EDC associated with the medical management of the subject.

6.1.3. Follow Up Period

The follow-up period is defined from Day 29 to Month 6. Subjects will be followed at 3 months, and 6 months, or until loss to follow-up, death, or withdrawal from study, whichever occurs first.

The study will be conducted in compliance with ICH Good Clinical Practices (GCPs) and in concordance with local Health Authority regulations.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as specified in the protocol, whichever is the later date.

6.1.4. Hospital Discharge

Hospital discharge is defined as the day a hospitalized subject is discharged. Hospital Discharge visit should be performed if a hospitalized subject is discharged on any day other than a scheduled study visit day.

Subjects who were treated in the Phase 1 portion of the study may be discharged on the day following the final planned CYNK-001 infusion (i.e., discharged on Study Day 8, where infusions occur on Days 1, 4, and 7 or discharged on Study Day 5 if only two doses were received on Days 1 and 4.)

As part of discharge criteria, the study team should assess for further monitoring of subjects who may be experiencing toxicity of Grade 3 and above (either related or unrelated to CYNK-001) at the time of discharge and consult with the treating physician and clinical site study team. The decision to discharge a subject should be in consultation with the treating physician. Physicians should follow best clinical practice to determine appropriate timing of hospital discharge.

Upon discharge, plans should be made for appropriately delegated staff to have telephone contact with subjects every day between hospital discharge through at least Day 15 visit for safety/AE monitoring. The discharge plan should include follow-up visit schedule as well as planned telehealth visit schedule.

Upon discharge, subjects will be provided with a thermometer, pulse oximeter, and blood pressure monitor for at home collection of temperature, oxygen saturation, and blood pressure with written instructions on their use as well as expectations for self-monitoring. These daily measurements will be reported via telephone to the clinical staff during each daily telehealth visit. During these daily telehealth visits, subjects are to report any new symptoms or worsening of symptoms associated with previously identified adverse events and will also provide the study team with daily vital sign measurements. Any vital signs outside of normal range will be escalated to the clinical site study team and evaluated for appropriate management.

The subject will be asked during each call to report any new or worsening symptoms that could be consistent with adverse events since the previous visit or telephone call. The investigator (or appropriately delegated study staff) will determine if medical attention or an unscheduled clinic visit is required. Each telephone call should be carefully documented with date and time of the call in the source documents and reported as appropriate.

Alternative person to contact in case of possible emergency or for planned daily calls from clinical site staff should also be collected prior to hospital discharge.

Consultation between the Medical Monitor and appropriately delegated site staff should occur every other day after hospital discharge up to Day 15 visit for ongoing review of the subject's clinical status. This communication may occur via telephone contact or written message (i.e., email) and should be documented accordingly.

6.1.5. Early Termination

Early Termination is defined as a subject who does not complete the 6-month Follow up visit. Early termination may be due to medical discharge without follow-up, loss to follow-up, withdrawal by a subject, or death.

6.2. Number of Subjects

This study will enroll up to 86 subjects, with 14 subjects in the Phase I portion and up to 72 subjects in the Phase II portion with 36 subjects given CYNK-001 and other 36 subjects who will be treated with the best supportive care only.

6.3. Dose Limiting Toxicity (DLT) Definition

Known pathologies associated with COVID-19 will be carefully considered and differentiated from potential CYNK-001-related effects in order to identify CYNK-001 related toxicities. Adverse events occurring up to Day 28 from the first dose of the CYNK-001 infusion will be included in the dose-limiting toxicity (DLT) determination.

A DLT is defined as the development of any new (not pre-existing) events:

- Grade 4 or 5 event in any organ system
- Grade 4 > 24 hour (Due to known organ damage associated with the COVID-19) in the following organ systems:
  - Cardiac
  - Pulmonary
  - Hepatic
  - Renal
  - Central Nervous System (CNS)
- Grade 3 or above allergic reaction that is suspected to be related to CYNK-001.
- Grade 3 or above GvHD event occurring within the first 28 days following CYNK-001 infusion (to Study Day 28).
- Grade 3 or above CRS event occurring within the first 28 days following the first CYNK-001 infusion (to Study Day 28).

All above events to be identified in discussion with the clinical study Medical Monitor and reportable to Drug Safety.

The events will be assessed for the first 3 subjects in Phase I and per the study stopping rules for the remaining subjects. Any such findings will be forwarded to the DMC for recommendation, review and confirmation as to whether or not the maximal tolerated dose (MTD) has been exceeded. If the MTD is confirmed by the DMC, no further CYNK-001 administration will occur within that dose level or at any higher dose level. For the remaining 11 subjects, DMC will be convened if the safety stopping rule is met. Overall, in case of 2 out of the 6 subjects had

experienced DLTs in the Phase I portion of this study, the DMC will be convened for safety evaluation.

During Phase II portion of the study, DMC will be convened at midpoint (after 18 subjects have received treatment) to evaluate safety for adverse event of interest such as shock, ARDS, and death in the treatment group versus the control group.

MTD is defined as the highest CYNK-001 dose level wherein it was deemed safe per the defined stopping rules or if the DMC recommends stopping the study due to DLTs suspected to be related to CYNK-001.

6.4. Treatment Assignment

Phase I:

Upon confirmation of eligibility during the Screening Period, eligible subjects will be sequentially assigned to the CYNK-001 group at the time of eligibility based on treatment slot availability.

Dose Level cohorts:

- Dose Level 1: CYNK-001 with an initial IV dose of 150 x 10^6 cells on Day 1 followed by 600 x 10^6 cells CYNK-001 IV on Days 4 and 7. After the first dose, subsequent infusions on Days 4 and 7 will be provided only if no toxicity of ≥ Grade 3 (either related or unrelated to CYNK-001) is observed for each subject. If any such ≥ Grade 3 toxicity is observed, the second and third doses will be delayed up to 48 hours until the noted event is resolved or reduced to Grade 1 toxicity level.
- Dose de-escalation Level -1: CYNK-001 with an initial IV dose of 150 x 10^6 cells on Day 1 followed by 600 x 10^6 cells CYNK-001 IV on Day 7 will be implemented due to potential safety concerns per the DMC recommendation.

A total of 14 subjects will be treated in the Phase I portion of the study.

Phase II:

For the Phase II portion of the study, up to 72 subjects will be randomized into the study with 1:1 ratio to either CYNK-001 or the control arm (best supportive care). The Phase II portion of the study is a randomized, open-label, multi-site study. Subjects will be randomized into either CYNK-001 group or Control group with 1:1 ratio stratified by age (< 45 vs. ≥ 45 years old).

6.5. Dose Adjustment Criteria

Dose adjustments may occur if clinically indicated by the treating physician. In general, the following should be followed:

- Dose reductions are not permitted in this study. If any DLTs were observed, the dose de-escalation treatment with reducing frequency of doses will be implemented per the DMC recommendation.
- Should dose delays for CYNK-001 be required:

- Day 1 will be the date of initial dose
- Day 4 dose may be delayed up to 48 hours
  - For non-safety reasons: If delayed longer than 48 hours, Day 4 dose will be skipped., and the subject will receive the Day 7 dose. If the Day 4 dose is given within 48 hours, the Day 7 dose will be delayed for three days from the actual day of when Day 4 dose was given (Ex: if Day 4 dose is given on Day 5, then Day 7 dose will be given on Day 8)
  - For safety reasons: Day 4 dose could be delayed if ≥ Grade 3 toxicity is observed after the first dose. In such cases, Day 4 dose is provided only if the event is resolved or reduced to Grade 1 toxicity level. If the toxicity did not resolve within 48 hours, the Day 4 dose will be skipped. If the Day 4 dose is given within 48 hours, the Day 7 dose will be delayed for three days from the actual day of when Day 4 dose given.
  - If the subject has worsening of illness, study medication will be stopped.
- Day 7 dose may be delayed up to 48 hours:
  - For non-safety reasons: If delayed longer than 48 hours, the subject will not receive additional therapy.
  - For safety reasons: If Day 4 dose was delayed but given within 48 hours of planned Day 4, then the Day 7 dose will be delayed for three days from the actual day of when Day 4 dose was given.

    If Day 4 dose was given as planned, Day 7 dose could be delayed if ≥ Grade 3 toxicity is observed after the second dose. If Day 4 dose was skipped, Day 7 dose could be delayed if ≥ Grade 3 toxicity is still observed after the first dose. In such cases, Day 7 dose is provided only if the event is resolved or reduced to Grade 1 toxicity level. If the toxicity did not resolve within 48 hours of the scheduled day, the Day 7 dose will not be administered.
  - If the subject has worsening of illness, study medication will be stopped.
- All subjects who receive any amount of CYNK-001 will be followed to 6 months or until loss to follow-up, death, or withdrawal from study, whichever occurs first.
- If subject has been found to be SARS-CoV-2 negative by rRT-PCR or the third dose is skipped per protocol allowances, and has received two doses of CYNK-001, the third dose is not mandatory. The subject may be discharged one day following the final planned dose of CYNK-001.

Consultation with the Medical Monitor is required prior to each CYNK-001 infusion if there is:

- An increase in supplemental oxygen of greater than or equal to 50% from baseline (for first CYNK-001 infusion) or from level at prior CYNK-001 infusion (for second and third CYNK-001 infusion) resulting in oxygen use of greater than 8L.

  -or-

- A change in the mode of supplemental oxygen delivery with the intention to deliver oxygen more efficiently.

The Medical Monitor will escalate to the Sponsor clinical and safety teams as appropriate per GCP guidelines to advise if a subject who is experiencing rapid worsening of disease should proceed to first or subsequent CYNK-001 infusion.

6.6. Duration of Study Participation

6.6.1. Treatment Discontinuation

Discontinuation from study medication does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE. The following events are considered sufficient reasons for discontinuing a subject from study medication:

- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued treatment with study medication would not be in the best interest of the participant.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation. Discussion with the Medical Monitor is recommended.
- Worsening of illness which requires discontinuation of study medication at the discretion of the treating physician.
- Subject withdrawal from treatment (subject no longer wants to receive study medication but is willing to have additional data collected), which must be documented in subject's medical record. It must be confirmed in documented communications whether or not AEs are leading the subject's choice to withdraw from the study medication.
- Death
- Protocol violation; discussion with the Medical Monitor is recommended.
- Pregnancy
- Loss to follow-up
- Completion of study treatment according to the study protocol.

Reason for study treatment discontinuation must be recorded in the electronic case report form (eCRF) and source documents.

6.6.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Subject withdrawal from study (subject no longer wants to participate in the study and is willing to have additional data collected), which must be documented in subject's medical record. It must be confirmed in documented communications whether or not AEs are leading the subject's choice to withdraw from the study.
- Significant study intervention non-compliance
- Death
- Loss to follow-up
- Protocol violation; discussion with the Medical Monitor is recommended

Reason for study discontinuation must be recorded in the eCRF and source documents.

6.6.3. Subject Withdrawal

Subjects may withdraw voluntarily from the study at any time upon request. Information related to the subject withdrawal must be well documented in the source document, including the documentation associated with any AEs the subject may or may not be experiencing at the time of the withdrawal.

Subjects who withdraw from the study after a single dose of CYNK-001 treatment will not be replaced.

6.7. Criteria for Study Termination

The study may be terminated for the following reasons:

- Study is completed as planned.
- The study is terminated based on lack of evidence of therapeutic benefit.

Celularity also reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (e.g., IRB/EC, regulatory authorities, and others as applicable).

In addition, the Investigator or Celularity has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment
- GCP non-compliance
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the study protocol
- Number of subjects not following the study protocol plan surpasses the statistical drop-out rate assumption resulting in the study being underpowered.

6.8. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as specified in the protocol, whichever is the later date.

