Brief protocol title	GLS27-005
Formal protocol title	Safety, Tolerability, Efficacy and Dose Response of GLS-1027 in the Prevention of Severe Pneumonitis caused by SARS-CoV-2 Infection
Regulatory Sponsor:	GeneOne Life Science Inc. 535 Pennsylvania Ave., Suite 200 Fort Washington, PA 19034 (610) 707-5671
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Version Summary

Initial version:	Version 3.0	11 Dec 2020
Amendment:		

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PROTOCOL ACKNOWLEDGEMENT

I have read this Protocol and agree that it contains all necessary details for carrying out the study described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and receive approval or a favorable opinion before implementation.

The signature of the Principal Investigator and Sponsor below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to the Declaration of Helsinki, GCP, ICH guidelines, local legal and regulatory regulations as well as to all stipulations of the protocol in both the clinical and administrative sections, including statements regarding confidentiality.

Investigator's printed name and signature	Date
	11 Dec 2020
Medical Monitor	Date

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CLINICAL PROTOCOL SYNOPSIS

Title of study: Safety, Tolerability, Efficacy and Dose Response of GLS-1027 in the Prevention of Severe Pneumonitis caused by SARS-CoV-2 Infection

Number of study participants: 132

Study Phase: II

Study Type: Randomized, double-blind, placebo-controlled

Research Hypothesis: GLS-1027 will be safe, well tolerated and reduce the incidence of treatment failure as characterized by 1) advancing to WHO COVID-19 Classification level ≥6 which includes the need for intubation with mechanical ventilation, initiation of extracorporeal mechanical oxygenation (ECMO), or death, in SARS-CoV-2 infected hospitalized patients, 2) need for institution of salvage therapy 72 hours after study entry with either an IL-6 monoclonal antibody or dexamethasone (≥6 mg/day), 3) withdrawing consent from the study, 4) becoming lost to follow-up, or 5) discontinuation of treatment for any reason other than decrease in renal function or pregnancy.

Primary study objectives and outcome variables:

- Incidence of serious adverse events relative to treatment group
- Incidence of treatment failure within 28 days from enrollment

Exploratory study objectives and outcome variables:

- Assess the number of days requiring ICU care relative to treatment group
- Assess the number of days of mechanical ventilation relative to treatment group
- Assess incidence of WHO COVID-19 Classification levels relative to baseline serum IL-6 level
- Assess incidence of WHO COVID-19 Classification levels relative to baseline serum ferritin level
- Assess incidence of WHO COVID-19 Classification levels relative to baseline CRP
- Assess trough level of GLS-1027 relative to serum creatinine
- Assess the maximal level of Positive End-Expiratory Pressure (PEEP) for subjects who are intubated relative to treatment group.
- Assess the number of days of PEEP > 5 cm H_2O for subjects who are intubated relative to treatment group
- Incidence of progression to WHO COVID-19 Classification level 6, or 7, or 8 (individually)
- Assess SARS-CoV-2 IgM antibody responses relative to treatment group

Table S1: Dosing arms and treatment regimen

Group	N	Treatment assignment	Study drug dose	Treatment schedule
1	44	Placebo + SOC	0 mg	Daily
2	44	GLS-1027 + SOC	120 mg	Daily
3	44	GLS-1027 + SOC	360 mg	Daily

Study design:

Phase II randomized, double-blind, placebo-controlled, study to assess 2 different doses of GLS-1027 in the prevention of treatment failure among participants admitted to hospital with PCR confirmed infection with SARS-CoV-2 (WHO classification 3 or 4). The enrollment period will extend to 72 hours from hospital admission. Participants will be randomized at a 1:1:1 ratio to either SOC plus placebo, or SOC plus GLS-1027 at either 120 mg or 360 mg daily. Participants will be administered drug until discharge or death for a maximum treatment period of 28 days. Clinical status will be monitored through 56 days from the initiation of treatment.

Sample Size:
Based early literature reports [1], it is anticipated that approximately 50% of subjects hospitalized with PCR-positive SARS-CoV-2 infections (WHO COVID-19 Classification level 3 or 4) will progress to WHO COVID-19 classification level of 6 or greater as defined by one or more of the following: the need for intubation or mechanical ventilation (level 6), the need for ECMO (level 7), or any cause death (level 8). The sample size estimate for this proof of concept is based on Fisher's Exact two-sided test for 2 proportions using NQuery 8 (www.statsols.com).

Although the interim analysis will utilize masked treatment assignments, the O'Brien Fleming group sequential sample size estimation confirms that a single interim look would retain a cumulative exit probability of 70% with a cumulative alpha =0.05 after the final analysis using the target enrollment of 132 (44 per group) to detect a reduction of those reaching the endpoint of treatment failure, which includes advancing to WHO COVID-19 Classification level ≥6 from 50% (SOC treated) to 25% in either treatment group of SOC plus GLS-1027. Other conditions also qualify a subject as treatment failure include: need for salvage therapy with IL-6 monoclonal antibody; or institution of salvage therapy with dexamethasone (≥ 6 mg/day), withdrawing consent from the study, becoming lost to follow-up, or discontinuation of treatment for any reason other than renal function or pregnancy. This study is not powered to assess statistically significant differences between GLS-1027 doses.

Study assessments:
Adverse events will be monitored and recorded throughout hospitalization from the point of enrollment. Daily assessments of vital signs and clinical laboratory parameters will be reviewed and recorded. Follow-up clinical status will be assessed to Day 56. The first 15 persons enrolled will be included in a pharmacokinetic sub-study assessment to determine elimination of GLS-1027, while trough levels will be monitored throughout the study.

Efficacy will be assessed by evaluating the difference in the proportion of treatment failures by group. Treatment failure will be defined as any of the following:

1) progression to WHO COVID-19 classification level of 6 or greater within the 28 days of treatment initiation,
2) need for salvage therapy with IL-6 monoclonal antibody; or institution of salvage therapy with dexamethasone (≥ 6 mg/day),
3) withdrawing consent from the study,
4) becoming lost to follow-up, or
5) discontinuation of treatment for any reason other than renal function or pregnancy.

A masked interim analysis will be performed when 22 subjects in each group have been assessed for the primary endpoint of treatment failure. The interim analysis is intended for blinded safety assessment. Unless safety is of concern, the study will not be stopped for futility and enrollment will continue to the targeted sample size of 132.

Study population:

Inclusion criteria for enrollment:

1. Age 18 years or older
2. Able to provide consent
3. Able and willing to comply with study procedures
4. Enrollment within 72 hrs of hospitalization with a diagnosis of PCR confirmed SARS-CoV-2
5. WHO COVID-19 classification level 3 or 4

Exclusion criteria for enrollment:

1. Pregnant or lactating
2. SpO2 less than 90% on room air or less than 95% if on supplemental oxygen
3. Calculated GFR < 60 (Cockcroft-Gault)

4. Meets hospital COVID-19 treatment algorithm for treatment with dexamethasone at a dose of 6 mg/day for a 10-day course. A single bolus dose of 6 mg of dexamethasone given in the Emergency Department and continued at a dose of ≤ 3.5 mg/day or less is allowed.
5. Meets treatment algorithm criteria for treatment with toclizumab or other anti-IL-6 agent
6. Treatment with an anti-IL-6 inhibitor, anti-IL-1 inhibitor, anti-TNF monoclonal antibody, or anti-JAK inhibitor (see Appendix A exclusionary period for specific drugs)
7. Participation in a COVID-19 clinical trial that includes prescription of a drug with anti-cytokine activity
8. Treatment within the past 60 days with a chemotherapeutic agent
9. Current treatment with systemic corticosteroids at a dose equivalent of 20 mg/day or greater of prednisone or prednisolone, 16 mg/day or greater of methylprednisolone, or 4 mg/day or greater of dexamethasone
10. Diagnosis of leukemia or lymphoma
11. WHO COVID-19 classification level of 5 or greater (use of high-flow oxygen, non-mechanical ventilation such as CPAP, mechanical ventilation)

