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MAJOR ARTICLE

Adjunctive Recombinant Human Plasma Gelsolin for Severe Coronavirus Disease 2019 Pneumonia

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Background. Excessive inflammation contributes to the morbidity and mortality of severe coronavirus disease 2019 (COVID-19) pneumonia. Recombinant human plasma gelsolin (rhu-pGSN) improves disease outcomes in diverse experimental models of infectious and noninfectious inflammation.

Methods. In a blinded, randomized study, 61 subjects with documented COVID-19 pneumonia having a World Health Organization (WHO) Severity Score of 4 to 6 and evidence of a hyperinflammatory state were treated with standard care and either adjunctive rhu-pGSN 12 mg/kg or an equal volume of saline placebo given intravenously at entry, 12 hours, and 36 hours. The prespecified coprimary outcomes were survival without major respiratory, hemodynamic, or renal support on Day 14 and the incidence of serious adverse events (SAEs) during the 90-day study period.

Results. All subjects receiving ≥1 dose of study drug were analyzed. Fifty-four of 61 subjects (88.5%) were WHO severity level 4 at entry. The proportions of subjects alive without support on Day 14 were 25 of 30 rhu-pGSN recipients (83.3%) and 27 of 31 placebo recipients (87.1%). Over the duration of the study, WHO Severity Scores improved similarly in both treatment groups. No statistically significant differences were observed between treatment groups at any time point examined. Two subjects died in each group. Numerically fewer subjects in the rhu-pGSN group had SAEs (5 subjects; 16.7%) or ≥ Grade 3 adverse events (5 subjects; 16.7%) than in the placebo group (8 subjects [25.8%] and 9 subjects [29.0%], respectively), mostly involving the lungs. Three rhu-pGSN recipients (10.0%) were intubated compared to 6 placebo recipients (19.4%).

Conclusions. Overall, subjects in this study did well irrespective of treatment arm. When added to dexamethasone and remdesivir, no definitive benefit was demonstrated for rhu-pGSN relative to placebo. Safety signals were not identified after the administration of 3 doses of 12 mg/kg rhu-pGSN over 36 hours. The frequencies of SAEs and intubation were numerically fewer in the rhu-pGSN group compared with placebo.

Keywords. COVID-19 pneumonia; efficacy; plasma gelsolin; safety.

Plasma gelsolin (pGSN) is an abundant protein in the blood of healthy individuals functionally distinct from the cytoplasmic isoform [1–3]. Upon injury, pGSN leaves the circulation to scavenge debris from ruptured cells that interferes with host defenses [4–15]. In the setting of infection, this process enhances bacterial uptake and killing by macrophages at the damaged site irrespective of the pathogen [16, 17]. Once extracellular actin and deoxyribonucleic acid are cleared, free pGSN can inhibit proinflammatory lipid and peptide mediators to foster resolution of the local inflammatory injury while limiting spread to distant uninvolved organs. Consequently, pGSN boosts the early innate immune response at the infected site while tempering the injurious consequences of excessively prolonged or distant inflammation [18, 19].

Circulating pGSN is consumed in serious conditions such as bacterial sepsis, major trauma, burns, prolonged hyperoxia, autoimmune diseases, and malaria associated with extensive tissue injury [20–29]. Observational studies of patients after a diverse spectrum of common insults have established a consistent relationship among the severity of the precipitating insult, the magnitude of resultant pGSN decline, and the subsequent likelihood of mortality or devastating complications. In particular, patients admitted with community-acquired pneumonia (CAP) who have the lowest pGSN levels at presentation have the worst outcomes [20].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents the emergence of a new pandemic type of CAP. Lung tissue is the major but not sole target of this novel coronavirus. Blunting of an overzealous inflammatory response can potentially improve respiratory outcomes independent of any direct antiviral effect [19, 30]. Acute coronavirus disease 2019 (COVID-19) pneumonia progresses through 2 sequential overlapping stages [31, 32]. The first stage

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is characterized by viral replication, followed in a subset of patients after 5–7 days by a second immune-mediated stage often associated with decreasing viral load but more intense tissue injury. The severe lung damage inflicted by COVID-19 is primarily mediated through this later excessive host response to the virus, not directly by the virus itself, sometimes culminating in a cytokine storm and disseminated coagulopathy injuring the lungs and blood vessels. Circulating levels of pGSN fall in proportion to the magnitude of damage in COVID and predict on a population level the likelihood of bad outcomes [27–29]. Interrupting or tempering this maladaptive process by repleting pGSN could limit further lung injury, restore immune equilibrium, and permit tissue repair [30, 33, 34]. We performed a double-blind, placebo-controlled, randomized superiority trial to assess the efficacy and safety of recombinant human pGSN (rhu-pGSN) plus standard of care (SOC) versus a saline placebo plus standard of care in the treatment of severe-critical COVID-19 pneumonia.

