A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PROOF-OF-CONCEPT STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RECOMBINANT HUMAN PLASMA GELSOLIN (RHU-PGSN) ADDED TO STANDARD OF CARE FOR TREATMENT OF SUBJECTS WITH SEVERE COVID-19 PNEUMONIA

Protocol Number:	BTI-202 NCT04358406
Investigational Product:	rhu-pGSN
IND Number:	N/A
EUDRA CT Number	2020-002460-31
Development Phase:	Phase 2
Indication Studied:	Severe pneumonia due to COVID-19
Sponsor Name and Address:	BioAegis Therapeutics, Inc. (BTI)
Responsible Medical Officer:	Mark J. DiNubile, MD FIDSA
Coordinating Investigators	Sandra Parra, MD and Antoni Castro, MD
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), and ICH GCP Guidelines. Essential study documents will be archived in accordance with applicable regulations.
Protocol Date:	09 June 2021
Version:	4.0

PROTOCOL APPROVAL SIGNATURE PAGE

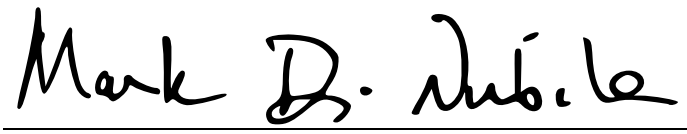
Protocol: BTI-202

Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept study to evaluate the Efficacy and Safety of Recombinant Human Plasma Gelsolin (rhu-pGSN) Added to Standard of Care for Treatment of Subjects with Severe COVID-19 Pneumonia

Date: 09 June 2021

Version: 4.0

Reviewed and Approved by:



09 June 2021

Mark J. DiNubile, MD
Chief Medical Officer
BioAegis Therapeutics, Inc.

Date

PROTOCOL ACCEPTANCE FORM

Protocol: BTI-202

Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept study to evaluate the Efficacy and Safety of Recombinant Human Plasma Gelsolin (rhu-pGSN) Added to Standard of Care for Treatment of Subjects with Severe COVID-19 Pneumonia

Date: 09 June 2021

Version: 4.0

I have carefully read the BTI-202 protocol and agree that it contains all of the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, ICH Guidelines for GCP, and all applicable regulatory requirements.

Investigator's Signature _____ Date _____

Name (printed) _____

1. SYNOPSIS

Name of Sponsor/Company:
BioAegis Therapeutics Inc.

Name of Investigational Product:
Recombinant Human Plasma Gelsolin (rhu-pGSN)

Name of Active Ingredient:
rhu-pGSN

Title of Study:
A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Trial to Evaluate the Efficacy and Safety of Recombinant Human Plasma Gelsolin (rhu-pGSN) Added to Standard of Care for Treatment of Subjects with Severe COVID-19 Pneumonia

Study center(s): 1-5 sites

Studied period (years):	**Phase of development:**
Estimated date first subject enrolled: 01 June 2020 Estimated date last subject completed: 21 October 2021	2 (Proof-of-Concept)

Objectives:

Primary

- To assess the efficacy (survival without organ failure on Day 14) of intravenous (IV) rhu-pGSN plus standard of care (SOC) vs placebo plus SOC (hereafter referred to as rhu-pGSN vs placebo) administered to hospitalized subjects with a primary diagnosis of coronavirus 2019 (COVID-19) pneumonia and in Part 1, a severity score of 4, 5, or 6, or for Part 2, intubated without extracorporeal membrane oxygenation (ECMO) with a severity score of 6 or 7 on the World Health Organization (WHO) 9-point severity scale
- To evaluate the safety (incidence of serious adverse events [SAEs]) of IV rhu-pGSN administered to hospitalized subjects with a primary diagnosis of COVID-19 pneumonia and in Part 1, a severity score of 4, 5, or 6, or for Part 2, intubated without ECMO with a severity score of 6 or 7 on the WHO 9-point severity scale

Secondary

- To further assess the efficacy of IV administered rhu-pGSN
- To measure changes in the WHO 9-point severity scale for SOC ± rhu-pGSN
- To evaluate the effect of administered rhu-pGSN on survival rates
- To assess the relationship of pGSN levels (and other biomarkers) at baseline with clinical outcomes
- To follow the pharmacokinetics (PK) of administered rhu-pGSN

Immunogenicity

- To investigate the development of antibodies against pGSN post-treatment in rhu-pGSN vs placebo recipients compared to baseline

Methodology:

This is a 2-part, randomized, double-blind, placebo-controlled, multicenter Phase 2 study to evaluate the efficacy and safety of rhu-pGSN plus SOC in subjects with severe COVID-19 pneumonia. Potential subjects hospitalized with pneumonia and laboratory-confirmed (reverse transcription polymerase chain reaction [RT-PCR$^+$]) or highly suspected (compatible with at least bilobar lung involvement without any other plausible diagnosis) COVID-19 etiology will be screened for Part 1 within 24 hours of reaching a WHO severity score of 4 to 6, whether the severity score is attained on admission or during hospitalization, or for Part 2, within 24 hours of intubation without ECMO with a WHO severity score of 6 or 7.

The 9-point WHO classification scheme for severe COVID-19 pneumonia will be applied to grade the severity of illness as follows:

8 Death
7 Mechanical ventilation or ECMO with either vasopressor support or dialysis/renal replacement therapy (RRT)
6 Intubation with mechanical ventilation, a mask with a reservoir or oxygen with high-flow nasal goggles but without vasopressor support or dialysis/RRT
5 Noninvasive ventilation (continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) or high-flow oxygen
4 Oxygen by mask or nasal
3 Hospitalized with no oxygen therapy
2 Limitation of activity
1 Infected without limitations
0 No clinical or virologic evidence of COVID-19 infection

Once informed consent is obtained, the following assessments/procedures will be performed:

1. Record medical history, including concomitant medications and current clinical status
2. Perform pregnancy test (urine or blood) for women of childbearing potential
3. Collect pretreatment blood samples for measurement of baseline pGSN level and for analysis of antibodies against pGSN
4. Calculate the CURB-65 score (**C**onfusion, **U**rea >7 mmol/L, **R**espiratory rate ≥30/min, **B**lood pressure systolic <90 or diastolic ≤60, and age ≥**65** years) at presentation
5. A RT-PCR test to confirm the diagnosis of COVID-19 should be documented during the current illness leading to the present hospitalization; if RT-PCR test is not done prior to screening, the test is to be performed during screening before randomization (result might not be available at randomization or start of study treatment). Perform physical examination (PE) and document radiographic evidence of pneumonia (chest x-ray [CXR] or computed tomography ([CT] scan if CXR is inadequate) if not already completed within the previous 48 hours per SOC
6. Obtain blood and sputum cultures and electrocardiogram (EKG) per SOC (if not already performed). The microbiology lab is encouraged to perform sputum (bacterial, viral, and mycobacterial, as indicated) and blood cultures, sputum Gram-stains, antigen detection on respiratory and urine specimens, and RT-PCR diagnostic tests as possible.
7. Measure routine lab tests and biomarkers, including ferritin, D-dimer, C-reactive protein (CRP) and procalcitonin level at local laboratory; collect aliquots of blood for subsequent biomarker assays (likely to include, but not limited to interleukin [IL]1[2] , IL6, IL10, tumor necrosis factor [TNF], etc.) for analysis at the central laboratory (see Table 5 Schedule of Assessments and

footnote ‘l’ for details).

8. If eligibility criteria are satisfied, subject to be randomized (1:1 to treatment arms rhu-pGSN:placebo) within 12 hours of informed consent (Part 1) or within 24 hours of intubation (Part 2).

Randomized subjects will receive the assigned dose of rhu-pGSN or an equal volume of sterile saline placebo as soon as possible (ASAP), but beginning no later than 12 hours of randomization. The rhu-pGSN dose will be based on actual body weight given at 12 mg/kg. After reconstitution, rhu-pGSN should not be kept at room temperature for >2 hours prior to beginning the infusion. The initial dose of study drug (Dose #1) will be followed by dosing at 12 (Dose #2) and 36 hours (Dose #3) after the initial administration. Study drug is administered as a slow IV bolus at a rate of 5-20 mL/min through a 0.2 μm filter. The syringe, in-line filter, and extension tubing for injection of study drug should be connected after disconnecting the IV as close to the subject as possible.

The primary efficacy endpoint will be assessed on Day 14, with secondary endpoints assessed on Days 7, 28, 60 (optional), and 90. Discharged subjects will return for follow-up evaluation on Days 14, 28, 60, and 90.

Screening laboratory and other tests can serve as baseline values for participants, they do not need to be repeated if performed within the prior 48 hours of randomization unless otherwise dictated by SOC; however, the blood sample for analysis of pGSN level must be repeated if not collected within 15 minutes of initiating the first dose of study drug. The day of first study drug administration will be used as baseline (Day 1) for analysis purposes.

Repeat CXRs, or CT scans if CXR is inadequate, and labs/cultures, etc. will be obtained during the hospitalization if/when indicated by SOC.

On Days 1 (predose), 28, and 90, blood samples for analysis of antibodies against pGSN will be collected.

If the patient expires, autopsy is encouraged.

Number of subjects (enrolled):

Part 1: A total of 60 evaluable participants randomized 1:1 to rhu-pGSN:placebo (30:30 subjects).

Part 2: A total of 20 evaluable participants randomized 1:1 to rhu-pGSN:placebo (10:10 subjects).

Although data will be examined both in total as well as grouped by baseline WHO score, subjects will not be formally stratified by severity group.

All reported deaths and treatment-emergent SAEs will be evaluated by the Data and Safety Monitoring Board (DSMB) within 4 working days of notification of the Contract Research Organization (CRO)/Sponsor.

In Part 1, periodic safety reviews will be conducted after 12, 24, 36, and 48 subjects have been fully dosed and completed assessment at Day 14. Only DSMB members will be provided with partially unblinded results separated into 2 groups by treatment without identifying the actual treatment. If all participants have completed study therapy before the last DSMB meeting involving review of 48 subjects after their Day 14 visit can be held, this meeting can be cancelled at the discretion of the DSMB chair. Data will be further unblinded and/or the study paused at the discretion of the DSMB chair; enrollment will continue during the safety analyses unless otherwise mandated by the DSMB chair.

Major inclusion criteria:

- Hospitalized with laboratory-confirmed (RT-PCR^{+}) or highly suspected (compatible with at least bilobar lung involvement without another plausible diagnosis) COVID-19
- Age ≥ 18 years
- **Part 1 only:** Weight ≤100 kg

- **Part 1 only:** Within 24 hours of reaching a WHO severity score of 4-6 either:
  - At admission
  - While already hospitalized.
- **Part 2 only:** Within 24 hours of intubation without ECMO with a WHO severity score of 6 or 7)
- Informed consent obtained from subject/next of kin/legal proxy
- Primary admitting diagnosis of pneumonia supported by a compatible clinical presentation with a documented infiltrate consistent with pneumonia on CXR or CT, as assessed by the admitting emergency department (ED), clinic, or ward physician or equivalent caregiver
- Recommended (not mandatory) guidance/discretionary criteria defining patients with pneumonia satisfying all 4 categories below:
  - At least 2 symptoms: difficulty breathing, cough, production of purulent sputum, or chest pain
  - At least 2 vital sign abnormalities: fever, tachycardia, or tachypnea (thresholds -- fever: body temperature >100.4°F [38°C]; heart rate >100 beats/min; respiratory rate >24/min)
  - At least one finding of other clinical signs and laboratory abnormalities: hypoxemia (O_2 saturation <90%), clinical evidence of pulmonary consolidation, or leukocytosis e $1.5x10^4$ or leukopenia $<4x10^3$
  - Chest imaging, or CT chest showing at least bilobar pulmonary infiltrates
    - Principal Investigator (PI) to note radiologic findings in the electronic case report form (eCRF)
    - Radiology report and conclusion should be summarized in the eCRF
    - A copy of the radiograph attached to be saved for review, if possible
- A hyperinflammatory status (defined by increased ferritin e 500 µg/L, D-dimer e 1000 ng/mL, or CRP e 75 mg/L)
- During the course of the study starting at screening and for at least 6 months after their final study treatment:
  - Female subjects of childbearing potential must agree to use 2 medically accepted birth control methods
  - Male subjects with a partner who might become pregnant must agree to use reliable forms of contraception (i.e., vasectomy, abstinence), or an acceptable method of birth control must be used by the partner
  - All subjects must agree not to donate sperm or eggs (ovocytes)

Major exclusion criteria:

- A negative RT-PCR test for COVID-19 in the absence of a positive test during the evaluation of the present illness (in the presence of a positive test during the current illness, preceding or subsequent negative tests do not disqualify the subject)
- Extracorporeal membrane oxygenation (ECMO)
- Pregnant or lactating women
- Active underlying cancer treated with systemic chemotherapy or radiation therapy during the last 30 days
- Transplantation of hematopoietic or solid organs
- Chronic mechanical ventilation or dialysis
- Otherwise unsuitable for study participation because of chronic, severe, end-stage, and life-

limiting underlying disease unrelated to COVID-19 likely to interfere with management and assessment of acute pneumonia, only comfort or limited (non-aggressive) care is to be given, or life expectancy <6 months unrelated to acute COVID infection in the opinion of the Investigator **Notes:** ➢ PK sampling is strongly encouraged. However, participants refusing some or all PK blood sampling can remain in the trial ➢ Participants with superinfection in addition to COVID-19 are eligible ➢ Caregivers can decide whether any other medications (investigational or otherwise) should be administered.
Investigational product, dosage and mode of administration: 10-mL vials containing 200 mg of lyophilized rhu-pGSN will be reconstituted to a volume of 5 mL with 4.56 mL of sterile water and drawn up into suitably sized syringes as dictated by the dose. • After reconstitution, rhu-pGSN can be refrigerated for up to 4 hours but should not be kept at room temperature for more than 2 hours. • Each subject will receive 3 doses of rhu-pGSN or placebo of equal volume, with the first dose administered ASAP but no later than 12 hours after randomization. Doses will be given within 4 total hours of reconstitution. • The drug will be administered by IV bolus at a rate between 5 and 20 mL/min through a standard 0.2-micron filter at 12 mg/kg (based on actual body weight) at 0, 12, and 36 hours (± 60 minutes).
Duration of treatment: 3 total doses starting with Dose #1 within 12 hours of randomization, Dose #2 12 hours later, and then Dose #3 after another 24 hours (36 hours after the initial dose [Dose #1]). Since pGSN is consumed more rapidly in patients with severe illness, the second dose is being given 12 hours (not 24 hours) after the first dose. **Duration of subject participation:** Day 14 post-first dose for the primary endpoint with daily assessments (including WHO severity score) from Day 1 until discharge and follow-up outpatient visits at Days 14, 28, 60 (if possible), and 90 days and as needed.
Reference therapy, dosage and mode of administration: Placebo (dosed at a volume of 0.30 mL/kg of 0.9% saline solution via IV push [matching the volume of rhu-pGSN for a patient of that size] injected at 5-20 mL/min though a standard 0.2-micron filter)
Concomitant medications: Subjects are treated according to the current SOC in the local facility. Subjects may continue their present medications as directed by their caregivers. Subjects may receive concomitant medications to treat symptoms, AEs, and inter-current illnesses that are medically necessary as standard care. All prior and concomitant medications, including generic name (if possible), and start date (if known) should be documented in the subject's file and in the eCRF.

Endpoints/Outcomes:

Primary

- Safety and tolerability
  - Incidence of SAEs in rhu-pGSN vs placebo groups
- Efficacy
  - Proportion of subjects alive not on vasopressors, mechanical ventilator, and dialysis on Day 14

Secondary

- Safety and tolerability
  - Incidence, causality, and severity of adverse events (AEs) (graded according to the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) in rhu-pGSN vs placebo groups
  - Frequencies of new or worsening clinically significant laboratory abnormalities in rhu-pGSN vs placebo groups
  - Mortality rate irrespective of cause at Days 28 and 90
- Efficacy
  - Daily change in 9-point WHO severity score through at least Day 14 (including after discharge, where feasible)
  - All-cause mortality at Days 28 and 90; time to death (Kaplan-Meier survival analysis)
  - Proportion of subjects alive on Days 7, 14, 28, 60, and 90 without:
    - Ongoing use of vasopressors
    - Ongoing intubation/mechanical ventilation
    - Ongoing residence in an intensive care unit (ICU)
    - New ongoing need for dialysis/RRT
  - Proportion of subjects discharged to home or immediate prior residence by Day 28
  - Days on the ventilator
  - Length of stay (LOS) in hospital and in ICU (days)
  - Re-admission to an acute-care hospital up to Day 90
- PK
  - PK for rhu-pGSN including maximum concentration (C_{max}), time to maximum concentration (T_{max}), terminal half-life ($T_{1/2}$), area under the curve from time zero to 8 hours (AUC_{0-8}), area under the curve from time 0 to infinity (AUC_{inf}) for Dose #1 within 15 minutes predose, and at 1 (±15 min), 2 (±15 min), 6 (±30 min), and 12 (±30 min) hours after end of administration (but prior to Dose #2); for Dose #3 within 15 minutes predose, and at 1 (±15 min), 2 (±15 min), 6 (±30 min), 12 (±30 min) and 24 (±30 min) hours after the end of administration (participants refusing these blood samplings can enter and remain in the trial).
- Immunogenicity
  - Presence of anti-pGSN antibodies on Days 1 (predose), 28, and 90

Exploratory

- Biomarkers
  - Changes in biomarkers and radiologic imaging over time with treatment

- Relationship of baseline biomarkers to clinical outcomes

Note: All deaths on-study must include cause of death as per investigator assessment and relationship to study drug and/or COVID-19.