6.9. Efficacy Endpoint Definitions

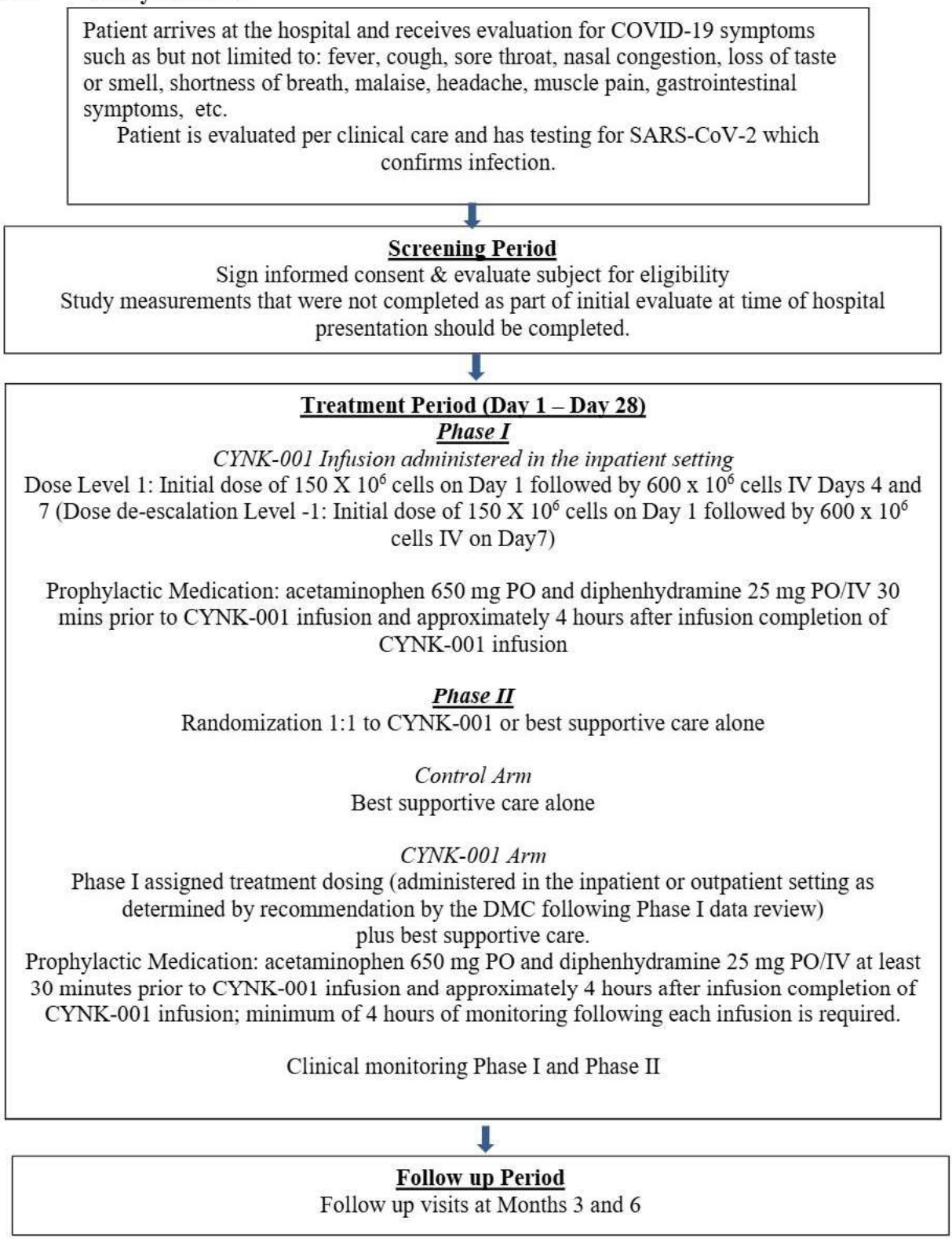
- **Time to Clinical Improvement by OSCI**: defined as the time from the date of randomization to the first date of clinical improvement measured by OSCI. (Appendix D). Clinical improvement is defined as an improvement at least by cross category (or Patient State improvement in Appendix D table, such as from Hospitalized Severe Disease to Hospitalized Mild Disease). Subjects who do not have clinical improvement on or before Study Day 28 will be censored at Study Day 28.
- **Clinical Status by OSCI**: defined by the Ordinal Scale score of 0 to 8 by OSCI (Appendix D).
- **Rate of Clinical Improvement by OSCI**: defined as the proportion of subjects who achieved clinical improvement by OSCI.
- **Time to Clearance of SARS-CoV-2**: defined as the time from the date of randomization to the clearance of SARS-CoV-2 by rRT-PCR by two negative results at least 24 hours apart, with the first negative as the start date of clearance. Specimens included are nasopharyngeal swab and oropharyngeal swab (if available). Subjects who do not have clearance on or before Day 28 will be censored at Day 28.
- **Rate of Clearance of SARS-CoV-2:** defined as the proportion of subjects with "negative" measurement of COVID-19 by rRT-PCR.
- **Time to Clinical Improvement by NEWS2:** defined as the time from the date of randomization to the first date of clinical improvement. Clinical improvement is defined as improvement of clinical symptoms as measured by the NEWS2 Score (Appendix C). Subjects who do not have clinical improvement on or before Study Day 28 will be censored at Study Day 28.
- **Rate of Clinical Improvement by NEWS2:** defined as the proportion of subjects who achieved clinical improvement.
- **Time to Pulmonary Clearance:** defined as the time of randomization to the date of pulmonary clearance. This is defined as disappearance of virus from LRT- specimen where it has previously been found (induced sputum if available, endotracheal aspirate if available). Subjects who do not have pulmonary clearance on or before Study Day 28 will be censored at Study Day 28.
- **Pulmonary Clearance Rate:** defined as the proportion of subjects who achieve pulmonary clearance.

- **Duration of Hospitalization:** defined as date of randomization to the date of medical discharge. Subjects who are not discharged on or before Study Day 28 will be censored at Study Day 28.
- **Ventilatory Support:** For those subjects requiring ventilatory support or supplemental oxygen during the treatment period:
  - Supplemental oxygen-free days
  - Proportion of subjects developing respiratory failure requiring invasive or noninvasive mechanical ventilation.
- **SOFA Score:** For those subjects evaluated by Sequential Organ Failure Assessment (SOFA) scores from ICU admission through ICU discharge (for subjects requiring intensive care). Mean arterial pressure should be measured with an arterial line. See Appendix A.
  - Organ support, according to the number of days within the 28 days starting from Day 1 when subjects do not receive specific forms of support:

a. Supplemental oxygen-free days
b. Renal replacement therapy-free days
c. Vasopressor-free days
d. Invasive or non-invasive mechanical ventilation free days
e. Organ support-free days (that is, days free of invasive mechanical ventilation, renal replacement therapy and vasopressors)
f. Extracorporeal circulation support-free days

- **Mortality Rate:** defined as the proportion of subjects who died by any cause.

Figure 2: Study Schema



7. TABLE OF EVENTS

Table 3: Table of Events

Event	Screen	Treatment Period						Follow-up period [w]			
	Baseline [a]	Day 1 [k]	Day 4 (+ 2 days) [k]	Day 7 (+ 2 days) [k]	Day 15 (± 2 days)	Day 21 (± 2 days)	Day 28 (± 2 days)	Day 90 (±14 days)	Day 180 (±14 days)	Hospital Discharge[v] (if applicable)	Early Termination [b]
Study Entry and General Assessments											
Study Informed Consent	X	-	-	-	-	-	-	-	-	-	-
Inclusion/Exclusion Assessment	X	-	-	-	-	-	-	-	-	-	-
Pre-ICF rRT-PCR (or other approved test per institutional practice) results confirming SARS-CoV-2	X	-	-	-	-	-	-	-	-	-	-
Demographics/Medical history	X	-	-	-	-	-	-	-	-	-	-
Treatment and Study Required concomitant medications											
Phase II only: Randomization to CYNK-001 or Best Supportive Care (1:1 ratio) after treatment eligibility is confirmed	X	-	-	-	-	-	-	-	-	-	-
CYNK-001 IV infusion[c,d]	-	X	X	X[e]	-	-	-	-	-	-	-
Best supportive care - Control group (Phase II only)	-	Control group to receive Best Supportive Care only						-	-	-	-
Acetaminophen 650mg PO pre- and post-medication[d]	-	X[f k]	X[f k]	X[e f k]	-	-	-	-	-	-	-

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

1. Subject has confirmed positivity for SARS-CoV-2 as measured by rRT-PCR or other approved test to detect SARS-CoV-2 per institutional practice.
2. Subject is experiencing any symptom/clinical sign of COVID-19 illness or has a positive disease-related chest x-ray/CT scan at screening.
3. Subject is ≥ 18 years of age at the time of signing the Study informed consent form (ICF).
4. Subject understands and voluntarily signs the Study ICF prior to any study-related assessments/procedures are conducted.
5. Subject is willing and able to adhere to the study schedule and other protocol requirements.
6. SpO2 ≥ 88% on room air; oxygen is permitted as delivered by nasal cannula and/or face mask at any flow rate to achieve this SpO2. Subjects must have an SpO2 ≥ 92% if on supplementary oxygen.
    - *(Note: Once eligibility is confirmed, to initiate CYNK-001 treatment, an increase of supplemental oxygen of greater than or equal to 50% from baseline/screening resulting in oxygen use of greater than 8L -or- a change in mode of supplemental oxygen delivery with the intention to deliver oxygen more frequently requires consultation with the medical monitor)*
7. Ability to be off immunosuppressive drugs for 3 days prior to infusion, unless clinically indicated. Steroids are permitted if clinically indicated and at the discretion of the treating physician. If clinically indicated, careful consideration should be taken regarding the timing and tapering of high-dose steroids.
8. Female of childbearing potential (FCBP)* must not be pregnant and agree to not becoming pregnant for at least 28 days following the last infusion of CYNK-001. FCBP must agree to use an adequate method of contraception during the treatment period.
    a. *FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
9. Male subjects must agree to use a condom during sexual contact for at least 28 days following the last infusion of CYNK-001, even if he has undergone a successful vasectomy.

8.2. Subject Exclusion Criteria

1. Subject requires supplemental oxygen delivered by mechanical ventilation, either invasive or bilevel positive airway pressure.