Table S2: Schedule of Events per Study Day

Tests and Observations	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	56[m]
Clinical Evaluations																														
Obtain written Informed Consent	X																													
Confirm Eligibility Criteria	X																													
Demographics	X																													
Medical History	X																													
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Medical Record	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
WHO COVID-19 Classification (Appendix B)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Evaluations																														
Record Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Vital Signs [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Hematology [b]	X	X	X	X	X	X	X							X							X							X		
Record Basic Metabolic Panel, LFTs [c]	X	X	X	X	X	X	X							X							X							X		
Record other labs [d] (for days available)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record Procalcitonin (baseline value) [e]	X																													
Record admission CXR	X																													
Record if care given in ICU setting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record whether nasal O_2 prescribed and dose level (L/min) [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record whether CPAP prescribed and expiratory pressure [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record if mechanically ventilated and level of PEEP, % FiO_2 [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record if treated by ECMO	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record admission ECG	X																													
Study Related Procedures																														
Administer assigned study drug [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	
Perform urine pregnancy test	X																													
Perform ECG (12-lead) [j]		X													X															
Collect serum for CPK, GGT [k]	X						X																							
Collect blood for plasma for PK assessment [l]		X																												
Collect blood for plasma for trough drug measurement (AM blood draw)		X	X	X					X							X							X				X		

Collect blood for serum (10mL red top,3 tubes)	X			X					X							X							X				X		
Collect blood for PBMCs (10mL ACD; 3 tubes)	X			X					X							X							X				X		
Blood volume for serum, PBMCs	**60**			**60**			**5**		**60**							**60**							**60**				**60**		

[a] Vital signs to be recorded daily to include maximal and minimal: temperature, respiratory rate, heart rate, systolic and diastolic blood pressure
[b] Hematology labs to be collected as necessary and recorded: Hemoglobin, hematocrit, platelets, neutrophils, band forms, lymphocytes, eosinophils
[c] Basic metabolic panel labs to be collected as necessary and recorded: Sodium, potassium, CO_2 (bicarbonate), creatinine, BUN, glucose, liver function tests (LFTs) that should be recorded include AST, ALT, bilirubin (direct), alkaline phosphatase, LDH, albumin . These labs are performed daily per the hospital COVID algorithm.
[d] Other labs to be recorded as available: Ferritin, CRP, IL-6, troponin, D-dimer
[e] Procalcitonin: record only initial measurement or within 48 hours of admission and/or SARS-CoV-2 diagnosis (may be performed prior to date of enrollment)
[f] Record maximal daily level of O_2 by nasal cannula prescribed, if applicable
[g] Record maximal daily level of end expiratory pressure delivered by CPAP prescribed, if applicable
[h] Record maximal daily level of PEEP and delivered FiO_2 by mechanical ventilation, if applicable
[i] Study drug administration will commence on the day of enrollment if treatment can be administered before 10 pm and then with AM medications thereafter, If, study drug cannot be administered prior to 10 pm on the day of enrollment, then the 1st day of treatment will occur on the day after enrollment.
[j] Perform a 12-lead ECG on the 2nd day of treatment with study drug between 75 and 90 minutes post-administration on day 2; and on day 15 (± 2 days)
[k] Serum is collected for CPK and GGT on day 1 and day 7, and weekly thereafter, if values on day 7 are abnormal until return to normal
[l] PK assessment will be performed for the initial 15 subjects enrolled. Blood (5 ml) will be collected for plasma collection at baseline (pre-treatment), and then at 1, 2, 4, and 8 hr. Trough measurements will be obtained as indicated for all study participants
[m] The clinical record should be reviewed through to Day 56 as relevant to denote date of discharge, date of death, or clinical status (WHO COVID-19 Classification Level) at Day 56

1. INTRODUCTION

This study will examine whether GLS-1027 is safe, tolerated and can reduce the risk treatment failure among patients admitted to hospital with confirmed Severe Acute Respiratory Syndrome coronavirus type 2 (SARS-CoV-2) infection and who require supplemental oxygen and assess if there appears to be a dose dependent response.

1.1 Background and Rationale

SARS-CoV-2 is a novel coronavirus first recognized in November 2019. Since discovery, greater than 60 million confirmed cases and greater than 1 million deaths have been documented globally, and greater than 13 million cases and greater than 250,000 deaths in the US, as of 30 November, 2020. Although coronaviruses typically cause a self-limited upper respiratory infection in the winter months, SARS-CoV-2 represents the third highly pathogenic coronavirus to emerge over the past 2 decades. SARS-CoV similarly was first recognized in 2002 and over the two-year period between 2002-2003 there were approximately 8,000 cases with a mortality rate of 10% and resulted in outbreaks and cases worldwide. The Middle East Respiratory Syndrome coronavirus (MERS-CoV) has resulted in fewer than 3,000 cases but with a mortality rate of 36-38%. Cases of MERS-CoV have been largely restricted to inhabitants of or travelers to the Arabian peninsula or neighboring countries.

Clinically, each of the pathogenic coronaviruses cause lower respiratory tract illness. For SARS-CoV-2, clinical illness typically starts with a viral prodrome characterized by malaise, muscle aches, and headache that can progress to a febrile illness with diaphoresis. Less usual, but pathognomonic signs are anosmia, ageusia, conjunctivitis, and perniosis. While most individuals will recover, progression to increasing respiratory compromise requiring oxygenation, high-flow oxygenation, intubation and mechanical ventilation, extracorporeal mechanical oxygenation (ECMO), or death may occur. Other complications of severe disease include renal failure and arterial thrombosis that may present as stroke, myocardial infarction, or peripheral arterial obstruction. Early studies reported that approximately 50% of those who require supplemental oxygenation after admission to hospital progress to needing mechanical ventilation at some time during hospitalization [1]. It is generally considered that as the level of acuity of admitted patients has increased, this percentage of those progressing to severe disease is likely higher. The mortality rate of those requiring mechanical ventilation has been reported as 50-80% [1] including recent data reported from New York City. Risk factors for severe disease and death include older age, diabetes mellitus, hypertension, cardiac disease, and chronic obstructive pulmonary disease. As was reported for both SARS-CoV and MERS-CoV, the fatality rate in men exceeds that for women.

Pulmonary disease associated with SARS-CoV-2 infection is characterized by a marked inflammatory component that was not described for either SARS-CoV or MERS-CoV. In fact, at presentation, minimally symptomatic patients may present with marked interstitial inflammatory changes on chest radiography presenting as “white-out” as described by colleagues treating infected patients in Seoul, Korea. Of interest, a similar presentation of severe pulmonary inflammatory disease despite a relatively low level of virus has been observed in ferrets). This inflammatory pneumonitis has been ascribed inflammatory

cytokine release. related to the release of multiple cytokines including TNFα, IL-1β, IL-6 and can lead to capillary leakage, hypotension, and myocardial dysfunction.

Treatment with anti-IL-6 monoclonal antibodies (mAb) such as tocilizumab or siltuximab for severe SARS-CoV-2 infection. Although anti-IL-6 mAbs appeared to be potentially beneficial, later studies did not bear this out. Moreover, anti-IL-6 mAbs are parenterally administered, difficult and expensive to manufacture, and are associated with potential serious adverse events including severe hypersensitivity and risk for opportunistic infection. A recent report provides critical insights as to why treatment directed against a single cytokine may be insufficient finding that the inflammatory effects were related to combinations of cytokines, especially TNFα plus IFNγ, whereas individual cytokines were not pathogenic [2].

GLS-1027 is an oral medication with high bioavailability that has inhibitory activity against multiple inflammatory cytokines including IL-6, IL-1β, TNFα, IL-17, and IL-23 and decreases Th17 T cell activity. As reviewed below, in pre-clinical studies, GLS-1027 is as potent in preventing inflammatory changes as dexamethasone. GLS-1027 is being assessed for the prevention of progression of severe respiratory disease among patients admitted to the hospital with documented SARS-CoV-2 infection and who require supplemental oxygen. The hypothesis being tested is whether daily oral treatment of GLS-1027 for those admitted to hospital at WHO COVID-19 Classification level of 3 or 4 will significantly reduce the number of SARS-CoV-2 infected patients who fail treatment. Pre-clinical and clinical experience with GLS-1027 are presented in the sections below.

