A PHASE 1B/2A, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF RECOMBINANT HUMAN PLASMA GELSOLIN (RHU-PGSN) ADDED TO STANDARD OF CARE IN SUBJECTS HOSPITALIZED FOR ACUTE COMMUNITY-ACQUIRED PNEUMONIA (CAP)

Protocol Number:	BTI-201
Investigational Product:	rhu-pGSN
IND Number:	120920
EUDRA CT Number	N/A
Development Phase:	Phase 1b/2a
Indication Studied:	Community-acquired pneumonia (CAP) requiring hospitalization
Sponsor Name and Address:	BioAegis Therapeutics, Inc. (BTI)
Responsible Medical Officer:	Mark J. DiNubile, MD FIDSA
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:	30 April 2018
Version:	Amendment 1

PROTOCOL APPROVAL SIGNATURE PAGE

Protocol:	BTI-201
Title:	A Phase 1b/2a, Double-blind, Placebo-controlled, Dose-escalation Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Recombinant Human Plasma gelsolin (rhu-pGSN) Added to Standard of Care in Subjects Hospitalized for Acute Community-acquired Pneumonia (CAP)
Date:	30 April 2018
Amendment:	Amendment 1

Reviewed and Approved by:

Mark J. DiNubile

May 20, 2018

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

Date

PROTOCOL ACCEPTANCE FORM

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I have carefully read the BTI-201 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 1b/2a, Double-blind, Placebo-controlled, Dose-escalation Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Recombinant Human Plasma gelsolin (rhu-pGSN) Added to Standard of Care in Subjects Hospitalized for Acute Community-acquired Pneumonia (CAP)

Study center(s): 4-8 sites in Australia

Studied period (years):	**Phase of development:**
Estimated date first subject enrolled: July 2018 Estimated date last subject completed: December 2018	1b/2a

Objectives:

Primary

- To evaluate the safety and tolerability of single and multiple ascending doses of rhu-pGSN administered by once-daily intravenous (IV) push to hospitalized subjects with a primary admitting diagnosis of community-acquired pneumonia (CAP)
- To identify the maximum tolerated dose (MTD) or recommended Phase 2b/3 dose

Secondary

- To characterize the pharmacokinetic (PK) profile of rhu-pGSN after single or multiple IV doses

Exploratory

- To assess the quantitative relationship of pGSN levels at baseline with clinical outcomes, changes in prognostic indices and inflammatory biomarkers, and etiologic pathogen type
- To assess the relationship between rhu-pGSN dose and clinical response and changes in surrogate biomarkers of efficacy

Immunogenicity:

- To investigate the post-treatment development of antibodies against rhu-pGSN by Day 28

Methodology:

Each dosing cohort will include 8 subjects randomized 3:1 rhu-pGSN:placebo (6 rhu-pGSN subjects:2 placebo subjects).

Dose will be based on actual body weight. Dose escalation will involve 3 dose levels of rhu-pGSN (6, 12, and 24 mg/kg) in patients admitted for CAP. Dose escalation will only occur after post-therapy safety information on all subjects in the prior cohort has been reviewed at Day 7 for the single-dose [SD] and multiple-ascending dose [MAD] arms).

The MAD portion of the study will commence once single doses of 6 mg/kg of rhu-pGSN are shown to be acceptably safe. The first 2 doses must be administered in the hospital, but the third dose can be given in a monitored outpatient setting where appropriate.

Discharged subjects will return for follow-up 7 days after the initiation of therapy (Day 7) and on Day 28 for the End-of-Study Visit.

To assess safety and tolerability starting at the initiation of study therapy, subjects will undergo physical examinations (PE; including vital sign measurements), adverse event (AE) assessments, concomitant medication assessments, safety laboratory testing, and electrocardiograms (EKG) completed locally, and other testing as per local custom.

Once informed consent is obtained:

1. Randomize to enrolling treatment arm.
2. Perform PE and document radiographic evidence of pneumonia if not previously completed in preceding 36 hours; calculate **C**onfusion, **U**rea >7 mmol/L, **R**espiratory rate ≥30/min, **B**lood pressure systolic <90 or diastolic ≤60, and age ≥**65** years (CURB-65), Sequential Organ Failure Assessment (SOFA), and Pneumonia Severity Index (PSI) scores.
3. Obtain blood and sputum cultures, routine/standard labs, and EKG per standard of care (SOC) (if not already performed). The microbiology lab is encouraged to also perform sputum Gram-stains, antigen detection, immunoassay, and genomic diagnostic tests when available.
4. Draw blood for baseline pGSN levels, C-reactive protein (CRP), procalcitonin level, and 10 mL aliquot to be frozen for subsequent biomarker assays.

Screening laboratory and other tests can serve as baseline values for participants (no need to repeat lab tests at entry if done within the prior 36 hours unless dictated by SOC).

Obtain repeat chest x-rays (CXRs), computed tomography (CT) scans, and labs/cultures, etc. during the hospitalization if/when indicated by SOC.

Recalculate CURB-65 and ΔSOFA scores and redraw procalcitonin, pGSN, and biomarker samples on Day 3 or 4 and Day 7.

Doses in the multiple-dose arms should be given at 24-hour (± 60-minute) intervals. For the one dose in the SD arm and the first 2 doses in the multiple-dose arms, blood will be drawn within 30 minutes predose, and 5-10 minutes after the end of administration, as well as 2, 8, 12 and/or 16, and 24 hours after the end of administration (± 30 minutes) for analysis of plasma 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}), and area under the curve from time zero to infinity (AUC_{inf}). Sampling at both the 12- and 16-hour time points is encouraged where feasible, but only one of these two times is required. Identical PK sampling is encouraged on Day 3 where feasible, but not required in the multiple-dose arms. In the multiple-dose arms, the sample at 24 hours after the prior dose must be drawn before the next dose is given and can serve as the predose sample for the next dose as long as administered within the subsequent 30 minutes.

The syringe, filter, and extension tubing should be connected after disconnecting the IV as close to the patient as possible. On Day 28, collect samples for analysis of pGSN levels and antibodies against pGSN.