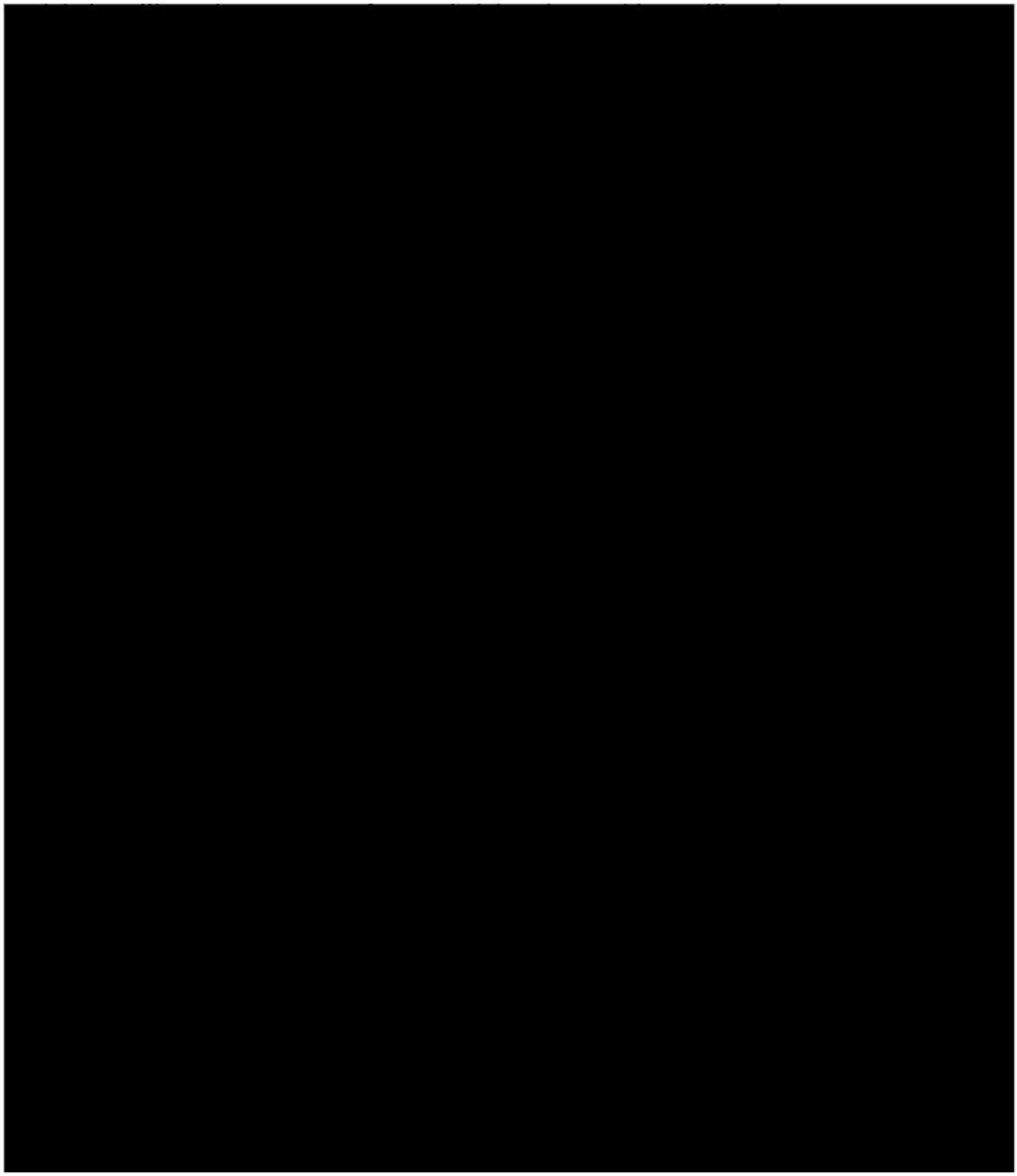
2. Subject admitted to Intensive Care Unit / Pulmonary Acute Care Unit designated area with severe pulmonary pneumonia, ARDS or Sepsis.
3. Subject is pregnant or breastfeeding.
4. Subject has a history of chronic asthma requiring ongoing medical therapy or other chronic pulmonary disease that, at the discretion of the treating physician, would contraindicate participation in this study.
5. Subject has any other organ dysfunction [Common Terminology Criteria for AEs (CTCAE) Version 5.0 Grade 3] that will interfere with the administration of the therapy according to this protocol.
6. Subject has inadequate organ function as defined below at time of Treatment Eligibility Period:
    a) Subject has aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase ≥ 5 x the upper limit of normal (ULN). (It is anticipated that the infection may impact liver.)
    b) Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 as calculated using the Modification of Diet in Renal Disease Study equation (Levey, 2006) or history of an abnormal eGFR < 60. A decline of > 15 mL/min/1.73 m2 below normal in the past year prior to infection. (It is anticipated that the infection may impact renal function.)
    c) Subject has a bilirubin level > 2 mg/dL (unless subject has known Gilbert's Syndrome).
7. Subject has a known sensitivity or allergy to treatment additives or diluent substances of dimethyl sulfoxide (DMSO), PlasmaLyte A or human serum albumin (HSA). Please refer to investigational brochure (IB).
8. Subject has active autoimmune disease other than controlled connective tissue disorder or those who are not on active therapy.
9. Subject is immunocompromised, has known human immunodeficiency virus (HIV) positivity, or has actively been treated with immunosuppressive products prior to being infected with SARS-CoV-2.
10. Subject has known active malignancy, unless the subject has been free of disease for ≥ 3 years from the date of signing the ICF. Exceptions include the following noninvasive malignancies:
    a. Basal cell carcinoma of the skin
    b. Squamous cell carcinoma of the skin
    c. Carcinoma in situ of the cervix
    d. Carcinoma in situ of the breast
    e. Incidental histological finding of prostate cancer (TNM stage of T1a or T1b)

11. Detection of other respiratory viruses from mucosal surfaces that, at the investigator's discretion, would interfere with the study treatment plan; detection of another respiratory virus is *not in itself* an exclusion criteria unless the investigator believes it would interfere with administration of CYNK-001.
12. Subjects must not have a history of unconsciousness or hemoptysis within 2 weeks of signing ICF.
13. Subjects must not have end stage liver disease and/or cirrhosis.
14. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
15. Subject has any condition including the presence of laboratory abnormalities which places the subject at unacceptable risk if he or she were to participate in the study.
16. Subject has any condition that confounds the ability to interpret data from the study.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

For full description of CYNK-001, refer to the Investigator's Brochure (IB).



9.1.2. CYNK-001 Overdose

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of CYNK-001 assigned to a given subject, regardless of any associated AEs or sequalae:

CYNK-001: 30% over the assigned protocol-specified dose of 600 x 10^6 cells.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the eCRF. (Refer to Section 12.3.1.1 for overdose reporting requirements).

9.2. Concomitant Medications

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments or clinical worsening. Supportive care, including but not limited to antiemetic medications, may be administered at the discretion of the physician. Use of high-dose steroids (greater than or equal to 0.5mg/kg per day prednisone equivalent) is not recommended during the Treatment Period, unless clinically indicated and at the discretion of the treating physician. High-dose steroids have been shown to interfere with the effectiveness of some adoptive cell therapies. If clinically indicated, careful consideration should be taken regarding the timing and tapering of high-dose steroids.

All concomitant treatments, including blood and blood products, used from 28 days prior to the first CYNK-001 infusion until completion of the study must be reported on the eCRF. All treatments administered for the purposes of providing care of COVID-19 including name and number of doses must be reported on the eCRF.

For information regarding other drugs that may interact with CYNK-001 and affect CYNK-001 activity, please see the IB.

9.2.1. Permitted Concomitant Medications

All subjects are to receive standard medical care for COVID-19 signs and symptoms, unless contraindicated.

During the Treatment Period and Follow-Up Period, the following Concomitant Medications are permitted:

- Prophylactic antibiotic and antifungal medication are permitted at the discretion of the treating physician. These treatments must be identified as prophylactic in the physical examination source documents.
- Diphenhydramine and acetaminophen are permitted to be used as indicated before and after CYNK-001 administration and as clinically indicated.
- Meperidine is permitted for the control of rigors and as clinically indicated.
- Steroids are permitted if clinically indicated and at the treating physician's discretion during the treatment period. If clinically indicated, careful consideration should be taken regarding the timing and tapering of high-dose steroids.
- Blood product transfusions may occur as clinically indicated greater than 24 hours before or greater than 24 hours after CYNK-001 infusion.
- Supplemental oxygen therapy is permitted if clinically indicated.
    - Note: Per NIH COVID-19 Treatment Guidelines dated 17 December 2020, the optimal target SpO2 in adults with COVID-19 is between 92% and 96%. (https://www.covid19treatmentguidelines.nih.gov/critical-care/oxygenation-and-ventilation/; NIH COVID-19 Treatment Guidelines: Oxygenation and Ventilation, 17 December 2020)
- Concomitant therapy with potential activity against COVID-19 is permitted.

9.2.2. Prohibited Concomitant Medications

- Blood product transfusions should not occur within 24 hours prior to and/or 24 hours after CYNK-001 infusion, unless clinically indicated.

9.2.3. Required Concomitant Medications

- The best supportive care treatments must be identified in the source documents and documented that they are administered for COVID-19. Prophylactic use of any treatment during the study must be documented as prophylactic treatment.
- Subjects should receive adequate medical therapy for control of hypertension, diabetes, and any other chronic medical conditions for which they require ongoing care.

- Acetaminophen and diphenhydramine are required concomitant medications to be administered prior to and following each CYNK-001 infusion.
- In some cases, tocilizumab, an anti-IL-6R-antibody, may be required to treat toxicities such as Cytokine Release Syndrome (CRS). Please refer to currently approved Actemra® package insert (Actemra, 2019). The recommended dose to intervene in subjects with CRS is 8 mg/kg; however, dosing is at the discretion of the treating physician. Other similarly available immune-modulatory drugs (targeted biologics), but not corticosteroids or more broadly-acting immunosuppressants) could be considered per physician discretion.