METHODS

Design and Objectives

In a double-blinded, proof-of-concept study (Supplemental Materials: Protocol), consenting eligible subjects ≥18 years of age with documented COVID-19 pneumonia having a World Health Organization (WHO) Severity Score of 4 to 6 (Table 1) and evidence of a hyperinflammatory state were randomized to receive SOC with either adjunctive rhu-pGSN 12 mg/kg or an equal volume of saline placebo given intravenously at entry, 12 hours, and 36 hours (ClinicalTrials.gov Identifier NCT04358406). The prespecified coprimary outcomes were survival without major respiratory, hemodynamic, or renal support on Day 14 and the incidence of serious adverse events (SAEs) during the 90-day study period. A second part of the study was planned to recruit sicker patients but was canceled before any enrollment when the number of COVID-19 admissions at the participating hospitals fell.

Table 1. World Health Organization COVID 9-Point Severity Scale

8	Death
7	Mechanical ventilation or ECMO with either vasopressor support or dialysis/RRT
6	**Intubation with mechanical ventilation but without vasopressors or renal replacement therapy**
5	**Noninvasive ventilation (CPAP or BiPAP) or high-flow oxygen**
4	**Oxygen by mask or nasal canula**
3	Hospitalized with no oxygen therapy
2	Limitation of activity
1	Infected without limitations
0	No clinical or virologic evidence of COVID-19 infection

Bold text shows the severity levels of subjects eligible for this trial.
Abbreviations: BiPAP, bilevel positive airway pressure; COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy.

Recombinant human pGSN (BioAegis Therapeutics, North Brunswick, NJ) was produced and purified from an *Escherichia coli* cell line. Sites were provided with 10-mL glass vials containing lyophilized powder for reconstitution to yield a 5-mL solution at a final concentration of 40 mg/mL rhu-pGSN in a proprietary stabilizing buffer. Subjects received 3 doses of rhu-pGSN as an intravenous infusion of 12 mg/kg based on actual body weight or an equal volume of 0.9% saline placebo administered at a rate between 5 and 20 mL/minute through a standard 0.2-micron filter.

The primary efficacy endpoint point was assessed on Day 14, with secondary endpoints assessed on Days 7, 14, 28, 60 (optional), and 90. Secondary objectives included evaluating changes in the WHO 9-point severity scale over time by treatment group, assessing the pharmacokinetics (PK) of administered rhu-pGSN in selected subjects, and investigating the development of antibodies against pGSN. Discharged subjects were to return for follow-up evaluations on Days 14, 28, 60, and 90.

Patient Consent Statement

Approval was obtained from an independent Ethics Committee for the conduct of the study at each site before recruitment of subjects. The committee was provided with the protocol, informed consent documents, and other written information given to the subjects. Written informed consent was obtained from each subject (or next of kin) before any study procedures. Enrolled subjects could withdraw from the study at any time at their discretion.

Eligibility Criteria and Randomization

The major inclusion criteria specified that participants were to be ≥18 years of age and weighing ≤100 kg hospitalized with laboratory-confirmed or highly suspected COVID-19 (with later confirmation) and a primary admitting diagnosis of pneumonia supported by a compatible clinical presentation with documented multilobar infiltrates on chest x-ray or computed tomography. Subjects were to be enrolled within 24 hours of reaching a severity score of 4–6 on the WHO 9-point scale (Table 1) either at admission or during the subsequent hospitalization. Demonstration of a hyperinflammatory state defined by increased blood levels of ferritin ≥500 μg/L, D-dimer ≥1000 ng/mL, and/or C-reactive protein (CRP) ≥0.075 g/L was also required.