Number of subjects (enrolled):

A total of 32 (6 rhu-pGSN and 2 placebo recipients per dose cohort x 4 dosing levels)

Major inclusion criteria:

1. Age ≥ 18 years

2. Gender: either
3. Informed consent obtained from subject
4. Domicile: home, assisted living, rehabilitation facility, or nursing home (as long as the prospective participant is capable of providing written informed consent)
5. Duration of infection precipitating hospitalization by history <14 days
6. Planned or actual admission to hospital with a primary diagnosis of CAP within 24 hours of presentation to the hospital
7. Primary admitting diagnosis of pneumonia supported by a compatible clinical presentation with a documented infiltrate consistent with pneumonia on chest radiograph 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 CAP:
     - At least 2 symptoms: difficulty breathing, cough, production of purulent sputum, chest pain
     - At least 2 vital sign abnormalities: fever, tachycardia, tachypnea
     - At least one finding of other clinical signs and laboratory abnormalities: hypoxemia, clinical evidence of pulmonary consolidation, an elevated total white blood cell (WBC) count or leukopenia
     - Chest imaging showing new (or presumed new or worsening) infiltrates
   - Receipt of antibiotic treatment prior to presentation does not exclude the patient

Major exclusion criteria:

1. Pregnant or lactating women
2. Intubation, vasopressor support, or admission to the intensive care unit (ICU) directly from the ED/office (fluids for responsive hypotension is not a reason for exclusion)
3. Use of any investigational drug in the past 30 days
4. Hospitalization during the last 30 days
5. Residence within the last 30 days in long-term care facility where the patient remains persistently unable to participate in the routine activities of daily living
6. Active underlying cancer treated with systemic chemotherapy or radiation therapy during the last 30 days
7. Known or suspected immunosuppressive disease or therapy (including steroid use equivalent to prednisone ≥20 mg/day for >7 days or known advanced human immunodeficiency virus (HIV) infection with CD4 count ≤200/mm^3; specific testing for HIV status or CD4 count is not required but can be done at the discretion of the caregivers)
8. Active congestive heart failure, myocardial infarction, or pulmonary embolism; cardiopulmonary arrest in last 30 days
9. Weight >100 kg
10. Otherwise unsuitable for study participation in the opinion of the investigator

Investigational product, dosage and mode of administration: 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. • SD: single IV push at a rate between 5 and 20 mL/min through a standard 0.2-micron filter at 6 mg/kg • MAD: once-daily IV push at a rate between 5 and 20 mL/min through a standard 0.2-micron filter for 3 days at 6 mg/kg, 12 mg/kg, or 24 mg/kg administered on 3 consecutive days approximately 24 hours (± 60 minutes) apart.
Duration of treatment: 1 day (SD) or 3 days (MAD) Subject screening: within 24 hours of presentation to hospital; enrollment and initiation of study treatment begun within 36 hours of presentation. **Duration of subject participation:** 28 days post-first dose
Reference therapy, dosage and mode of administration: Placebo (dosed at a volume of 0.15, 0.30, or 0.60 mL/kg [depending on the dosing arm] up to 60 mL normal saline solution [NSS] via IV push [to match the volume of rhu-pGSN for a patient of that size in the specific dosing arm] injected at 5-20 mL/min through a standard 0.2-micron filter)

Endpoints/Outcomes:

Primary

- Incidence, causality, and severity of AEs and SAEs graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (or equivalent); clinically significant laboratory and/or EKG abnormalities; death irrespective of cause; cause of death per investigator, including relationship to study drug; use of vasopressors, intubation, or transfer to the ICU or equivalent through Day 7

Secondary

- PK for rhu-pGSN including, but not limited to: C_{max}, T_{max}, $T_{1/2}$, AUC_{0-8}, AUC_{inf} (levels measured within 30 minutes predose, 5-10 minutes after the end of administration, and 2, 8, 12 and/or 16, and 24 hours (± 30 minutes) after each dose (Day 3 sampling in multiple-dose arms is optional)
- Incidence, causality, and severity of AEs and serious adverse events (SAEs) graded according to the NCI CTCAE version 4.03 (or equivalent); clinically significant laboratory and/or EKG abnormalities as required by SOC; death irrespective of cause; cause of death per investigator, including relationship to study drug; use of vasopressors, intubation, or transfer to the ICU or equivalent through Day 28 (secondary time point)

Exploratory

- Baseline and sequential pGSN levels
- Clinical outcomes: 28-day survival; ICU days; days on ventilator or pressers; days on antibiotics; duration of hospitalization; ΔSOFA and CURB-65 scores
- Temporal profiles of inflammatory biomarkers
- Pathogen type (bacterial; viral; other; unknown) determined per customary work-up at each site

Immunogenicity

- Presence anti-rhu-pGSN antibodies at Day 28

Enrollment Procedure:

After informed consent, subjects with a primary diagnosis of CAP to be admitted to the medical wards will be screened for eligibility as soon as possible. Medical history, including concomitant medications and current clinical status, will be recorded.

- Pregnancy test (urine/blood) for women of childbearing potential
- A CXR and/or CT of the chest if not previously completed in preceding 36 hours
- If inclusion and exclusion criteria are satisfied, the subject will be enrolled and assigned to a baseline risk group CURB-65 ≤3 or >3. Randomization will not be stratified by risk group. Screening labs can be used for baseline values. The day of admission will be used as baseline (Day 1) for analysis purposes. Subjects will receive rhu-pGSN or placebo at the assigned dose within 36 hours of presentation.

Subject Replacement

Only subjects missing doses or discontinuing at random (non-informative) before the primary visit on Day 7 will be replaced as originally randomized to receive rhu-pGSN or placebo. Safety data from all subjects treated with ≥1 dose will be collected. Subjects discontinuing the study after the Day-7 Visit will not be replaced.

Data and Safety Monitoring Board:

MDN, SO, Clinical Research Organization (CRO) monitor.

Statistical Methods and Sample Size Rationale for Power Calculations:

All subjects given ≥1 dose of study drug will be included in the intention-to- treat population; missing values will not be imputed but safety data (death and other AEs) will be carried forward. Subjects receiving all 3 doses and evaluable at Day 7 will constitute the per-protocol population. The expectation is that both populations will be almost identical.