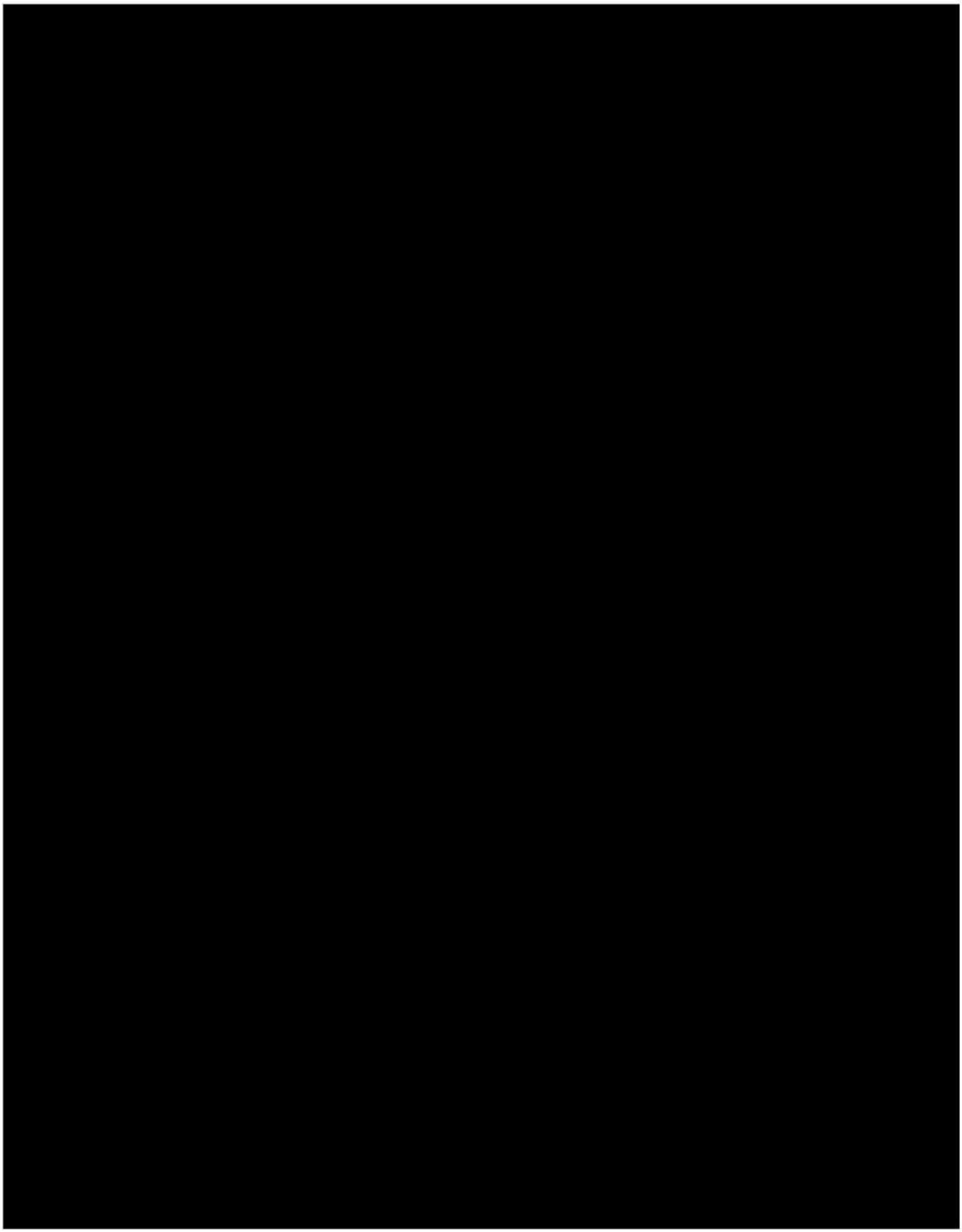
9.3. Treatment Compliance

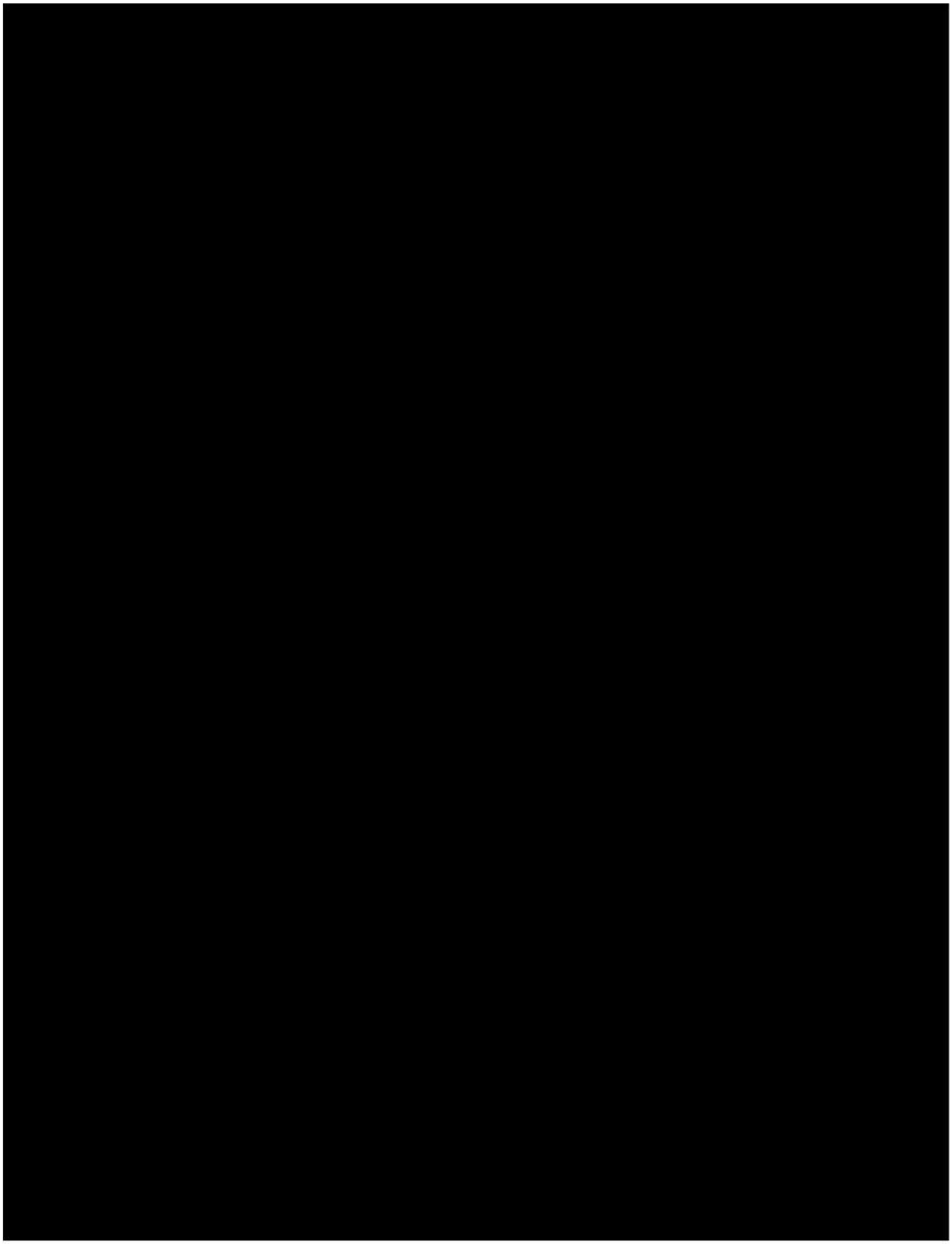
CYNK-001 is to be administered IV at the clinical study site. Study personnel will review the dosing treatment allocation and ensure treatment is administered according to the subject's treatment plan. Treatment compliance will be noted on the appropriate CRFs and source records based on administration records.

- Dose reductions are not permitted in this study.
- Dose delays are permitted. See Section 6.5
- Concomitant therapies
    - Blood product transfusions should not occur within 24 hours prior to and/or 24 hours after CYNK-001 infusion.
    - Use of steroids is permissible if clinically indicated and at the discretion of the treating physician.

10. STUDY DRUG MATERIALS AND MANAGEMENT

[redacted]





For the second and third doses (6×10^8 cells each), inspect the contents of the prepared

[redacted]

11. ASSESSMENT OF EFFICACY

This study will explore the potential clinical efficacy of CYNK-001 by evaluating:

- **OSCI**: OSCI will be recorded daily in hospital and outpatient by phone contact. See Appendix D for the definition of the ordinal scale for clinical improvement.
- **Clearance of SARS-CoV-2**: defined as the time from the date of randomization to the clearance of SARS-CoV-2 by rRT-PCR by two negative results at least 24 hours apart. Specimens included are nasopharyngeal swab and optional oropharyngeal swab.
- **Pulmonary Clearance**: defined as the time from randomization to the date of pulmonary clearance. This is defined as disappearance of virus from LRT specimen where it has previously been found (induced sputum if available, endotracheal aspirate if available).
- **Duration of Hospitalization**: defined as the date of hospitalization to the date of medical discharge.
- **Ventilatory Support:** For those subjects requiring ventilatory support or supplemental oxygen during the treatment period:
    - Supplemental oxygen-free days
    - The development of respiratory failure requiring invasive or noninvasive mechanical ventilation.
- **SOFA Score:** For those subjects evaluated by Sequential Organ Failure Assessment (SOFA) scores at ICU admission through ICU discharge (for subjects requiring intensive care; mean arterial pressure to be measured with an arterial line). See Appendix A
    - Organ support, according to the number of days within the 28 days starting Day 1 when subjects do not receive specific forms of support:

a. Supplemental oxygen-free days
b. Renal replacement therapy-free days
c. Vasopressor-free days
d. Invasive or non-invasive mechanical ventilation free days
e. Organ support-free days (that is, days free of invasive mechanical ventilation, renal replacement therapy and vasopressors)
f. Extracorporeal circulation support-free days

- **Mortality**: defined as the death within 28 days and 6 months of any cause.
- **NEWS2 Score:** NEWS2 Score will be calculated based on data collected in the EDC for assessment of clinical symptoms including respiration, oxygen saturation, blood pressure, pulse, consciousness, and temperature (Royal College of Physicians, 2017, Section 19). See Appendix C.
- **Radiologic Evaluation:** Chest x-ray and/or CT scans will be evaluated at timepoints outlined in the Table of Events Section 7 Table 3. In an effort to apply objective, semi-quantitative methods for radiologic evaluation, the following binary scoring system will be implemented:
    - Score A: Chest x-ray or CT scan: normal (score 0) versus abnormal (score 1)

- Score B: Pleural Effusion: absence (score 0) versus presence (score 1)
- Radiologic Evaluation Score: the sum of Score A and B.

12. ASSESSMENT OF SUBJECTS

12.1. Study Activities and Evaluations

Subject safety will be assessed in all subjects who receive any amount of CYNK-001 and will include AEs, vital signs, body weight measurements, physical examination findings, clinical laboratory test results, infusion site assessments, x-ray or computerized tomography (CT) scan results, electrocardiogram (ECG) interpretations, electroencephalography (EEG) if clinically indicated, pregnancy testing for FCBP, and concomitant medications and procedures will be tabulated and summarized by cohort. Timing of evaluations will be assessed as outlined in the Table of Events, Section 7 Table 3.

All AEs will be reported and recorded in the electronic case report form (eCRF). For serious adverse events (SAEs), an expedited reporting procedure will be used. The rate of AEs, SAEs, abnormal laboratory AEs and vital signs (graded according to the NCI CTCAE Version 5.0) will be measured while the subject is on study.

The ASTCT Consensus Grading for CRS and Neurologic Toxicity Associated with Immune Effector Cells will be used for the purposes of grading of CRS considered associated with CYNK-001 by the Investigator. CRS Grading can be found in Section 12.6.2. Any new CRS event or worsening of a pre-existing CRS event at any grade is an expected event and immediately reportable.

Subjects will be monitored for safety from the time of signing ICF through end of study and will be collected in the eCRF.

12.1.1. Study Informed Consent and Eligibility Assessment

Once a subject has been identified due to testing positive for COVID-19, they may be approached for Informed Consent. Once the informed consent has been signed, the subject will be evaluated for eligibility and additional research procedures may be performed as needed.

12.1.2. Demographic/Medical History

Demographics (initials, date of birth, gender, race, and ethnicity – if allowed by local regulations)

Complete medical history (all relevant medical conditions diagnosed/occurring prior to screening should also be included). Baseline signs and symptoms will be recorded as medical history. Where possible, grading of medical history by CTCAE, version 5.0 criteria should be included.

12.1.3. Physical Examination, Performance Status, and Infection Symptoms Assessment

A complete physical examination will be conducted and documented appropriate for the clinical status of the subject's health and infection burden.

It is important that during the course of the physical examination the subject should be assessed for symptoms related to their COVID-19 infection. COVID-19 symptoms include but are not limited to the following: fever, cough, sore throat, nasal congestion, loss of taste or smell, shortness of breath, wheezing, chest pain, ear pain, myalgia, arthralgia, malaise, headache, gastrointestinal symptoms. Given that symptoms associated with infection are critical to study

endpoints, symptoms associated with COVID-19 should be documented at baseline and grade according to CTCAE, version 5.0.
Subject's overall wellbeing and illness related symptoms must be monitored during the study for improvement and/or worsening and should be captured in the EDC. Symptom worsening is to be reported as an AE.
SOFA score must be documented for subjects requiring intensive care (See Appendix A). Karnofsky Performance Status (KPS) score will also be collected (See Appendix B). For subjects receiving CYNK-001, the site of infusion will be assessed as outlined in the Table of Events, Section 7 Table 3.

12.1.4. Vital Signs

Vital signs will be measured, including temperature, systolic and diastolic blood pressure, respiration rate, and pulse and oxygen saturation (SpO2), per standard institutional practice as outlined in the Table of Events.

Vital signs to be collected from medical record during hospitalization. Once subject is discharged the vital signs should be collected in the outpatient facility where the subject is seen.

Upon discharge, plans should be made for appropriately delegated study staff to have telephone contact with subjects every day between hospital discharge through at least Day 15 visit for safety/AE monitoring. Subjects will be provided with a thermometer, pulse oximeter, and blood pressure monitor for at home collection of temperature, oxygen saturation, and blood pressure with written instructions on their use as well as expectations for self-monitoring. These daily measurements will be reported via telephone to the clinical staff during each daily telehealth visit. During these daily telehealth visits, subjects are to report any new symptoms or worsening of symptoms associated with previously identified adverse events and will also provide the study team with daily vital sign measurements. Any vital signs outside of normal range will be escalated to the clinical site study team and evaluated for appropriate management. The subject will be asked during each call to report any new or worsening symptoms that could be consistent with adverse events since the previous visit or telephone call. The investigator (or appropriately delegated study staff) will determine if medical attention or an unscheduled clinic visit is required. Each telephone call should be carefully documented with date and time of the call in the source documents and reported as appropriate.

On each day of CYNK-001 infusion, vital signs to be collected pre-infusion, approximately 30 minutes after the start of infusion, and approximately 4 hours after the completion of infusion.

On non-infusion days where multiple vital signs are collected throughout the day, vital signs should be captured in the EDC once per day and the worst vitals should be recorded.

Note: Subjects must be monitored for at least 4 hours after completion of each CYNK-001 infusion.

Note: CYNK-001 infusion should be paused or discontinued if there are any signs of an infusion site reaction or signs of an allergic reaction to the study drug. In the case an infusion site reaction or allergic reaction is suspected, the CYNK-001 infusion should be stopped, and vital signs should be taken. Treatment should be provided as clinically indicated and the patient should be monitored for at least 4 hours after the infusion.