Data and Safety Monitoring Board

See charter.

Statistical Methods and Sample Size Rationale for Power Calculations:

All subjects given e 1 dose of study drug will be included in the Full Analysis Set (FAS) according to actual drug received; non-completers will be counted as failures in the primary efficacy analysis. Subjects receiving all 3 doses and evaluable for the primary Day 14 endpoint will constitute the per-protocol population for efficacy assessment. WHO severity score will be recorded daily while the subject is hospitalized, after discharge through Day 14, where feasible, and at each follow-up visit.

AE data will be summarized for the FAS by actual drug received using counts and proportions of subjects having an AE, each AE type, and an AE of each System Organ Class. SAEs and reasons for any early discontinuation will be summarized similarly. All deaths will be categorized by cause of death as per investigator assessment and relationship to study drug and/or COVID-19.

Immunogenicity will be assessed on Days 1 (predose), 28, and 90 days in all participants. Antibodies against pGSN will be assayed from frozen specimens to determine whether the investigational product induces an antibody response in recipients.

For Part 1, binary efficacy endpoints will be compared between treatments via stratified Cochran-Mantel-Haenszel (CMH) test and, to accommodate continuous covariates, via logistic regression. Continuous efficacy and biochemical endpoints will be compared between treatments via mixed model repeated measures analysis or analysis of covariance, depending on whether repeated measures are available or not. Time-to-event analysis via stratified log rank test and Cox proportional hazards model may also be carried out as supplemental analyses.

For Part 1, exploratory analyses to compare the efficacy endpoint data from the rhu-pGSN group from this study to that of external control data may be carried out if appropriate. Sample size may be increased to improve the precision of the estimates of between-treatment comparisons if appropriate and if drug supplies are available.

The primary endpoint is difference between treatments in the proportion of surviving subjects off vasopressors, the ventilator, and dialysis on Day 14. For Part 1, the power for the study is computed for the expected increase in proportion of surviving subjects without these supports at Day 14 after start of study treatment. A total sample size of N=54 has ~80% power to yield a statistically significant (alpha=0.2 1-sided) difference if the TRUE underlying proportions are 20% and 5% for placebo plus SOC and rhu-pGSN plus SOC, respectively. The minimum OBSERVED difference from placebo plus SOC proportion 20% that yields statistical significance is 8.4% (20% vs 11.6%). As this is a pilot Phase 2 proof-of-concept (POC) trial in an infection with no approved therapy and false negative error (100% minus power) is equally as important as false positive error, the one-sided type 1 error is set at 0.2. Thus, the trial is adequately powered for its primary POC objective.

For Part 2, only descriptive statistics will be provided for exploratory analyses. Binary efficacy endpoints will be summarized by counts, percentages, and 95% confidence intervals (CIs) for each treatment group. Differences in percentages between treatment groups will be summarized by 95% CIs. Continuous efficacy and biochemical endpoints will be summarized by counts, means, standard deviations, median, minimum, maximum by treatment group. Differences in means between treatment groups will be summarized by 95% CIs. Natural log transformation may be necessary to better approximate a bell-shaped distribution for the continuous endpoints. Time-to-event endpoints will be summarized by

Kaplan-Meier plots, medians, quartiles, minimum, and maximum by treatment group. Bayesian posterior probabilities that differences from zero toward beneficial treatment effect for these summary statistics may be computed.

2. TABLE OF CONTENTS AND LIST OF TABLES

TABLE OF CONTENTS

LIST OF TABLES

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
ACE-2	angiotensin-converting enzyme 2
AE	adverse event
ALT	alanine aminotransferase
ASAP	as soon as possible
AST	aspartate aminotransferase
AUC_{0-8}	area under the curve from time zero to 8 hours
AUC_{inf}	area under the curve from time zero to infinity
BioAegis	BioAegis Therapeutics, Inc. or Sponsor
BiPAP	bilevel positive airway pressure
BUN	blood urea nitrogen
CAP	community-acquired pneumonia
CBC	complete blood count
CI	confidence interval
C_{max}	maximum concentration
CMH	Cochran-Mantel-Haenszel
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus 2019
CPAP	continuous positive airway pressure
CPK	creatine phosphokinase
CRO	Contract Research Organization
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CURB-65	Confusion, Urea >7 mmol/L, Respiratory rate e30/min, Blood pressure systolic <90 or diastolic d60, and age e65 years
CXR	chest x-ray
CYP450	cytochrome P450
DSMB	Data and Safety Monitoring Board

Abbreviation or Specialist Term	Explanation
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
ED	emergency department
EDC	electronic data capture
EKG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
f-actin	filamentous actin
FAS	Full Analysis Set
g-actin	globular actin
GCP	Good Clinical Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Independent Ethics Committee
IL	interleukin
INR	international normalized ratio
IRB	Institutional Review Board
IRR	injection-related reaction
IUD	intrauterine device
IV	intravenous
LDH	lactate dehydrogenase
LOS	length of stay
MV	mechanical ventilation
NCI	National Cancer Institute
NSAIDS	non-steroidal anti-inflammatory drugs
PDF	portable document format
PE	physical examination
PEEP	positive end-expiratory pressure

Abbreviation or Specialist Term	Explanation
pGSN	plasma gelsolin
PI	Principal Investigator The Investigator who leads the study conduct at an individual study site. Every study site has a Principal Investigator.
PK	pharmacokinetics
POC	proof of concept
rhu-pGSN	recombinant human plasma gelsolin
RRT	renal replacement therapy
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SDV	source data verification
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TNF	tumor necrosis factor
US	United States
VP	vasopressor
WHO	World Health Organization

4. INTRODUCTION

4.1. Coronavirus 2019 (COVID-19) Pneumonia

Pneumonia is an inflammatory condition of the lung primarily affecting the alveoli. It is usually caused by infection with viruses or bacteria and less commonly other microorganisms. Certain drugs and other conditions such as autoimmune diseases may cause a similar clinical picture.

Typical symptoms include a cough, chest pain, fever, and difficulty breathing. Diagnostic tools include chest x-rays (CXRs), serology, microscopy of a sputum smear and culture of the sputum. Treatment depends on the underlying cause. Pneumonia documented or presumed to be viral, bacterial, or fungal is treated with appropriate agents when available. If the pneumonia is severe, the affected person is admitted to hospital.

Pneumonia is classified according to the etiologic organism and where the infection was acquired (community or hospital facility).

Community-acquired pneumonia (CAP) is the most common type of pneumonia, and may be caused by pyogenic bacteria, atypical bacteria, viruses or fungi which often cannot be identified in real time. CAP may also have non-infectious etiologies, including allergic, immune-mediated, toxins, or drugs. CAP occurs throughout the world and is a leading cause of illness and death.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the angiotensin-converting enzyme 2 (ACE-2) receptors located to certain epithelial and endothelial cell surfaces. Lung tissue is the major, but not sole target of this novel coronavirus. The agent can cause fatal infections by eliciting an over-exuberant immune response leading to injurious lung inflammation +/- a cytokine storm. Patients may die from acute lung injury/acute respiratory distress syndrome or survive with debilitating pulmonary fibrosis. Interventions have been proposed as treatment modalities to decrease the viral load and/or to modulate the intense host reaction. Blunting of an overzealous inflammatory response can potentially improve respiratory outcomes independent of any direct antiviral effect. A coagulopathy that may result in large part from endothelial cell disruption can contribute to the pathogenesis by predisposing to disseminated microthrombi and large vessel thromboemboli. Older, hypertensive, and diabetic patients are at highest risk for complications and serious outcomes.

Plasma gelsolin (pGSN), an abundant, naturally occurring, circulating protein depleted in severe inflammatory conditions, offers similar promise in aborting lung injury, and offers a possible novel therapeutic agent in this time of crisis. Since recombinant human pGSN (rhu-pGSN) is a pathogen-indifferent treatment acting primarily on host inflammatory responses, the microbial etiology of life-threatening pneumonia is not particularly relevant.

4.2. Current Treatment of COVID-19 Pneumonia

Possible treatments for COVID-19 pneumonia include corticosteroids; lopinavir/ritonavir; chloroquine or hydroxychloroquine +/- azithromycin; remdesivir; ACE-2 blockers; interleukin (IL)-1 and IL-6 inhibitors; kinase inhibitors; interferons; and passive antibody either convalescent plasma-derived or monoclonal; granulocyte-macrophage colony-stimulating factor (GM-CSF); anti-coagulants; among others. With the possible exceptions of remdesivir and

corticosteroids, the evidence that specific therapies favorably impact the course of the disease has not been persuasively demonstrated. Some interventions seem to be helpful early but not later in the course of illness, such as monoclonal antibodies directed against COVID-19 surface proteins. Antiviral agents may also be more effective before disease becomes too advanced.

Proof-of-concept (POC) for rhu-pGSN therapy in human conditions has not yet been established but there are abundant animal data demonstrating survival benefits with tissue protection in diverse infectious and non-infectious inflammatory conditions. The recombinant human formulation (rhu-pGSN) developed by BioAegis Therapeutics, Inc. (BioAegis or Sponsor) has already been administered to patients with mild community-acquired pneumonia (CAP) in a small dose-ranging trial supporting safety and tolerability (https://clinicaltrials.gov/ct2/show/NCT03466073).

4.3. Plasma Gelsolin

Plasma gelsolin (pGSN) is a human protein produced and secreted by virtually every cell type, and it circulates at high levels in the blood of healthy individuals. At normal levels of 200-300 mg/L, it is the fourth most abundant protein in the circulation.

The therapeutic protein developed by BioAegis is rhu-pGSN and was formerly referred to as BG9385. It is identical to the complete natural protein and is comprised of 755 amino acids. The protein, like the natural protein, is non-glycosylated. The protein consists of six repeated domains, which make up three distinct actin binding sites, two that bind globular actin (G-actin) and one that binds filamentous actin (F-actin). Domain 1 plus the first 10 amino acids of domain 2 of gelsolin is the minimal fragment size required for its actin severing activity. Rhu-pGSN contains multiple calcium binding sites that regulate its activity. It is a highly conserved protein, as far back as drosophila.

Plasma gelsolin modulates inflammation while at the same time, boosting the body's ability to clear pathogens. It functions through mechanisms quite distinct from anti-inflammatory agents, which are antagonists of specific mediators or inhibitors of specific enzymes. Plasma gelsolin functions through a pleiotropic mechanism of action, scavenging toxic actin, binding inflammatory mediators and enhancing pathogen clearance. pGSN levels decrease markedly in a variety of clinical conditions such as acute respiratory distress syndrome, sepsis, major trauma, prolonged hyperoxia, malaria, and liver injury. The strength of the correlation between magnitude of decline in pGSN and likelihood of mortality is especially striking (Lee et al, 2006; 2008; 2009; Osborn et al, 2008). Specifically, a study of adult patients hospitalized with CAP showed that lower pGSN concentrations were significantly associated with more severe clinical outcomes (Self et al, 2018). Repletion of depressed plasma gelsolin levels with rhu-pGSN is expected to benefit patients through four distinct mechanisms that have been described in the literature:

1. Sequestration of released actin from sites of damage. This sequestration causes local depletion of pGSN while leaving large stores of pGSN continuing to circulate in healthy individuals. Modest reduction of systemic pGSN levels is then restored after healing is complete (Haddad et al, 1990; Lee et al, 1992).

2. Prevention of the escape of mediators of inflammation from the local site. Local depletion allows appropriate inflammation/healing to proceed while high circulating levels keep the mediators local (Bucki et al, 2005, 2008, and 2010; Piktel et al, 2020). pGSN binds and dampens pro- inflammatory mediators such as platelet-activating factor, lysophosphatidic acid, and bacterial products (Goetzel et al, 2000; Vasconcellos and Lind, 1993; Bucki et al, 2005; Bucki et al, 2008; Bucki et al, 2010; Osborn et al, 2007). pGSN can also bind fibronectin (Lind et al, 1984) and fibrin (and possibly pro-inflammatory fibrinopeptides) (Smith et al, 1987), and may 'escort' or delay binding of lysophosphatidic acid and other mediators to their receptors (Goetzel et al, 2000; Bucki et al, 2010).

3. Enhanced uptake of gram + and gram – bacteria by tissue macrophages. It has been shown that actin inhibits bacterial uptake and that pGSN reverses that inhibition. Excess actin in seriously ill individuals may account for immune suppression seen in these patients.

4. Improved killing of gram + and gram – bacteria by tissue macrophages. This function is distinct from the function that enhances bacterial uptake. It has been shown to be mediated by induction of NOS3 and is absent in NOS3 knock-out mice (Yang et al, 2015).

The development of rhu-pGSN was initiated in the 1990s and included development of the original *E. coli* cell bank and conduct of non-clinical and first clinical studies with the protein produced from culture of aliquots of this cell bank. BioAegis took over the development of rhu-pGSN, established a new *E. coli* cell line for the production of rhu-pGSN, and implemented improvements in the manufacturing process of the therapeutic protein.

4.4. Preclinical and Clinical Experience

4.4.1. Preclinical Experience

The preclinical studies of pGSN have revealed no safety concerns related to its mechanism of action or formulation. No functional effects on the respiratory system and no systemic toxicity attributed to rhu-pGSN or the formulation excipient, 0.1% polysorbate 80 (Tween-80), were observed in these studies at the highest achievable doses. No clinically relevant pathological effects were evident in rats or monkeys following administration of pGSN or 0.1% polysorbate 80 vehicle for up to 28 days by inhalation or for 14 days by intravenous (IV) injection.

Exposures to the lower respiratory tract of rats and monkeys in the repeat-inhalation dose toxicity studies were up to approximately 75 and 250 times, respectively, the estimated level at the proposed starting dose to be administered to patients with CAP. Based upon the lack of test article-related effects, safety margins are estimated to be in excess of 4.5 and 30 times (for rat and monkey, respectively) the highest planned clinical dose.

The pharmacokinetic (PK) profile of rhu-pGSN following inhalation, intratracheal, IV, or oral administration is consistent with that of a relatively stable, high molecular weight protein. Detectable systemic absorption of rhu-pGSN following inhalation exposure is not extensive. No changes in endogenous plasma gelsolin levels were detected using an enzyme-linked immunosorbent assay (ELISA) following aerosol administration of pGSN to monkeys at presented dose levels up to 9,550 mg/kg. The half-life of rhu-pGSN-related radioactivity in the lung was approximately 10 to 16 hours in normal rats and monkeys, respectively, following pulmonary exposure.

Test article-related effects observed following repeat aerosol administration of pGSN under conditions of continuous pulmonary exposure was limited to minimal microscopic changes in the lungs of monkeys. The microscopic change is attributed to an immunogenic response as evidenced by the detection of antibodies to rhu-pGSN. The antibodies appeared to be directed against the human-specific epitopes of intact rhu-pGSN and caused no clinical or pathological signs of serum sickness. Thus, the immunogenic reaction to rhu-pGSN in monkeys appears to be a species-specific response and, therefore, is not considered to be clinically relevant.

No cardiovascular effects were noted in monkeys receiving pGSN by either inhalation or IV administration.

No eye or skin irritation was noted in rabbits after acute exposure to the product.

In a murine model of influenza A/PR/8/34, male CD1 mice were treated with subcutaneous rhu-pGSN ranging in dose from 0.5 to 5 mg where treatment was initiated 3 or 6 days after intranasal viral challenge (Yang et al, 2020). Overall, when combining all doses regardless of the day treatment was initiated, mice treated with rhu-pGSN had a significantly higher survival rate ($p=0.000001$) on day 12 than those treated with vehicle. Improved survival was observed regardless of the day treatment was initiated.

In a murine model of pneumococcal pneumonia, male CD1 mice were treated with intraperitoneal rhu-pGSN ranging in dose from 5 to 10 mg (Yang et al, 2019). Treatment was initiated either 2 or 3 days after intranasal challenge with *Streptococcus pneumoniae* type 3 or 24 hours after infection with an antibiotic-resistant pneumonia strain, type 14, and treated for 9 days. In both models, treatment with rhu-pGSN increased survival and reduced morbidity and weight loss.

Lastly, another murine model of multidrug-resistant *Pseudomonas aeruginosa* pneumonia was used to evaluate the effect of rhu-pGSN on survival and lung injury (DiNubile et al, submitted for publication in 2020). Neutropenic BALB/c mice were treated subcutaneously with different meropenem doses ± 12 mg/day of intraperitoneal rhu-pGSN commencing 1 day before intratracheal challenge with multidrug-resistant *P. aeruginosa*. Mice were treated for 5 days and assessed on day 7. Overall survival was 35/64 (55%) and 46/64 (72%) in mice given meropenem without or with rhu-pGSN, respectively [” (95% confidence interval) = 17% (1, 34)]. In control mice receiving meropenem 1250 mg/kg/day where the majority died, addition of rhu-pGSN increased survival from 5/16 (31%) to 12/16 (75%) [” = 44%]. Survival with minor lung injury was found in 26/64 (41%) mice receiving only meropenem versus 38/64 (59%) in mice given meropenem plus rhu-pGSN [” (95% confidence interval) = 19% (2, 36)]. Overall, both mortality and lung injury were reduced by the addition of rhu-pGSN to meropenem against carbapenem-resistant *P. aeruginosa*, most prominently in situations where meropenem alone was highly inefficacious.

In summary, the preclinical profile of pGSN supports continued evaluation of rhu-pGSN in humans and suggests that the drug is well tolerated with a low risk of respiratory or systemic toxicity.

4.4.2. Clinical Experience

Rhu-pGSN has been previously evaluated in 4 clinical studies.