Exclusion criteria included failure to test positive for SARS-CoV-2. Patients on extracorporeal membrane oxygenation at screening were excluded. Pregnant or lactating women, patients with active underlying cancer treated with systemic chemotherapy or radiation therapy during the last 30 days or having received a transplant of hematopoietic or solid organs, or patients on chronic mechanical ventilation or dialysis were also ineligible. Patients were deemed unsuitable for study

participation if chronic, severe, end-stage, and life-limiting underlying disease unrelated to COVID-19 was likely to interfere with management and assessment of acute pneumonia, only comfort or limited (nonaggressive) care were to be given, or life expectancy was estimated to be <6 months unrelated to acute COVID infection in the opinion of the investigator.

If eligible after screening, prospective subjects were randomized in a 1:1 ratio to receive an equal volume of rhu-pGSN or placebo. Randomization was done centrally using manual methods. A pharmacist unblinded to treatment assignment prepared the study drug. The subject, caregivers, investigators, and sponsor were kept blinded to treatment allocation. Masking was maintained because the placebo solution was virtually indistinguishable from the active product. Three doses were administered: Dose number 1 within 12 hours of enrollment and randomization, Dose number 2 12 hours later, and then Dose number 3 after another 24 hours (36 hours after the initial dose). The duration of follow up was 90 days after the first dose.

Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) was established to review the safety data after each group of 12 subjects had been treated and observed for at least 14 days. The DSMB comprised 4 members, including 3 clinicians with relevant expertise and an experienced biostatistician. Treatment group data without specifying the specific treatment arm was provided to the DSMB. The study could have been stopped and/or unblinded data requested at any time during the study at the discretion of the DSMB chair.

Specialized Assays

Plasma gelsolin levels were measured using a proprietary sandwich enzyme-linked immunosorbent assay (ELISA) [35]. This assay was specific for the plasma isoform but did not distinguish between endogenous and recombinant pGSN. Other inflammatory biomarkers were analyzed using commercial kits. The presence of antidrug antibodies (ADAs) against rhu-pGSN was determined on Days 1 (baseline before dosing), 28, and 90 using a MESO Scale Diagnostics (MSD)-based electrochemiluminescent immunoassay. A screening cut point was determined from the analysis of normal human serum samples from treatment-naive subjects, but an in-study cut point was not feasible. If the addition of pGSN could reduce the apparent ADA, the sample was then diluted to determine the presumed antibody titer.

Statistical Considerations

Power was computed for the expected increase in proportion of surviving subjects without support at Day 14. A total sample size of $N = 54$ would have ~80% power to yield a statistically significant (1-sided alpha = 0.2) difference if the true underlying proportions of subjects failing the primary outcome were 20% and 5% for placebo plus SOC and rhu-pGSN plus SOC, respectively.

The full analysis set (FAS) consisted of all subjects given ≥1 dose of study drug according to the actual drug received. In the end, no subject was cross-treated. The FAS was used for the primary efficacy and safety analyses. Noncompleters were counted as failures in the efficacy analysis. The Cochran-Mantel-Haenszel method was applied to identify an association between treatment group and the primary outcome. Subjects without major protocol violations receiving all 3 doses and evaluable for the primary Day 14 endpoint constituted the per-protocol population for efficacy assessment as a sensitivity analysis. The PK population included only those subjects who agreed to provide blood specimens for PK analysis.

RESULTS

Participant Accounting and Baseline Characteristics

The study was conducted at 2 sites in Spain and 1 site in Romania from August 5, 2020 to May 25, 2021. Overall, 69 potential participants were screened after informed consent (Supplementary Figure 1), but 5 failed to meet inclusion criteria regarding weight, the diagnosis of pneumonia, or withdrawal of consent. The other 64 subjects were enrolled and randomized, but 3 then refused study therapy, leaving 61 subjects (30 in the rhu-pGSN group and 31 in the placebo group) who were treated with at least 1 dose of study drug. Of these, 54 completed the study, 4 died, and 3 were lost to follow up.