Results will be summarized via summary statistics separately for each pGSN dose level in the SD and in the MAD portions of the trial, and for all placebo subjects pooled. No data will be excluded from the summary statistics and analyses, and missing data will not be imputed.

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 separately by dose group and placebo subjects (all placebo subjects combined), and for all study subjects combined.

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 each dose and placebo (all placebo subjects combined). SAEs will be summarized similarly. Reasons for any early discontinuations will be summarized similarly.

Biomarker, clinical outcome, and laboratory data 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. Details will be in the statistical analysis plan (SAP).

To complete the PK analyses, plasma specimens will be periodically sampled relative to study drug administration and stored frozen for pGSN measurements. For the 1 dose in the SD arm and the first 2 doses in the MAD arms, blood will be drawn for analysis of C_{max}, C_{max}, $T_{1/2}$, AUC_{0-8}, and AUC_{inf}. Identical PK sampling is encouraged on Day 3 where feasible (but not required) in the multiple-dose arms.

The immunogenicity will be assessed at the last visit on Day 28 ± 2 days. Antibodies against rhu-pGSN will be assayed from frozen specimens to determine whether the investigational product induces an antibody response in recipients.

The table below presents the Minimum Sample Size such that there is 90% probability of observing at least 1 AE of a certain type if the TRUE underlying AE rate.

Sample Size	**TRUE underlying AE rate**
6 (each pGSN dose level)	32%
8 (pooled placebo)	21%
24 (pooled pGSN)	10%

With each sample size presented in the table above, if zero AEs of a certain type are observed, one could be "90% confident" the TRUE underlying rate for that AE is at most the rate indicated above.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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
AE	Adverse event
ALT	Alanine aminotransferase
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
CAP	Community-acquired pneumonia
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
C_{max}	Maximum concentration
COPD	Chronic obstructive pulmonary disease
CPK	Creatinine phosphokinase
CRO	Contract Research Organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
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
CXR	Chest x-ray
eCRF	Electronic case report form
CT	Computed tomography
DSMB	Data and Safety Monitoring Board
ED	Emergency department
EDC	Electronic data capture
EKG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
f-actin	Filamentous actin
g-actin	Globular actin
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Explanation
HIV	Human immunodeficiency virus
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRR	Injection-related reaction
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
MAD	Multiple-ascending dose
MMSE	Mini-Mental State Examination
MTD	Maximum tolerated dose
MV	Mechanical ventilation
NCI	National Cancer Institute
NSAIDS	Non-steroidal anti-inflammatory drugs
NSS	Normal saline solution
PD	pharmacodynamic
PDF	Portable document format
PE	Physical examination
PI	Principal Investigator The investigator who leads the study conduct at an individual study site. Every study site has a principal investigator.
PK	Pharmacokinetics
PSI	Pneumonia Severity Index
rhu-pGSN	Recombinant human plasma Gelsolin
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Single dose
SOC	Standard of care
SOFA	Sequential Organ Failure Assessment
$T_{1/2}$	Terminal half-life

Abbreviation or Specialist Term	Explanation
Tmax	Time to maximum concentration
US	United States
VP	Vasopressor
WBC	White blood cell
WHO	World Health Organization

4. INTRODUCTION

4.1. Community-Acquired 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.

According to the World Health Organization (WHO), pneumonia due to infection affects approximately 450 million people globally per year, seven percent of the population, and results in about 4 million deaths, mostly in third-world countries; however, it remains a serious issue in the developed world, as well. In the United States (US), 1.1 million are hospitalized each year, resulting in over 52,000 deaths at a ratio of 16.8 deaths per 100,000 (Centers for Disease Control and Prevention [CDC], 2010; Kochanek et al, 2015).

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.

The following outcome prediction models will be used in the current study:

- CURB-65:a simple five-point score in which one point is allocated to the presence of each of the following: **C**onfusion, **U**rea >7 mmol/L, **R**espiratory rate ≥30/min, **B**lood pressure systolic <90 or diastolic ≤60, and age ≥**65** years (Appendix A; British Thoracic Society, 1987; Neill et al, 1996; Niederman et al, 2001; Lim et al, 2003; Richards et al, 2011).
- Pneumonia Severity Index (PSI): calculates the probability of morbidity and mortality among patients with CAP (Appendix C; Richards et al, 2011).
- Sequential Organ Failure Assessment (SOFA): calculates the number and the severity of organ dysfunction in six organ systems (respiratory, coagulation, liver, cardiovascular, renal, and neurologic) (Appendix D) (Singer et al, 2016).

4.2. Current Treatment of CAP

CAP antibiotic, anti-fungal or anti-viral agents are administered based on organisms present in sputum, bacteriologic culture, serum antibody results or clinical impression of the infecting organism until resolution of sepsis and clinical symptoms and radiographic improvement has occurred, typically of 5- to 14-days duration. Patients with CURB-65 score ≥3 have an unacceptably high mortality despite standard-of-care (SOC) therapy and should be admitted to

hospital and may need intensive care (Richards et al, 2011). Any associated organ dysfunction is supported in an intensive care unit (ICU) and may include vasopressors and fluids for shock and mechanical ventilation for respiratory failure. Oral antibiotic therapy may be continued after discharge from hospital.

4.3. Plasma Gelsolin and Treatment of CAP

Plasma gelsolin 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 being developed by BioAegis Therapeutics, Inc. (BioAegis or Sponsor) is recombinant human plasma gelsolin (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). 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, 2000; 2005; 2008; 2010). 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 some 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 summary, the preclinical profile of pGSN suggests that this drug will be well tolerated by humans and that the risk of respiratory or systemic toxicity is low.

4.4.2. Clinical Experience

Rhu-pGSN has been previously evaluated in 3 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 per day (Day 1 and 2), 10 mg per day (Day 3 and 4) and 25 mg per day (Day 5 to 9). Sixteen patients were randomized to rhu-pGSN and five patients to placebo (randomization ratio 3:1). Rhu-pGSN was well tolerated and no safety concerns were raised. 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 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.