Study 96-900 was a Phase 1, double-blind, randomized, controlled, within-subject, dose-escalation study in 24 healthy volunteers conducted in the United Kingdom. Patients were dosed via nebulization up to a maximum dose of 32 mg given twice per day. Adverse events (AEs) were minor and none were consistently attributed to treatment. No formation of antibodies to rhu-pGSN was observed.

Study C96-901 was a randomized, double-blind, placebo-controlled, dose-escalating, tolerability study of inhaled rhu-pGSN in 21 patients with cystic fibrosis conducted at one clinical site in Canada. Rhu-pGSN or placebo was administered via nebulization at 3.0 mg/day (Day 1 and 2), 10 mg/day (Day 3 and 4) and 25 mg/day (Day 5 to 9). Sixteen patients were randomized to rhu-pGSN and 5 patients to placebo (randomization ratio 3:1). Rhu-pGSN was well tolerated with no safety concerns. No patients withdrew from the study. There was no negative effect on pulmonary function. There were no serious adverse events (SAEs) and no AEs were considered likely or definitely related to treatment.

Study CBC-101 was a randomized, double-blind, placebo-controlled, ascending dose, infusion trial of the PK of rhu-pGSN in patients with decreased natural gelsolin levels. This Phase 1b/2a study was conducted in Hong Kong and enrolled patients admitted to the ICU. Twenty-eight patients were enrolled; 21 patients received rhu-pGSN and 7 received placebo. The 4 cohorts were treated with ascending doses of rhu-pGSN via IV infusion according to the following scheme:

Cohort 1: Single infusion of 3 mg/kg rhu-pGSN (10 patients) or placebo (3 patients)

Cohort 2: Single infusion of 6 mg/kg rhu-pGSN (3 patients) or placebo (2 patients)

Cohort 3: Daily infusion of 6 mg/kg rhu-pGSN for 3 days (6 patients) or placebo (2 patients)

Cohort 4: Daily infusion of 6 mg/kg rhu-pGSN for 3 days (2 patients with severe multiple organ failure)

The dose escalation over the successive cohorts was supervised by an independent Data and Safety Monitoring Board (DSMB). The DSMB had to document the safety profile of the drug before allowing the study to proceed to a higher dose and/or exposure. No safety concerns associated with rhu-pGSN were raised by the DSMB. Seven patients died during the 3-month observation period (Table 2); none of the deaths were assessed as related to study treatment. No patient who received placebo died. The incidence of death in the rhu-pGSN-treated patients (7/21; 33%) is within the limits of expectation for patients admitted in intensive care unit (ICU) with similar diagnoses. However, the incidence of death was lower than expected in the placebo group, most probably due to imbalances in multiple baseline clinical prognostic factors in favor of the placebo group when compared to the rhu-pGSN group.

Table 2: Summary of Deaths

Subject	Cohort	Age	pGSN mU/mL	Admission diagnosis[1]	VP	MV	Day of admission relative to infusion[2]	Day of death[3]

G004	1	84	921	Fecal peritonitis, emergency rectosigmoidectomy, renal insufficiency	Yes	Yes	-10	5
G006	1	69	1892	Pneumonia with hepatitis	No	Yes	-10	3
G012	1	79	524	Sigmoid perforation, emergency rectosigmoidectomy	No	No	-6	26
G015	2	79	1161	Pneumonia, COPD	Yes	Yes	-15	21
G017	2	78	963	Peritonitis with terminal cholangiocarcinoma	No	No	-10	16
G018	2	85	1128	Pneumonia with renal insufficiency	Yes	Yes	-10	66
G401	4	83	780	Pneumonia with renal insufficiency	Yes	Yes	-4	7

[1] Diagnosis established at ICU admission
[2] Represents the day of hospitalization (irrespective of ICU or not) relative to day of infusion
[3] Day of death relative to first infusion
COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; MV = mechanical ventilation; pGSN = plasma gelsolin; VP = vasopressor.

Study BTI-201 was a Phase 1b/2a, double-blind, placebo-controlled, single- and multiple-ascending dose escalation study to evaluate the safety, PK, and pharmacodynamics of rhu-pGSN added to standard of care (SOC) in non-ICU patients hospitalized for mild CAP. Eligible subjects were randomized 3:1 to receive adjunctive IV rhu-pGSN or placebo. Thirty-three subjects were treated: 8 received a single dose of rhu-pGSN 6 mg/kg, and 25 received a daily rhu-pGSN dose of 6, 12, or 24 mg/kg over 3 consecutive days.

Overall, AEs were mild in both treatment groups irrespective of dose. AEs were reported more frequently in the lowest rhu-pGSN dose cohorts and the less frequently in the highest rhu-pGSN dose cohorts. Treatment-emergent adverse events (TEAEs) that were reported in more than 1 subject in the rhu-pGSN groups were: nausea (11.1% rhu-pGSN; 0% placebo) and blood pressure increased (11.1% rhu-pGSN; 0% placebo). No injection-related reactions were reported. Of the subjects treated with rhu-pGSN, no subject experienced a TEAE assessed as drug-related and no subject discontinued due to a TEAE.

Two subjects experienced SAEs: 1 SAE was reported in 1 subject who received a single dose of rhu-pGSN and 2 SAEs were reported in 1 subject who received placebo in the multiple-ascending dose phase. One subject who received a single dose of rhu-pGSN had an SAE of pneumonia (Grade 5, not related) after being withdrawn from the study; and 1 subject who received placebo had SAEs of pneumonia (Grade 4, not related) and pulmonary embolism (Grade 5, not related).

Pharmacokinetic analyses showed that the median rhu-pGSN half-life exceeded 17 hours with all dosing regimens. Overall, rhu-pGSN was well tolerated in patients admitted to non-ICU beds with CAP.

4.5. Rationale for Study

The damage inflicted by COVID-19 is primarily mediated through an overly exuberant host response to the virus, not directly by the virus itself. This overblown reaction consists of excessive and prolonged inflammation culminating in a cytokine storm and disseminated coagulopathy injuring the lungs and blood vessels. Interrupting or tempering this maladaptive process lessens further organ injury, restoring immune equilibrium and allowing tissue repair.

Plasma gelsolin plays a central regulatory role (“master switch”) in diverse inflammatory pathways. A dual-pronged attack on COVID-19 concurrently reducing the inciting virus (with remdesivir or other antiviral agents) and quelling the inflammatory tsunami (with a non-toxic but powerful anti-inflammatory drug) could theoretically synergize in shutting down the COVID-19 attack better than either modality alone. The action of pGSN on multiple pathways effectively blocks unbridled immune activation without inducing undesired side-effects or dangerous immunosuppression.

The study protocol was amended to include Part 2 to evaluate rhu-pGSN in 10 subjects (compared to 10 placebo subjects) who are intubated without extracorporeal membrane oxygenation (ECMO) and therefore score as level 6 or 7 on the WHO scale. Recent data in the “steroid era” have suggested that immunomodulators may exert their most beneficial effects in critically ill patients which were not captured in the original recruitment for this study. Compassionate use in a single patient who scored as level 7 on the WHO scale in April 2021 resulted in quick and dramatic improvement temporally related to rhu-pGSN administration. Accordingly, intubated patients may be an appropriate target population for rhu-pGSN.

4.6. Rationale for Starting Dose

The dosage for this trial was extrapolated from efficacious doses in animal studies of severe pneumonia. A Phase 1b/2a dose escalation study showed no drug-related or SAEs in patients with CAP administered 3 daily doses of rhu-pGSN at 6, 12, and 24 mg/kg of actual body weight.

4.7. Risk/Benefit Assessment

4.7.1. Known Potential Risks

The safety database is limited to a total of 24 rhu-pGSN recipients. Some of these subjects developed apparent anti-drug antibodies, although no untoward effects were recognized.

4.7.2. Known Potential Benefits

Rhu-pGSN may temper excessive tissue inflammation and thereby limit organ damage.

4.7.3. Assessment of Potential Risks and Benefits

Because rhu-pGSN is a naturally occurring blood protein, there is little a priori concern about intrinsic toxicity. Furthermore, experimental data support benefit in uncontrolled inflammatory states. Overall, the drug is expected to have a favorable risk:benefit ratio.

5. TRIAL OBJECTIVES AND ENDPOINTS

5.1. Objectives

5.1.1. Primary Objective

- To assess the efficacy (survival without organ failure on Day 14) of IV rhu-pGSN plus SOC vs placebo plus SOC (hereafter referred to as rhu-pGSN vs placebo) administered to hospitalized subjects with a primary diagnosis of COVID-19 pneumonia and in Part 1, a severity score of 4, 5, or 6, or for Part 2, intubated without ECMO with a severity score of 6 or 7 on the World Health Organization (WHO) 9-point severity scale
- To evaluate the safety (incidence of SAEs) of IV rhu-pGSN administered to hospitalized subjects with a primary diagnosis of COVID-19 pneumonia and in Part 1, a severity score of 4, 5, or 6, or for Part 2, intubated without ECMO with a severity score of 6 or 7 on the WHO 9-point severity scale

5.1.2. Secondary Objectives

- To further assess the efficacy of IV administered rhu-pGSN
- To measure changes in the WHO 9-point severity scale for SOC ± rhu-pGSN
- To evaluate the effect of administered rhu-pGSN on survival rates
- To assess the relationship of pGSN levels (and other biomarkers) at baseline with clinical outcomes
- To follow the PK of administered rhu-pGSN

5.1.3. Immunogenicity Objective

- To investigate the development of antibodies against pGSN post-treatment in rhu-pGSN vs placebo recipients compared to baseline

5.2. Endpoints

5.2.1. Primary Endpoint

- Safety and tolerability
    - Incidence of SAEs in rhu-pGSN vs placebo groups
- Efficacy
    - Proportion of subjects alive not on vasopressors, mechanical ventilator, and dialysis on Day 14

5.2.2. Secondary Endpoints

- Safety and tolerability
    - Incidence, causality, and severity of AEs (graded according to the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) in rhu-pGSN vs placebo groups
    - Frequencies of new or worsening clinically significant laboratory abnormalities in rhu-pGSN vs placebo groups
    - Mortality rate irrespective of cause at Days 28 and 90
- Efficacy
    - Daily change in 9-point WHO severity score through at least Day 14 (including after discharge, where feasible)
    - All-cause mortality at Days 28 and 90; time to death (Kaplan-Meier survival analysis)
    - Proportion of subjects alive on Days 7, 14, 28, 60, and 90 without:
        - Ongoing use of vasopressors
        - Ongoing intubation/mechanical ventilation
        - Ongoing residence in an ICU
        - New ongoing need for dialysis/renal replacement therapy (RRT)
    - Proportion of subjects discharged to home or immediate prior residence by Day 28
    - Days on the ventilator
    - Length of stay (LOS) in hospital and in ICU (days)
    - Re-admission to an acute-care hospital up to Day 90
- PK
    - PK for rhu-pGSN including maximum concentration (C_{max}), time to maximum concentration (T_{max}), terminal half-life ($T_{1/2}$), area under the curve from time zero to 8 hours (AUC_{0-8}), area under the curve from time 0 to infinity (AUC_{inf}) for Dose #1 within 15 minutes predose, and at 1 (±15 min), 2 (±15 min), 6 (±30 min), and 12 (±30 min) hours after end of administration (but prior to Dose #2); for Dose #3 within 15 minutes predose, and at 1 (±15 min), 2 (±15 min), 6 (±30 min), 12 (±30 min) and 24 (±30 min) hours after the end of administration (participants refusing these blood samplings can enter and remain in the trial).
- Immunogenicity
    - Presence of anti-pGSN antibodies on Days 1 (predose), 28, and 90

5.2.3. Exploratory Endpoints

- Biomarkers
    - Changes in biomarkers and radiologic imaging over time with treatment
    - Relationship of baseline biomarkers to clinical outcomes

Note: All deaths on-study must include cause of death as per investigator assessment and relationship to study drug and/or COVID-19.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a 2-part, randomized, double-blind, placebo-controlled, multicenter Phase 2 study to evaluate the efficacy and safety of rhu-pGSN plus SOC in subjects with severe COVID-19 pneumonia. Potential subjects hospitalized with pneumonia and laboratory-confirmed (reverse transcription polymerase chain reaction [RT-PCR$^+$]) or highly suspected (compatible with at least bilobar lung involvement without any other plausible diagnosis) COVID-19 etiology will be screened for Part 1 within 24 hours of reaching a WHO severity score of 4 to 6, whether the severity score is attained on admission or during hospitalization, or for Part 2, within 24 hours of intubation without ECMO with a WHO severity score of 6 or 7.

The 9-point WHO classification scheme for severe COVID-19 pneumonia will be applied to grade the severity of illness as follows:

8 Death

7 Mechanical ventilation or ECMO with either vasopressor support or dialysis/RRT

6 Intubation with mechanical ventilation, a mask with a reservoir or oxygen with high-flow nasal goggles but without vasopressor support or dialysis/RRT

5 Noninvasive ventilation (continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) or high-flow oxygen

4 Oxygen by mask or nasal

3 Hospitalized with no oxygen therapy

2 Limitation of activity

1 Infected without limitations

0 No clinical or virologic evidence of COVID-19 infection

Once informed consent is obtained, the following assessments/procedures will be performed:

1. Record medical history, including concomitant medications and current clinical status
2. Perform pregnancy test (urine or blood) for women of childbearing potential
3. Collect pretreatment blood samples for measurement of baseline pGSN and for analysis of antibodies against pGSN
4. Calculate the CURB-65 score (**C**onfusion, **U**rea >7 mmol/L, **R**espiratory rate ≥30/min, **B**lood pressure systolic <90 or diastolic ≤60, and age ≥**65** years) at presentation (Appendix A)
5. A RT-PCR test to confirm the diagnosis of COVID-19 should be documented during the current illness leading to the present hospitalization; if RT-PCR test is not done prior to screening, the test is to be performed during screening before randomization (result might

not be available at randomization or start of study treatment). Perform physical examination (PE) and document radiographic evidence of pneumonia (CXR or computed tomography ([CT] scan if CXR is inadequate) if not already completed within the previous 48 hours per SOC

6. Obtain blood and sputum cultures and electrocardiogram (EKG) per SOC (if not already performed). The microbiology lab is encouraged to perform sputum (bacterial, viral, and mycobacterial, as indicated) and blood cultures, sputum Gram-stains, antigen detection on respiratory and urine specimens, and RT-PCR diagnostic tests as possible.
7. Measure routine lab tests and biomarkers, including ferritin, D-dimer, C-reactive protein (CRP) and procalcitonin level at local laboratory; collect aliquots of blood for subsequent biomarker assays (likely to include, but not limited to IL1[2] , IL6, IL10, tumor necrosis factor [TNF], etc.) for analysis at the central laboratory (see Table 5 Schedule of Assessment and footnote 'l' for details).
8. If eligibility criteria are satisfied, subject to be randomized (1:1 to treatment arms rhu-pGSN:placebo) within 12 hours of informed consent (Part 1) or within 24 hours of intubation (Part 2).

Randomized subjects will receive the assigned dose of rhu-pGSN or an equal volume of sterile saline placebo as soon as possible (ASAP), but beginning no later than 12 hours of randomization. The rhu-pGSN dose will be based on actual body weight given at 12 mg/kg. After reconstitution, rhu-pGSN should not be kept at room temperature for >2 hours prior to beginning the infusion. The initial dose of study drug (Dose #1) will be followed by dosing at 12 (Dose #2) and 36 hours (Dose #3) after the initial administration. Study drug is administered as a slow IV bolus at a rate of 20 mL/min through a 0.2 μm filter. The syringe, filter, and extension tubing for injection of study drug should be connected after disconnecting the IV as close to the subject as possible.

The primary efficacy endpoint will be assessed on Day 14, with secondary endpoints assessed on Days 7, 28, 60, and 90. Discharged subjects will undergo follow-up evaluation on Days 14, 28, 60, and 90.

Screening laboratory and other tests can serve as baseline values for participants, they do not need to be repeated if performed within the prior 24 hours of randomization unless otherwise dictated by SOC; however, the blood sample for analysis of pGSN levels must be repeated if not collected within 15 minutes of initiating the first dose of study drug. The day of first study drug administration will be used as baseline (Day 1) for analysis purposes. Screening should be done on Day -1 up to the time of randomization.

Repeat CXRs, or CT scans if CXR is inadequate, and labs/cultures, etc. will be obtained during the hospitalization if/when indicated by SOC.

On Days 1 (predose), 28, and 90, blood samples for analysis of antibodies against pGSN will be collected.

If the patient expires, autopsy is encouraged.

6.2. Data and Safety Monitoring Board

An independent DSMB will be established to closely monitor the safety of subjects. The primary mission of the DSMB is to ensure that decisions are made that serve the best interests of patients volunteering for the study.

The independent DSMB will be comprised of 4 voting members: 3 academicians/clinicians with expertise in pulmonary care, critical care, and/or infectious diseases as related to COVID-19 pneumonia, and a statistician. Representatives from the Contract Research Organization (CRO) and Sponsor's Chief Medical Officer will be able to attend the open meetings to provide information and administrative support to the DSMB. However, they will not have any voting rights and will not attend the closed meeting where unblinded data may be discussed.

No SAEs have been associated with the investigational medicinal product. Thus, all SAEs will be considered as unexpected for reporting purposes. All reported deaths and treatment-emergent SAEs will be sent by EastHORN Safety to the DSMB within 2 working days of notification of the CRO/Sponsor by the sites. The events will be evaluated by the DSMB and comments returned to EastHORN Safety within 2 working days of notification of the DSMB. A DSMB meeting does not necessarily need to be convened. Ad hoc meetings will be convened whenever felt appropriate by a DSMB member.