The 2 treatment groups were generally well matched (Table 2). The majority of subjects were white with a slight predominance of males (57.4%). The median age was 64 years, and body mass index was moderately elevated in both treatment groups (overall mean/median of 28.3/27.4 kg/m^2). The most frequently reported comorbidities were dyslipidemia (47.5%), hypertension (41.0%), and diabetes mellitus (32.8%), which were each more common in the placebo than in the rhu-pGSN group. Fifty-four (88.5%) of the 61 subjects were WHO severity level 4 on entry, the other 7 being level 5 (3 rhu-pGSN and 4 placebo recipients). Subjects were generally in a hyperinflammatory state at baseline, as evidenced by elevated mean levels of ferritin (1113.7 ± 848.0 μg/L), D-dimer (932.5 ± 845.2 μg/dL), and CRP (0.12 ± 0.07 g/L). All subjects received corticosteroids (mostly dexamethasone), and remdesivir was given to every subject except 1 rhu-pGSN recipient; other immunomodulatory therapies were used rarely if at all.

Efficacy Analyses

The proportions of subjects alive without support on Day 14 were 25 rhu-pGSN recipients (83.3%) and 27 placebo recipients (87.1%) (adjusted Δ = −7.5% [−30.5%, +15.5%]). The corresponding proportions of subjects alive without support at the

Table 2. Demographics and Baseline Characteristics of Treated Subjects[a]

Characteristics	rhu-pGSN (*N* = 30)	Placebo (*N* = 31)	Total (*N* = 61)
Age (years)			
Mean (SD)	63.3 (11.91)	61.1 (11.38)	62.1 (11.60)
Median	63.5	64.0	64.0
Interquartile range	56–73	54–70	56–71
Minimum, maximum	34, 80	36, 78	34, 80
Sex, *n* (%)			
Male	16 (53.3)	19 (61.3)	35 (57.4)
Female	14 (46.7)	12 (38.7)	26 (42.6)
Females of child bearing potential	2 (14.3)	2 (16.7)	4 (15.4)
Ethnicity, *n* (%)			
Hispanic or Latino	5 (16.7)	1 (3.2)	6 (9.8)
Not Hispanic or Latino	25 (83.3)	30 (96.8)	55 (90.2)
Race, *n* (%)			
American Indian or Alaskan Native	0	1 (3.2)	1 (1.6)
Black or African American	3 (10.0)	2 (6.5)	5 (8.2)
Mixed or multiple races	1 (3.3)	1 (3.2)	2 (3.3)
White	26 (86.7)	27 (87.1)	53 (86.9)
Weight (kg)			
Mean (SD)	77.3 (12.25)	83.1 (12.80)	80.2 (12.77)
Median	76.5	85.3	80.7
Minimum, maximum	55, 100	50, 102	50, 102
BMI (kg/m^2)			
Mean (SD)	28.1 (4.45)	28.5 (4.83)	28.3 (4.58)
Median	27.1	28.6	27.4
Minimum, maximum	22.3, 36.4	19.1, 36.5	19.1, 36.5
WHO Severity Score, *n* (%)			
Score 6	0	0	0
Score 5	3 (10.0)	4 (12.9)	7 (11.5)
Score 4	27 (90.0)	27 (87.1)	54 (88.5)
Temperature (Celsius)			
Mean (SD)	36.5 (0.87)	36.5 (0.66)	36.5 (0.76)
Median	36.6	36.5	36.5
Minimum, maximum	35.0, 39.0	35.0, 38.0	35.0, 39.0
Heart Rate (Beats/Minute)			
Mean (SD)	79.8 (10.4)	79.0 (11.7)	79.4 (11.0)
Median	80.0	78.0	80.0
minimum, Maximum	57, 102	46, 102	46, 102
Respiratory Rate (Breaths/Minute)			
Mean (SD)	22.1 (4.7)	21.9 (5.3)	22.0 (5.0)
Median	22.0	20.0	22.0
Minimum, maximum	14, 35	14, 36	14, 36
Oxygen Saturation (%)[b]			
Mean (SD)	95.2 (3.1)	94.3 (5.2)	94.7 (4.3)
Median	95.5	95.0	95.0
Minimum, maximum	86, 100	72, 100	72, 100
Plasma Gelsolin (μg/mL)			
n	30	31	61
Mean (SD)	39.3 (8.6)	39.5 (8.6)	39.4
Median	38.7	38.7	38.7
Minimum, maximum	25.2, 57.5	23.7, 56.0	23.7, 57.5
Ferritin (μg/L)			
n	19	25	44
Mean (SD)	1042.7 (773.9)	1167.7 (912.2)	1113.73 (848.0)
Median	770.6	944.2	893.3
Minimum, maximum	90.0, 2391.0	60.9, 3714.0	60.9, 3714.0
D-dimer (μg/dL)[c]			