1.1.1 Pre-clinical experience with GLS-1027

There is extensive literature regarding the use of GLS-1027 in either *in vitro* or *in vivo* animal models of inflammatory and autoimmune diseases with greater than 25 papers published by more than 15 groups of investigators. In the scientific literature, the GLS-1027 molecule is also known as VGX-1027 or GIT-27. For simplicity, the summaries below will only use the designation of GLS-1027. Those papers relevant to this study are presented in detail below.

In vitro, GLS-1027 was shown to prevent development of carragenen-induced pleuritis in mice with treatment effects similar to a monoclonal antibody against TNFα [3] and was equal to dexamethasone to prevent the development of collagen-induced arthritis [3] in mice and to prevent LPS-induced uveitis in rats [4]. The therapeutic effect of GLS-1027 correlated with inhibition of IL-1β, IL-6, and TNFα.

Unpublished data have also shown that GLS-1027 can successfully treat dogs with steroid-resistant autoimmune uveitis.

Of note, dexamethasone is the only treatment that has prevented progression of COVID-19 disease that has borne the test of time.

1.1.1.1. GLS-1027 protects mice from LPS-induced acute lung injury

Zhang et al. studied a model of lipopolysaccharide (LPS) induced acute lung injury in mice [5]. Following intranasal infusion of 10 μg of LPS mice were treated intraperitoneally an hour later with either atractylenolide I at doses of 5, 10, or 20 mg/kg or GLS-1027 at 0.5 mg/mouse (approximately 20 mg/kg).

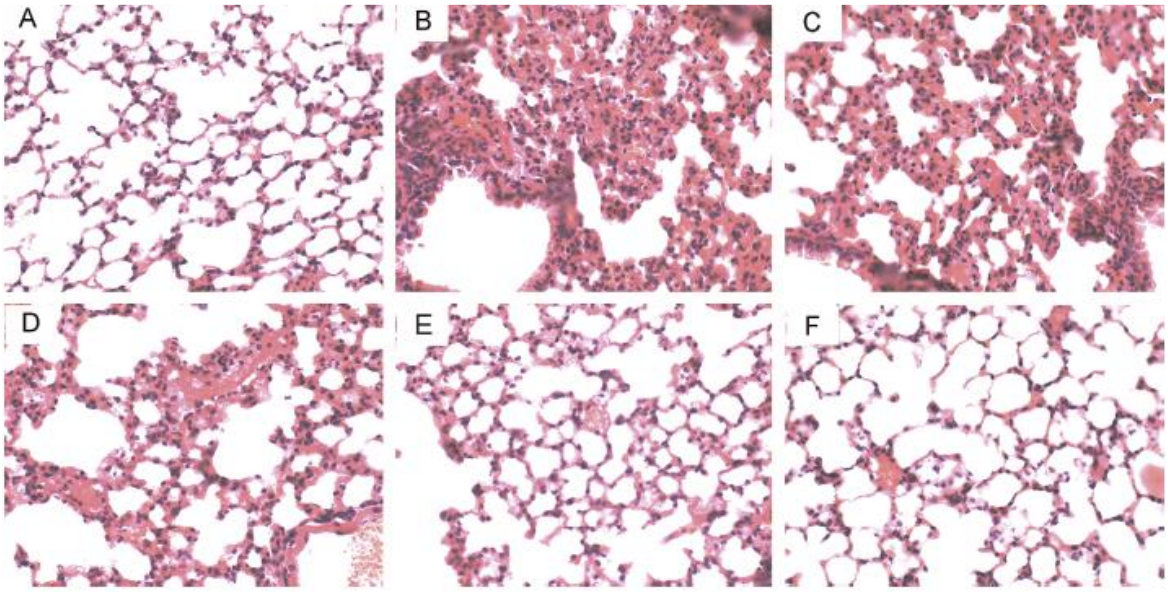

Figure 1.1.1.1-1: Pulmonary LPS-induced inflammation is inhibited by GLS-1027
Effects of AO-I on histopathological changes in lung tissues in LPS-induced ALI mice. Mice were given an intraperitoneal injection of AO-I (5,10 and 20 mg/kg) 1h after administration of LPS. Lungs tissues from each experimental group were processed for histological evaluation at 6h after LPS challenge. Representative histological changes of lung obtained from mice of different groups. A:Control group, B:LPS group, C:LPS + AO-I (5mg/kg) group, D:LPS +A O-I (10mg/kg) group, E:LPS + AO-I (20mg/kg) group, F: LPS + VGX-1027 (0.5mg/mouse) (Hematoxylin and eosin staining, magnification 200).

As shown in Figure 1.1.1.1-1 (Fig 1 from paper), compared to control untreated mice (Panel A), LPS induced significant inflammatory changes with thickened interstitial membranes and small alveolar spaces. Whereas atractylenolide showed a dose-related effect with near-normal lung histology at the highest dose (Panel E), animals treated with GLS-1027 had normal lung histology (Panel F). GLS-1027 treatment was also associated with significant decreases in neutrophil and macrophage influx into the lungs relative to LPS. Importantly, the anti-inflammatory effect of GLS-1027 was associated with significantly lower levels of IL-6, IL-13, TNFα, and IL-1β (Figure 1.1.1.1-2 panels A-D respectively, called VGX-1027 in Fig 5 from paper). The inflammatory changes related to

SARS-CoV-2 infection are expected to mirror the pathogenesis of LPS induced lung injury demonstrating a potential benefit of GLS-1027 treatment.