4.5. Rationale for Study and Starting Dose

The dosing for this study starts at the highest daily dose evaluated in the CBC-101 study performed in Hong Kong, followed by incrementally increased multiple doses for 3 consecutive days. The actual dose will be based on actual body weight. The placebo will be the equivalent volume on a weight basis of normal saline solution.

5. TRIAL OBJECTIVES AND ENDPOINTS

5.1. Objectives

5.1.1. Primary Objective

- To evaluate the safety and tolerability of single and multiple ascending doses of rhu-pGSN administered by once-daily IV push to hospitalized subjects with a primary admitting diagnosis of CAP
- To identify the maximum tolerated dose (MTD) or recommended Phase 2b/3 dose

5.1.2. Secondary Objectives

- To characterize the PK profile of rhu-pGSN after single or multiple IV doses

5.1.3. Exploratory Objectives

- To assess the quantitative relationship of pGSN levels at baseline with clinical outcomes, changes in prognostic indices and inflammatory biomarkers, and etiologic pathogen type
- To assess the relationship between rhu-pGSN dose and clinical response and changes in surrogate biomarkers of efficacy

5.1.4. Immunogenicity Objective

- To investigate the post-treatment development of antibodies against rhu-pGSN by Day 28

5.2. Endpoints

5.2.1. Primary Endpoint

- Incidence, causality, and severity of AEs and SAEs graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (or equivalent), clinically significant laboratory and/or electrocardiogram (EKG) abnormalities, death irrespective of cause, cause of death per investigator, including relationship to study drug; use of vasopressors, intubation, or transfer to the ICU or equivalent through Day 7

5.2.2. Secondary Endpoints

- PK for rhu-pGSN including, but not limited to 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 zero to infinity (AUC_{inf}) (levels measured within 30 minutes predose, 5-10 minutes after the end of administration, and 2, 8, 12 and/or 16, and 24 hours (± 30 minutes) after each dose (Day 3 sampling in multiple-dose arms is optional)

- Incidence, causality, and severity of AEs and SAEs graded according to the NCI CTCAE version 4.03 (or equivalent); clinically significant laboratory and/or EKG abnormalities as required by SOC; death irrespective of cause; cause of death per investigator, including relationship to study drug; use of vasopressors, intubation, or transfer to the ICU or equivalent through Day 28 (secondary time point)

5.2.3. Exploratory Endpoints

- Baseline and sequential pGSN levels
- Clinical outcomes: 28-day survival; ICU days; days on ventilator or pressers; days on antibiotics; duration of hospitalization; ΔSOFA and CURB-65 scores
- Temporal profiles of inflammatory biomarkers
- Pathogen type (bacterial; viral; other; unknown) determined per customary work-up at each site

5.2.4. Immunogenicity Endpoints

- Presence of anti-rhu-pGSN antibodies at Day 28

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

Study BTI-201 is a Phase 1b/2a, double-blind, placebo-controlled, dose-escalation study to evaluate the safety, PK, and pharmacodynamics of rhu-pGSN added to SOC in subjects hospitalized for acute CAP. Each dosing cohort will include 8 subjects randomized 3:1 rhu-pGSN:placebo (6 rhu-pGSN subjects:2 placebo subjects).

Dose will be based on actual body weight. Dose escalation will involve 3 dose levels of rhu-pGSN (6, 12, and 24 mg/kg) in patients admitted for CAP. Dose escalation will only occur after post-therapy safety information on all subjects in the prior cohort has been reviewed at Day 7 for the single-dose [SD] and multiple-ascending dose [MAD] arms.

The MAD portion of the study will commence once single doses of 6 mg/kg of rhu-pGSN are shown to be acceptably safe. The first 2 doses must be administered in the hospital, but the third dose can be given in a monitored outpatient setting where appropriate.

Discharged subjects will return for follow-up 7 days after the initiation of therapy (Day 7) and on Day 28 for the End-of-Study (EOS) Visit.

To assess safety and tolerability, subjects will undergo physical examinations (PE; including vital sign measurements), AE assessments, concomitant medication assessments, safety laboratory testing and EKGs (completed locally), and other testing as per local custom. See Table 5 and Table 6 for schedules of all study events.

6.2. Study Enrollment Plan

After informed consent, subjects with a primary diagnosis of CAP to be admitted to the medical wards will be screened for eligibility as soon as possible. Medical history, including concomitant medications and current clinical status, will be recorded. Initial assessments include:

- Pregnancy test (urine/blood) for women of childbearing potential
- A CXR and/or computed tomography (CT) of the chest if not previously completed in preceding 36 hours
- If inclusion and exclusion criteria are satisfied (Section 7.2 and Section 7.3), the subject will be enrolled and assigned to a baseline risk group CURB-65 ≤3 or >3. Randomization will not be stratified by risk group. Screening labs can be used for baseline values and need not be repeated unless the caregivers deem necessary. The day of admission will be used as baseline (Day 1) for analysis purposes. Subjects will receive rhu-pGSN or placebo at the assigned dose within 36 hours of presentation.

6.3. Doses and Schedule of Administration

In the SD arm, subjects will receive one dose of rhu-pGSN or placebo on Day 1 as an IV push at 6 mg/kg.

In the MAD arms, subjects will receive once-daily doses approximately 24 hours apart of rhu-pGSN or placebo on Days 1 through 3 as an IV push at 6, 12, or 24 mg/kg. The first 2 doses

must be administered in the hospital, but the third dose can be given in a monitored outpatient setting where appropriate.

6.4. Data and Safety Monitoring Board

An 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 CAP.

Safety through Day 7 of the study will be evaluated after the completion of each dosing arm to determine if it is safe to initiate the next cohort according to the safety criteria for stopping doses (Section 6.5).

Further details will be included in the DSMB charter.

6.5. Safety Criteria for Stopping Doses

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.

6.5.1. Management of rhu-pGSN Injection-Related Reactions

Injection-related reactions (IRRs) (Table 3) will be defined according to the NCI-CTCAE, version 4.03 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 ≤24 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 ≤Grade 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 1 hour, 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.