12.1.5. Weight

Weight will be measured at baseline and thereafter monitored as outlined in the Table of Events.

12.1.6. Height

Height is requested to be taken at Screening/Baseline as outlined in the Table of Events.

12.1.7. Prior and Concomitant Medications and Procedures

Prior and concomitant medications (including those taken within 28 days of signing ICF, and including contraceptive measures and over-the-counter products), must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

Relevant prior and all concomitant procedures should be recorded. Any intervention associated with SOFA should be carefully documented. Oxygen therapy is permitted and should be carefully documented, including daily level of oxygenation requirements from time of hospital admission to time of hospital discharge.

Note: Consultation with the Medical Monitor is required prior to each CYNK-001 infusion if there is:

- an increase in supplemental oxygen of greater than or equal to 50% from baseline (for first CYNK-001 infusion) or from level at prior CYNK-001 infusion (for second and third CYNK-001 infusion) resulting in oxygen use of greater than 8L. -or-
- a change in the mode of supplemental oxygen delivery with the intention to deliver oxygen more efficiently.

The Medical Monitor will escalate to the Sponsor as appropriate to advise if a subject who is experiencing rapid worsening of disease should proceed to first or subsequent CYNK-001 infusion.

12.1.8. Chest X-Ray

A chest x-ray will be performed at baseline to assess the overall pulmonary health of the subject. Subjects are anticipated to have pulmonary infiltrates associated with their infection. Continued monitoring by chest x-ray is anticipated to occur as outlined in the Table of Events. On days when CYNK-001 treatment is administered, it is preferred that this be performed prior to treatment. Information from these procedures will be collected.

12.1.9. Chest Computed Tomography (CT-Scan)

In some cases, it is anticipated that a chest x-ray will not be sufficient for the clinical diagnosis and monitoring of subjects. A chest CT scan may be performed in lieu or in conjunction with chest x-rays, as deemed appropriate by the treating physician. In the event that a CT scan is performed, it is recommended that this be continued at least weekly if clinically indicated to confirm radiological measurements. Information from these procedures will be collected.

12.1.10. Electrocardiogram (ECG)

12-lead ECG. An ECG will be done as part of the subject's Treatment Eligibility screen and thereafter monitored as outlined in the Table of Events. The ECG will be reviewed by a qualified physician (paper or electronic tracing) and will be available for comparison with subsequent ECGs. The following will be recorded on the eCRF:

- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- QTcB (Bazett's formula) and/or QTcF (Fridericia's formula) interval (msec)
- Heart rate (BPM)
- RR interval (msec)
- Overall interpretation of ECG

12.1.11. Electroencephalography (EEG)

In the event that Neurotoxicity is identified, and if indicated, electroencephalography may be performed to clinically assess the nature of the AE. Subjects may have electroencephalography changes, such as generalized or frontal slowing or frontal intermittent rhythmic delta activity, which should not be considered seizures (Lee, 2019).

12.1.12. Laboratory Assessments

All laboratory assessments are to be tested either locally or centrally as indicated in the Table of Events, Section 7, Table 3. Screening laboratory values must demonstrate subject eligibility; screening laboratory values may be repeated within the screening window if necessary.

12.1.12.1. Real-Time Reverse-Transcriptase-Polymerase-Chain-Reaction (rRT-PCR)

For initial diagnostic and follow-up testing for COVID-19, there are varied specimen options for analysis. The CDC recommends collecting and testing upper respiratory (nasopharyngeal and oropharyngeal (if possible) swabs), and lower respiratory (sputum, if possible) for those subjects with productive coughs. Induced sputum may be collected if institutional practice allows. Testing may also be performed on blood (serum) samples. Institutional practices for the collection procedures and appropriate precautionary practices for avoiding transmission must be followed at all times.

For intubated subjects, endotracheal aspirate should be collected as outlined in the Table of Events.

Refrigerate specimen at 2-8°C until testing can be performed. Samples for screening should be prioritized on for testing as the results are required in order to intervene in a timely manner.

Note: Baseline testing for the detection of SARS-CoV-2 to confirm eligibility should be performed using rRT-PCR or other approved test based on institutional practice. All subsequent testing for the detection of SARS-CoV-2 should be performed by rRT-PCR.

12.1.12.1.1. Nasopharyngeal and Oropharyngeal (optional) swabs

Using only synthetic fiber swabs with plastic shafts. Nasopharyngeal swab: Insert a swab into the nostril parallel to the palate. Leave the swab in place for a few seconds to absorb secretions. Swab both nasopharyngeal areas with the same swab. Optional Oropharyngeal swab: Swab the posterior pharynx, avoiding the tongue.

Do not use calcium alginate swabs or swabs with wooden shafts, as they may contain substances that inactivate some viruses and inhibit PCR testing. Place swabs immediately into sterile tubes containing 2-3 ml of viral transport media. Nasopharyngeal and oropharyngeal specimens should be kept in separate vials and labeled accurately.

12.1.12.1.2. Optional Sputum

The subject should rinse the mouth with water and then expectorate a deep cough sputum directly into a sterile, leak-proof, screw-cap sputum collection cup or sterile dry container. Samples should be labeled accurately.

12.1.12.1.3. Serum

Collect 1 tube (5-10 mL) of whole blood in a serum separator tube. Serum separator tubes should be stored upright for at least 30 minutes, and then centrifuged at 1000-1300 relative centrifugal force (RCF) for 10 minutes before removing the serum and placing it in a separate sterile tube for testing. Samples should be labeled accurately. Serum is not required to be collected during the Follow Up Period if the prior sample tested negative.

12.1.12.1.4. Endotracheal Aspirate

Endotracheal aspirate should be collected for intubated subjects only as outlined in Table of Events, Section 7, Table 3. Sample should be collected per institutional practice. Samples should be labeled accurately.

12.1.12.2. Hematology

Hematology panel including complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count (with differential), platelet count, and mean platelet volume (MPV) will be collected as outlined in Table of Events, Section 7, Table 3.

12.1.12.3. Blood Chemistry

Chemistry panel including sodium, potassium, calcium, carbon dioxide (bicarbonate) CO_2, chloride, blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase will be collected as outlined in Table of Events, Section 7, Table 3.

Estimated Glomerular Filtration Rate (eGFR) will be calculated as part of the treatment eligibility assessment.

12.1.12.4. Coagulation

Coagulation tests including, prothrombin time (PT), partial thromboplastin time (PTT), International normalized ratio (INR) or activated partial thromboplastin time (aPTT), and fibrinogen will be measured locally at Treatment Eligibility Period and prior to first CYNK-001 infusion by local lab, then as clinically indicated, as outlined in the Table of Events, Section 7, Table 3.

12.1.12.5. Immunological/Inflammation Assessments

IL-6, C-reactive protein (CRP), ferritin, D-dimer, and procalcitonin (tested locally) will be measured as biomarkers of CRS as indicated in the Table of Events, Section 7 Table 3.

Note: CRS management and grading relies primarily on clinical signs and symptoms, these laboratory measurements will be collected as biomarkers to support CRS diagnosis/monitoring.

12.1.12.6. Pregnancy Screen

Pregnancy test is required for all female subjects of childbearing potential. Serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed at Screening and at Day 28. Negative results are required for CYNK-001 administration to be initiated.

12.1.12.7. Exploratory laboratory testing

Please refer to Section 13 for more information on these assessments.

12.1.12.8. Urinalysis

Urinalysis (dipstick) will be assessed if clinically indicated as outlined in the Table of Events, Section 7, Table 3.

12.2. Best Supportive Care Treatment

Subjects are expected to receive best supportive care as defined by the institution during the course of this study starting Day 1. The specific medication and duration of therapy is at the discretion of the treating physician. These medications must be documented in the source documents as treatment for COVID-19.

12.3. Adverse and Serious Adverse Events

12.3.1. Definition of Adverse Events

12.3.1.1. Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF. (See Section 9.1.2 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for CYNK-001 overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. **Infusion related reactions (IRRs) will be documented for the first 72 hours of CYNK-001 infusion at every dose**. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs that occur after any subject has been enrolled, before treatment, during treatment, or within 28 days following the first CYNK-001 infusion (to Study Day 28), whether or not they are related to the study, must be recorded on forms provided by Celularity.

12.3.1.2. Serious Adverse Event (SAE)

A SAE is an AE occurring during the conduct of the study, and at any dose of the investigational product that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur after any amount of treatment with CYNK-001, must be recorded on forms provided by Celularity.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (i.e., planned prior to start of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to the CYNK-001, action taken regarding the CYNK-001, and outcome.

12.3.1.3. Suspected Unexpected Serious Adverse Drug Reaction (SUSAR)

SUSAR is an adverse drug reaction that is both serious and unexpected (per the IB) which, based on the opinion of the investigator and/or sponsor, is felt to have a reasonable suspected causal relationship to an investigational product.

12.3.1.4. Anticipated Event

Adverse experiences (serious or non-serious) that commonly occur in the study population or background regimen. Such events include known consequences of the underlying disease (disease-related) or condition under investigation (e.g., symptoms, disease progression) and events unlikely to be related to the underlying disease or condition under investigation but common in the study population independent of drug therapy (e.g., non-acute death observed in a trial with cancer patients). For reporting purposes, anticipated events are not “expected” because they are not listed in the IB.

12.3.1.5. Unexpected Event

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. This also means that events listed in the investigator brochure is considered "expected".

12.3.1.6. Adverse Event of Special Interest (AESI)

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

In this study, Immune receptor cell associated Neurotoxicity syndrome (ICANS) and hypersensitivity reactions are the noted AESIs. CRS is listed in the IB as an expected event.

12.3.1.7. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for AEs (CTCAE, version 5.0);

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Following CYNK-001 infusion, AEs will be included up to Day 28 post first CYNK-001 infusion. Subjects will be monitored for AEs throughout the study. Importantly, the symptoms associated with the subject's CRS should be captured independently from the CRS designation and graded using CTCAE, version 5.0 to facilitate greater understanding of CRS associated with CYNK-001.

The AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is

based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

12.3.1.8. Causality

The Investigator must determine the relationship between the administration of CYNK-001 and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

- Not suspected: a causal relationship of the AE to CYNK-001 administration is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
- Suspected: there is a reasonable possibility that the administration of CYNK-001 caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between CYNK-001 and the AE.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional CYNK-001 that has not been manufactured or provided by Celularity, please provide the name of the manufacturer when reporting the event.

12.3.1.9. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

12.3.1.10. Action Taken

The Investigator will report the action taken with CYNK-001 as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption, or dose reduction of CYNK-001, as appropriate) and report if concomitant and/or additional treatments were given for the event.

12.3.1.11. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

12.3.1.12. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of CYNK-001 dose, or any other therapeutic intervention; or

- is judged to be of significant clinical importance, e.g., one that indicates a new disease process and/or organ toxicity or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

Laboratory analyses will occur both centrally and locally. In the event that locally drawn laboratory testing identifies abnormal results, these data will be collected in the eCRF. In the event that multiple blood draws occur on the same day, only the most clinically relevant draw of the day should be collected.

12.3.1.13. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or a male subject whose partner is of childbearing potential are immediately reportable events.

i. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on CYNK-001, or within 28 days of first treatment with CYNK-001, are considered immediately reportable events. Investigational product is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy and must notify Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in-utero exposure to the CYNK-001 should also be reported to Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

ii. Male Subjects

If a female partner of a male subject taking CYNK-001 becomes pregnant, the male subject taking CYNK-001 should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

12.4. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method (e.g., via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to CYNK-001) that occur during the study (from the time the subject signs Study ICF until Study Day 28) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to CYNK-001. SAEs occurring prior to treatment (Screening Period) will be captured in the EDC.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celularity and the IRB/EC.

12.5. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Drug Safety will determine the expectedness of events suspected of being related to CYNK-001 based on the IB.