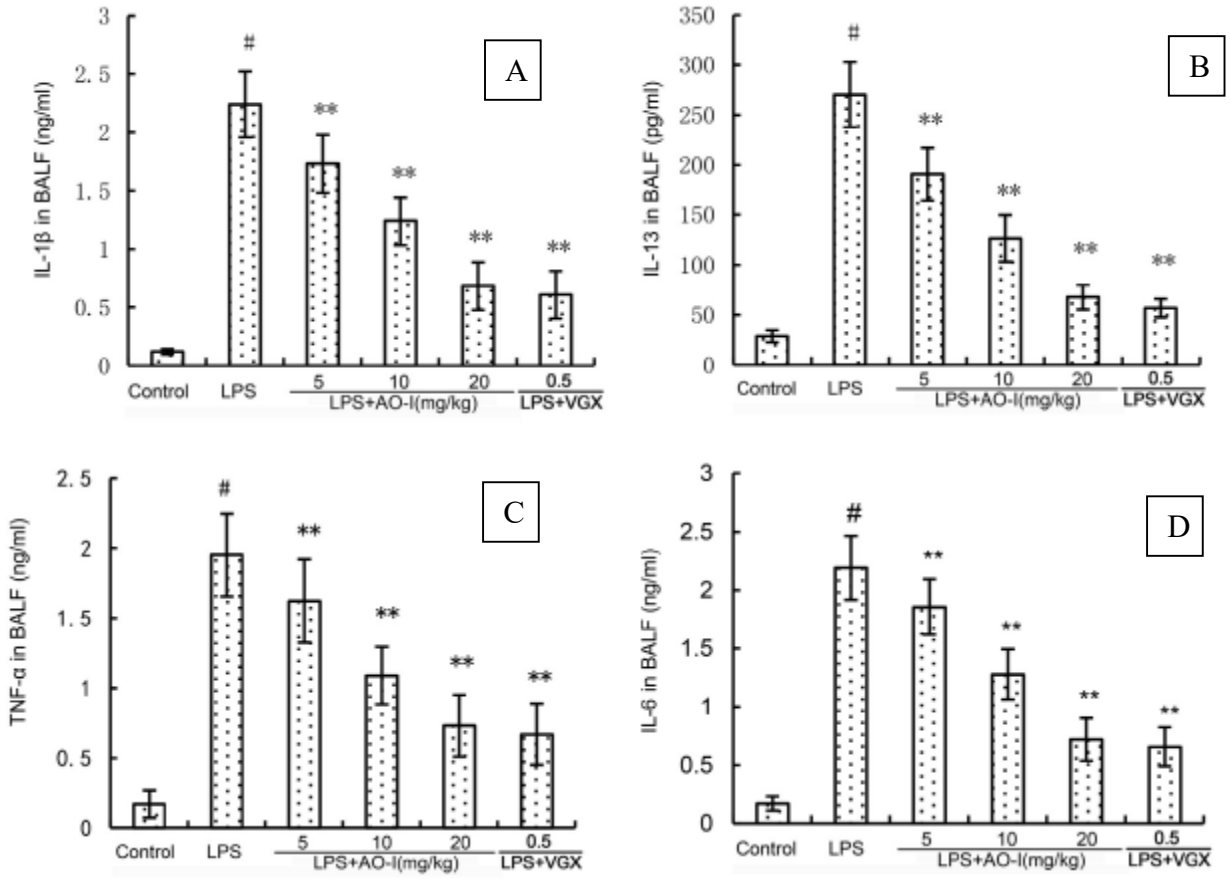

Figure 1.1.1.1-2: Pulmonary LPS-induced inflammation is inhibited by GLS-1027 Effects of AO-I and GLS(VGX)-1027 on TNF-α, IL-6, IL-1β, IL-10, IL-13, and MIF production in the BALF of LPS-induced ALI mice. BALF was collected a t 6 h following LPS challenge to analyze the inflammatory cytokines TNF-α, IL-6, IL-1β, IL-10, IL-13 and MIF. The values presented are mean +- S.D. (n = 12 in each analysis) of three independent experiments. $P^{\#}$ <0.01 vs control group, P* < 0.05, P** < 0.01 vs LPS group.

1.1.1.2. Lung inflammation induced by $PM_{2.5}$ particulates is prevented by GLS-1027; Potential role for particulate enhancement of SARS-CoV and SARS-CoV-2 related disease

Xu et al. examined whether GLS-1027 could prevent $PM_{2.5}$ particulate induced lung inflammation [6]. The deleterious pulmonary effects of air pollution are associated with fine particular matter of a size less than 2.5 μm, referred to as $PM_{2.5}$, which leads to multiple respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and lung cancer.

Mice pretreated with GLS-1027 (25 mg/kg given intraperitoneally) were exposed to $PM_{2.5}$ particulates (7.8 mg/kg) over two consecutive days. Whereas $PM_{2.5}$ exposed, untreated mice developed significant inflammatory changes in the lungs and bronchi consisting of infiltration of mononuclear cells and thickened alveoli, $PM_{2.5}$ exposed, GLS-1027 treated animals did not akin to PBS treated controls. Bronchoalveolar lavage fluid demonstrated that alveolar inflammation was associated with marked increases in TNFα, IL-1β, and IL-6; increases blocked by GLS-1027 as correlated with mRNA transcriptional reductions (Figure 1.1.1.2-1, Fig 3 from paper).

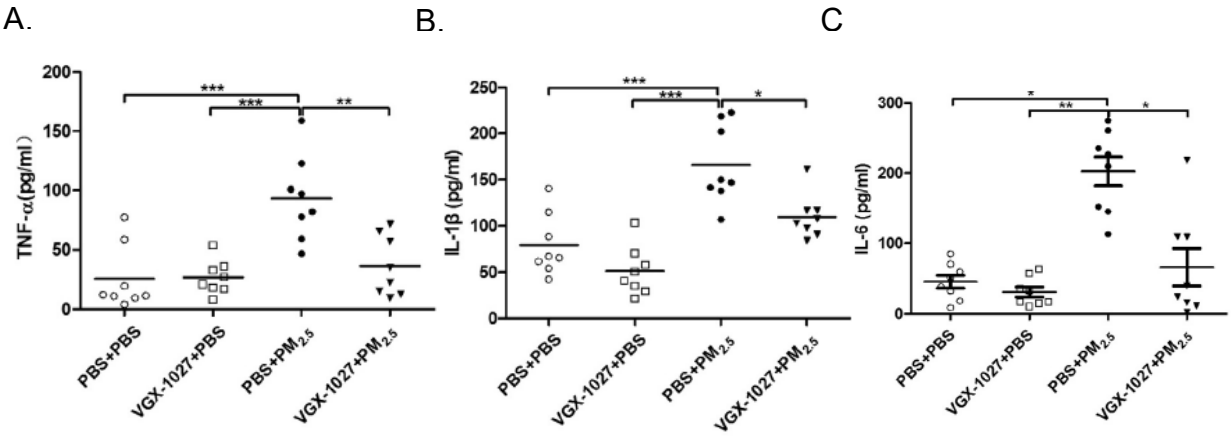

Figure 1.1.1.2-1: GLS-1027 inhibits $PM_{2.5}$ induced inflammatory cytokine expression Effect of PM $_{2.5}$ (7.8 mg/kg) exposure and of VGX-1027 (25 mg/kg) pretreatment on individual and mean levels of TNF-α (A), IL-1β (B) and IL-6 (C) in bronchoalveolar lavage (BAL) fluid. *P < 0.05, **P < 0.01, ***P < 0.001 compared with PBS-pretreated $PM_{2.5}$-instilled mice

The therapeutic effect of GLS-1027 in $PM_{2.5}$ exposed mice yielded lower pulmonary inflammation scores (Figure 1.1.1.2-2, panel A; VGX-1027 in Fig 4E from paper). Moreover, GLS-1027 treatment lowers $PM_{2.5}$ induced airway resistance (Figure 1.1.1.2-2, panel B; VGX-1027 in Fig 1C from paper) – a factor that is a critical determinant in being able to effectively oxygenate persons after airway intubation. GLS-1027 also reduced levels of IL-18, caspase-1 and NLRP3 inflammasome mRNA.

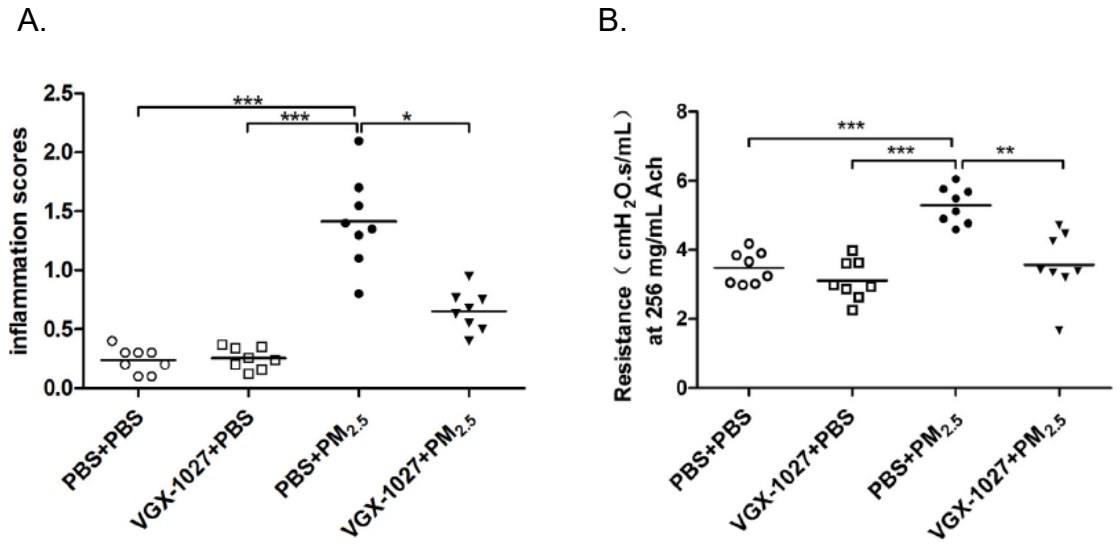

Figure 1.1.1.2-2: GLS-1027 lowers $PM_{2.5}$ induced lung inflammation and airway resistance Effect of $PM_{2.5}$ (7.8 mg/kg) exposure and of VGX-1027 (25 mg/kg) pretreatment on lung inflammation (A) and airway resistance (B). A. Individual and mean values of inflammation scores measured from H&E-stained sections. *P<0.05, **P<0.01, ***P<0.001 compared with PBS-pretreated $PM_{2.5}$-instilled mice. B. Individual and mean airway resistance at 256 mg/mL. *P<0.05, **P<0.01, ***P<0.001 compared with PBS-pretreated $PM_{2.5}$-instilled mice.