In Part 1, periodic safety reviews will be conducted after 12, 24, 36, and 48 subjects have been fully dosed and completed assessment at Day 14. Only DSMB members will be provided with partially unblinded results separated into 2 groups by treatment without identifying the actual treatment. If all participants have completed study therapy before the last DSMB meeting involving review of 48 subjects after their Day 14 visit can be held, this meeting can be cancelled at the discretion of the DSMB chair.

Data may be further unblinded and/or the study paused at the discretion of the DSMB chair; otherwise, enrollment will continue during the safety review.

Please refer to the DSMB Charter for further details.

6.3. Dose Discontinuation Criteria

Dosing of rhu-pGSN may be stopped during the study at the discretion of the DSMB. In general, doses should not be interrupted for Grade 1 AEs, but treatment to control symptoms should be provided, if applicable.

6.4. Management of rhu-pGSN Injection-Related Reactions

Injection-related reactions (IRRs) (Table 3) will be defined according to the NCI CTCAE, version 5.0 or higher.

Table 3: Definition of Injection-Related Reactions

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
IRR	Mild transient reaction; injection interruption not indicated; intervention not indicated	Therapy or injection interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for d24 hours	Prolonged (i.e., not rapidly responsive to symptomatic medication, brief interruption of injection, or both); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated

Abbreviations: IRR=injection-related reaction; IV=intravenous; NSAIDs=non-steroidal anti-inflammatory drugs.

Management of Grade 1 IRRs

If a subject presents with a Grade 1 IRR:

- The injection may be continued; however, the rate may be reduced to 50% at the discretion of the Investigator.
- If the symptoms resolve, the injection can be increased, as tolerated, to the baseline rate.
- The subject may receive appropriate further treatment for IRRs if clinically indicated per the site's standard practice for management of IRRs.

Management of Grade 2 IRRs

If a subject presents with a Grade 2 IRR:

- The injection should be stopped immediately.
- The subject should receive appropriate further treatment with an antihistamine and/or acetaminophen (paracetamol) if clinically indicated per the site's standard practice for management of IRRs. Further medications can be administered if necessary.
- Once the symptoms have been resolved or reduced to Grade 1, the injection can be continued at an injection rate of 50%.
- If a subject who developed a Grade 2 IRR receives further injections, then premedication following the site's standard practice for premedication for IRR should be given before all subsequent injections of rhu-pGSN given at a rate of 50% of the original rate.

Management of Grade 3 IRRs

If a subject presents with a Grade 3 IRR:

- The injection should be stopped immediately.
- The subject must receive appropriate treatment with an antihistamine and/or acetaminophen (paracetamol) and/or methylprednisolone (or equivalent) and, if necessary, further medications (i.e., epinephrine, bronchodilator).
- Only after the complete resolution to dGrade 1, and after having received appropriate prophylactic medication(s) as described above, the injection may be resumed at an injection rate of 25%. If, after 20 minutes, the subject's symptoms do not return and vital signs are stable, the injection rate may be increased to a maximum of 50%.
- If, after the resumption of injection, symptoms return (irrespective of grade), the injection must be stopped immediately, and the injection tubing should be disconnected from the subject.
- Subjects experiencing a Grade 3 IRR may only receive further injections of study drug, provided clinically appropriate precautions are undertaken and agreed upon by Investigator and Medical Monitor.

Management of Grade 4 IRRs

If a subject presents with a Grade 4 IRR:

- The injection should be stopped immediately, and the injection tubing should be disconnected from the subject.
- The subject should receive appropriate treatment with an antihistamine and/or acetaminophen (paracetamol) and/or methylprednisolone (or equivalent) and, if necessary, further medications (i.e., epinephrine, bronchodilator).
- The subject must not receive further injections of rhu-pGSN if rhu-pGSN is judged by the Investigator to be the cause of the IRR.

6.5. Study Duration

Subjects will be treated with 3 doses over 36 hours: after the initial dose is administered (Dose #1), then next dose (Dose #2) is administered 12 hours later, and the last dose is administered 24 hours later (Dose #3 administered 36 hours after Dose #1).

Subject screening will occur for Part 1 within 24 hours of determination of WHO severity score of 4 to 6, whether the severity score is attained on admission or during current ongoing hospitalization, or for Part 2, within 24 hours of intubation without ECMO with a WHO severity score of 6 or 7. Eligible subjects will be randomized within 12 hours of informed consent (Part 1) or 24 hours of intubation (Part 2), and dosed within 12 hours of randomization (both parts).

Subjects are followed for safety and efficacy through Day 90.

6.6. Total Duration of Subject Participation

Subjects will be observed for the primary efficacy endpoint with daily assessments (including WHO severity score) from Day 1 through Day 14. If a subject is discharged prior to Day 14, he/she will be assessed, if feasible, by phone daily through Day 14, and then at follow-up visits, on Days 28, 60, and 90, and as needed.

6.7. End of Study Definition

End of study (EOS) will be defined as the date the last subject completes the EOS Visit (Day 90). The Sponsor will notify all applicable regulatory agencies in accordance with local requirements when the study has ended.

6.8. Criteria for Treatment Discontinuation

Subjects are free to discontinue their participation in the study at any time and without prejudice to further treatment. The Investigator must withdraw any subject from the study if that subject requests to be withdrawn, or if it is determined that continuing in the study would result in a significant safety risk to the subject.

The subject's participation in this study may be discontinued for the following reasons:

- Subject withdrew consent
- Unacceptable AE
- Subject is unwilling or unable to continue the study or is lost to follow up
- Subject is non-compliant with study procedures/study protocol
- Investigator decides that withdrawal from the study is in the best interest of the subject
- Any clinically significant change in subject’s medical condition (at the discretion of the Investigator)
- Sponsor decision to end the study

If a subject withdraws from the study prematurely, assessments scheduled for the EOS Visit should be performed ASAP. If a subject refuses further assessment, the subject should be contacted for safety evaluations (AE/concomitant medications/potential pregnancy) approximately 28 and 90 days after study withdrawal.

If such withdrawal occurs, or if the subject refuses to participate in the EOS Visit, the Investigator must determine the primary reason for a subject’s withdrawal from the study and record the information on the electronic case report form (eCRF). If the reason for withdrawal is an AE, monitoring should continue until the outcome is evident. The specific event or test result(s) must be recorded in the eCRF. At the discretion of the Sponsor, subjects may also be removed from the study.

It should be clearly documented in the source data whether a subject withdrew his/her consent and will not enter the follow-up phase, or if a subject withdrew his/her consent for study drug treatment but will continue further participation in the study.

6.9. Subject Replacement

Only subjects missing doses or discontinuing at random (non-informative) before the primary visit on Day 14 will be replaced as originally randomized to receive rhu-pGSN or placebo. Safety data from all subjects treated with e 1 dose will be collected. Subjects discontinuing the study after the Day 14 visit will not be replaced.

6.10. Criteria for Study Termination

The Sponsor reserves the right to discontinue the study at any time for any reason. Such reasons may be any of, but not limited to, the following:

- Occurrence of AEs unknown to date in respect to their nature, severity, and duration, or the unexpected incidence of known AEs
- Medical or ethical reasons affecting the continued performance of the study

If the study is prematurely terminated, the Investigator is to promptly inform the study subjects and Independent Ethics Committee (IEC) and should ensure appropriate follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (e.g., study drug, etc.) must be destroyed or returned to the Sponsor.

7. STUDY POPULATION

7.1. Number of Subjects

Part 1: A total of 60 evaluable participants randomized 1:1 to rhu-pGSN:placebo (30:30 subjects).

Part 2: A total of 20 evaluable participants randomized 1:1 to rhu-pGSN:placebo (10:10 subjects).

7.2. Subject Inclusion Criteria

To be considered eligible to participate in this study, a subject must meet all the inclusion criteria listed below:

1. Hospitalized with laboratory-confirmed ($RT\text{-}PCR^{+}$) or highly suspected (compatible with at least bilobar lung involvement without another plausible diagnosis) COVID-19
2. Age $\geq$ 18 years
3. **Part 1 only:** Weight $\leq$100 kg
4. **Part 1 only:** Within 24 hours of reaching a WHO severity score of 4-6 either:
    a) At admission
    b) While already hospitalized.
5. **Part 2 only:** Within 24 hours of intubation without ECMO with a WHO severity score of 6 or 7)
6. Informed consent obtained from subject/next of kin/legal proxy
7. Primary admitting diagnosis of pneumonia supported by a compatible clinical presentation with a documented infiltrate consistent with pneumonia on CXR or CT, as assessed by the admitting emergency department (ED), clinic, or ward physician or equivalent caregiver
    - Recommended (not mandatory) guidance/discretionary criteria defining patients with pneumonia satisfying all 4 categories below:
        - At least 2 symptoms: difficulty breathing, cough, production of purulent sputum, or chest pain
        - At least 2 vital sign abnormalities: fever, tachycardia, or tachypnea (thresholds -- fever: body temperature >100.4°F [38°C]; heart rate >100 beats/min; respiratory rate >24/min)
        - At least one finding of other clinical signs and laboratory abnormalities: hypoxemia (O_2 saturation <90%), clinical evidence of pulmonary consolidation, or leukocytosis $\geq 1.5x10^4$ or leukopenia $<4x10^3$
        - Chest imaging or CT chest showing at least bilobar pulmonary infiltrates
            - Principal Investigator (PI) to note radiologic findings in the eCRF
            - Radiology report and conclusion should be summarized in the eCRF

- A copy of the radiograph attached to be saved for review, if possible

8. A hyperinflammatory status (defined by increased ferritin ≥ 500 µg/L, D-dimer ≥ 1000 ng/mL, or CRP ≥ 75 mg/L)
9. During the course of the study starting at screening and for at least 6 months after their final study treatment:
    a) Female subjects of childbearing potential must agree to use 2 medically accepted birth control methods
    b) Male subjects with a partner who might become pregnant must agree to use reliable forms of contraception (i.e., vasectomy, abstinence), or an acceptable method of birth control must be used by the partner
    c) All subjects must agree not to donate sperm or eggs (ovocytes)

7.3. Subject Exclusion Criteria

To be eligible for entry into the study, the subject must not meet any of the exclusion criteria listed below:

1. A negative RT-PCR test for COVID-19 in the absence of a positive test during the evaluation of the present illness (in the presence of a positive test during the current illness, preceding or subsequent negative tests do not disqualify the subject)
2. Extracorporeal membrane oxygenation (ECMO)
3. Pregnant or lactating women
4. Active underlying cancer treated with systemic chemotherapy or radiation therapy during the last 30 days
5. Transplantation of hematopoietic or solid organs
6. Chronic mechanical ventilation or dialysis
7. Otherwise unsuitable for study participation because of chronic, severe, end-stage, and life-limiting underlying disease unrelated to COVID-19 likely to interfere with management and assessment of acute pneumonia, only comfort or limited (non-aggressive) care is to be given, or life expectancy <6 months unrelated to acute COVID infection in the opinion of the Investigator

Notes:

- PK sampling is strongly encouraged. However, participants refusing some or all PK blood sampling can remain in the trial.
- Participants with superinfection in addition to COVID-19 are eligible.
- Caregivers can decide whether any other medications (investigational or otherwise) should be administered.

7.4. Subjects or Partners of Subjects of Reproductive Potential

Pregnancy is an exclusion criterion. Women of childbearing potential (<60 years of age and/or not post-hysterectomy) must avoid getting pregnant during the study. Female subjects of childbearing potential must have a negative serum or urine pregnancy test within 24 hours prior to start of study drug. A serum or urine pregnancy test will be performed at the EOS Visit.

Women of childbearing potential should not become pregnant while on this study, or for 6 months after receiving the last dose of study treatment. Females that can become pregnant must agree to use two medically accepted birth control methods during the study starting at screening and for at least 6 months after their final study treatment. Medically accepted forms of birth control include condoms, diaphragm, cervical cap, the placement of an intrauterine device (IUD), birth control pills, hormone implants or injections, or partners who have undergone a vasectomy (surgical sterility). Unless sterilized, one of these methods must be a barrier method such as a condom or diaphragm. Abstinence at certain times of a menstrual cycle and partner withdrawal are not acceptable methods of birth control. The subject should consult with her study doctor about the contraceptive methods that are available, and which might be the best for her.

Male subjects with a partner who might become pregnant must use reliable forms of contraception (i.e., vasectomy, abstinence) during the study starting at screening and for at least 6 months after their final study treatment, or an acceptable method of birth control must be used by the partner (i.e., oral contraceptive, IUD, hormonal implants, contraceptive injection, or a double- barrier method).

Subjects will be instructed to notify the Investigator if pregnancy is discovered either during or within 6 months of the last dose of study drug.

Subjects must agree not to donate sperm or eggs (ovocytes) during the study starting at screening and for at least 6 months after their final study treatment.

7.5. Waivers of Inclusion/Exclusion Criteria

No waivers of these inclusion or exclusion criteria (Section 7.2 and Section 7.3) will be granted by the Investigator and/or the Sponsor or its designee for any subject enrolling into the study.

8. DESCRIPTION OF STUDY TREATMENT

8.1. Description of Study Drug

Study drug is a recombinant human plasma gelsolin (rhu-pGSN) powder for solution (Table 4).

Study drug will be administered to subjects randomized to rhu-pGSN as an IV bolus at a rate between 5 and 20 mL/min through a standard 0.2-micron filter at 12 mg/kg (based on actual body weight) at 0, 12, and 36 hours (± 60 minutes).

rhu-pGSN drug product is provided as lyophilized powder containing 200 mg rhu-pGSN plus excipients. It is provided in 10-mL glass vials to be reconstituted to a volume of 5 mL with 4.56 mL of sterile water yielding a final concentration of 40 mg/mL of rhu-pGSN, 2% glycine, 4% trehalose, 0.5% arginine, and 0.1% poloxamer 188 in a 10-mM phosphate buffer, pH 7.

Table 4: Investigational Product

	Investigational Product
Product Name:	rhu-pGSN
Dosage Form:	Powder for solution filled as a 5 mL fill in 10-mL glass vials
Unit Dose	rhu-pGSN reconstituted to a volume of 5 mL with 4.56 mL of sterile water
Route of Administration	Intravenous
Physical Description	Lyophilized powder
Storage Conditions	2 to 8 °C
Manufacturer	Drug Product: Integrity Bio, Inc., Camarillo, CA USA

Vials containing rhu-pGSN study drug will be labeled according to national regulations for investigational products.

8.2. Description of Placebo

Placebo will be normal saline solution and will be dosed at a volume of 0.30 mL/kg of 0.9% saline solution via IV push [matching the volume of rhu-pGSN for a subject of that size] injected at 5 to 20 mL/min though a standard 0.2-micron filter at 0, 12, and 36 hours (± 60 minutes). The placebo requires no special manipulation.

8.3. Preparation of Study Drug for Administration

The Investigator or designee will be responsible for administering the appropriate dose of IV rhu-pGSN to subjects. rhu-pGSN must be stored refrigerated at 2 to 8 °C in its original package in an appropriate storage facility accessible only to the pharmacist(s), the Investigator, or a duly designated person.

This person will determine the dose (mg) of rhu-pGSN, calculate the volume of rhu-pGSN solution needed, and reconstitute each vial of study drug to a volume of 5 mL with 4.56 mL of sterile water.

The individual rhu-pGSN IV push will be prepared under aseptic conditions and administered at the study site according to the directions of the Sponsor, which will be provided in a Pharmacy Manual. Any powder remaining in the vial must be discarded. After dilution, administration of rhu-pGSN should be initiated ASAP (within 4 hours, including no more than 2 hours at room temperature). Maximum allowed storage times and conditions will be detailed in the Pharmacy Manual.

8.4. Subject Monitoring During rhu-pGSN Administration

Vital signs should be measured as outlined in Section 9.2.2. All supportive measures consistent with optimal patient care will be provided throughout the study according to institution standards.

Precautions for anaphylaxis should be observed during rhu-pGSN administration. Emergency resuscitation equipment and medications should be readily available. Additional supportive measures should also be available and may include, but are not limited to, epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen (paracetamol).

8.5. Study Drug Administration

The subject will receive an IV bolus at the time points specified in Table 5 at a rate between 5 to 20 mL/min. The syringe, filter, and extension tubing should be connected after disconnecting the IV as close to the subject as possible.

Subjects are to be monitored for administration site reactions during study drug administration and for 1 hour after its completion. Injection-site reactions will be recorded as AEs using the appropriate coding terms on the eCRF.

8.6. Shipment of Study Drug

Prior to study treatment, study medications will be supplied to the clinical trial site's pharmacy or equivalent by the Sponsor or its designee.

Shipment of study drug supplies for the study will be accompanied by a shipment form describing the contents of the shipment, drug information, and other appropriate documentation. The shipment form will assist in maintaining current and accurate inventory records.

8.7. Receipt and Storage of Study Drug

All study supplies should arrive at the pharmacy or equivalent in sufficient quantity and in time to enable dosing as scheduled. The pharmacist or designee must ensure the acknowledgement of receipt of the clinical trial material (i.e., study drug) at the site, including that the material was received in good condition.

The Sponsor or its designee must notify the pharmacist or designee prior to dispatch of drug supplies, with the anticipated date of their arrival, addressed to the site's pharmacy.

The investigational drug will be stored in the pharmacy or equivalent, refrigerated at 2 to 8 ºC. The Sponsor should be notified for any deviation from the storage conditions.

8.8. Accountability, Handling, and Disposal of Study Drug

The study site must maintain accurate records documenting dates and amount of study drug received. The trial site's pharmacy or equivalent will be responsible for ensuring the supervision of the storage and allocation of these supplies. When a shipment is received, the pharmacist or designee verifies the quantities received and the accompanying documentation and provides acknowledgement of receipt.