Table 2. Continued

Characteristics	rhu-pGSN (*N* = 30)	Placebo (*N* = 31)	Total (*N* = 61)
n	27	28	55
Mean (SD)	971.5 (943.1)	894.9 (754.5)	932.5 (845.2)
Median	583.0	640.0	590.0
Minimum, maximum	190, 3900	340, 3721	190, 3900
CRP (g/L)			
n	29	29	58
Mean (SD)	0.13 (0.07)	0.12 (0.07)	0.12 (0.07)
Median	0.12	0.10	0.12
Minimum, maximum	0.01, 0.34	0.02, 0.30	0.01, 0.34
Procalcitonin (ng/mL)[d]			
n	22	22	44
Mean (SD)	632.0 (2545.4)	4927.5 (20 875.8)	2779.7 (14 856.5)
Median	0.27	0.21	0.24
Minimum, maximum	0.04, 12 000.0	0.05, 98 000.0	0.04, 98 000.0

Abbreviations: BMI, body mass index; CRP, C-reactive protein; rhu-pGSN, recombinant human plasma gelsolin; SD, standard deviation; WHO, World Health Organization.

[a]Of the 61 treated subjects constituting the full analysis set, 58 (95.1%) were enrolled from the 2 sites in Spain and 3 (4.9%) from the 1 site in Romania. Screening laboratory tests could serve as baseline values. Tests were not repeated if performed within the prior 24 hours of randomization unless otherwise dictated by standard of care.

[b]Subjects may have already been receiving supplemental oxygen by the time when baseline oxygen saturation was measured.

[c]Three additional subjects had D-dimer measured in μFEU/mL: 1 in the rhu-pGSN group (0.36 μFEU/mL) and 2 in the placebo group (0.42 and 0.58 μFEU/mL).

[d]Three additional subjects had procalcitonin measured in %: 1 in the rhu-pGSN group (1.33%) and 2 in the placebo group (0.75% and 0.19%).

7, 28, 60, and 90-Day visits were numerically higher in placebo than rhu-pGSN recipients but were never statistically significant. All-cause mortality during the study was low with 2 subjects dying in each group. Death occurred on study days 6 and 84 in the 2 rhu-pGSN recipients and on study days 25 and 31 in the 2 placebo recipients (Supplementary Figure 2). Only 1 subject <75 years of age died; she was a 35-year-old placebo recipient with progressive pneumonia.

Over the duration of the study, WHO Severity Scores improved similarly in each treatment group (Supplementary Figure 3). No significant differences were observed between treatment groups at any time point examined other than the pGSN levels on Day 3 after rhu-pGSN treatment (Figure 1). The pGSN concentrations in the placebo control group did not noticeably change over time during the first week. In both groups, pGSN levels gradually increased toward normal from Day 14 through Day 60. Findings in the per-protocol population mirrored the results in the FAS.

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) occurred in 16 rhu-pGSN recipients (53%) and 16 placebo recipients (52%) (Supplementary Table 1). Only 1 transient mild adverse event ([AE] eye irritation) was considered as probably related to rhu-pGSN. Numerically fewer subjects in the rhu-pGSN group had SAEs (5 subjects; 16.7%) or ≥ Grade 3 AEs (5 subjects; 16.7%) than in the placebo group (8 subjects [25.8%] and 9 subjects [29.0%], respectively) (Table 3), mostly involving the lungs. The median duration of hospitalization was approximately 11 days in both groups (Table 4). Eight rhu-pGSN recipients and 7 placebo recipients spent a median of 15 and 14 days, respectively, in an intensive care unit (ICU). During the study, 3 rhu-pGSN subjects (10.0%) and 6 placebo subjects (19.4%) were intubated with the mean time on mechanical ventilation being longer for the rhu-pGSN than the placebo recipients.