1.1.1.3. Particulate exposure is associated with increased mortality SARS-CoV and SARS-CoV-2

Lung pollution has also been associated with greater morbidity and mortality with severe coronavirus infection. Cui et al. examined the mortality during the 2002-2003 SARS-CoV epidemic in China [7]. They found a 2-fold increase in mortality between regions experiencing either short-term or long-term exposure to environmental particulates yielding an air pollution index > 100 relative to an index < 75. Moreover, analysis of Chinese provinces reveals a near linear relationship (R^2 = 0.86) between air pollution index and SARS-CoV case fatality rate (Figure 1.1.1.3-1; Fig. 1 from paper). A similar association is being anecdotally reported for SARS-CoV-2 infection and has been postulated by many as a risk factor for greater mortality.

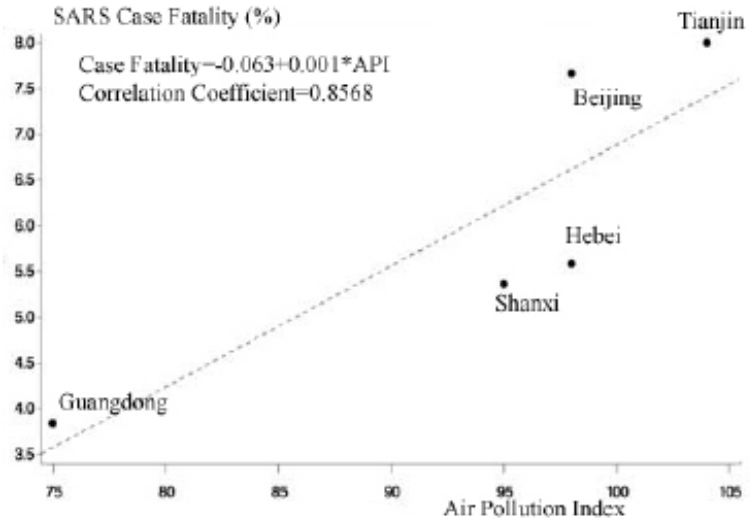

Figure 1.1.1.3-1: SARS-CoV case-fatality relative to provincial air pollution index The correlation and association between short-term exposure to ambient air pollution and case fatality of SARS in People's Republic of China.

The data showing that GLS-1027 reduces airway inflammation related to $PM_{2.5}$ air pollution provides a potential second important anti-inflammatory effect of GLS-1027 that may be associated with lower progression to severe pulmonary disease. Moreover, the fact that $PM_{2.5}$ exposure was associated with greater airway resistance, an effect blocked by GLS-1027 in mice, raises the possibility that, for those individuals who progress to requiring mechanical ventilation, continued GLS-1027 treatment may increase ventilatory effectiveness and possibly reduce the level of positive end-expiratory pressure (PEEP) required to maintain oxygenation status. Note, that in general, higher levels of PEEP are considered as a negative prognostic factor for survival. Thus, an additional exploratory goal of this study will be to determine whether those patients who do progress to intubation and mechanical ventilation differ in the level of PEEP required relative to treatment group.

1.1.1.4. Biomaterial induced thrombosis is TLR2/4 mediated

Langadec et al. investigated the pathogenesis of biomaterial induced thrombosis [8]. Some observations from this study have relevance to the use of GLS-1027 in SARS-CoV-2 disease. The study showed that pathogenesis of thrombogenesis was initiated through a classic inflammatory response involving NF-κB translocation resulting in induction of TNFα and pro-IL-1β release, the latter then cleaved to IL-1β through caspase-1 cleavage. In addition, there is formation of the NLRP3 inflammasome that together with the inflammatory cytokines IL-1β, IL-6, and IL-18 serves as the initial triggering mechanism to start a thrombotic response. The investigators demonstrated the critical role of IL-6 in this process and demonstrated that GLS-1027 was able to effectively block the initiating inflammatory cytokine IL-1B and IL-6 activation pathways.

It is of interest that there have been a large number of recent reports of relatively healthy, young patients presenting with SARS-CoV-2 infection complicated by intracerebral and

peripheral arterial thromboses resulting in stroke (including fatal strokes) and vascular compromise leading to amputation of legs and myocardial infarction.

Whether the thrombotic complications associated with SARS-CoV-2 infection are related to an inflammatory priming event is, as yet, unknown. However, should such a mechanism ultimately be proven, it provides yet another inflammatory complication of SARS-CoV-2 infection that may be benefitted by GLS-1027. Thus, this study as an exploratory goal will additionally determine whether thrombotic complications differ relative to treatment group.

1.1.1.5. GLS-1027 inhibits IL-6 mediated neuroinflammation in TBI and autism models

Additional studies documented the ability of GLS-1027 to inhibit IL-6, IL-1β, and TNFα in neuroinflammatory models.

The study by Laird et al. investigated the role of GLS-1027 to reduce cerebral edema and neuroinflammation following traumatic brain injury (TBI) [9]. In this study, the investigators found that high mobility group box protein-1 (HMGB1) is released from damaged neurons following traumatic brain injury in mice. HMGB1 in turn activates TLR4 on microglial cells and induces release of aquaporin-4, a water channel, that results in cerebral edema. This pathway is IL-6 mediated and was blocked by pharmacologic treatment of mice with GLS-1027. Thus, a common secondary complication of increased cerebral edema that can occur following cerebral thrombosis and stroke may additionally be benefitted by treatment with GLS-1027. Since vascular complications are considered to be seen in a minority of study subjects, with stroke representing only a subset of patients, any potential treatment effects of GLS-1027 in preventing or ameliorating cerebral edema will be observed and catalogued but will not be included as an exploratory aim of the study. Should such complications be observed then they will be catalogued as part of the Clinical Study Report (CSR) and published with clinical trial results.

Ahmad et al. studied the effect of GLS-1027 on neuroinflammation in BTPR Itpr3^{tf}/J mice, a model of human autism [10]. As with other studies, GLS-1027 was observed to down-regulate inflammatory cytokines IL-1β, IL-6, and TNFα in peripheral mononuclear cells. Of note, GLS-1027 was also able to down regulate the same inflammatory response in neural tissue, confirming that the drug was able to penetrate the blood brain barrier and limit neuroinflammation.

1.1.2 Human experience with GLS-1027

GLS-1027 has completed two Phase I safety and pharmacodynamic studies: CAT-001 (NCT00627120) and CAT-002 (NCT00760396). The compound was then called VGX-1027. Both human clinical studies, as well as pre-clinical pharmacokinetic (PK) studies, were published together in 2016 by Lee et al. [11]. More detailed information regarding these clinical trials is presented in the GLS-1027 Investigator's Brochure.

CAT-001 was a single-ascending dose study of GLS-1027. Six subjects each received single doses of drug at 0, 1, 10, 100, 200, 400, and 800 mg in a fasted state with 72-96 hours between administration of successive doses. An additional sub-study was conducted to determine PK of a 100 mg dose given in a fasted or fed state. CAT-002 was a multiple-ascending dose study of GLS-1027 administered at doses of either 0, 40, 100,

200 mg daily, or 200 mg twice daily over a 5-day period. Adverse events and PK were assessed during the trial.