Accountability logs will be provided to assist the pharmacist or designee in maintaining current and accurate inventory records covering receipt, dispensing, and disposition of the study drug. An unblinded study monitor will examine inventory during the study. Accountability records must be readily available and may be subject to inspection by regulatory authorities or independent auditors at any time.

Drug administration will be recorded in source documents and in the eCRFs.

At the end of the study, delivery records of study drug will be reconciled with used / unused supplies. A disposition form will be completed as per local regulation, since used/partially used vials might be required to be destroyed after use. Unused vials should be returned to the Sponsor. One copy of all accountability records and the disposition form will be retained by the Investigator for the study files.

8.9. Concomitant Medications

To date, there are no known drug interactions with rhu-pGSN. Because rhu-pGSN has no effect on the cytochrome p450 (CYP450) system, subjects may continue their present medications as directed by their caregivers. Subjects may receive concomitant medications to treat symptoms, AEs, and inter-current illnesses that are medically necessary as standard care.

Medications administered within 1 month prior to screening and concomitant medications, including generic name (if possible), and start date if known should be documented in the subject's file and in the eCRF.

8.10. Method of Assigning Subjects to Treatment Groups

Subjects will be randomized in a 1:1 ratio to receive SOC plus IV rhu-pGSN or placebo during the treatment period. See Section 8.12 for details regarding randomization.

8.11. Treatment Compliance

The study drug will be administered by personnel at the study site to ensure compliance.

8.12. Randomization and Blinding

Following screening, subjects qualified for study entry will be randomized to receive rhu-pGSN or placebo during the treatment period. Randomization will be done centrally using manual methods. All eligible subjects will be assigned a randomization number.

The investigational site team and the subject will be kept blinded to the treatment allocation of each participant. Only the designated pharmacist(s) or designee(s) will be unblinded to the treatment allocation. A manual system to randomly assign a treatment allocation. The treatment allocation will be available to the unblinded pharmacist(s).

8.12.1. Unblinding

The unblinded pharmacist(s) or designees will prepare sterile syringes with filters consisting of 12 mg/kg rhu-pGSN or normal saline (Section 8.3) according to the treatment allocation for each subject.

There is no antidote for rhu-pGSN. Unblinding should only be performed if knowledge of the treatment assignment will change the planned management of a medical condition. If possible, prior to unblinding, the need to unblind should be discussed with the Medical Monitor or Sponsor's Chief Medical Officer; however, this should not delay unblinding if the Investigator believes it is necessary. Each case of unblinding will be documented and documentation will be stored separately by the unblinded pharmacist or designee.

Subjects that are unblinded may be withdrawn from the study. The decision to withdraw a subject from the study because of unblinding should be discussed with the Sponsor. If the subject is withdrawn, the Investigator or designee must record the date and reason for withdrawal on the appropriate eCRF for that subject.

9. STUDY ASSESSMENTS

The procedures and assessments that will be conducted during this study are described in this section and summarized in the Schedule of Assessments (Table 5). Detailed instructions regarding all laboratory procedures, including collection and handling of samples, will be included in the study Laboratory Manual provided by the Sponsor or its designee.

Informed consent must be granted by each subject/next of kin/legal proxy according to hospital procedures and local regulations prior to the initiation of any study procedure or assessment (other than those considered SOC).

Table 5: Schedule of Assessments

Visit	Screening	Baseline/ Treatment	Continued Treatment	Follow-up Visits					Early Term/ End of Study Visit
Day	**-1[a]**	**1[a]**	**2**	**3**	**7 ± 1**	**14 ±2**	**28 ±2**	**60 ±2**	**90 ± 4**
Informed consent	X								
Eligibility assessment	X	X							
Randomization if appropriate		X							
Medical history/signs and symptoms	X	X[b]							
WHO Severity Score[c]	X	X	X	X	X	X	X	X	X
Sputum culture[d, e]	X								
Blood or urine pregnancy	X (for women of childbearing potential only)						X		X (for women of childbearing potential only)
HIV	Not required (can be done at the discretion of caregivers)								
Confirm COVID-19 pneumonia (CXR or CT, RT-PCR for COVID-19)[e, f]	X					X	X		
CURB-65 score	X			X	X	X	X	X	
Physical exam[g]	X	X[b]	X	X	X	X	X	X	X
Abbreviated Mental Test Score	X			X	X	X	X	X	

Visit	Screening	Baseline/ Treatment	Continued Treatment	Follow-up Visits					Early Term/ End of Study Visit
Day	**-1[a]**	**1[a]**	**2**	**3**	**7 ± 1**	**14 ±2**	**28 ±2**	**60 ±2**	**90 ± 4**
Vital signs, including pulse oximetry[h]	X	X	X	X	X	X	X	X	X
EKG [e, i]	X	X	X	X					X
Sampling for pGSN levels (including PK)[j]		X	X	X[k]	X	X	X	X	X
CBC with differential and reticulocyte count; PT (INR)/aPTT [e]	X	X[b]	X	X	X	X	X	X	X
Comprehensive metabolic profile (including amylase or lipase) [e]	X	X[b]	X	X	X	X	X	X	X
Biomarker sampling[l]		X		X	X	X	X	X	
Anti-rhu-pGSN antibody sampling (immunogenicity)[m]		X					X		X
Study drug administration[n]		X[o]	X[p]						
AEs/SAEs[q]	X	X	X	X	X	X	X	X	X
Con meds	X	X	X	X	X	X	X	X	X

Abbreviations: AEs=adverse events; CBC=complete blood count; Con meds=concomitant medications; CRP=C-reactive protein; CT=computed tomography; CURB-65=**C**onfusion, **U**rea >7 mmol/L, **R**espiratory rate ≥30/min, **B**lood pressure systolic <90 or diastolic ≤60, and age ≥**65** years (score); CXR=chest x-ray; EKG=electrocardiogram; HIV=human immunodeficiency virus; IL=interleukin; INR=international normalized ratio; PEEP=positive end-expiratory pressure; PK=pharmacokinetic; PT=prothrombin time; aPTT=activated partial thromboplastin time; RT-PCR=reverse transcription polymerase chain reaction; SOC=standard of care; Term=termination; TNF=tumor necrosis factor; WHO=World Health Organization.

[a] Day 1 is the first day of study treatment. Baseline tests (including blood draws) should be performed prior to administration of the first dose. Screening tests may also be performed on Day 1 prior to study treatment if necessary, as long as these tests cannot affect eligibility. If Dose 1 is administered in the evening of Day 1, Dose 2 would be given on the second calendar day and Dose 3 would be given on the third calendar day,

[b] Test/assessment does not have to be repeated if performed within the prior 24 hours unless dictated by SOC.

[c] Assess daily from screening through Day 14 during hospitalization and after discharge, where feasible, and then at Days 28, 60, and 90.

[d] Collect sputum sample as soon as possible if not collected at the time of hospital admission. The microbiology lab is encouraged to also perform sputum Gram-stains, antigen detection, immunoassay, and RT-PCR diagnostic tests when available. If fevers or chills are present, 2 sets of blood cultures are recommended at the discretion of the caregivers.

[e] To be performed if/when indicated by SOC.

[f] At screening, document radiographic evidence (CXR, or CT scan if CXR is inadequate) of COVID-19 pneumonia if not already completed in the previous 48 hours per SOC. On Days 14 and 28, repeat RT-PCR for COVID-19 and repeat CXR, or CT scan if CXR is inadequate, are encouraged but not mandatory.

[g] Height and weight only to be measured at screening or baseline and as per SOC thereafter. In Part 2, height is not required at screening and weight may be obtained via bed scale, if possible, or estimated.

[h] Record blood pressure, body temperature, respiration rate, and heart rate, as well as pulse oximetry. In Part 2, while the subject is intubated, the respiratory rate and the ventilator settings (i.e., tidal volume, inspired oxygen, inspiratory pressure, and PEEP) should be documented. To be measured during study drug administration at the following time points: predose, at the end of administration, and 30 minutes after the end of administration.

[i] When EKGs are to be collected at the same time point as a blood collection, EKGs should be collected first. At screening, 3 serial, resting, supine 12-lead EKGs are to be conducted within 10 minutes total time. All other ECGs are single recordings.

[j] Blood for PK will be drawn for Dose #1 within 15 minutes predose, and at 1 (±15 min), 2 (±15 min), 6 (±30 min), and 12 (±30 min) hours after the end of administration (but prior to Dose #2); and for Dose #3 within 15 minutes predose, and at 1 (±15 min), 2 (±15 min), 6 (±30 min), 12 (±30 min), and 24 (±30 min) hours after the end of administration. Samples should be spun and plasma frozen and sent to a central lab for analysis.

[k] Blood for PK will be collected 24 hours after the end of study drug administration given on Day 2 so the last sample will be obtained Day 3.

[l] Collect blood for measurement of ferritin, D-dimer, CRP, and procalcitonin for evaluation at local laboratory; save an approximate 10 mL aliquot of blood plasma or serum to be frozen at -20°C for subsequent biomarker assays (likely to include, but not limited to IL1², IL6, IL10, TNF, etc.) for analysis at the central laboratory.

[m] Sample to be sent to a central lab for analysis.

[n] Study drug to be administered at 0, 12, and 36 hours (± 60 minutes). Subjects are to be monitored for administration site reactions during study drug administration and for 1 hour after its completion.

[o] Initial dose must be administered no later than 12 hours after randomization. A second dose on Day 1 is to be administered 12 hours after the initial dose.

[p] Day 2 dose to be administered 24 hours after last dose administration on Day 1 (36 hours after Dose #1).

[q] From informed consent to first administration of study drug, AEs related to study procedures and all SAEs will be recorded. During and after first administration of study drug, all AEs and SAEs will be recorded through Day 14. After Day 14, only SAEs will be recorded through study completion.

9.1. Screening Assessments

Potential subjects hospitalized with COVID-19 pneumonia will be screened for Part 1 within 24 hours of reaching a WHO severity score of 4 to 6, whether the severity score is attained on admission or during hospitalization, or for Part 2, within 24 hours of intubation without ECMO with a WHO severity score of 6 or 7.

Prior to screening, all subjects/next of kin/legal proxy must provide informed consent for study participation, per Section 13.5. The following assessments will be performed according to the time points in the Schedule of Assessments (Table 5).

9.1.1. WHO Severity Score

During screening and at the time points presented in the Schedule of Assessments (Table 5), each subject's WHO severity score according to the 9-point scale (Section 6.1) will be recorded on the appropriate eCRF. WHO severity scores should be documented daily through Day 14 (during hospitalization and after discharge, where feasible).

9.1.2. HIV Testing

Subjects are not required to have a negative serology test for HIV to participate in the study. Testing is not required but could be done as part of SOC at the discretion of caregivers.

9.1.3. Confirmation of COVID-19 Pneumonia

Subjects are required to have pneumonia (confirmed clinically and documented on CXR or CT), with RT-PCR^{+} confirmed or highly suspected COVID-19 etiology at screening. If documentation is not available, the subject must undergo CXR, or a CT scan if CXR is inadequate, to confirm COVID-19 pneumonia. At screening, radiographic evidence (CXR, or CT scan) of COVID-19 pneumonia may have been completed in the previous 48 hours per SOC. If not already obtained and documented during the current illness leading to the present hospitalization, a RT-PCR test is to be performed during screening before randomization (result might not be available at randomization or start of study treatment).

On Days 14 and 28, repeat RT-PCR for COVID-19 and repeat CXR, or CT scan if CXR is inadequate, are encouraged but not mandatory.

9.1.4. Pregnancy Test

All females of childbearing potential are required to have a negative serum or urine pregnancy test at screening to participate in the study.

9.2. Safety Assessments

The following assessments will be performed according to the time points in the Schedule of Assessments (Table 5).

9.2.1. Demographic/Medical History

A review of demographic parameters, including age, gender, race, and ethnicity will be performed at screening.

Relevant past and present medical history will be recorded. Any ongoing condition or signs and symptoms observed prior to the initiation of study treatment should be recorded as medical history.

9.2.2. Vital Signs

Vital signs will include blood pressure, body temperature, respiration rate, and heart rate, as well as pulse oximetry. In Part 2, while the subject is intubated, the respiratory rate and the ventilator settings (i.e., tidal volume, inspired oxygen, inspiratory pressure, and PEEP) should be documented. Vitals signs will be measured during study drug administration at the following time points: predose, at the end of administration, and 30 minutes after the end of administration. Significant findings noticed after the start of study drug that meet the definition of an AE must be recorded in the eCRF.

9.2.3. Physical Examination

All PEs, including measurement of body weight, will be performed by a study physician or designee. In Part 1, height and weight need only be measured at screening or baseline. In Part 2, height is not required at screening and weight may be obtained via bed scale, if possible, or estimated. The initial body weight measured at enrollment will be used to calculate rhu-pGSN dosing for all doses (so that an individual subject will always receive the same dose). Body weight can be repeated per SOC thereafter where possible. The physical examination includes skin, head, ears, eyes, nose, throat, heart, lungs, abdomen, and neurologic system, where possible. Additional examination may be performed as found relevant by the Investigator.

9.2.4. Outcome Prediction Models

The CURB-65 (Appendix A) test will be utilized at screening. The cognitive status of the subject will be assessed for incorporation in the CURB-65 score by using the abbreviated mental test score; Appendix B.

9.2.5. Electrocardiogram

All EKGs will be conducted and read locally. When EKGs are to be collected at the same time point as a blood collection, EKGs should be collected first. At screening, 3 serial, resting, supine, 12-lead EKGs will be conducted within 10 minutes total time. The mean of the triplicate EKG measurements performed at screening will serve as the subject's baseline corrected QT (QTc) value for all post-dose comparisons. All other ECGs will be collected as a single recording.

EKG parameters to be evaluated include heart rate, the time from the onset of the P wave to the start of the QRS complex (PR), the duration of the entire cardiac cycle, measured in seconds (RR), the combination of three of the graphical deflections (QRS complex), the measure of the time between the start of the Q wave and the end of the T wave (QT) intervals, and the QT interval corrected for heart rate using Fridericia's formula (QTcF).

9.2.6. Laboratory Assessments

All routine clinical laboratory assessments will be performed by the hospital laboratory or equivalent per SOC. Where indicated, handling and shipping clinical laboratory samples to a central laboratory will be outlined in the Laboratory Manual.

Screening laboratory and other tests can serve as baseline values for participants, they do not need to be repeated if performed within the prior 24 hours of randomization unless otherwise dictated by SOC; however, the blood sample for analysis of pGSN antibodies must be repeated if not collected within 30 minutes of initiating the first dose of study drug.

The laboratory evaluations will include:

1. Hematology: complete blood count with differential white count and reticulocyte count, and platelet count; PT (INR)/aPTT
2. Comprehensive metabolic profile including chemistries/electrolytes, total protein/albumin, blood urea nitrogen (BUN)/creatinine, CRP, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, alkaline phosphatase, and amylase or lipase
3. Respiratory function (oxygen saturation by pulse oximetry; arterial blood gas tests only at the caregiver's discretion)

Abnormal laboratory test results considered clinically significant by the Investigator or that require treatment should be reported as AEs in the eCRF according to the AE reporting instructions in Section 10.6.

9.3. Pharmacokinetic Assessments

Blood for PK will be drawn at the following time points:

- For Dose #1: within 15 minutes predose, and at 1 (±15 min), 2 (±15 min), 6 (±30 min), and 12 (±30 min) hours after the end of dose administration (but prior to Dose #2)
- For Dose #3: within 15 minutes predose, and at 1 (±15 min), 2 (±15 min), 6 (±30 min), 12 (±30 min) and 24 (±30 min) hours after the end of dose administration

Samples should be spun and plasma frozen and sent to a central lab for analysis. Plasma samples will be analyzed for maximum concentration (C_{max}), time to maximum concentration (T_{max}), terminal half-life ($T_{1/2}$), area under the curve from time zero to 8 hours (AUC_{0-8}), area under the curve from time 0 to infinity (AUC_{inf}).

Participants who refuse some or all PK blood samplings can remain in the trial. However, PK sampling is to be highly encouraged.

For Dose #3, the last PK sample will occur on Day 3 (i.e., 24 hours after the end of third study drug administration which was initiated 36 hours after the first dose).

9.4. Pharmacodynamic Assessments

On the study days indicated in Table 5, blood will be collected for measurement of ferritin, D-dimer, CRP, and procalcitonin level at local laboratory. Save aliquots of blood for subsequent analysis. Analyses are likely to include, but are not limited to, the following:

- Biomarkers including, but not limited to, IL1[2] , IL6, IL10, TNF, etc. (see Table 5 Schedule of Assessments and footnote 'l' for details).

Blood samples may be stored for analysis for up to 5 years in the event that new biomarkers are discovered.

9.5. Other Assessments

Other analyses to be performed include:

- Blood, sputum, and other cultures as clinically indicated per SOC (note that a sputum culture is mandatory if a sputum specimen can be obtained and blood cultures are strongly encouraged at entry into the study)

10. ADVERSE EVENT MANAGEMENT

10.1. Definition of Adverse Events

10.1.1. 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 casually related to the product.

All AEs that occur during or after a subject has been administered study drug, or within 14 days following the last study drug administration, whether or not they are related to the study, must be recorded on forms provided by the Sponsor.

10.1.2. Serious Adverse Event (SAE)

An SAE is an AE occurring during any study phase (i.e., baseline, treatment, or follow up), and at any dose of the investigational product, comparator or placebo, 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 the subject/next of kin/legal proxy has given informed consent and has been randomized, including before or during treatment and within 90 days following the last dose of study drug, whether or not judged to be related to the study, must be recorded on forms provided by the Sponsor.