6.6. Study Duration

Subjects in the SD arm of the study will be treated for 1 day. Subjects in the MAD arms of the study will be treated for 3 consecutive days.

Subject screening: within 24 hours of presentation to hospital; enrollment and initiation of study treatment within 36 hours of presentation.

Subjects are followed for safety and efficacy through Day 28 for a total duration of approximately 1 month.

6.7. Total Duration of Subject Participation

Subjects will be observed for 28-days post-first dose.

6.8. End of Study Definition

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

6.9. 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 as soon as possible. If a subject refuses further assessment, the subject should be contacted for safety evaluations (AE/concomitant medications/potential pregnancy) approximately 28 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 (Section 6.6).

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.

6.10. Subject Replacement

Only subjects missing doses or discontinuing at random (non-informative) before the primary visit on Day 7 will be replaced as originally randomized to receive rhu-pGSN or placebo. Safety data from all subjects treated with ≥1 dose will be collected. Subjects discontinuing the study after the Day-7 Visit will not be replaced.

6.11. 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

A total of 32 (6 rhu-pGSN and 2 placebo recipients per dose cohort x 4 dosing levels).

7.2. Subject Inclusion Criteria

1. Age: ≥ 18 years
2. Gender: Either
3. Informed consent obtained from subject
4. Domicile: home, assisted living, rehabilitation facility, or nursing home (as long as the prospective participant is capable of providing written informed consent)
5. Duration of infection precipitating hospitalization by history <14 days
6. Planned or actual admission to hospital with a primary diagnosis of CAP within 24 hours of presentation to the hospital
7. Primary admitting diagnosis of pneumonia supported by a compatible clinical presentation with a documented infiltrate consistent with pneumonia on chest radiograph 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 CAP:
     - At least 2 symptoms: difficulty breathing, cough, production of purulent sputum, chest pain
     - At least 2 vital sign abnormalities: fever, tachycardia, tachypnea
     - At least one finding of other clinical signs and laboratory abnormalities: hypoxemia, clinical evidence of pulmonary consolidation, an elevated total white blood cell (WBC) count or leukopenia
     - Chest imaging showing new (or presumed new or worsening) infiltrates
   - Receipt of antibiotic treatment prior to presentation does not exclude the patient.

7.3. Subject Exclusion Criteria

1. Pregnant or lactating women
2. Intubation, vasopressor support, or admission to the ICU directly from the ED/office (fluids for responsive hypotension is not a reason for exclusion)
3. Use of any investigational drug in the past 30 days
4. Hospitalization within the past 30 days
5. Residence within the last 30 days in long-term care facility where the patient remains persistently unable to participate in the routine activities of daily living

6. Active underlying cancer treated with systemic chemotherapy or radiation therapy during the last 30 days
7. Known or suspected immunosuppressive disease or therapy (including steroid use equivalent to prednisone ≥20 mg/day for >7 days or known advanced human immunodeficiency virus (HIV) infection with CD4 count ≤200/mm^3; specific testing for HIV status or CD4 count is not required but can be done at the discretion of the caregivers)
8. Active congestive heart failure, myocardial infarction, or pulmonary embolism; cardiopulmonary arrest in last 30 days
9. Weight >100 kg
10. Otherwise unsuitable for study participation in the opinion of the investigator

7.4. Subjects or Partners of Subjects of Reproductive Potential

Pregnancy is an exclusion criterion and women of childbearing potential (<60 years of age and/or post-hysterectomy) must not be considering getting pregnant during the study. Female subjects of childbearing potential must have a negative serum or urine pregnancy test within 36 hours prior to start of study drug. A serum or urine pregnancy test will be performed at the EOS Visit.

Women of childbearing potential must practice an acceptable method of birth control starting at screening and continuing at least 4 weeks after the last study treatment. Acceptable methods of birth control in this study include: true sexual abstinence (i.e., completely refraining from heterosexual intercourse throughout the study), hormonal methods (e.g., "the pill", hormone injections, implants), barrier methods (e.g., condom or diaphragm), intrauterine device (IUD or "coil"), or sex exclusively with a sterilized partner.

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 4 weeks after the last 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.

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.

In the SD arm, study drug will be administered as a single IV push at a rate between 5 and 20 mL/min through a standard 0.2-micron filter at 6 mg/kg.

In the MAD arms, study drug will be administered as a once-daily IV push at a rate between 5 and 20 mL/min through a standard 0.2-micron filter for 3 consecutive days approximately 24 hours apart at 6, 12, or 24 mg/kg.

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

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. Method of Assigning Subjects to Treatment Groups

Subjects will be randomized in a 3:1 ratio to receive an IV push of rhu-pGSN or placebo (up to 60 mL normal saline solution [NSS]) during the treatment period. See Section 8.11 for details regarding randomization.

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 as soon as possible (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.

Placebo (dosed at a volume of 0.15, 0.30, or 0.60 mL/kg (depending on the dosing arm) up to 60 mL normal saline solution [NSS] via IV push [to match the volume of rhu-pGSN for a patient of that size in the specific dosing arm] injected at 5-20 mL/min through a standard 0.2-micron filter).

rhu-pGSN is administered as an IV push. The placebo is NSS and requires no special manipulation. The placebo will be the equivalent volume on a weight basis of normal saline solution.

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 a single IV push at a rate between 5 and 20 mL/min at 6 mg/kg in the SD arm. Doses in the MAD arms will be administered as a daily IV push at a rate between 5 and 20 mL/min at 6, 12, or 24 mg/kg of study drug for 3 days. The syringe, filter, and extension tubing should be connected after disconnecting the IV as close to the patient 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 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 in sufficient quantity and in time to enable dosing as scheduled. The Investigator must ensure the acknowledgement of receipt of the clinical trial material (i.e., study drug and placebo) at the site, including that the material was received in good condition.

The Sponsor or its designee must notify the Investigator/study staff 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, 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 will be responsible for ensuring the supervision of the storage and allocation of these supplies. When a shipment is received, the pharmacist verifies the quantities received and the accompanying documentation and provides acknowledgment of receipt via the interactive web response system (IWRS).