In the United States, all SUSARs will be reported in an expedited manner in accordance with 21 CFR 312.32.

Events of PD for the disease under study (including deaths due to PD for indications that are considered to be fatal) will be assessed as anticipated AEs and will not be reported as expedited safety reports to regulatory authorities.

Celularity or its authorized representative shall notify the Investigator of the following information.

- Any AE suspected of being related to the use of CYNK-001 in this study or in other studies that is both serious and unexpected (i.e., SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celularity and the IRB/EC.

12.6. Potential Risks and Management of Treatment Toxicities

12.6.1. Graft Versus Host Disease (GvHD) Target Organ Staging

AEs that are related to GvHD should be monitored for at least 100 days after last CYNK-001 infusion and evaluated for severity/intensity according to guidelines outlined by the Mount Sinai Acute GvHD International Consortium as outlined in Table 6 (Harris, 2016).

Table 6: GvHD Staging

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper Gastrointestinal (GI)	Lower Gastrointestinal (GI) (stool output/day)
0	No active (erythematous) GvHD rash	< 2 mg/dL	No or intermittent nausea, vomiting, or anorexia	< 500 mL/day or < 3 episodes/day
1	Maculopapular rash < 25% body surface area	2 to 3 mg/dL	Persistent nausea, vomiting, or anorexia	500-999 mL/day or 3 to 4 episodes/day
2	Maculopapular rash 25% to 50% body surface area	3.1 to 6 ml/dL		1000 to 1500 mL/day or 5 to 7 episodes/day
3	Maculopapular rash > 50% body surface area	6.1 to 15 mg/dL		> 1500 mL/day or > 7 episodes/day
4	Generalized erythroderma (> 50% body surface area) plus bullous formation and desquamation > 50% body surface area	> 15% mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

Source: Harris, 2016

12.6.2. Cytokine Release Syndrome (CRS)

CYNK-001 is a cryopreserved formulation of PNK-007 and testing has found these products to be comparable. Administration of PNK-007 has been associated with CRS. A CRS is a nonantigen-specific toxicity that occurs as a result of high-level immune activation. The magnitude of immune activation typically required to mediate clinical benefit using modern immunotherapies exceeds levels of immune activation that occur in more natural settings. As immune-based therapies have become more potent, this syndrome is becoming increasingly recognized (Lee, 2014).

CRS is characterized by high fever, fatigue, nausea, vomiting, diarrhea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, anorexia, and neurologic abnormalities (e.g., altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity). Timing of symptom onset and CRS severity depends on the inducing agent and the magnitude of immune cell activation (Lee, 2014).

Subjects at high risk of developing severe CRS (sCRS) include those who develop the following (Davila, 2014):

- Fever (≥ 38 ºC) for at least 3 consecutive days
- Changes in 2 different cytokines of at least 75-fold or a maximum change in 1 cytokine of at least 250-fold
- One or more clinical signs of toxicity such as:
    - Hypotension (requiring vasopressor support)
    - Hypoxia (pO2 < 90%)
    - Neurologic disorders (including mental status changes, obtundation, and seizures)

Elevated CRP (≥ 20 mg/dL) levels are also a reliable indicator of sCRS (Davila, 2014). Thus, close observation of these subjects is strongly recommended.

A proposed American Society for Transplantation and Cellular Therapy [(ASTCT); formerly American Society of Bone and Marrow Transplant (ASBMT)] consensus definition and grading for CRS and ICANS was released in December 2018 (Lee, 2019). Recognizing the disparity in published grading schemes and the need for harmonization of definitions and grading systems for immune effector cell-associated CRS and neurotoxicity seen after immune effector cell therapies including Chimeric Antigen Receptor (CAR) Thymus cell (T cell) therapy, 49 experts from all aspects of the field met in Arlington, VA on June 20-21, 2018, at a meeting supported by the ASBMT. Attendees included leaders from major academic centers involved in CAR T cell therapy research as well as representatives from industry, the Center for International Blood and Marrow Transplant Research (CIBMTR), the American Society of Hematology (ASH), and the National Cancer Institute (NCI). In addition, these guidelines were presented at the CIBMTR CT Registry Forum on October 25, 2018, for discussion and comment.

It was highlighted by this group that CRS is observed not just with CAR T and other immune effector cell therapies. Preclinical studies suggest that CRS could be observed with CAR NK cell therapy as well.

The CRS was re-defined by this group as a "'supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction'. CRS should be applied to any immune effector cell-engaging therapy, not just with CAR T cells." (Lee 2019)

12.6.2.1. Cytokine Release Syndrome Diagnosis

Common symptoms of CRS are not unique to CRS and hence, practitioners must be cautious and exclude other causes of fever, hypotension, hemodynamic instability, and/or respiratory distress,

such as an overwhelming infection. A reasonable temporal relationship to the cell therapy must be present. The group had excluded the immune effector cell-associated neurotoxicity from the definition of the CRS. They did describe Immune Effecter Cell Associated Neurotoxicity Syndrome (ICANS) as part of the ASTCT consensus grading. (Lee, 2019)

12.6.2.2. Cytokine Release Syndrome Grading

For the purposes of this study, the ASTCT CRS consensus Grading will be used.

Table 7: ASBMT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥ 38° Celsius	Temperature ≥ 38° Celsius	Temperature ≥ 38° Celsius	Temperature ≥ 38° Celsius
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or†				
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Abbreviations: BiPAP = Bilevel positive air pressure; CPAP = Continuous positive air pressure; CRS = cytokine release syndrome
*Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
†CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

12.6.2.3. Cytokine Release Syndrome Management

During the ASTCT consensus on the CRS grading, a need for variation in practitioner intervention for CRS treatment was recognized. The below Algorithm provides one of the key recommendations for CRS treatment while allowing investigators to maintain their usual practice.

Figure 3: Cytokine Release Syndrome Treatment Algorithm

Adapted/modified from Lee, 2014

All subjects at time of CYNK-001 treatment:
- Monitor for CRS symptoms (fever, fatigue, anorexia, neurologic changes)
- Follow serum CRP, ferritin, and coagulation as clinically indicated

Grade 1 CRS
- Evaluate fever, take surveillance cultures, give antibiotics per institutional guidelines
- Admit and monitor closely for organ dysfunction, include neurologic exams if clinically indicated
- Follow CRP, ferritin, and coagulation daily
- Symptomatic support (e.g., antipyretics)
- If rapid progression from time of first fever, and/or CRP rising quickly within 96 hours, recommend Tocilizumab

Grade 2 CRS
- Frequent inpatient monitoring until fever and symptom resolution, include neurologic evaluations if clinically indicated
- Follow CRP, ferritin, and coagulation daily
- Symptomatic, hemodynamic, and respiratory support
- Initiate seizure prophylaxis if clinically indicated, consider EEG monitoring
- Recommend Tocilizumab
- If CRS rapidly progressing (progressive hypotension, neurologic symptoms, and/or rapid rise in CRP) or refractory to tocilizumab, recommend corticosteroids

Grade 3 CRS
- ICU-level monitoring until stable, include neurologic exams if clinically indicated
- Follow CRP, ferritin, and coagulation daily
- Symptomatic, hemodynamic, and respiratory support
- Initiate seizure prophylaxis if clinically indicated, consider EEG monitoring
- Recommend Tocilizumab
- Recommend corticosteroids every 12 to 24 hours
- If CRS rapidly progressing recommend increased dose and frequency of corticosteroids and/or other IL-6 blocking agents

Grade 4 CRS
- ICU-level monitoring until stable, include neurologic exams if clinically indicated
- Follow CRP, ferritin, and coagulation daily
- Symptomatic, hemodynamic, and respiratory support
- Initiate seizure prophylaxis if clinically indicated, consider EEG monitoring
- Recommend Tocilizumab
- Recommend corticosteroids every 6 to 12 hours
- If CRS persists, recommend increased dose and frequency of corticosteroids and/or other IL-6 blocking agents

Abbreviations: CRP = C-reactive protein; CRS = cytokine release syndrome; EEG = electroencephalogram; IL = interleukin; ICU = intensive care unit

12.6.3. Immune Effector Cell-associated neurotoxicity syndrome (ICANS)

Immunotherapies that function through activation of immune effector cells might be associated with neurological toxicity. Per ASTCT consensus, ICANS is defined as "a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.

12.6.3.1. ICANS Grading

For the purposes of this study, the ASTCT ICANS consensus Grading will be used. In this grading system, the final ICANS grade is determined by the most severe event among the different domains.

Table 8: ASTCT Neurotoxicity Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

(Lee, 2019) EEG = Electroencephalography; ICE = Immune effector cell; ICP = Increased cranial pressure; N/A = Not applicable;

12.6.3.2. ICANS Management

The supportive care should be provided per standard institutional guidelines after other causes for neurological symptoms were excluded.

14. STATISTICS

14.1. Statistical Overview

The objectives of the Phase I portion are to evaluate the safety and efficacy (for lack of efficacy) of CYNK-001.

The overall clinical benefit in the Phase II portion of the study will be evaluated by comparing therapeutic effect of CYNK-001 versus the control group (best supportive care alone). Safety and tolerability by adverse events, labs, vital signs, etc. will also be evaluated.

A detailed Statistical Analysis Plan (SAP) will be provided in a separate document.

14.2. Study Population Definitions

The following analysis populations are planned for this study:

- Safety Population – include all subjects who receive any amount of CYNK-001 or who enroll into the control group.
- ITT Population – include all randomized subjects.

14.3. Baseline and Demographic Characteristics

Baseline and demographic characteristics will be summarized. Continuous variables will be summarized using descriptive statistics such as mean, median, minimum, and maximum, while gender, race, and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

14.4. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

14.5. Safety Analysis

Safety analysis will be based on the Safety Population. Descriptive statistics will be provided for AEs, vital sign measurements, physical examination findings, clinical laboratory test results, infusion site assessments, and concomitant medications and procedures.

AEs observed will be classified using the MedDRA classification system (MedDRA version 23.0). The severity of the toxicities will be graded according to the NCI CTCAE, version 5.0 whenever possible. Adverse events will be summarized by MedDRA system organ class and preferred terms, and separate tabulations also will be produced for related adverse events, SAEs, discontinuations due to adverse events, and events of at least Grade 3 severity. A summary of the number and severity of CRS AEs will also be produced. AEs will be summarized by study period for those events that occur during the study periods.

Vital signs data and laboratory data will be tabulated for changes over time.

Laboratory parameters will be summarized for changes across study using descriptive statistics including shifts relative to CTCAE criteria for laboratory abnormalities. Laboratory measures will also be compared with their corresponding normal ranges, and the incidence of abnormally high and abnormally low laboratory values will be summarized.

Graphical displays may be provided where useful in the interpretation of results.

14.6. Efficacy Analysis

Phase I efficacy data will be summarized by descriptive analyses. The efficacy endpoints used in the lack of efficacy tests is the responses at Day 15 of the clinical improvement by OSCI. If efficacy is not established in 2 out of the 14 subjects, the study will be terminated. If efficacy is noted in 2 or more subjects, the study will move forward to the Phase II portion.

Efficacy endpoints are defined in Section 6.9 .

[redacted]

No interim analysis will be implemented in this study.

14.8. Sample Size and Power Considerations

Phase I:

Fourteen (14) subjects will be treated by CYNK-001 in the Phase I portion. Based on clinical judgement for this coronavirus disease and the current treatment status, this sample size is

appropriate to evaluate the safety of CYNK-001, and to evaluate the lack of efficacy before starting Phase II portion. This number is not based on hypothesis testing and power calculation.

Phase II

[redacted]

14.9. Subject Replacement

Subjects will not be replaced.

14.10. Study Stopping Rules

Phase I of the study:

a. Safety Stopping Rules:

In addition to the evaluation of vital signs, performance status, a Consultation with the Medical Monitor is required prior to each CYNK-001 infusion if there is:

- an increase in supplemental oxygen of greater than or equal to 50% from baseline (for first CYNK-001 infusion) or from level at prior CYNK-001 infusion (for second and third CYNK-001 infusion) resulting in oxygen use of greater than 8L.