10.2. Clarifications to Serious Adverse Event Reporting

Death is an outcome of an SAE and not an SAE in itself. When death is an outcome, report the event(s) resulting in death as the SAE term (e.g., “pulmonary embolism”). If the cause of death is unknown, report “Death, unknown cause” as the SAE term.

10.3. Assessment of Causality

The relationship of each AE to the study drug administration will be assessed by the Investigator after careful consideration of all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to receipt of the study medication and de-challenge or re-challenge according to the following guidelines:

YES (possible, probably or definitely related): there is a reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of study drug.
- The event could not be reasonably attributed to the known characteristics of the subject's clinical state, environment or toxic factors or other modes of therapy administered to the subject.
- The event follows a known pattern of response to study drug.
- The event disappears or decreases on cessation or reduction in dose of the study drug. In some situations, an AE will not disappear or decrease in intensity upon discontinuation of the study drug despite other clear indications of relatedness.

NO (probably not related or definitely not related): There is no reasonable possibility that the study drug caused the event and none of the criteria from the previous section apply; one or more of the following criteria apply:

- The event does not follow a reasonable temporal sequence from administration of study drug.
- The event could be reasonably attributed to the known characteristics of the subject's clinical state, concurrent illness, environment or toxic factor or other modes of therapy administered to the subject.
- The event does not follow a known pattern of response to study drug.
- The event does not disappear or decrease on cessation or reduction in dose of the study drug, and it does not reappear or worsen when the study drug is re-administered.

10.4. Assessment of Severity

The severity rating of an AE refers to its intensity. The severity of each AE will be categorized using the NCI CTCAE, version 5.0. For any term that is not specifically listed in the CTCAE scale, intensity should be assigned a grade of 1 through 5 using the following CTCAE guidelines:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 10.1.2. An AE of severe intensity may not be considered serious.

10.5. Pregnancy or Drug Exposure during Pregnancy

If a subject becomes pregnant during the study, administration of study drug is to be discontinued immediately.

Pregnancies must be reported within 24 hours of the Investigator's knowledge using the Sponsor's pregnancy form.

Pregnancy in itself is not regarded as an AE or SAE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

10.6. Laboratory Abnormalities

To the extent possible, all laboratory abnormalities observed during the course of the study will be included under a reported AE term describing a clinical syndrome (e.g., elevated BUN and creatinine in the setting of an AE of "renal failure"). In these cases (e.g., an AE of renal failure), the laboratory abnormality itself (e.g., elevated creatinine) does not need to be recorded as an AE.

If a laboratory abnormality cannot be reported as a clinical syndrome, AND if the laboratory abnormality results in a therapeutic intervention (i.e., concomitant medication or therapy), is a dose-limiting toxicity, or is judged by the Investigator to be of other clinical relevance, then the laboratory abnormality should be reported as an AE.

Subjects experiencing AEs or clinically significant laboratory abnormalities will be assessed and appropriate evaluations performed until all parameters have returned to baseline levels or are consistent with the subject's then-current physical condition.

10.7. Reporting Adverse Events

All AEs, serious and nonserious, will be fully documented on the appropriate eCRF. For each AE, the Investigator must provide its duration (start and end dates or ongoing), intensity, assessment of causality and whether specific action or therapy was required.

All AEs that occur from informed consent until the first dose of study drug should be recorded on the AE eCRF page only if the event was related to a study procedure. All other AEs/findings prior to first dose of study drug should be recorded as medical history on the applicable eCRF page. AEs occurring from the first dose of study drug until 14 days after the last dose of study drug must be recorded on the AE eCRF. An ongoing AE identified prior to 14 days after the last study drug administration will be followed if possible until resolution.

All SAEs occurring any time (baseline, treatment, or follow up) during the study (related or unrelated) must be reported to EastHORN Safety within 24 hours of the Investigator's knowledge. This should be done in accordance with the instructions on SAE Report Form completion and reporting

Investigators must follow subjects with AEs/SAEs until the event has resolved, the condition has stabilized, withdrawal of consent, the subject is lost to follow up or death OR until the EOS Visit, whichever occurs first. An ongoing SAE identified by EOS will be followed if possible until resolution. If the subject dies, this should be captured as the outcome of the AE unless no link between the AE and the subject death can be established, in which case the AE will be marked as ongoing and the death will be reported as a separate event.

If a subject is lost to follow up, this should be captured accordingly within the AE eCRF and on the follow up SAE report.

The Sponsor or designee is responsible for notifying the relevant regulatory authorities of applicable suspected unexpected serious adverse reactions (SUSARs) as individual notifications or through periodic line listings. It is the PI's responsibility to notify the Institutional Review Board (IRB) or IEC of all SAEs that occur at his or her site according to the local regulations. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial.

11. STATISTICS

11.1. General Overview

All subjects given e 1 dose of study drug will be included in the Full Analysis Set (FAS) according to actual drug received; non-completers will be counted as failures in the primary efficacy analysis. Subjects receiving all 3 doses and evaluable for the primary Day 14 endpoint will constitute the per-protocol population for efficacy assessment. WHO severity score will be recorded daily while the subject is hospitalized, after discharge through Day 14, where feasible, and at each follow-up visit.

AE data will be summarized for the FAS by actual drug received using counts and proportions of subjects having an AE, each AE type, and an AE of each System Organ Class. SAEs and reasons for any early discontinuation will be summarized similarly. All deaths will be categorized by cause of death as per investigator assessment and relationship to study drug and/or COVID-19

Immunogenicity will be assessed on Days 1(predose), 28, and 90 days in all participants. Antibodies against pGSN will be assayed from frozen specimens to determine whether the investigational product induces an antibody response in recipients.

For Part 1, binary efficacy endpoints will be compared between treatments via stratified Cochran-Mantel-Haenszel (CMH) test and, to accommodate continuous covariates, via logistic regression. Continuous efficacy and biochemical endpoints will be compared between treatments via mixed model repeated measures analysis or analysis of covariance, depending on whether repeated measures are available or not. Time-to-event analysis via stratified log rank test and Cox proportional hazards model may also be carried out as supplemental analyses.

For Part 1, exploratory analyses looking at biomarkers and outcomes in each treatment arm will be conducted. Other exploratory analysis to compare the efficacy endpoint data from the rhu-pGSN group from this study to that of external control data may be carried out if appropriate. Sample size may be increased to improve the precision of the estimates of between-treatment comparisons if appropriate and if drug supplies are available.

For Part 2, only descriptive statistics will be provided for exploratory analyses. Binary efficacy endpoints will be summarized by counts, percentages, and 95% confidence intervals (CIs) for each treatment group. Differences in percentages between treatment groups will be summarized by 95% CIs. Continuous efficacy and biochemical endpoints will be summarized by counts, means, standard deviations, median, minimum, maximum by treatment group. Differences in means between treatment groups will be summarized by 95% CIs. Natural log transformation may be necessary to better approximate a bell-shaped distribution for the continuous endpoints. Time-to-event endpoints will be summarized by Kaplan-Meier plots, medians, quartiles, minimum, and maximum by treatment group. Bayesian posterior probabilities that differences from zero toward beneficial treatment effect for these summary statistics may be computed.

Data from Part 1 and Part 2 of the study will be analyzed separately.

11.2. Sample Size and Power Calculations

The primary endpoint is difference between treatments in the proportion of surviving subjects off vasopressors, the ventilator, and dialysis on Day 14. For Part 1, the power for the study is computed for the expected increase in proportion of surviving subjects without these supports at Day 14 after start of study treatment. A total sample size of N=54 has ~80% power to yield a statistically significant (alpha=0.2 1-sided) difference if the TRUE underlying proportions are 20% and 5% for placebo plus SOC and rhu-pGSN plus SOC, respectively. The minimum OBSERVED difference from placebo plus SOC proportion 20% that yields statistical significance is 8.4% (20% vs 11.6%). As this is a pilot Phase 2 POC trial in an infection with no approved therapy and false negative error (100% minus power) is equally as important as false positive error, the one-sided type 1 error is set at 0.2. Thus, the trial is adequately powered for its primary POC objective.

For Part 2, a sample size of 20 subjects was chosen to generate an estimate of any clinically relevant treatment effect.

11.3. Analysis Populations

The Full Analysis Set (FAS) will include subjects given e 1 dose of study drug according to actual drug received.

11.4. Criteria for Evaluation and Statistical Methods

11.4.1. Safety

AE data will be summarized by counts and proportions of subjects having an AE, each AE type, and an AE of each System Organ Class. These summaries will be provided for the rhu-pGSN and placebo groups separately. SAEs will be summarized similarly. Reasons for any early discontinuations will be summarized similarly.

Laboratory data in relation to normal range values will be summarized via counts and percentages of subjects below, within, and above the respective normal range, and by summary statistics (N, mean, median, standard deviation, minimum, maximum, 90% confidence intervals, etc.) for baseline, each observed time point, and change from baseline at each observed time point for continuous lab endpoints.

11.4.2. Baseline Characteristics

Demographics and disease-related characteristics will be summarized via counts and percentages of subjects for categorical variables, and by N, mean, median, standard deviation, minimum, maximum for continuous variables. Summaries will be performed for the rhu-pGSN and placebo groups separately, and for all subjects combined.

11.4.3. Pharmacokinetics and Immunogenicity

To complete the PK analyses, plasma specimens will be periodically sampled relative to study drug administration and stored frozen for pGSN measurements. See Table 5 and Section 9.3 for collection time points. Plasma samples will be analyzed for C_{max}, T_{max}, $T_{1/2}$, AUC_{0-8}, AUC_{inf}.

Immunogenicity will be assessed on Day 1(predose), 28, and 90. Antibodies against rhu-pGSN will be assayed from frozen specimens to determine whether the investigational product induces an antibody response in recipients.

11.4.4. Pharmacodynamics

Biomarker and clinical outcomes will be summarized via counts and percentages of subjects for categorical variables, and by summary statistics (N, mean, median, standard deviation, minimum, maximum, 90% confidence intervals, etc.) for baseline, each observed time point, and change from baseline at each observed time point for continuous variables. Data will be assessed via graphical and Shapiro-Wilk statistic for closeness to normal distribution and if substantial departure is observed, transformation (e.g., natural log, reciprocal, square root, ranks) may be employed to derive the summary statistics.

12. DATA RECORDING, RETENTION AND MONITORING

12.1. Case Report Forms

Data will be collected using an electronic data capture (EDC) system at the clinical site. The Investigator or designee will record data specified in the protocol using eCRFs. Changes or corrections to eCRFs will be made by the Investigator or an authorized member of the study staff according to the policies and procedures at the site and the eCRF completion guidelines.

It is the responsibility of the Investigator to ensure eCRFs are complete and accurate. Following review and approval, the Investigator or designee will electronically sign and date the pages. This signature certifies that the Investigator has thoroughly reviewed and confirmed all data on the eCRF. Regardless of whether this responsibility has been delegated, the Investigator is personally responsible for the accuracy and completeness of all data included in the eCRF.

The Sponsor or designee will provide a portable document format (PDF) file of the eCRFs to the site for archiving after all data have been monitored and reconciled.

12.2. Records Retention

Per Good Clinical Practice (GCP) guidelines regarding records retention, study documents are to be retained at the site until at least 2 years after the last approval of a marketing application in an International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) region or at least 2 years have elapsed since the formal discontinuation of clinical development of study drug. The Sponsor will notify the site of the date when study documentation may be destroyed.

12.3. Data Monitoring

This study will be closely monitored by representatives of the Sponsor throughout its duration. Monitoring will include personal visits with the Investigator and study staff, remote monitoring visits including Remote Source Data Verification (remote SDV) only in case onsite visits are not allowed in the BTI-202 study during the public health crisis due to COVID-19 as well as appropriate communications by telephone, fax, mail, email or use of the EDC system, if applicable. It is the responsibility of the monitor to inspect eCRFs at regular intervals throughout the study to verify the completeness, accuracy and consistency of the data and to confirm adherence to the study protocol and to GCP guidelines. The Investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of this study are resolved promptly. The Investigator and site will permit study-related monitoring, audits, IEC review and regulatory inspection, including direct access to source documents.

It is understood that study monitors and any other personnel authorized by the Sponsor and/or Sponsor representatives may contact and visit the Investigator and will be permitted to inspect all study records (including eCRFs and other pertinent data) on request, provided that subject confidentiality is maintained and that the inspection is conducted in accordance with local regulations.

Every effort will be made to maintain the anonymity and confidentiality of subjects during this study. However, because of the experimental nature of this treatment, the Investigator agrees to allow representatives of the Sponsor as well as authorized representatives of regulatory authorities to inspect the facilities used in the conduct of this study and to inspect, for purposes of verification, the hospital or clinic records of all subjects enrolled in the study.

Remote monitoring is an alternative mechanism of the Sponsor oversight activities that allows remote evaluation of accumulating data, performed with the same frequency as onsite monitoring visits.

In this study, remote SDV of data is a part of this remote monitoring visit and will be considered only when onsite visits will not be allowed during COVID-19 pandemic.

It will focus on the quality control of critical data such as primary efficacy data and important safety data. Only the data that are necessary for this purpose will be accessed.

Remote SDV may include a combination of the following:

1. Sharing pseudonymized copies of trial related source documents with the monitor; this may be done electronically where manageable by the site staff;
2. Direct, suitably controlled remote access to trial participants' electronic medical records; The provision for source data verification to take place remotely;
3. Video review of medical records with clinical site team support, without sending any copy to the monitor and without the monitor recording images during the review.

It will be confirmed with the Principal Investigator (PI) / designee at each site to establish whether remote SDV would be allowed, feasible and manageable for this site and what the practicalities could be.

It will be discussed with the PI and site Data Privacy Officer and decision should be taken which option of remote SDV, that is in line with national law, will be possible for particular site.

Every effort will be made to maintain the anonymity, confidentiality, and protection of study participants rights during remote SDV.

12.4. Quality Control and Quality Assurance

The study site may be audited by a quality assurance representative of the Sponsor or its designee for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor and/or auditor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

The Investigator should contact the Sponsor or designee immediately if contacted by a regulatory agency about an inspection.

13. REGULATORY, ETHICAL, AND LEGAL OBLIGATIONS

13.1. Good Clinical Practice

The study will be performed in accordance with the protocol, guidelines for GCP established by the ICH, and applicable local regulatory requirements and laws.

13.2. Independent Ethics Committee Approval

The Investigator must inform and obtain approval from the IEC for the conduct of the study at named sites, the protocol, informed consent documents and any other written information that will be provided to the subjects and any advertisements that will be used. Written approval must be obtained prior to recruitment of subjects into the study and shipment of study drug.

The Investigator is responsible for informing the IEC of any amendment to the protocol in accordance with local requirements. Amendments may be implemented only after a copy of the approval letter from the IEC has been transmitted to the Sponsor. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor or IEC approval. However, in this case, approval must be obtained ASAP after implementation.

Per GCP guidelines, the Investigator will be responsible for ensuring that an annual update is provided to the IEC to facilitate continuing review of the study and that the IEC is informed about the end of the study. Copies of the update, subsequent approvals and final letter must be sent to the Sponsor.

13.3. Regulatory Authority Approval

The study will be performed in accordance with regional regulatory requirements and will also meet all of the requirements of ICH GCP guidance. Amendments to the protocol will be submitted to the appropriate regulatory agency/agencies prior to implementation in accordance with applicable regulations.

13.4. Other Required Approvals

In addition to IEC and regulatory authority approval, all other required approvals (e.g. approval from the local research and development board or scientific committee) will be obtained prior to recruitment of subjects into the study and shipment of study drug.

13.5. Informed Consent

It is the responsibility of the Investigator (or designee) to obtain written informed consent from each subject/next of kin/legal proxy after adequate explanation of the aims, methods, and potential hazards of the study and before any study procedures are initiated. If written consent cannot be obtained prior to enrollment due to clinical circumstances, oral consent will be documented and written consent will be obtained later, when possible. The subject/next of kin/legal proxy should be given the opportunity to ask questions and allowed time to consider the information provided. Each subject/next of kin/legal proxy should be given a copy of the

informed consent document and associated materials. Documentation of informed consent must be retained at the site and is subject to inspection by representatives of the Sponsor or regulatory authorities.

Substantial changes to the study protocol may necessitate modifications to the ICF. If an amended informed consent document is issued during a subject's participation in the study, the subject/next of kin/legal proxy is required to provide informed consent using the updated consent form prior to continuing with study-related activities.

A subject/next of kin/legal proxy unable or unwilling to provide informed consent will not be enrolled in the study.

13.6. Subject Confidentiality

The Investigator must ensure that subjects' privacy is maintained. On the eCRF or other documents submitted to the Sponsor, subjects will be identified by a subject number or a subject number and initials only. Documents that are not submitted to the Sponsor (e.g., signed informed consent documents) should be kept in a strictly confidential file by the PI.

The Investigator shall permit authorized representatives of the Sponsor, regulatory authorities and IECs to review the portion of the subject's medical record that is directly related to the study. As part of the required content of informed consent documents, the subject must be informed that his/her records will be reviewed in this manner.

13.7. Disclosure of Information

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The PI may use this information for the purposes of the study only.

It is understood by the PI that the Sponsor will use information obtained in this clinical study in connection with the clinical development program, and therefore may disclose it as required to other clinical Investigators and to regulatory authorities. In order to allow the use of the information derived from this clinical study, the PI understands that he/she has an obligation to provide complete test results and all data obtained during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

14. PUBLICATION POLICY

The results of this study will be posted on ClinicalTrials.gov and submitted for peer reviewed publication within one year after the end of study.