Accountability logs will be provided to assist the pharmacist 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 to verify that all used, unused or partially used supplies have been returned or destroyed following appropriate accountability review by the monitor. 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.

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.

8.10. Treatment Compliance

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

8.11. 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 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. The treatment allocation will be available to the unblinded pharmacist(s).

8.11.1. Unblinding

The unblinded pharmacist(s) will prepare sterile syringes with filters consisting of either 6, 12, or 24 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.

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 and Table 6). 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.

Written informed consent must be granted by each subject prior to the initiation of any study procedure or assessment (other than those considered SOC).

Table 5: Schedule of Assessments: Single-Dose Phase

Visit	Screening	Baseline/ Randomization/ Pre-Treatment	Follow-up days				Early Term/ End-of-Study Visit
Day	**-1 to 0**	**1[h]**	**2**	**3 or 4**	**7 ± 1**	**14 ±2**	**28 ± 4**
Informed consent	X						
Eligibility assessment	X						
Medical history/signs and symptoms	X	X[i]					
Sputum culture[a]	X						
Blood or urine pregnancy	X (for women of childbearing potential only)						X
Hepatitis B and C, HIV	Not required (could be done at the discretion of caregivers)						
Confirmation of CAP (CXR or CT)	X						
PSI score	X			X	X		X
SOFA score	X			X	X		X
CURB-65 score	X			X	X		X
Physical exam	X	X[i]	X	X	X	X	X
MMSE (Abbreviated Mental Test Score)	X	X[i]	X	X	X	X	X
Vital signs, including pulse oximetry[b]	X	X	X	X	X	X	X

Visit	Screening	Baseline/ Randomization/ Pre-Treatment	Follow-up days				Early Term/ End-of-Study Visit
Day	**-1 to 0**	**1**[h]	**2**	**3 or 4**	**7 ± 1**	**14 ±2**	**28 ± 4**
EKG[c]	X	X[i]					X
PK sampling for pGSN levels[d]		X	X				
CBC with differential and reticulocyte count; PT/PTT	X	X[i]	X	X	X	X	X
Comprehensive metabolic profile (including amylase or lipase)	X	X[i]	X	X	X	X	X
Biomarker sampling [e]		X	X	X	X	X	X
Anti-rhu-pGSN antibody sampling (immunogenicity)[f]							X
Study drug administration[g]		X					
AEs		X	X	X	X	X	X
Con meds	X	X	X	X	X	X	X

Abbreviations: AEs=adverse events; CAP=community-acquired pneumonia; CBC=complete blood count; Con meds=concomitant medications; 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; MMSE= mini-mental state examination; PD=pharmacodynamic; PK=pharmacokinetic; PSI=pneumonia severity index; PT=prothrombin time; PTT=partial thromboplastin time; SOFA= sequential organ failure assessment (score); Term=termination.

[a] 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 genomic diagnostic tests when available. If fevers or chills are present, 2 sets of blood cultures are recommended at the discretion of the caregivers.

[b] Record blood pressure, oral temperature, respiration rate, and heart rate, as well as pulse oximetry. 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.

[c] When EKGs are to be collected at the same time point as a blood collection, EKGs should be collected first. Three serial, resting, supine 12-lead EKGs are to be conducted within 10 minutes total time.

[d] Blood for PK will be drawn within 30 minutes predose, 5-10 minutes after the end of administration, and 2, 8, 12 and/or 16, and 24 hrs (± 30 minutes) after the end of administration. Sampling at both the 12- and 16-hour time points is encouraged where feasible, but only one of these two times is required. The last PK sample (i.e., 24 hours after the end of administration) will occur on Day 2. Samples are spun and plasma frozen and sent to a central lab for analysis.

[e] A 10-mL aliquot (equal parts serum and plasma) will be frozen for subsequent biomarker analysis including, but not limited to, procalcitonin, pGSN, TNFα, TGFβ, IL1β, IL1ra, IL2, IL4, IL6, IL10, IL17a levels and sent to a central lab for analysis.

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

[g] Subjects are to be monitored for administration site reactions during study drug administration and for 1 hour after its completion.

[h] Day 1 is the first day of study treatment. Baseline tests (including blood draws) should be performed prior to administration of the first dose.

[i] Test/assessment does not have to be repeated if performed within the prior 36 hours unless dictated by standard of care.

Table 6: Schedule of Assessments: Multiple-Ascending Dose Phase

Visit	**Screening**	**Baseline/ Randomization/ Pre-Treatment**	**Follow-up days**					**Early Termination/ End-of-Study Visit**
Day	**-1 to 0**	**1[j]**	**2**	**3**	**4**	**7 ± 1**	**14 ±2**	**28 ± 4**
Informed consent	X							
Eligibility assessment	X							
Medical history/ signs and symptoms	X	X[k]						
Sputum culture[a]	X							
Blood or urine pregnancy	X (for women of childbearing potential only)							X
Hepatitis B and C, HIV	Not required (could be done at the discretion of caregivers)							
Confirmation of CAP (CXR or CT)	X							
PSI score	X				X	X		X
SOFA score	X				X	X		X
CURB-65 score	X				X	X		X
Physical exam	X	X[k]	X	X	X	X	X	X
MMSE (Abbreviated Mental Test Score)	X	X[k]	X	X	X	X	X	X

Visit	Screening	Baseline/ Randomization/ Pre-Treatment	Follow-up days					Early Termination/ End-of-Study Visit
Day	**-1 to 0**	**1[j]**	**2**	**3**	**4**	**7 ± 1**	**14 ±2**	**28 ± 4**
Vital signs, including pulse oximetry[b]	X	X	X	X	X	X	X	X
EKG[c]	X	X[k]						X
PK sampling for pGSN levels[d]		X	X	X[e]	X[e]			
CBC with differential and reticulocyte count; PT/PTT	X	X[k]	X	-	X	X	X	X
Comprehensive metabolic profile, including amylase or lipase	X	X[k]	X	-	X	X	X	X
Biomarker sampling [f]		X	X	X	X	X	X	X
Anti-rhu-pGSN antibody sampling (immunogenicity)[g]								X
Study drug administration[h]		X	X	X[i]				
AEs		X	X	X	X	X	X	X
Con meds	X	X	X	X	X	X	X	X

Abbreviations: AEs=adverse events; CAP=community-acquired pneumonia; CBC=complete blood count; Con meds=concomitant medications; 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; MMSE= mini-mental state examination; PD=pharmacodynamic; PK=pharmacokinetic; PSI=pneumonia severity index; PT=prothrombin time; PTT=partial thromboplastin time; SOFA= sequential organ failure assessment (score).