Immunogenicity and Pharmacokinetics

In the ADA studies, 7 rhu-pGSN and 7 placebo recipients had positive tests at some timepoint. However, 9 of 14 positive subjects had positive predose baseline samples. Five of the 6 rhu-pGSN recipients available for follow-up testing were positive at low titer on Day 28, and 2 subjects were positive on Day 90. Overall, only 1 placebo recipient and 1 pGSN recipient were ADA positive at both follow-up times. The ADA positivity could not be associated with any immune-related AEs.

In a subset of 7 subjects who agreed to provide specimens for PK analysis, blood levels of pGSN were maintained in the supraphysiological range with dosing of rhu-pGSN at 12 mg/kg of actual body weight at 0, 12, and 36 hours throughout the treatment period without drug-related serious adverse events (Supplementary Figure 4). Accumulation of pGSN was modest (~25%) for the third dose relative to first dose. The half-life after the first dose was estimated to be approximately 13.5 hours. Compared to the modestly ill subjects hospitalized in our earlier study of community-acquired pneumonia treated with 3 doses of rhu-pGSN of 12 mg/kg over 72 hours [33], the total pGSN levels were lower and the half-life of rhu-pGSN was shorter in the sicker COVID-infected subjects in the current trial despite more compressed dosing (Supplementary Table 2). This finding is consistent with pGSN being consumed faster in sicker patients.

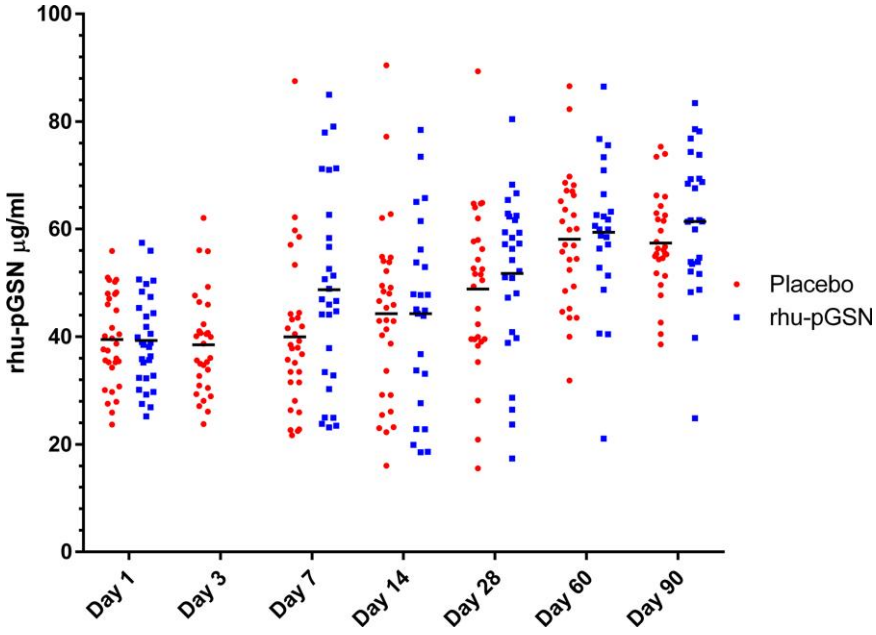

Figure 1. Scatterplot of plasma gelsolin (pGSN) levels over time. The top part of the scale on the y-axis has been truncated at 100 µg/mL. All the posttreatment pGSN levels in the recombinant human pGSN (rhu-pGSN) recipients on Day 3 were >100 µg/mL and are not shown given the scale of the figure. Median pGSN concentrations from healthy adult volunteers is 56.8 µg/mL (interquartile range, 52.6–65.4 µg/mL).

Table 3. Serious Adverse Events in Treated Subjects

Study Treatment	Age	SAE	Grade	Study Treatment-Related?	Outcome
rhu-pGSN	79	ARDS/VAP	3	No	Recovered
rhu-pGSN	65	ARDS/VAP	4	No	Recovered
rhu-pGSN	75	ARDS	5	No	Died
rhu-pGSN	73	ARDS	3	No	Sequelae
rhu-pGSN	80	Diarrhea with hypokalemia; CVA	5	No	Died
PBO	54	Lung adenocarcinoma metastatic to brain	3	No	Sequelae
PBO	78	ARDS/bacterial superinfection/septic shock	5	No	Died
PBO	49	ARDS	3	No	Recovered
PBO	65	ARDS	3	No	Sequelae
PBO	55	Readmitted with pneumonia	3	No	Recovered
PBO	73	ARDS	3	No	Recovered
PBO	63	ARDS	3	No	Recovered
PBO	36	Worsening pneumonia leading to intubation	5	No	Died

Abbreviations: ARDS, acute respiratory distress syndrome; CVA, cerebrovascular accident; PBO, placebo; Rhu-pGSN, recombinant human plasma gelsolin; SAE, serious adverse event; VAP, ventilator-associated pneumonia.