Overall, in the multiple ascending dose study, 15 of the 40 subjects experienced one or more adverse events. Among those receiving study drug, grade 1 hypertension was observed in 4 subjects at each of the three highest doses of 100, 200, and 200 mg BID. Each of these subjects had borderline elevations in systolic blood pressure (>145). Additionally, two subjects in the single ascending dose study (100, 200 mg) experienced neutropenia. Both subjects were of African American ethnicity and had low baseline neutrophil counts. Headache was observed in two individuals in the multiple dose study (200, 200 mg BID). Hypersomnia was observed in two individuals in the single dose study who received 10 mg of GLS-1027, however, it was also observed in two placebo subjects in the single dose study.

The pharmacokinetic profile of GLS-1027 showed proportionate increases in peak serum concentration and AUC relative to dose with normalized C_{max} of approximately 60 µg/L/mg and normalized AUC of 450-500 µg-hr/L/mg. Serum C_{max} and AUC was increased by a factor of approximately 1.4-1.5 in the fed state. The serum half-life was approximately 7 hours with no drug accumulation observed over the 5-day period at any dose level. Drug was highly bioavailable with 90% excreted unchanged in the urine. Separate pre-clinical toxicology studies showed no evidence of hepatic metabolism or interaction with the cytochrome P_{450} enzymes.

GLS-1027 was safe and well-tolerated in these two Phase I studies with a PK profile that demonstrated high bioavailability, renal excretion, and pharmacodynamics that support daily dosing.

1.2 Investigational Agent

GLS-1027, the therapeutic agent in this study, is an isoxazole compound. The structure of GLS-1027, [S,R]-3-phenyl-4,5-dihydro-isoxazoleacetic acid, is shown below (Figure 1.2-1).

Microcrystalline cellulose will be used as the placebo in this study. The structure of microcrystalline cellulose is shown below (Figure 1.2-2).

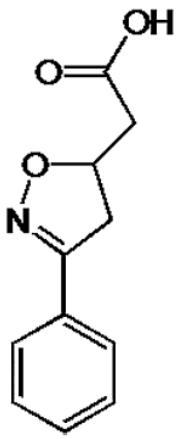

Figure 1.2-1: Structure of GLS-1027

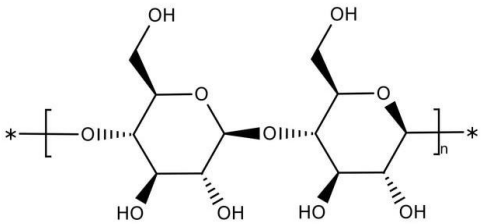

Figure 1.2-2: Structure of microcrystalline cellulose

1.3 Dose and Regimen Rationale

The doses of GLS-1027 used in this clinical trial are 120 mg or 360 mg given orally once daily. Pre-clinical studies have found that the effective dose in mice of 20 mg/kg would correlate to a human dose of 1.626 mg/kg, or 113 mg for a 70 kg person. This study will assess doses of 120 mg and 360 mg given in the fasting state to determine whether there is a dose effect. Treatment will commence on the day of enrollment (or the following day if drug administration would be after 10 pm) and then once daily, given with daily AM medications through the period of hospitalization to a maximum treatment period of 28 days.

1.4 Risk/Benefit Assessment

In accordance with the International Conference on Harmonization (ICH), this study has been designed to minimize the risk to study participants. The potential benefit of treatment is to reduce the incidence of progression to severe disease is consistent with the known risks and adverse events known to occur with GLS-1027. Since patients will be monitored in an in-patient setting, daily changes in clinical status can be assessed and changes to drug regimens made as clinically indicated.

GLS-1027 has been well tolerated in Phase I clinical studies. The doses chosen conform to those already studied and known to be tolerated. The maximal dose level is below the 800 mg/day maximal dose in the single ascending dose study (CAT-001) or the 400 mg/day maximal dose in the multiple ascending dose study (CAT-002).

An initial PK assessment of GLS-1027 will be conducted for the initial 15 enrollees. For all subjects, trough dosing will be assessed throughout the study. Modifications to drug dosing will be made based on changes in renal function as warranted, as described in Section 5.4.

2. HYPOTHESIS AND STUDY OBJECTIVES

2.1 Hypothesis

GLS-1027 will be safe, well tolerated and, for those admitted to hospital with PCR confirmed SARS-CoV-2 infection at WHO COVID-19 classification level of 3 or 4, will reduce likelihood for progression to WHO COVID-19 classification level of 6 or greater (defined as severe pneumonitis characterized by the need for intubation with mechanical ventilation, initiation of ECMO, or death) or need for salvage treatment started 72 hours after study entry with either an IL-6 monoclonal antibody or dexamethasone at a dose of ≥ 6 mg/day.

2.2 Primary Objectives and Outcome Variables

- Incidence of serious adverse events relative to treatment group
- Incidence of treatment failure within 28 days from enrollment

2.3 Exploratory Objectives

- Assess the number of days requiring ICU care relative to treatment group
- Assess the number of days of mechanical ventilation relative to treatment group
- Assess incidence of WHO COVID-19 Classification levels relative to baseline serum IL-6 level
- Assess incidence of WHO COVID-19 Classification levels relative to baseline serum ferritin level
- Assess incidence of WHO COVID-19 Classification levels relative to baseline CRP
- Assess trough level of GLS-1027 relative to serum creatinine
- Assess the maximal level of Positive End-Expiratory Pressure (PEEP) for subjects who are intubated relative to treatment group.
- Assess the number of days of PEEP > 5 cm H_2O for subjects who are intubated relative to treatment group
- Incidence of progression to WHO COVID-19 Classification level 6, or 7, or 8 (individually)
- Assess SARS-CoV-2 IgM antibody responses relative to treatment group

3. STUDY DESIGN

This is a Phase II, randomized, double-blind, placebo-controlled study to assess 2 dose levels of GLS-1027 for the prevention of treatment failure among participants admitted to hospital with PCR confirmed infection with SARS-CoV-2 (WHO classification 3 or 4). The enrollment period will extend to 72 hours from hospital admission.

Participants will be randomized to placebo or GLS-1027 at either 120 mg or 360 mg daily in a 1:1:1 ratio as adjunctive to standard of care based on the hospital COVID-19 treatment algorithm and/or local COVID-19 treatment practices. Participants will be administered study drug for a maximum treatment period of 28 days or until discharge or

death, whichever comes first. Follow-up will continue through to Day 56 to document AEs and outcome as to discharge, death, or WHO COVID-19 classification level if subject remains hospitalized.

3.1 Safety Monitoring

Participants will be monitored by hospital personnel as per protocol. Clinical adverse events (AEs) will be reviewed daily through to discharge or the end of the treatment period. Safety monitoring will also include laboratory assessment of hematology, chemistry and ECG as per the Schedule of Events. Serum trough levels of GLS-1027 will be assessed at select times throughout the trial as per the Schedule of Events. Participants will also be followed for up to 56 days post-enrollments for health status and adverse events.

3.2 Data and Safety Monitoring Board (DSMB)

In addition to internal monitoring of safety data by the site PI and medical monitor, an independent data and safety monitoring board (DSMB), consisting of expert members not related to the clinical trial or sponsor staff will provide safety oversight. The DSMB will include at a minimum three members: a physician specializing in either Infectious Disease or Pulmonary / Critical Care, a second health-care practitioner who may be a physician, and someone with statistical experience (physician or non-physician).

The DSMB will meet at the start of the clinical trial to review and finalize the DSMB charter. At a minimum, the DSMB will meet to review interim data when 50% of the target enrollees (66 subjects) have completed the primary observation period to discharge, death, discontinuation or 28 days of treatment. The DSMB will review safety data and outcomes for enrolled subjects in a blinded manner. Unless a safety signal has been encountered, enrollment will continue through to at least 44 per group (total N=132).