[a] 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 genomic diagnostic tests when available. If fevers or chills are present, 2 sets of blood cultures are recommended at the discretion of the caregivers.

[b] Record blood pressure, oral temperature, respiration rate, and heart rate, as well as pulse oximetry. 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.

[c] When EKGs are to be collected at the same time point as a blood collection, EKGs should be collected first. Three serial, resting, supine 12-lead EKGs are to be conducted within 10 minutes total time.

[d] Doses in the multiple-dose arms should be given at 24-hour (± 60-minute) intervals. Blood for PK will be drawn within 30 minutes predose, 5-10 minutes after the end of administration, and 2, 8, 12 and/or 16, and 24 hrs (± 30 minutes) after the end of administration. Sampling at both the 12- and 16-hour time points is encouraged where feasible, but only one of these two times is required. In the multiple-dose arms, the sample at 24 hours after the prior dose must be drawn before the next dose is given and can serve as the predose sample for the next dose as long as administered within the subsequent 30 minutes. Samples are spun and plasma frozen and sent to a central lab for analysis.

[e] Identical blood collection for PK analysis is encouraged on Day 3 but not required. Where feasible, the last PK sample would occur on Day 4 (i.e., 24 hours after the end of administration on Day 3); otherwise, because there is no study drug administered after Day 3, no further PK sampling would be done on Day 4. Samples are spun and plasma frozen and sent to a central lab for analysis.

[f] A 10-mL aliquot (equal parts serum and plasma) will be frozen for subsequent biomarker analysis including, but not limited to, procalcitonin, pGSN, TNFα, TGFβ, IL1β, IL1ra, IL2, IL4, IL6, IL10, IL17a levels and sent to a central lab for analysis.

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

[h] Subjects are to be monitored for administration site reactions during study drug administration and for 1 hour after its completion.

[i] The third dose of study drug may be given in a monitored outpatient setting where appropriate.

[j] Day 1 is the first day of study treatment. Baseline tests (including blood draws) should be performed prior to administration of the first dose.

[k] Test/assessment does not have to be repeated if performed within the prior 36 hours unless dictated by standard of care.

9.1. Screening Assessments

Prior to screening, all subjects 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 tables (Table 5 and Table 6).

9.1.1. HIV Testing

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

9.1.2. Confirmation of CAP

Subjects are required to have a confirmed CAP diagnosis at screening. If confirmation is not available, the subject must undergo testing to confirm CAP.

9.1.3. 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 tables (Table 5 and Table 6).

9.2.1. Demographic/Medical History

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

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, oral temperature, respiration rate, and heart rate, as well as pulse oximetry. 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 physical examinations, including measurement of body weight, will be performed by a study physician or designee. 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). The physical examination includes skin, head, ears, eyes, nose, throat, heart, lungs, abdomen, and neurologic system. Additional examination may be performed as found relevant by the Investigator.

9.2.4. Outcome Prediction Models

The CURB-65 (Appendix A), PSI (Appendix C), and SOFA (Appendix D) tests will be administered. The cognitive status of the subject will be informally assessed for incorporation in the CURB-65 score by using the mini-mental state examination (MMSE; also referred to as the abbreviated mental test score; Appendix B). If the caregivers are concerned about abnormalities of cognition, subjects will be further evaluated at the discretion of the caregivers, which may involve being asked questions according to the MMSE or similar tool to assess cognitive function.

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. Three 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.

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, when appropriate. 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 (no need to repeat lab tests at entry if done within the prior 36 hours unless dictated by SOC).

The laboratory evaluations will include:

1. Hematology: complete blood count with differential white count and reticulocyte count, and platelet count; PT/PTT
2. Comprehensive metabolic profile (including chemistries/electrolytes, TP/albumin, BUN/creatinine, C-reactive protein (CRP), lactose dehydrogenase (LDH), creatine phosphokinase (CPK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, 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.

9.3. Pharmacokinetic Assessments

For the one dose in the SD arm and the first 2 doses in the MAD arms, blood will be drawn within 30 minutes predose, and 5-10 minutes after the end of administration, as well as 2, 8, 12 and/or 16, and 24 hours after the end of administration (± 30 minutes) for analysis of plasma for C_{max}, T_{max}, $T_{1/2}$, AUC_{0-8}, AUC_{inf}. Sampling at both the 12- and 16-hour time points is encouraged where feasible, but only one of these two times is required. Identical PK sampling is encouraged on Day 3 where feasible but not required in the multiple-dose arms.

9.4. Pharmacodynamic Assessments

A 10-mL aliquot (equal parts serum and plasma spun from 20 mL of whole blood) collected on study days indicated in Table 5 and Table 6 will be frozen for subsequent analysis of the following:

- Biomarkers including, but not limited to, procalcitonin, pGSN, TNFα, TGFβ, IL1β, IL1ra, IL2, IL4, IL6, IL10, IL17a levels

9.5. Other Assessments

Other analyses to be performed include:

- Blood, sputum, and other cultures as clinically indicated (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)
- Sputum neutrophil elastase (where feasible at entry and near the conclusion of study therapy)

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 worsening of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product.

10.1.2. Serious Adverse Event (SAE)

A serious adverse event (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 a subject has signed the consent form and has been randomized, including before or during treatment and within 28 days following the cessation of treatment, 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; 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, v 4.03 (or higher). 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 DLT, 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 the signing of the informed consent form (ICF) 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. All AEs occurring from the first dose of study drug until 28 days after the last dose of study drug must be recorded on the AE eCRF.