DISCUSSION

In subjects with severe COVID-19 pneumonia requiring oxygen supplementation, our small, randomized, double-blinded trial did not demonstrate a benefit of rhu-pGSN over placebo when added to standard of care. Plasma gelsolin plays a central regulatory role in diverse inflammatory pathways (Supplemental Materials: Clinical Study Report) [3, 34, 35]. When appropriately timed, a dual-pronged attack on COVID-19 reducing the inciting virus early (with remdesivir or other antiviral agents) and moderating the later exuberant inflammatory reaction might theoretically synergize in shutting down COVID-19 progression better than either modality alone. Repletion of pGSN could effectively block unbridled and injurious immune activation without inducing undesired side-effects or dangerous immunosuppression.

No unexpected safety signals were apparent during this trial with the incidence of SAEs numerically (but not statistically) lower in rhu-pGSN than placebo recipients. To establish the safety profile of rhu-pGSN without confounding comorbidities, we had conducted our first dose-escalation study in 33 mildly ill patients

Table 4. Hospital Course

Study Treatment	Median Days in Hospital	Number in Intensive Care Unit	Median Days in Intensive Care Unit	Number Intubated	Median Days on Ventilator
Rhu-pGSN	10.5	8	15.0	3	27.0
Placebo	11.0	7	14.0	6	13.5

Abbreviations: Rhu-pGSN, recombinant human plasma gelsolin.

hospitalized with CAP outside an ICU (ClinicalTrials.gov Identifier NCT03466073) [36]. Dosing was escalated from 6 mg/kg once up to 24 mg/kg daily for 3 consecutive days. Recombinant human pGSN appeared to be generally safe and well tolerated. None of the AEs in the rhu-pGSN arms were considered related to study treatment. Two subjects died during the study: 1 rhu-pGSN recipient in the single-dose phase and 1 placebo recipient in the multidose phase. Neither death was attributed to study interventions.

In the current trial, we explored the efficacy and safety of rhu-pGSN added to standard-of-care treatment in a small, blinded, placebo-controlled study of 61 treated subjects, most of whom entered the study at WHO stage 4. Subjects received standard-of-care treatment with steroids and remdesivir. Recipients of rhu-pGSN had numerically fewer SAEs (mostly related to COVID-19 pneumonia/acute respiratory distress syndrome) and subsequent intubation than placebo recipients. The rhu-pGSN-dosing regimen of 12 mg/kg× 3 doses given over 36 hours maintained levels in the supraphysiological range for the entire dosing period without any drug-related SAEs.

CONCLUSIONS

This study did not demonstrate a clear benefit of rhu-pGSN in this population of 61 subjects with hyperinflammatory COVID-19 pneumonia who were overall not critically ill and concurrently receiving standard-of-care therapy with steroids and remdesivir. Most subjects required conventional oxygen therapy by mask or nasal canula at entry, whereas patients needing noninvasive ventilation or high-flow oxygen may represent the ideal target population for immunomodulatory anti-inflammatory therapy [37, 38]. No safety signals were apparent, and there was no convincing evidence of enduring ADA development in rhu-pGSN-treated subjects. Whether a benefit from rhu-pGSN might become evident with a larger study, more critically ill subjects, or a longer dosing period of rhu-pGSN remains unanswered. Fewer serious or severe AEs generally attributable to the underlying pneumonia (including intubations) were seen in rhu-pGSN than placebo recipients, perhaps hinting at possible yet-to-be demonstrated efficacy against COVID-related lung injury.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. S. L. L. and M. J. D. are employees of BioAegis Therapeutics, which is developing recombinant human plasma gelsolin (rhu-pGSN) for clinical use. S. L. L. is the Chief Executive Officer and M. J. D. is the Chief Medical Officer, both of whom own stock in the company. S. P. and A. C. S. declare no conflicts of interest.

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