A summary of all AEs and SAEs will be provided to the DSMB as masked treatment groups by an independent statistician together with a summary rates of retention in the study, and other relevant events. Reports will include a summary of participants' baseline characteristics, early study discontinuations, and a summary of participants who reach primary endpoint and/or end of study follow-up. The DSMB may recommend corrective measures, up to termination of the study for safety concerns. Study termination can be implemented by the Project PI, FDA, Sponsor, or site-specific or other supervising IRBs. Conference call or video conference meetings are allowed as necessary.

Additional details can be found in the DSMB Charter.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Recruitment of Participants

4.2 Inclusion Criteria for enrollment

1. Age 18 years or older
2. Able to provide informed consent
3. Able and willing to comply with study procedures
4. Enrollment within 72 hrs of hospitalization with a diagnosis of PCR confirmed SARS-CoV-2 infection
5. WHO COVID-19 classification level of 3 or 4

4.3 Exclusion Criteria for enrollment

1. Pregnant or lactating
2. SpO2 less than 90% on room air or less than 95% on supplemental oxygen
3. Calculated GFR < 60 (Cockcroft-Gault)
4. Meets hospital treatment algorithm for treatment with dexamethasone at a dose of 6 mg/day for a 10 day course. A single bolus dose of 6 mg of dexamethasone given in the Emergency Department and continued at a dose of ≤ 3.5 mg/day or less is allowed.
5. Meets treatment algorithm criteria for treatment with toclizumab or other anti-IL-6 agent
6. Treatment with an anti-IL-6 inhibitor, anti-IL-1 inhibitor, anti-TNF monoclonal antibody, or anti-JAK inhibitor (see Appendix A for exclusionary period for individual drugs)
7. Participation in a COVID-19 clinical trial that includes prescription of a drug with anti-cytokine activity
8. Treatment within the past 60 days with a chemotherapeutic agent
9. Current outpatient treatment with systemic corticosteroids at a dose equivalent of 20 mg/day or greater of prednisone or prednisolone, 16 mg/day or greater of methylprednisolone
10. Diagnosis of leukemia or lymphoma
11. WHO COVID-19 classification level of 5 or greater (use of high-flow oxygen, non-mechanical ventilation such as CPAP, mechanical ventilation)

4.4 Discontinuation/Withdrawal of Study Participants

The Informed Consent will require that subjects allow follow-up for the primary outcome and safety through to 56 days post-enrollment or death. A subject may withdraw from the study by withdrawing consent to continue participation. If a subject withdraws consent from participating in the study at any time after enrollment, but prior to the final scheduled study visit, the investigator will make every effort to have the participant complete all assessments at the time of withdrawal. All data collected up to the time of withdrawal will be used for data analyses. The request to withdraw consent must be documented.

Discontinuing treatment is not a reason for withdrawing from participating in the study. Subjects who discontinue treatment for any reason should be followed until 56 days post-enrollment or death, whichever comes first.

Reasons for treatment discontinuation are defined below.

- The PI or Medical Monitor consider that continuation of treatment may pose a safety risk to the subject. Treatment discontinuation will be considered a treatment failure, unless the subject discontinues treatment due to pregnancy or renal insufficiency. The subject should however continue to be monitored as per protocol for outcome measures through to study end (Day 56).
- Adverse event (Adverse Reaction): clinical or laboratory events that in the medical judgement of the investigator are grounds for discontinuation of treatment. This will be considered as a treatment failure. Subjects should however continue to be monitored as per protocol for outcome measures through to study end (Day 56).
- Lost to follow-up: for subjects who are discharged from the hospital within 28 days of treatment initiation who cannot be contacted after multiple attempts, will be

considered as Lost to Follow-up for purposes of Long-term outcomes (56 days). Otherwise, without relapse of COVID-19 symptoms, discharge within 28 days of enrollment is considered a treatment success. For subjects who are discharged from the hospital, every effort should be made to contact the subject to determine clinical status and adverse events post-discharge.

- Transfer of subject to another hospital. All transfers will be considered treatment failures.

4.5 Treatment with dexamethasone post-enrollment

Treatment with dexamethasone at a dose of 6 mg/day for 10 days is currently considered as part of the standard of care for COVID-19 at many institutions, however, the specifics of treatment and whether such treatment is formally algorithm based varies between institutions. Moreover, it is recognized that dexamethasone treatment may be ordered as part of clinical care for some subjects after enrollment into the study.

Enrollment into the study is allowed for individuals who have not been treated with dexamethasone since hospital admission. Enrollment into the study is also allowed for those have received a single bolus dose of 6 mg of dexamethasone at presentation to the hospital with or without continuation of dexamethasone at a dose of 3.5 mg/day or less.

Enrolled subjects for whom dexamethasone is initiated within 72 hours of the time of 1st dose of study drug will be considered to have required dexamethasone at the time of presentation to hospital and will be treated the same as those who received a single bolus dose of 6 mg at presentation to the hospital. Unless dexamethasone is prescribed for 10 days at 6 mg, sSuch subjects will not be considered to have met the definition of the need for salvage therapy, and will not be considered as meeting a study endpoint for failure.

Enrolled subjects for whom dexamethasone is ordered at a dose of ≥ 6 mg per day and is initiated 72 hours or later after the 1st dose of study drug will be considered to have met the definition of need for salvage therapy and thus have met a study endpoint for failure. Initiation of treatment with dexamethasone at a dose of less than 6 mg/day after enrollment in the study will not be considered as treatment failure.

Subjects will be subgrouped for summary by concomitant bolus dexamethasone within 72 hours of enrollment versus no concomitant dexamethasone with 72 hours of enrollment.

5. STUDY PRODUCT

5.1 Investigational Product

GLS-1027 is a small molecule with a chemical structure as shown in Figure 1.2-1 and has a molecular weight of 205.21 g/mol. GLS-1027 will be formulated in capsules at a dose of 120 mg per capsule.

Microcrystalline cellulose, the placebo used in this study, has a chemical structure as shown in Figure 1.2-2 and has a molecular weight of 658.7 g/mol. Microcrystalline cellulose will be formulated in capsules at a dose of 105 mg per capsule.

5.2 Packaging and Labeling

GLS-1027 will be supplied to the investigational pharmacy in bottles of 50 capsules, while the placebo will be supplied in bottles of 100 capsules. Drug will be dispensed by pharmacy personnel to study participants as part of daily medication dispensing to maintain blinding of other study personnel.
Drug product vial label is shown below in Table 5.2-1.

Table 5.2-1. GLS-1027 and Placebo drug product vial labels

GLS-1027	PLACEBO
GLS-1027 Capsules, 120 mg Protocol No. GLS27-005 Lot No. xxxx Quantity: 50 capsules (Caution New Drug Limited by Federal (United States) Law to Investigational Use Keep out of reach from children: Take as directed Store at 25ºC (77°F) excursion permitted to 15°-30°C (56° - 86°F) Sponsor: GeneOne Life Science Mfd by CoreRx Inc., 14205 Myerlake Circle, Clearwater FL 33760	Placebo Capsules, 105 mg Protocol No. GLS27-005 Lot No. xxxx Quantity: 100 capsules (Caution New Drug Limited by Federal (United States) Law to Investigational Use Keep out of reach from children: Take as directed Store at 25ºC (77°F) excursion permitted to 15°-30°C (56° - 86°F) Sponsor: GeneOne Life Science Mfd by CoreRx Inc., 14205 Myerlake Circle, Clearwater FL 33760

5.3 Handling of Study Drug

Study drug will be stored at 25°C (ambient temperature, range 15°C to 30°C) in the hospital Investigational Drug Service. Investigational product must be stored in a secure area according to local regulations.

5.4 Dispensing of Study Drug

Pharmacy service will provide 3 capsules per day (GLS-1027 or matching placebo) based on randomization assignment. The randomization treatment code will be provided to the site pharmacists from a web-based system. How to access the randomization system is covered in a separate Pharmacy Manual. It is the responsibility of the Investigators that study drug is dispensed only to study participants by hospital nursing personnel. Authorized personnel are the only ones to dispense product according to local regulation and study specific Delegation Log. Study drug administration is to be discontinued for periods when subject either has an eGFR < 60 mL/min/1.73 m^2, is unable to take medications orally, or reaches a study endpoint (WHO COVID-19 classification of 6 or greater).