15. LIST OF REFERENCES

Bucki R, Georges P, Espinassous Q, et al. Inactivation of endotoxin by human plasma gelsolin. Biochemistry 2005; 44:9590–7.

Bucki R, Byfield F, Kulakowska A, et al. Extracellular Gelsolin Binds Lipoteichoic Acid and Modulates Cellular Response to Proinflammatory Bacterial Wall Components. J Immunol 2008; 181:4936- 44.

Bucki R, Kulakowska A, Byfield FJ, et al. Plasma gelsolin modulates cellular response to sphingosine 1-phosphate. Am J Physiol, Cell Physiol. 2010; 299:C1516–23.

DiNubile, M., Levinson SL, Stossel TP, et al. Recombinant human plasma gelsolin (rhu-pGSN) improves survival and attenuates lung injury in a murine model of multi-drug resistant Pseudomonas aeruginosa pneumonia. Manuscript submitted for publication in 2020, in review.

Goetzel EJ, Lee H, Azuma T, et al. Gelsolin Binding and Cellular Presentation of Lysophosphatidic Acid. J Biol Chem 2000; 275:14573-8.

Haddad JG, Harper KD, Guoth M, et al. Angiopathic consequences of saturating the plasma scavenger system for actin. Proc Natl Acad Sci USA. 1990; 87:1381-5.

Lee WM, Galbraith RM. The extracellular actin-scavenger system and actin toxicity. N Engl J Med 1992; 326:1335-41.

Lee P, Drager L, Stossel T, et al. Relationship of plasma gelsolin levels in outcomes of critically ill surgical patients. Ann Surg 2006; 243:399-403.

Lee PS, Patel S, Christiani DC, et al. Plasma gelsolin depletion and circulating actin in sepsis: a pilot study. PLoS ONE 2008; 3:e3712.

Lee P, Sampath K, Karumanchi S, et al. Plasma Gelsolin and Circulating Actin Correlate with Hemodialysis Mortality. J Am Soc Nephrol 2009; 20:1140-8.

Lind SE, Janmey PA. Human plasma gelsolin binds to fibronectin. J Biol Chem 1984; 259:13262-6.

Osborn TM, Dahlgren C, Hartwig JH, et al. Modifications of cellular responses to lysophosphatidic acid and platelet-activating factor by plasma gelsolin. Am J Physiol Cell Physiol 2007; 292:C1323-30.

Osborn T, Verdrengh M, Stossel T, et al. Decreased levels of the gelsolin plasma isoform in patients with rheumatoid arthritis. Arthritis Res Ther 2008, 10:R117.

Piktel E, Wnorowska U, Cie[luk M, et al. Recombinant human plasma gelsolin stimulates phagocytosis while diminishing excessive inflammatory responses in mice with *Pseudomonas aeruginosa* sepsis. Int J Mol Sci 2020; 21:pii:E2551.

Self WH, Wunderink RG, DiNubile MJ, et al. Low admission plasma gelsolin concentrations identify community-acquired pneumonia patients at high risk for severe outcomes. Clin Infect Dis 2019; 69:1218-25.

Smith DB, Janmey PA, Herbert TJ, et al. Quantitative measurement of plasma gelsolin and its incorporation into fibrin clots. J Lab Clin Med 1987; 110:189-95.

Vasconcellos CA and Lind SE. Coordinated inhibition of actin-induced platelet aggregation by plasma gelsolin and vitamin D-binding protein. Blood 1993; 82:3648-57.

Yang Z, Chiou T, Stossel T, et al. Plasma gelsolin improves lung host defense against pneumonia by enhancing macrophage NOS3 function. Am J Physiol Lung Cell Mol Physiol 2015; 309: L11–L16.

Yang Z, Bedugnis A, Levinson S, et al. Delayed administration of recombinant plasma gelsolin improves survival in a murine model of severe influenza [version 2] F1000Research 2020; 8:1860.

Yang Z, Bedugnis A, Levinson S, et al. Delayed administration of recombinant plasma gelsolin improves survival in a murine model of penicillin-susceptible and penicillin-resistant pneumococcal pneumonia. J Infect Dis 2019; 220:1498-1502.

16. APPENDICES

Appendix A: CURB-65 Score

The score is an acronym for each of the risk factors measured. Each risk factor scores one point, for a maximum score of 5:

- Confusion of new onset (defined by the Abbreviated Mental Test Score [see Appendix B] of 8 or less [2 or more incorrect answers])
- Blood Urea nitrogen greater than 7 mmol/l (19 mg/dL)
- Respiratory rate of 30 breaths per minute or greater
- Blood pressure less than 90 mmHg systolic or diastolic blood pressure 60 mmHg or less
- Age 65 or older

Appendix B: Abbreviated Mental Test Score

The following or similar questions (adapted per country) are put to the patient. Each question correctly answered scores one point. A score of 8 or less suggests cognitive impairment at the time of testing, although further and more formal tests are necessary to confirm a diagnosis of dementia, delirium or other causes of cognitive impairment.

Question	**Score**
What is your age? (1 point)	
What is the time to the nearest hour? (1 point)	
Give the patient an address and ask him or her to repeat it at the end of the test. (1 point) e.g. 42 West Street	
What is the year? (1 point)	
What is the name of the office or doctor you are seeing today? (1 point)	
Can the patient recognize two persons (the doctor, nurse, home help, etc.)? (1 point)	
What is your date of birth? (day and month sufficient) (1 point)	
In what year was the 9-11 terrorist attack? (1 point) (other dates can be used, with a preference for dates sometime in the past)	
Name the present president of the USA. (1 point)	
Count backwards from 10 down to 1. (1 point)	

Appendix C: Protocol Amendment Summaries of Changes

Appendix C1: Summary of Changes v1.0 to v2.0

Summary of Changes to Protocol BTI-202 Ver 1.0 to 2.0
29 June 2020

Page # of Redline Version	Section	Old Text	New Text	Rationale
Global		14 May 2020 version 1.0	29 June 2020 version 2.0	Protocol amendment
1	**Title Page**	EUDRA CT Number: N/A	EUDRA CT Number: 2020-002460-31	Updated to add EUDRA CT number.
6, 28/29	**Synopsis (Number of subjects) and Section 6.2**	p. 6, "All SAEs and deaths and unexpected treatment-emergent SAEs will be evaluated by the Data and Safety Monitoring Board (DSMB) within 96 hours of occurrence. Periodic safety reviews will be conducted after enrollment of 12, 24, 36, and 48 patients. Data will be unblinded and/or the study paused at the discretion of the DSMB chair; enrollment will continue during the interim analyses unless otherwise mandated by the DSMB chair.	p. 6, "All deaths and unexpected treatment-emergent SAEs will be evaluated by the Data and Safety Monitoring Board (DSMB) within 4 working days of occurrence. Periodic safety reviews will be conducted after enrollment of 12, 24, 36, and 48 patients. Data will be unblinded and/or the study paused at the discretion of the DSMB chair; enrollment will continue during the safety analyses unless otherwise mandated by the DSMB chair."	Clarified definition of SAEs to be evaluated by DSMB and the timing to be implemented.
		p. 28/29 "A DSMB will be established to monitor safety of subjects. The DSMB will be comprised of 3 members: a representative of the Contract Research Organization (CRO), a representative of the Sponsor, and an independent expert in COVID-19	p. 28/29, "An independent DSMB will be established to closely monitor the safety of subjects. The primary mission of the DSMB is to ensure that decisions are made that serve the best interests of patients volunteering for the study. The independent DSMB will be comprised of 4 voting members: 3	

		pneumonia. All SAEs and deaths will be evaluated by the DSMB within 96 hours of occurrence. Periodic safety reviews will be conducted after enrollment of 12, 24, 36, and 48 patients. Data will be unblinded and/or the study paused at the discretion of the DSMB chair; enrollment will continue during the interim analyses unless otherwise mandated by the DSMB chair. Further details will be included in the DSMB charter."	academicians with expertise in pulmonary care, critical care, and/or infectious diseases as related to COVID-19 pneumonia and a statistician. Representatives from the CRO and Sponsor's Chief Medical Officer will be able to attend the open meetings to provide information and administrative support to the DSMB. However, they will not have any voting rights and will not attend the closed meeting where unblinded data may be discussed. All deaths and unexpected treatment-emergent SAEs will be evaluated by the DSMB within 4 working days of occurrence, but a DSMB meeting does not necessarily need to be convened. Ad hoc meetings will be convened whenever felt appropriate by a DSMB member. Periodic safety reviews will be conducted after the last enrolled subject in each group of 12, 24, 36, and 48 patients has reached the primary Day 14 timepoint. Data may be unblinded and/or the study paused at the discretion of the DSMB chair; otherwise, enrollment will continue during the safety review. Please refer to the DSMB Charter for further details."	
39, 40	**Section 8.8 and 8.12**	p. 39 "When a shipment is received, the pharmacist verifies the quantities	p. 39 "When a shipment is received, the pharmacist verifies the quantities	IWRS system is not to be implemented in the

		received and the accompanying documentation and provides acknowledgement of receipt via the interactive web response system (IWRS)."	received and the accompanying documentation and provides acknowledgement of receipt."	study.
		p. 40 "Randomization will be done centrally using the IWRS. All eligible subjects will be assigned a randomization number. The investigational site team and the subject will be kept blinded to the treatment allocation of each participant. Only the designated pharmacist(s) will be unblinded to the treatment allocation. The unblinded pharmacist will utilize the IWRS system to randomly assign a treatment allocation."	p. 40 "Randomization will be done centrally using manual methods. All eligible subjects will be assigned a randomization number. The investigational site team and the subject will be kept blinded to the treatment allocation of each participant. Only the designated pharmacist(s) will be unblinded to the treatment allocation. A manual system to randomly assign a treatment allocation."	
44	**Table 5 Schedule of Assessments Footnote 'a'**	Footnote 'a': "Day 1 is the first day of study treatment. Baseline tests (including blood draws) should be performed prior to administration of the first dose. Screening tests may also be performed on Day 1 prior to study treatment if necessary, as long as these tests cannot affect eligibility."	Footnote 'a': "Day 1 is the first day of study treatment. Baseline tests (including blood draws) should be performed prior to administration of the first dose. Screening tests may also be performed on Day 1 prior to study treatment if necessary, as long as these tests cannot affect eligibility. If Dose 1 is administered in the evening of Day 1, Dose 2 would be given on the second calendar day and Dose 3 would be given on the third calendar day,"	Clarified timing of doses if given at specific times on Day 1.

Appendix C2: Summary of Changes v2.0 to v3.0

Summary of Changes to Protocol BTI-202 Ver 2.0 to 3.0
29 January 2021

Page # of Redline Version	Section	Old Text	New Text	Rationale
Global		29 June 2020 version 2.0	29 January 2021 version 3.0	Protocol amendment
4	**Synopsis**	Estimated date last subject completed: 30 September 2020	Estimated date last subject completed: 01 May 2021	Enrollment not as fast as expected.
4, 8, 9, 25, 26, 35, 48	**Synopsis (Objectives, Notes, Endpoints/ Outcomes) and Sections 5.1.2, 5.2.2, 7.3, 9.3**	p.4 & 25, "[Optional] To follow the pharmacokinetics (PK) of administered rhu-pGSN."	p. 4 & 25, "To follow the pharmacokinetics (PK) of administered rhu-pGSN."	Clarifies that PK sampling is not mandatory but is strongly encouraged.
		p.8, 35, & 48 "Participants refusing PK blood samplings can remain in the trial."	p. 8, 35, & 48, "PK sampling is strongly encouraged. However, participants refusing some or all PK blood sampling can remain in the trial."	
		p.9 & 26, "PK(Optional)"	p. 9 & 26, "PK"	
5, 27	**Synopsis, Section 6.1**	• Mechanical ventilation or extracorporeal membrane oxygenation (ECMO), vasopressor support, dialysis/renal replacement therapy (RRT). • Intubation with mechanical	• Mechanical ventilation or extracorporeal membrane oxygenation (ECMO) with either vasopressor support or dialysis/renal replacement therapy (RRT) • Intubation with mechanical	Either vasopressor support or dialysis/renal replacement therapy (RRT) define WHO 7; both are excluded from WHO 6.

		ventilation, a mask with a reservoir or oxygen with high-flow nasal goggles	ventilation, a mask with a reservoir or oxygen with high-flow nasal goggles but without vasopressor support or dialysis/RRT	
5, 27/28, 46	**Synopsis, Section 6.1, 9.1.3**	p.5 & 27/28, "Perform physical examination (PE) and document radiographic evidence of pneumonia (chest x-ray [CXR] or computed tomography ([CT] scan if CXR is inadequate) if not already completed within the previous 48 hours per SOC"	p. 5 & 27/28, "A RT-PCR test to confirm the diagnosis of COVID-19 should be documented during the current illness leading to the present hospitalization; if RT-PCR test is not done prior to screening, the test is to be performed during screening before randomization (result might not be available at randomization or start of study treatment). Perform physical examination (PE) and document radiographic evidence of pneumonia (chest x-ray [CXR] or computed tomography ([CT] scan if CXR is inadequate) if not already completed within the previous 48 hours per SOC."	Added to indicate that an RT-PCR test to confirm COVID-19 is needed during screening if not done prior to screening, even if the result is to be available only after screening. A CXR or CT chest is needed at or within 48 hours of entry. Both are necessary to fulfill the inclusion criterion of being "Hospitalized with laboratory-confirmed (RT-PCR+) or highly suspected (compatible with at least bilobar lung involvement without another plausible diagnosis) COVID-19.
		p. 46, "Subjects are required to have a laboratory-confirmed (RT-PCR^{+}) or highly suspected COVID-19 pneumonia at screening. If confirmation is not available, the subject must undergo CXR, or a CT scan if CXR is inadequate, to confirm COVID-19 pneumonia. At screening, radiographic evidence (CXR, or CT scan) of COVID-19 pneumonia may have been	p.46, "Subjects are required to have pneumonia (confirmed clinically and documented on CXR or CT), with RT-PCR^{+} confirmed or highly suspected COVID-19 etiology at screening. If documentation is not available, the subject must undergo CXR, or a CT scan if CXR is inadequate, to confirm COVID-19 pneumonia. At screening,	

		completed in the previous 48 hours per SOC."	radiographic evidence (CXR, or CT scan) of COVID-19 pneumonia may have been completed in the previous 48 hours per SOC. If not already obtained and documented during the current illness leading to the present hospitalization, a RT-PCR test is to be performed during screening before randomization (result might not be available at randomization or start of study treatment)."	
5/6, 28, 49	**Synopsis, Section 6.1, 9.4**	"Save an approximate 10 mL aliquot of blood plasma or serum to be frozen at -20° C for subsequent biomarker assays (likely to include, but not limited to interleukin [IL]1², IL6, IL10, tumor necrosis factor [TNF], etc.) for analysis at the central laboratory."	"Collect aliquots of blood for subsequent biomarker assays (likely to include, but not limited to interleukin [IL]1², IL6, IL10, tumor necrosis factor [TNF], etc.) for analysis at the central laboratory (see Table 5 Schedule of Assessments and footnote 'l' for details)."	The detail of volume and storage was omitted for simplicity. It is mentioned later in the schedule of assessment in what is now footnote 'l'.
6, 29	**Synopsis and section 6.2**	p.6 & 29, "All deaths and unexpected treatment-emergent SAEs will be evaluated by the Data and Safety Monitoring Board (DSMB) within 4 working days of occurrence"	p.6, "All reported deaths and treatment-emergent SAEs will be evaluated by the Data and Safety Monitoring Board (DSMB) within 4 working days of notification of the Contract Research Organization (CRO)/Sponsor." p.29, "No SAEs have been associated with the investigational medicinal product. Thus, all SAEs will be considered as unexpected for reporting purposes. All reported	Because the CRO and Sponsor are not always immediately notified when SAEs occur. This change is intended to allow enough time for the DSMB to receive notification of and evaluate the SAEs.

			deaths and treatment-emergent SAEs will be sent by EastHORN Safety to the DSMB within 2 working days of notification of the CRO/Sponsor by the sites. The events will be evaluated by the DSMB and comments returned to EastHORN Safety within 2 working days of notification of the DSMB."	
6, 29	**Synopsis and section 6.2**	p.6, "Periodic safety reviews will be conducted after enrollment of 12, 24, 36, and 48 patients. Data will be unblinded and/or the study paused at the discretion of the DSMB chair." p.29," Periodic safety reviews will be conducted after the last enrolled subject in each group of 12, 24, 36 and 48 patients has reached the primary Day 14 time point. Data may be unblinded and/or the study paused at the discretion of the DSMB chair"	p.6 & 29, "Periodic safety reviews will be conducted after 12, 24, 36, and 48 subjects have been fully dosed and completed assessment at Day 14. Only DSMB members will be provided with partially unblinded results separated into 2 groups by treatment without identifying the actual treatment. If all participants have completed study therapy before the last DSMB meeting involving review of 48 subjects after their Day 14 visit can be held, this meeting can be cancelled at the discretion of the DSMB chair. Data will be further unblinded and/or the study paused at the discretion of the DSMB chair."	Clarifies that periodic safety reviews should be performed after a specified number of patients in each group have reached assessment Day 14 and NOT after they were enrolled. Depending on the enrolment progress, the DSMB meeting after 48 patients might not be performed if all subjects required for the study are fully dosed at the time of the DSMB meeting to review the preceding 48 subjects.
7, 34, 47	**Synopsis, Sections 7.2, 9.2.2**	p. 7 & 34, "oral or core temperature" p. 47, "oral temperature"	p. 7, 34 & 47 "body temperature"	The change is to permit body temperature to be taken as is customary at the site, not necessarily by the oral route.