-or-

- a change in the mode of supplemental oxygen delivery with the intention to deliver oxygen more efficiently.

The Medical Monitor will escalate to the Sponsor clinical and safety team as appropriate per GCP guidelines to advise if a subject who is experiencing rapid worsening of disease should proceed to first or subsequent CYNK-001 infusion.

b. Study Stopping Rules:

- During Phase I, 3 subjects will be initially monitored for any potential DLTs until 24 hours after the final dose given to the 3rd subject. If any DLTs occur, the DMC will be convened. Study will proceed to enroll the remaining 11 subjects if it is deemed safe in the first 3 subjects. For the remaining 11 subjects, DMC will be convened if the safety stopping rule which is defined as death in any of the subjects irrespective of relatedness to the product is met. Overall, in case of 2 out of the 6 subjects had experienced DLTs in the Phase I portion of this study, the DMC will be convened for safety evaluation.

- The study will be stopped, and DMC will be convened, if death in any of the 14 subjects had occurred by Study Day 15 from the first dose of CYNK-001infusion irrespective of relatedness to CYNK-001. If no such events have occurred in all 14 subjects, it is deemed safe to proceed to Phase II of the study.
- All other serious adverse events assessed as "Related to product" will be tracked and sent for DMC review and recommendation but will not trigger the study to be stopped unless recommended by the DMC Chair.
- Worsening of a condition in any subject will be tracked and sent for DMC review and recommendation but will not trigger the study to be stopped unless recommended by the DMC Chair.

b. Efficacy (Futility) Stopping Rules:

By Day 15 of CYNK-001 infusion in the Phase I, the study may stop for futility if there is less than 2 subjects with clinical improvement of at least one "Patient State" category as defined by the OSCI (Appendix D).

If at least 2 out of the 14 subjects by Day 15 demonstrated efficacy in the Phase I portion of the study, the study will move forward to the Phase II.

Phase II of the study:

- The study will be stopped, and DMC will be convened: if death had occurred by Study Day 15 of CYNK-001 infusion irrespective of relatedness to the product.
- DMC will be convened at midpoint (after 18 subjects have received treatment) during this portion of the study to evaluate safety for adverse event of interest such as shock, ARDS, and death in the treatment group versus the control group.
- All other serious adverse events assessed as "Related to product" will be tracked and sent for DMC review and recommendation.
- Worsening of a condition in any subject will be tracked and sent for DMC review and recommendation but will not trigger the study to be stopped unless recommended by the DMC Chair.

14.11. Other Topics

14.11.1. Dose Limiting Toxicity (DLT)

For the purposes of DLT assessments for the Phase I portion of the study, AEs will be collected up to Day 28 post first dose of CYNK-001 infusion. Please refer to Section 6.3 for definitions.

14.11.2. Data Monitoring Committee (DMC)

A DMC will monitor the safety and efficacy information to ensure subject safety in accordance with a separate charter. The DMC may be comprised of external members who may not be involved in the day-to-day activities of the CYNK-001study team but will be physicians and/or Clinical Research Experts with experience treating coronavirus infections and/or clinical trial involvement with this specific subject population. The DMC will recommend whether dose de-escalation is required, whether modifications to the protocol design are necessary or whether to end dosing and/or further enrollment to the study is required. The DMC will make their determinations based on available clinical data. The decisions of the DMC will be documented in meeting minutes.

An initial DMC meeting to introduce the DMC members to the Celularity study team, relevant other parties and provide an overview of the overall study plan with applicable documentation will be conducted. The DMC will be convened for subsequent meetings:

- Upon completion of 24 hours after the final dose was provided to the 3rd subject in the Phase I portion of the study to evaluate the safety data.
- Upon an event that met the safety study stopping rules in both Phase I and Phase II of the study (Section 14.10).
- After Day 15 of the final subject treated in the Phase I portion of the study is complete, DMC will meet for review of safety and efficacy data and to recommend moving forward with the Phase II portion of the study.
- Upon completion of the study.
- In the event that during the course of the Phase I or Phase II portions of the study, even if a single subject experiences an event listed below, the DMC Chair will be notified within 24 hours of the sponsor being informed. The DMC chair may review the case and if deemed necessary request that a meeting be convened to evaluate the event. If specified, the site may be placed on investigational medicinal product (IMP) treatment hold until the event is investigated.
    - A DLT event during 28 days from first dose of CYNK-001 infusion (to Study Day 28).
- When the DMC chair requests an ad hoc meeting (e.g., when an Urgent Safety Measure requires).
- Closed session may be held during the DMC meeting per request from the DMC Chair.

- Participation of treating investigators in the DMC meetings is optional. DMC may request treating investigators to attend DMC meeting and provide additional information for subject under review.
- Data outputs for review should be provided to the DMC via email at least 2 weeks prior to scheduled meeting.

At a minimum, the scope of the meeting/suggested agenda for subsequent DMC meetings is as follows:

a. Overview of current study enrollment status including but not limited to, recruitment, ineligibility rate and site status.
b. Overview of subject status including but not limited to, baseline characteristics, safety/adverse event profile and known subject outcomes.
c. Cumulative data for all subjects enrolled into the study, including safety and efficacy information.
d. Suggestions for modifications to any of the documents listed below
    a. Format of interim reports to the DMC
    b. Method and timing of the delivery of the report to the DMC members prior to the meeting
    c. Protocol
    d. Master informed consent document
    e. Case report forms
    f. Other important study documents
e. Conclusions/Recommendation Rationale for moving forward with the study
f. In the event of an ad hoc meeting, the scope of the information will be defined by the event that lead to the meeting request (e.g., Urgent Safety Measure)

The Sponsor will take appropriate action based upon the recommendations of the DMC and this will be communicated to the Investigator. The Investigator will be responsible for notifying their IRB/EC.

14.12. Exploratory Analysis

Descriptive statistics will be provided for collected biomarker data. The analysis plan and the analyses will be documented in a separate document and will be reported separately.

15. REGULATORY AND ETHICAL CONSIDERATIONS

15.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celularity, its authorized representatives, and Investigators abide by Good Clinical Practice (GCP), as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines. The Investigator will conduct all aspects of this study in accordance with the study protocol, applicable national, state, and local laws of the pertinent regulatory authorities.

15.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celularity staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celularity information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an ICF and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celularity on public registry websites) is considered Celularity confidential information. Only information that is previously disclosed by Celularity on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celularity protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celularity. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celularity for review and approval, providing at least 10 business days for review.

At the time results of this study are made available to the public, Celularity will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

15.3. Institutional Review Board (IRB) / Ethics Committee (EC) Review and Approval

Before the start of the study, the study protocol (or protocol amendment, if applicable), ICF, IB, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

The final study protocol (or protocol amendment, if applicable), including the final version of the ICF, and any other appropriate documents must be approved or given a favorable opinion in writing by an IRB/EC as appropriate. The study will receive approval from an IRB/EC prior to commencement. The investigator must submit written approval to Celularity before he or she can enroll any subject into the study. Formal approval by the IRB/EC should mention the Investigator name, protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

CYNK-001 can only be supplied to an Investigator by Celularity or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celularity or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP Guidelines. For example, the IRB General Assurance Number may be accepted as a substitute for this list.

Any amendment to the protocol must be approved by the Celularity prior to distribution to sites. The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments will be submitted to the IRB/EC for written approval. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised. Written approval must be obtained before implementation of the amended version occurs.

Amendments that are administrative in nature do not require IRB/EC approval but will be submitted to the IRB/EC for information purposes.

Any advertisements used to recruit subjects for the study must be reviewed by Celularity and the IRB/EC prior to use.

The Principal Investigator is responsible for informing the IRB/EC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/EC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB/EC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB/EC with reports of any reportable serious adverse drug reactions with the investigational product provided by Celularity to the Principal Investigator, according to IRB/EC reporting requirements.

If required by legislation or the IRB/EC, the Investigator must submit progress reports and notifications of serious adverse drug reactions to the IRB/EC accordingly.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

15.4. Written Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative (LAR) prior to any study related procedures. The investigator or his/her representative will explain the nature of the study to the participant or his/her LAR and answer all questions regarding the study. Participants must be informed that their participation is voluntary. Participants or their LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

Documentation that informed consent occurred prior to the study subject's entry into the study, of the informed consent process, and date the written consent was obtained should be recorded in the study subject's source documents including the date.

The original ICF signed and dated by the study subject (or the subject's LAR) and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF unless otherwise specified by the IRB/EC approval. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Many COVID-19 patients have shown symptoms of confusion, disorientation, and fatigue, which may render them less than fully capable to provide informed consent. This may necessitate the increased use of subject's LAR for consent purposes for this clinical trial. In accordance with the principles outlined in the NIH guideline "Research Involving Individuals with Questionable Capacity to Consent: Points to Consider, November 2009", clinic staff will assess a subject's capacity to provide informed consent. If found incapable, staff may engage the patient's family or other individuals given durable power of attorney for health care, to determine whether an LAR appointment is in the interest of the patient. LAR appointment will be documented and comply with all state laws and regulations. LARs will be informed about the role of an LAR and provided information about the health status of the research subject.

If informed consent is given via a subject's LAR, the initial study procedures will be performed. During the course of the study, continuous assessment of informed consent will be maintained. Techniques will be used to maintain informed consent and enhance study information

comprehension. These techniques will include repeated assessment of the subject's consent capacity, oral repetition of study information, and presentation of graphical and animated/narrated forms of study information and the informed consent process. All materials used will be submitted to the IRB for approval prior to their use.

Impairment in a subject's capacity to give informed consent due to COVID-19 is expected to be partial or fluctuating. If a subject is enrolled in the study by way of LAR consent, and during the study becomes competent to give consent, informed consent will be obtained again directly from the subject.

15.5. Confidentiality

Celularity requires the Investigator to permit Celularity's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws. Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

Celularity affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent).

16. DATA HANDLING AND RECORDKEEPING

16.1. Records and Reports

All participant data relating to the study will be recorded in the eCRFs. The Investigator / Institution must maintain accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects in a manner that will allow for adequate oversite of the study activities. The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, legible, filed and retained. Examples of study records and source documents include but are not limited to: hospital records; clinic and office charts; administrative study files; correspondence files; master subject list; appointment books; sign-in logs; screening lists; AE reporting forms (e.g., Study specific SAE report forms or MedWatch forms where applicable; laboratory notes; memoranda; subject's diaries or evaluation checklists; quality of life questionnaires, dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy and cell therapy dispensing unit, and the laboratories, as well as copies of eCRFs or CD-ROM. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

16.2. Retention of Records

The Principal Investigator / Institution must maintain all documentation relating to the study for a period of time outlined in the clinical trial agreement associated with this study or according to local laws or requirements, whichever is longer.

Study related documentation relating to the study may include but are not limited to the following:

- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Record of all communications between the Investigator, Celularity, and their authorized representative(s);
- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Study Drug accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Principal Investigator / Institution must notify Celularity if he/she wishes to remove these documents to another location, assign document responsibility to someone else or is unable to retain them for a specified period. The Principal Investigator must obtain approval in writing from Celularity prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celularity for permission to make alternative arrangements. Details of these arrangements should be documented. The Principal Investigator / Institution should take measures to prevent accidental or premature destruction of study related documents.

If it becomes necessary for Celularity or applicable Regulatory Authorities to review any documentation relating to the study, the Investigator / Institution must permit access to such records at any time during or post-study.

16.3. Data Collection and Management

Data will be collected via eCRF and entered into the clinical database per Celularity designated standard operating procedures (SOPs) and in accordance with the study specific clinical trial database/s. This data will be electronically verified through use of programmed edit checks specified by the clinical team as well as manual reviews of data in accordance with study related plans. Identified discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these identified issues will be reflected in the database. An audit trail within the system will track all changes made to the data in accordance with applicable regulations. Upon completion of the study, compact disc contains all documents of the eCRFs, complete with the audit trails for documentation of data would be generated and archived. All documents of the eCRFs will be reviewed, validated and quality controlled to ensure that everything in the database is successfully transferred into the acceptable compact disc for storage.

17. SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

17.1. Direct access to source data/documents

All aspects of the study will be carefully monitored by Celularity or its authorized representative for compliance with applicable government regulations with respect to current GCP and Celularity designated SOPs. Celularity ensures that appropriate monitoring procedures are performed before, during and after the study.

17.2. Study Monitoring

All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Before an investigational site can enter a patient into the study, a representative of Celularity will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Celularity or its representatives. This will be documented in a Clinical Study Agreement between Celularity and the Investigator.
- Prior to enrolling subjects into the study, a Celularity representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. The site will provide Celularity with applicable documentation associated with location of study conduct as well as location of any source documentation that will be used to verify data. Ongoing and supplemental training will be provided as requested during the conduct of the study.

Celularity and/or its designees will be allowed to conduct on-site visits to the investigation facilities for the purpose of monitoring any aspect of the study. In the event that remote monitoring is available, this would be permitted after written approval by the investigational site and Celularity or its representatives. During the study, a monitor from Celularity or representative will have regular contacts with the investigational site. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. Monitoring will include but not be limited to the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed.

- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to Celularity.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Celularity and those SAEs that met criteria for reporting have been forwarded to the IRB.
- Confirm that documentation associated with delegation of responsibilities and associated training of site study personnel.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

17.3. Audits and Inspections

Authorized representatives of Celularity, a regulatory authority, an IRB/EC may visit the site to perform audits or inspections, including source data verification. The purpose of a Celularity audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact Celularity immediately if contacted by a regulatory agency about an inspection.

The Investigator and/or Study site is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulator authorities (e.g., FDA, European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA), Health Canada (HC) and Celularity authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory agency regarding an inspection, he/she should contact Celularity immediately.

17.4. Institutional Review Board (IRB)

The Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the informed consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities. All materials approved by the IRB/EC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for to the monitor.

18. PUBLICATION POLICY

With exception to the information provided by Celularity on the public registry websites and/or Celularity approved recruitment material, any information regarding this clinical study is considered confidential and/or proprietary and is not to be used in any publications, press releases or other public disclosure without the written approval from an authorized representative of Celularity. Celularity protocol-related information proposed for use in a publication must be submitted to Celularity for review and written approval prior to publication, as agreed and described in the Clinical Trial Agreement.

Celularity will ensure that Celularity-sponsored studies are considered for publication in scientific literature in a peer-reviewed journal, irrespective of the results. This applies to results of all Phase 3 clinical studies, and any other study results of significant medical importance, at a minimum. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses and may be used for scientific exchange and teaching purposes. This study and its results may be submitted for inclusion in appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable), and contribution to abstract, presentation and/or publication development.

19. LIST OF REFERENCES

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APPENDIX A. SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE

SOFA score	**1**	**2**	**3**	**4**
Respiration [a]				
PaO_2/FIO_2 (mm Hg)	<400	<300	<220	<100
SaO_2/FIO_2	221-301	142-220	67-141	<67
Coagulation				
Platelets x $10^3/mm^3$	<150	<100	<50	<20
Liver				
Bilirubin (mg/dL)	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular [b]				
Hypotension	MAP <70	Dopamine ≤5 or dobutamine (any)	Dopamine >5 or norepinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1
Central Nervous System				
Glasgow Coma Score	13-14	10-12	6-9	<6
Renal				
Creatinine (mg/dL) or urine output (mL/d)	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

Abbreviations: MAP, mean arterial pressure; SaO_2, peripheral arterial oxygen saturation

[a] PaO2/FIO2 ratio was used preferentially. If not available, the SaO_2/FIO_2 ratio was used

[b] vasoactive mediations administered for at least 1 hour (dopamine and norepinephrine µmg/kg/min).

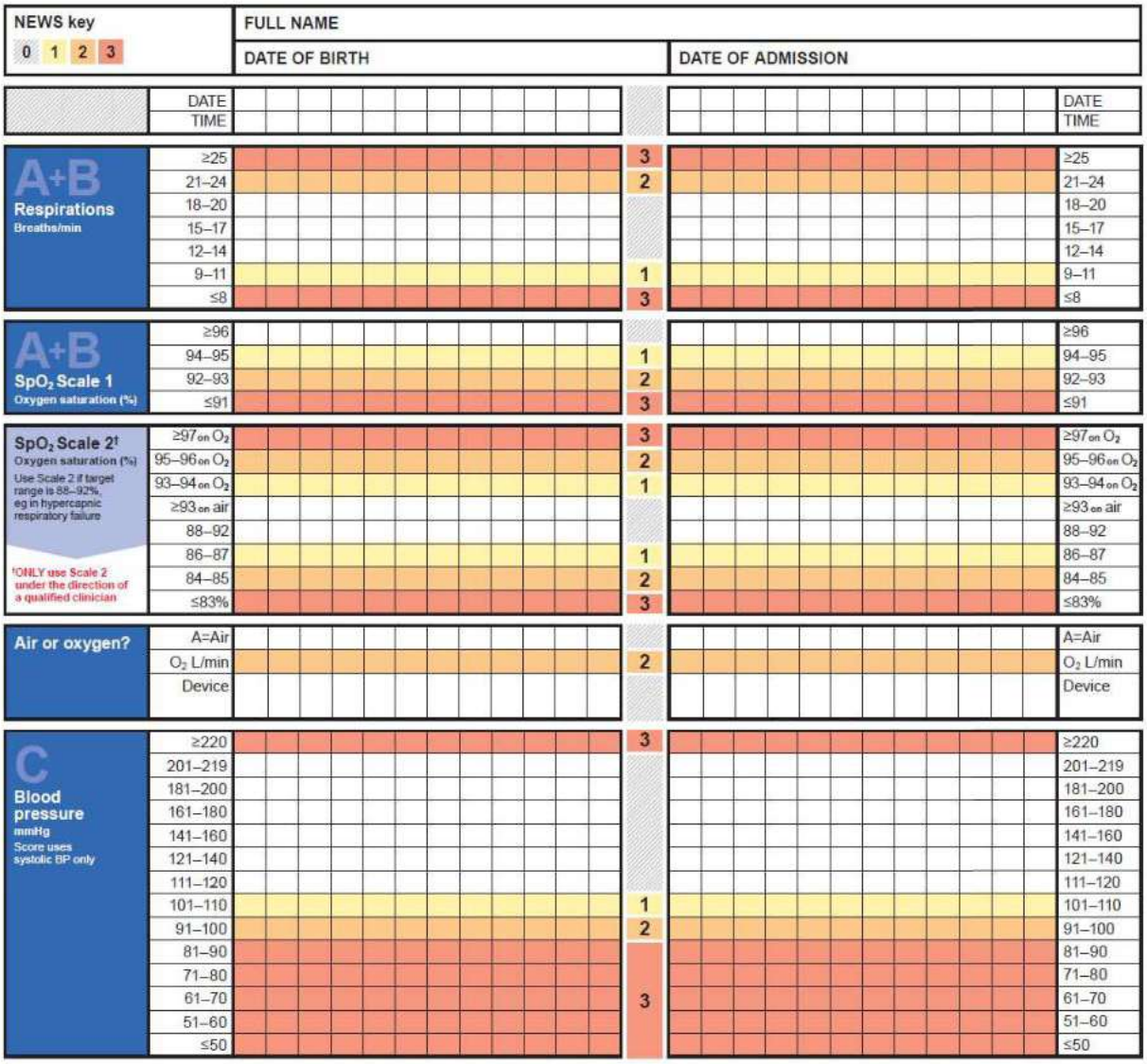
Source: Jones, 2009

APPENDIX B. KARNOFSKY PERFORMANCE STATUS

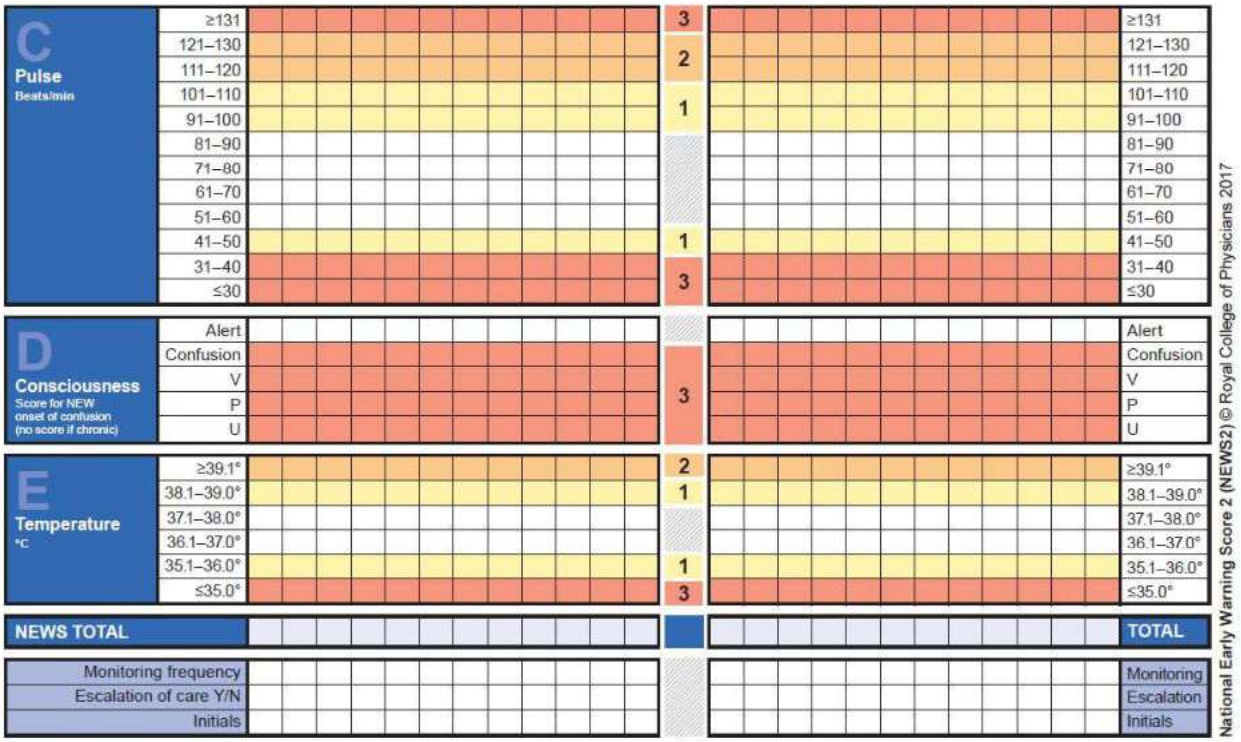
100	Normal; No complaints; No evidence of disease. Able to work.
90	Able to carry on normal activity, Minor symptoms. Able to work.
80	Normal activity with effort; Some symptoms. Able to work.
70	Cares for self; Unable to carry on normal activity. Independent; not able to work.
60	Disabled; dependent. Requires occasional assistance; cares for most needs.
50	Moderately disabled; dependent. Requires considerable assistance and frequent care.
40	Severely disabled; dependent. Requires special care and assistance.
30	Severely disabled. Hospitalized, death not imminent.
20	Very sick. Active supportive treatment needed.
10	Moribund. Fatal processes are rapidly progressing

Source: Mor 1984

APPENDIX C. NATIONAL EARLY WARNING SCORE 2 (NEWS2) SCORE



Sample NEWS2 Score calculation: Page 1 of 2
Source: Royal College of Physicians 2017



Sample NEWS2 Score calculation: Page 2 of 2
Source: Royal College of Physicians 2017

APPENDIX D. ORDINAL SCALE FOR CLINICAL IMPROVEMENT

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Source: World Health Organization (WHO) R&D Blueprint novel Coronavirus; COVID-19 Therapeutic Trial Synopsis, 2020.