All SAEs (related and unrelated) must be reported to the Sponsor within 24 hours of the Investigator's knowledge. This should be done by faxing/emailing the completed SAE Report Form to the number provided on the SAE Report Form. After the EOS Visit, only new treatment-related SAEs need to be captured on the AE eCRF and reported to the Sponsor.

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. New and ongoing treatment-related SAEs should be followed beyond the EOS Visit. 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 Principal Investigator's responsibility to notify the Institutional Review Board (IRB) or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

11. STATISTICS

11.1. General Overview

All subjects given ≥1 dose of study drug will be included in the intention-to- treat population; missing values will not be imputed but safety data (death and other AEs) will be carried forward. Subjects receiving all 3 doses and evaluable at Day 7 will constitute the per-protocol population. The expectation is that both populations will be almost identical.

Results will be summarized via summary statistics separately for each pGSN dose level in the SD and MAD portions of the trial; pooled for all placebo subjects. Additional details will be provided in a separate Statistical Analysis Plan (SAP).

11.2. Sample Size and Power Calculations

The sample size of N=6 rhu-pGSN recipients per dose level and combined placebo in the SD and MAD portions of the trial were chosen based on limiting exposure to pGSN in this initial study in the current development program. The sample sizes in this trial have the following properties in relation to interpretation of AE incidence rates (Table 7).

Table 7 presents the Minimum Sample Size such that there is 90% probability of observing at least 1 AE of a certain type if the TRUE underlying AE rate.

Table 7: Minimum Sample Size Calculations

Sample Size	TRUE underlying AE rate
6 (each pGSN dose level)	32%
8 (pooled placebo)	21%
24 (pooled pGSN)	10%

With each sample size presented in the table above, if zero AEs of a certain type are observed, one could be "90% confident" the TRUE underlying rate for that AE is at most the rate indicated above.

11.3. Analysis Populations

No data will be excluded from the summary statistics and analyses, and missing data will not be imputed. AEs, including death, will be carried forward. As a sensitivity analysis to the intention-to-treat population, a per-protocol population excluding subjects who missed doses and/or randomly discontinued the study before the primary Day-7 Visit will be analyzed.

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 each dose and placebo (all placebo subjects combined). Serious AEs 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 separately by dose group and placebo subjects (all placebo subjects combined), 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. For the 1 dose in the SD arm and the first 2 doses in the MAD arms, blood will be drawn within 30 minutes predose, and 5-10 minutes after the end of administration, as well as 2, 8, 12 and/or 16, and 24 hours after the end of administration (± 30 minutes) for analysis of C_{max}, C_{max}, $T_{1/2}$, $AUC_{0\text{-}8h}$, and AUC_{inf}. Identical PK sampling is encouraged on Day 3 where feasible (but not required) in the multiple-dose arms.

Immunogenicity will be assessed at the last visit on Day 28 ± 2 days. 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 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.

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 as soon as possible 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 after adequate explanation of the aims, methods and potential hazards of the study and before any study procedures are initiated. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. Each subject should be given a copy of the informed consent document and associated materials. The original copy of the signed and dated informed consent document must be retained at the site and is subject to inspection by representatives of the Sponsor or regulatory authorities; the subject should be given a copy of the signed ICF.

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

Subjects unable or unwilling to provide written 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 Principal Investigator.

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 Principal Investigator may use this information for the purposes of the study only.

It is understood by the Principal Investigator 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 Principal Investigator 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.

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15. 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:

- **C**onfusion of new onset (defined by the Mini-Mental Status Exam Score [Abbreviated Mental Test Score; see Appendix B] of 8 or less [2 or more incorrect answers])
- Blood **U**rea nitrogen greater than 7 mmol/l (19 mg/dL)
- **R**espiratory rate of 30 breaths per minute or greater
- **B**lood pressure less than 90 mmHg systolic or diastolic blood pressure 60 mmHg or less
- Age **65** or older

APPENDIX B: MINI-MENTAL STATE EXAM (ABBREVIATED MENTAL TEST SCORE)

The following questions 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 some time in the past.)	
Name the present president of the USA. (1 point)	
Count backwards from 10 down to 1. (1 point)	

APPENDIX C: PSI (PORT SCORE)

The Pneumonia Severity Index (PSI) algorithm is detailed below. An online, automated PSI calculator is available on the US Agency for Healthcare Research and Quality website.

Step 1: Stratify to Risk Class I vs. Risk Classes II-V	
Presence of:	
Over 50 years of age	Yes/No
Altered mental status	Yes/No
Pulse ≥125/minute	Yes/No
Respiratory rate >30/minute	Yes/No
Systolic blood pressure <90 mm Hg	Yes/No
Temperature <35 °C or ≥40 °C	Yes/No
History of:	
Neoplastic disease	Yes/No
Congestive heart failure	Yes/No
Cerebrovascular disease	Yes/No
Renal disease	Yes/No
Liver disease	Yes/No
If any "Yes", then proceed to Step 2	
If all "No" then assign to **Risk Class I**	
Step 2: Stratify to Risk Class II vs III vs IV vs V	
Demographics	**Points Assigned**
If Male	+Age (yr)
If Female	+Age (yr) - 10
Nursing home resident	+10
Comorbidity	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical Exam Findings	
Altered mental status	+20
Pulse ≥125/minute	+10
Respiratory rate >30/minute	+20

Systolic blood pressure <90 mm Hg	+20
Temperature <35 °C or ≥40 °C	+15
Lab and Radiographic Findings	
Arterial pH <7.35	+30
Blood urea nitrogen ≥30 mg/dl (9 mmol/liter)	+20
Sodium <130 mmol/liter	+20
Glucose ≥250 mg/dl (14 mmol/liter)	+10
Hematocrit <30%	+10
Partial pressure of arterial O2 <60mmHg	+10
Pleural effusion	+10
∑ <70 = **Risk Class II**	
∑ 71-90 = **Risk Class III**	
∑ 91-130 = **Risk Class IV**	
∑ >130 = **Risk Class V**	

APPENDIX D: SOFA SCORE

The SOFA score is assessed as below (source: Singer et al, 2016).

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.