7, 34	**Synopsis, Section 7.2**	"Radiology report to be placed in the eCRF"	"Radiology report and conclusion should be summarized in the eCRF"	Changed to reflect that a formal report does necessarily need to be included but at least a summary of the report and findings should be included in the eCRF.
7, 35	**Synopsis, Section 7.3**	"A negative RT-PCR test for COVID-19 during the evaluation of the present illness."	"A negative RT-PCR test for COVID-19 in the absence of a positive test during the evaluation of the present illness (in the presence of a positive test during the current illness, preceding or subsequent negative tests do not disqualify the subject)."	Added to indicate that a negative RT-PCR test is not an automatic disqualifier from the study provided there are other positive tests during the current illness.
9, 10, 26, 32, 44, 46, 54	**Synopsis, sections 5.2.2, 6.6, 9, 9.1.1, 11.1**	p. 9 & 26, "Daily change in 9-point WHO severity score through at least Day 14."	p.9 & 26, "Daily change in 9-point WHO severity score through at least Day 14 (including after discharge, where feasible)."	Added to avoid missing data after discharge when possible regarding daily assessment of the 9-point WHO score, should a subject be discharged before Day 14.
		p.10 & 54, "WHO severity score will be recorded daily as long as the subject is hospitalized, and at each follow-up visit."	p.10 & 54, "WHO severity score will be recorded daily while the subject is hospitalized, after discharge through Day 14, where feasible, and at each follow-up visit."	

		p. 32, “Subjects will be observed through Day 14 for the primary efficacy endpoint with daily assessments (including WHO severity score) from Day 1 through discharge, and then follow-up visits at Days 14, 28, 60 (if possible), and 90, and as needed.”	p. 32, “Subjects will be observed for the primary efficacy endpoint with daily assessments (including WHO severity score) from Day 1 through Day 14. If a subject is discharged prior to Day 14, he/she will be assessed, if feasible, by phone daily through Day 14, and then at follow-up visits, on Days 28, 60, and 90, and as needed.”	
		p. 44, Footnote “c” was added in Table 5: Schedule of Assessment: "Assess daily from screening through Day 14 during hospitalization and after discharge, where feasible, and then at Days 28, 60, and 90.” Corresponding superscript was added in Row 5 “Who Severity Score” of Table 5.		
		p. 46, “During screening and at the time points presented in the Schedule of Assessments (Table 5), each subject’s WHO severity score according to the 9-point scale (Section 6.1) will be recorded on the appropriate eCRF.”	p. 46, “During screening and at the time points presented in the Schedule of Assessments (Table 5), each subject’s WHO severity score according to the 9-point scale (Section 6.1) will be recorded on the appropriate eCRF. WHO severity scores should be documented daily through Day 14 (during hospitalization and after discharge, where feasible).”	

39	**Section 8.8**	"A disposition form will be completed to verify that all used, unused or partially used supplies have been returned or destroyed following appropriate accountability review by the monitor."	"A disposition form will be completed as per local regulation, since used/partially used vials might be required to be destroyed after use. Unused vials should be returned to the Sponsor."	Provides clarity that disposition of used/partially used drug should be done according to local regulation and that unused drug vials should be returned to the Sponsor.
39	**Section 8.9**	"All prior and concomitant medications, including generic name (if possible), and start date if known should be documented in the subject's file and in the eCRF."	"Medications administered within 1 month prior to screening and concomitant medications, including generic name (if possible), and start date if known should be documented in the subject's file and in the eCRF."	Provides guidance for the timeline of medications taken before screening that need to be reported.
41, 46, 50, 52, 58, 59	**Sections 9, 9.1, 10.1.2, 10.7, 13.5**	p. 41, "Written informed consent must be granted by each subject prior to the initiation of any study procedure or assessment (other than those considered SOC)."	p. 41, "Written or oral informed consent must be granted by each subject/next of kin/legal proxy according to hospital procedures and local regulations prior to the initiation of any study procedure or assessment (other than those considered SOC)."	Corrected to be consistent with inclusion criteria that states that the next of kin or legal proxy can provide consent and clarifies that informed consent can be either written or oral which was changed as an adaptation to the COVID-19 crisis in case informed consent cannot be given by writing.
		p.46, "Prior to screening, all subjects must provide informed consent"	p.46, "Prior to screening, all subjects/next of kin/legal proxy must provide informed consent"	
		p.50, "All SAEs that occur after any subject has signed the consent form and has been randomized, …"	p.50, "All SAEs that occur after the subject/next of kin/legal proxy has given written or oral consent and has been randomized, …."	

		p.52, "All AEs that occur from the signing of the informed consent form (ICF) until the first dose…"	p.52, "All AEs that occur from informed consent until the first dose…"	
		In section 13.5 in p. 58 & 59,"/next of kin/legal proxy" was added next to the word "Subject" when mentioned and "or oral" was added next to the word "written"		
42	**Section 9: Table 5**	Remove what is now superscript "d" (was part of "c") from *Confirm COVID-19 pneumonia (CXR or CT, RT-PCR for COVID-19)* row		Footnote "d" that refers to collecting sputum is not applicable for confirming COVID-19 pneumonia.
42	**Section 9: Table 5**	Remove superscripts of what is now footnote "f" (was "e") from time points in *Confirm COVID-19 pneumonia (CXR or CT, RT-PCR for COVID-19* row columns "Screening" and "Follow up visits 14 and 28")		Removed for simplicity as the footnote "f" itself describes when the indicated tests should be done.
42, 44 & 47	**Section 9: Table 5, Section 9.2.3**	Add footnote "g": "Height and weight only to be measured at screening or baseline and as per SOC thereafter" and corresponding superscript in the table, row *Physical exam*		Added to emphasize that weight does not necessarily need to be repeated after screening or baseline unless dictated by SOC.
		p. 47, "Height need only be measured at the screening examination. The initial body weight measured at enrollment will be used to calculate rhu-pGSN dosing for all doses (so that an individual subject will always receive the same dose). Body weight can be repeated per SOC thereafter where possible."	p. 47, "Height and weight need only be measured at screening or baseline. The initial body weight measured at enrollment will be used to calculate rhu-pGSN dosing for all doses (so that an individual subject will always receive the same dose). Body weight can be repeated per SOC thereafter where possible."	

43	**Section 9: Table 5**	Remove footnote "b" from *Biomarker sampling* row		Samples are required to be collected at baseline.
43	**Section 9: Table 5**	Remove superscript of footnote "b" from *Anti-rhu-pGSN antibody sampling (immunogenicity)* row, column "Baseline/Treatment"		Footnote "b" refers to tests done as dictated by SOC. Since immunogenicity is not part of SOC, "b" superscript was removed.
43	**Section 9: Table 5**	Remove superscript "n" (was previously "l") from *Study drug administration* row, column "Baseline/Treatment"		Footnote "n" (previously "l") is not applicable as it is a general description of study treatment at all days of treatment and not just at Day 1.
43 & 45	**Section 9: Table 5**	Row 21 "AEs (only SAEs after Day 14)"	Row 21: "AEs/SAEs[q]"	Clarify that after Day 14, only SAEs will be recorded throughout the remainder of the study.
		Added footnote "q": "From informed consent to first administration of study drug, related AEs and any SAEs will be recorded. During and after first admin of study drug, all AEs and SAEs will be recorded through Day 14. After Day 14, only SAEs will be recorded through study completion"		
		Row 21"AEs/SAEs [q]": Added "X" in "Screening" Column		
46	**Section 9.1.2**	"Testing could be done at the discretion of caregivers."	"Testing is not required but could be done as part of SOC at the discretion of caregivers."	Added to clarify that HIV testing is not required per protocol.
48	**Section 9.2.6**	"Comprehensive metabolic profile including chemistries/electrolytes, total protein/albumin, blood urea nitrogen (BUN)/creatinine, CRP,	"Comprehensive metabolic profile including chemistries/electrolytes, total protein/albumin, blood urea nitrogen (BUN)/creatinine, CRP,	LDH indicates "lactate" (not "lactose") dehydrogenase. Tests re: lipid parameters

		lactose dehydrogenase (LDH), creatine phosphokinase (CPK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, and amylase or lipase."	lactate dehydrogenase (LDH), creatine phosphokinase (CPK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, alkaline phosphatase, and amylase or lipase."	highlighted were added as requested by one of the investigators.
53	**Section 10.7**	All SAEs occurring any time (baseline, treatment, or follow up) during the study (related or unrelated) must be reported to the Sponsor and the responsible person at the CRO within 24 hours of the Investigator's knowledge.	All SAEs occurring any time (baseline, treatment, or follow up) during the study (related or unrelated) must be reported to EastHORN Safety within 24 hours of the Investigator's knowledge.	Added to clarify to whom SAEs should be first reported.
56, 57	**Section 12.3**	p. 56, "Monitoring will include personal visits with the Investigator and study staff, as well as appropriate communications …"	p. 56, "Monitoring will include personal visits with the Investigator and study staff, remote monitoring visits including Remote Source Data Verification (remote SDV) only in case onsite visits are not allowed in the BTI-202 study during the public health crisis due to COVID-19 as well as appropriate communications…"	Allows for remote data monitoring which was implemented as an adaptation to the COVID-19 pandemic.
		A paragraph was added at the end of this section in p. 57 to explain the specifics of remote data monitoring: "Remote monitoring is an alternative mechanism....and protection of study participants rights during remote		

		SDV”	

Other changes:

- Few additional language corrections were included in different places in the text.
- Some background about COVID19 was updated as shown in Section 4.2.
- Footnote lettering of Table 5: Schedule of Assessments was updated as required by insertions and deletions.
- Starting with Section 8.7, “or designee” was added next to “pharmacist” and “equivalent” next to “pharmacy” to accommodate local practices if necessary.

Appendix C3: Summary of Changes v3.0 to v4.0

Summary of Changes to Protocol BTI-202 Ver 3.0 to 4.0
09 June 2021

Page # of Redline Version	Section	Old Text	New Text	Rationale
Global	**Global**	~~29 January~~ 2021 version ~~3~~.0	09 June 2021 version 4.0	Protocol amendment
Global	**Global**	(see protocol)	(see protocol)	Updated abbreviations on first use and added new abbreviations, as needed.
Global	**Global**	(N/A)	**Defined criteria subjects in Part 1:** …in Part 1, a severity score of 4, 5, or 6,… **Defined criteria for subjects in Part 2:** …or for Part 2, intubated without extracorporeal membrane oxygenation (ECMO) with a severity score of 6 or 7 on the World Health Organization (WHO) 9-point severity scale	The study was amended to include subjects who are intubated without ECMO with a WHO severity score of 6 or 7. To distinguish this group of subjects, the study was divided into 2 parts and the differences between subjects in the 2 parts is defined throughout the protocol.
4	**Synopsis**	~~01 May~~ 2021	21 October 2021	Estimated last subject completion date updated to reflect addition of new subjects in Part 2.
5, 36, 40, 55	**Synopsis, Section 6.1, Section 6.5, Section 9.1**	…within 24 hours of reaching a WHO severity score of 4 to 6, whether the severity score is attained on admission or during hospitalization.	…for Part 1 within 24 hours of reaching a WHO severity score of 4 to 6, whether the severity score is attained on admission or during hospitalization, or for Part 2, within 24 hours of intubation without ECMO with a WHO severity	Specified the time within which subjects in Part 2 must be screened.

			score of 6 or 7.	
5, 37, 40	**Synopsis, Section 6.1, Section 6.5**	…subject to be randomized (1:1 to treatment arms rhu-pGSN:placebo) within 12 hours of informed consent	…subject to be randomized (1:1 to treatment arms rhu-pGSN:placebo) within 12 hours of informed consent (Part 1) or within 24 hours of intubation (Part 2)…	Specified the time within which subjects in Part 2 must be randomized.
6, 43	**Synopsis, Section 7.1**	A total of 60 evaluable participants randomized 1:1 to rhu-pGSN:placebo (30:30 subjects).	Part 1: A total of 60 evaluable participants randomized 1:1 to rhu-pGSN:placebo (30:30 subjects). Part 2: A total of 20 evaluable participants randomized 1:1 to rhu-pGSN:placebo (10:10 subjects).	Updated to reflect the addition of Part 2 and 20 additional subjects.
6, 38	**Synopsis, Section 6.2**	Periodic safety reviews will be conducted after 12, 24, 36, and 48 subjects have been fully dosed and completed assessment at Day 14.	In Part 1, periodic safety reviews will be conducted after 12, 24, 36, and 48 subjects have been fully dosed and completed assessment at Day 14.	Updated to clarify that the listed time points for periodic safety reviews apply to only Part 1.
6, 43	**Synopsis, Section 7.2**	- Weight d100 kg - Within 24 hours of reaching a WHO severity score of 4-6 either: o At admission o While already hospitalized.	- **Part 1 only:** Weight d100 kg - **Part 1 only:** Within 24 hours of reaching a WHO severity score of 4-6 either: o At admission o While already hospitalized. - **Part 2 only:** Within 24 hours of intubation without ECMO with a WHO severity score of 6 or 7)	Updated inclusion criteria to reflect that the weight limit only applies to subjects in Part 1 and to distinguish between the severity of disease required for subjects enrolled in Part 1 vs. Part 2.
10, 63	**Synopsis, Section 11.1**	(Added "For Part 1" to existing text; see protocol)	For Part 2, only descriptive statistics will be provided for exploratory analyses. Binary efficacy endpoints will be summarized by counts, percentages, and 95% confidence intervals (CIs) for each treatment group. Differences in percentages between treatment groups will be summarized by 95% CIs. Continuous efficacy and biochemical	Updated statistical analyses to reflect distinctions between analyses to be performed in Part 1 vs. Part 2.

			endpoints will be summarized by counts, means, standard deviations, median, minimum, maximum by treatment group. Differences in means between treatment groups will be summarized by 95% CIs. Natural log transformation may be necessary to better approximate a bell-shaped distribution for the continuous endpoints. Time-to-event endpoints will be summarized by Kaplan-Meier plots, medians, quartiles, minimum, and maximum by treatment group. Bayesian posterior probabilities that differences from zero toward beneficial treatment effect for these summary statistics may be computed.	
31	**Section 4.5**	(N/A)	The study protocol was amended to include Part 2 to evaluate rhu-pGSN in 10 subjects (compared to 10 placebo subjects) who are intubated without extracorporeal membrane oxygenation (ECMO) and therefore score as level 6 or 7 on the WHO scale. Recent data in the "steroid era" have suggested that immunomodulators may exert their most beneficial effects in critically ill patients which were not captured in the original recruitment for this study. Compassionate use in a single patient who scored as level 7 on the WHO scale in April 2021 resulted in quick and dramatic improvement temporally related to rhu-pGSN administration. Accordingly, intubated patients may be an appropriate target population for rhu-pGSN.	Added the rationale for the addition of Part 2 to the study.

40	**Section 6.5**	Eligible subjects will be…dosed within 12 hours of randomization.	Eligible subjects will be…dosed within 12 hours of randomization (both parts).	Updated to specify that subjects in both parts of the study must be dosed within 12 hours of randomization.
50, 59, 69	**Section 9, Section 10.1.2, Section 13.5**	~~Written or oral~~ informed consent…	Informed consent…	Updated to reflect that subjects in Part 2 may not be able to provide written consent initially.
53, 56	**Schedule of Assessments Table 5, Section 9.2.3**	Height and weight only to be measured at screening or baseline and as per SOC thereafter.	(In Part 1, h)Height and weight only to be measured at screening or baseline and as per SOC thereafter. In Part 2, height is not required at screening and weight may be obtained via bed scale, if possible, or estimated.	Added text to clarify the different measurement requirements for height and weight in Part 1 vs. Part 2.
53, 56	**Schedule of Assessments Table 5, Section 9.2.2**	Record blood pressure, body temperature, respiration rate, and heart rate, as well as pulse oximetry.	Record blood pressure, body temperature, respiration rate, and heart rate, as well as pulse oximetry. In Part 2, while the subject is intubated, the respiratory rate and the ventilator settings (i.e., tidal volume, inspired oxygen, inspiratory pressure, and PEEP) should be documented.	Added text to specify which settings related to intubation should be documented in Part 2.
56	**Section 9.2.3**	The physical examination includes skin, head, ears, eyes, nose, throat, heart, lungs, abdomen, and neurologic system.	The physical examination includes skin, head, ears, eyes, nose, throat, heart, lungs, abdomen, and neurologic system, where possible.	Added "where possible" to the body parts/systems to be examined to reflect that there may be differences in physical examinations for subjects in Part 1 vs. Part 2.
63-64	**Section 11.2**	(Added "For Part 1" to existing text; see protocol)	For Part 2, a sample size of 20 subjects was chosen to generate an estimate of any clinically relevant treatment effect.	Clarified the rationale for sample size in Part 2.
68	**Section 13.5**	It is the responsibility of the Investigator (or designee) to obtain written ~~or oral~~ informed consent from each subject/next of kin/legal proxy after adequate explanation of the aims, methods, and	It is the responsibility of the Investigator (or designee) to obtain written informed consent from each subject/next of kin/legal proxy after adequate explanation of the aims, methods, and	Updated to reflect that in Part 2, written consent may not be possible to obtain prior to enrollment due to clinical circumstances, but

		potential hazards of the study and before any study procedures are initiated.	potential hazards of the study and before any study procedures are initiated. If written consent cannot be obtained prior to enrollment due to clinical circumstances, oral consent will be documented and written consent will be obtained later, when possible.	oral consent will be documented and written consent obtained later, when possible.