5.5 Precautions with Investigational Medicinal Product

Medication should not be taken by children or anyone outside of the current clinical trial.

5.6 Preparation of Investigational Product

No preparation of Investigational Product is required.

5.7 Record of Investigational Product Disposition at Site

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Investigational Pharmacy and/or Hospital Pharmacy records or logs must comply with applicable regulations and guidelines.

5.8 Return and Destruction of Investigational Product

Remaining study drug at the hospital investigational drug service will be returned to GeneOne Life Science accompanied with relevant return log(s).

6. STUDY PROCEDURES AND TREATMENTS

6.1 Procedures by Visit (also see Table S2)

6.1.1 Day 1: Review Study and Eligibility Criteria; Obtain Informed Consent, Enrollment

Subjects will be recruited and Study staff will review the protocol with the prospective participant and obtain written informed consent. One copy of the informed consent form (ICF) will be maintained with the investigative team, and the other given to the participant. Study procedures that will be completed include:

- Document review of ICF process and that copy was provided to participant
- Review and record medical history, demographics
- Review concomitant medications
- Record physical exam, height, weight, vital signs from medical record
- Record baseline ECG
- Record COVID-19 PCR result
- Record baseline CBC and Basic Metabolic Profile (BMP), liver function tests (LFTs), CRP, IL-6, troponin, D-dimer, procalcitonin, admission CXR
- Determine and record baseline WHO COVID-19 Classification (Appendix B)
- Record whether participant is prescribed supplemental nasal O_2 and flow rate or O_2 via facemask and Fi O_2
- Perform urine pregnancy test if person is of child-bearing potential
- Collect blood for CPK and GGT
- Alert Pharmacy to enrollment to direct administration of study drug per randomization (if drug administration would occur after 10 pm, then start study drug on Day 2)
- Collect serum and PBMCs as indicated in the Schedule of Events

6.1.2 Day 2 (PK sub-study participants ONLY)

- For the 15 persons enrolled, additional blood samples (5 ml) will be collected as follows
    - Pre-Dose
    - Post-Dose 1, 2, 4, 8 hr

6.1.3 Day 2 through 29 (or until discharge or death)

- Administer study drug with AM medications if calculated creatinine clearance is ≥ 60.
- Determine and record WHO COVID-19 classification level (Appendix B)

- Review new concomitant medications
- Record past 24 hour maximal and minimal temperature (°C), respiratory rate, heart rate, systolic and diastolic BP
- Record potential co-morbid complications of SARS-CoV-2 infection to include shortness of breath, arterial thrombosis (myocardial infarction, stroke, peripheral blood clot), mental confusion, death
- Record adverse effects
- Collect and Record labs as indicated in the Schedule of Events: CBC, BMP, LFTs, CRP, ferritin, D-dimer, CPK, IL-6
- Record if care given in ICU setting
- Record ventilatory status: O_2 use, CPAP use, ventilator, ECMO
- Record O_2 flow rate, FiO_2 % (if intubated), CPAP pressure (as relevant), PEEP setting (as relevant)
- Perform ECG (12 lead) on day 2 at 75-90 minutes post dose, and on day 15 ± 2 days
- Collect serum for CPK and GGT (Day 7) and, if abnormal, then weekly until values normalize
- Collect blood for plasma for GLS-1027 trough measurement as indicated in the Schedule of Events
- Collect blood for serum and PBMCs as indicated in the Schedule of Events
- Pharmacy to review patient creatinine and calculated creatinine clearance daily.

6.1.4 Day 56

- Review medical record to document date of discharge or death, as relevant
- Determine and record WHO COVID-19 classification level (Day 56)
- If hospitalized, review chart to document intercurrent AEs
- If not hospitalized, query participant to document intercurrent AE's from the end of the primary study period

6.2 Timing and Evaluations

6.2.1 Informed Consent (Day 1)

Study personnel will meet with prospective study participants, explain the study, and provide them with an informed consent form (ICF) that describes the eligibility criteria for entering the study, study treatments, randomization, and follow-up procedures. An informed consent must be signed prior to any study related procedures being performed. A copy of the signed and dated consent form will be given to the participant.

6.2.2 Enrollment (Day 1)

Participants who consent to be in the study will be assigned a unique participant identification designation number (PID#). PID#'s consist of a 3 digit site code followed by a 3-digit subject number. Subject numbers are assigned in numerical order of enrollment (i.e., 1st subject is assigned XXX-001, 2nd subject is assigned XXX-002 with XXX a placeholder for the site number). Once assigned, PID numbers cannot be reused for any reason. Information regarding participant's PID# will also be documented on a screening log. Study personnel will alert pharmacy to enrollment for drug administration and review medical record for study related procedures.

Medical History

Investigators should document all significant illnesses that the participant has experienced as Medical History in the last 6 months. Illnesses' first occurring or detected during the study and/or worsening of an existing illness that occurs after the first administration of study drug are documented as AEs on the electronic case report form (eCRF).

Prior and Concomitant medications

Prior treatments, defined as administered up to 4 months prior to the time of enrollment with designation as to whether the drug was prescribed as an outpatient or only since admission, will be recorded in the eCRF as prior medications. Concomitant treatments, defined as continuing or new treatments taken at or after the signing of the informed consent, will be recorded in the eCRF as concomitant medications.

Review and record baseline labs

The medical record will be reviewed and labs from the day of enrollment recorded. Labs and evaluations such as procalcitonin, CXR, D-dimer, troponin will be recorded from the 1st recorded instance in the medical record if not repeated through to the time of or on the day of enrollment.

Determine and record WHO COVID-19 classification level

Determine from the clinical record the WHO COVID-19 classification level (Appendix B) and record. This will be determined and recorded on a daily basis.

Review and record oxygenation status

Document that participant is prescribed nasal O_2 and the flow rate.
If mechanically ventilated, record level of PEEP and %FiO2
Record if CPAP prescribed and expiratory pressure
Record if given ECMO treatment

Contact pharmacy for study drug administration

Contact the investigational pharmacy regarding study recruitment for assignment of randomization code and to dispense study drug to inpatient ward.

6.2.3 Safety Assessments

6.2.3.1 SARS-CoV-2 associated events

The medical record will be reviewed daily for the occurrence of SARS-CoV-2 associated events, which include shortness of breath and arterial thrombosis (myocardial infarction, stroke, peripheral blood clot).

6.2.3.2 Adverse events

The medical record will be reviewed daily for the occurrence of any adverse events, change in clinical status, or death. These will be graded as per the NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

6.2.3.3 Vital Signs

Vital signs will be recorded from the medical record daily to include maximal and minimal temperature (°C), respiratory rate, heart rate, and systolic and diastolic blood pressure.

6.2.3.4 Weight and Height

Height and as listed in the medical record at the time of admission will be recorded at the time of enrollment.

6.2.3.5 12-lead ECG

The results of the participant's baseline or first 12-lead ECG from the admission will be recorded. A repeat ECG will be performed on Day 2 at 75-90 minutes post-dose and Day 15 of the study (± 2 days).

6.2.3.6 Laboratory Evaluations

Laboratory evaluations to include CXR, CBC, biochemistries, CPK; and ferritin, CRP, IL-6 (if ordered at site), D-dimer, and procalcitonin as available; are recorded as per the Schedule of Events.

6.3 Assessment of Laboratory Abnormalities

Serum chemistries (complete metabolic panel) and complete blood count with differential blood count will be graded as noted in Section 7.1.

6.4 Assessment of Clinical Adverse Events

The Investigator will grade clinical AEs (based on discussions with study participants) using the CTCAE v5.0.

6.5 Plasma for PK sub-study and/or trough level determination of GLS-1027

Blood will be collected for plasma as per the Schedule of Events for measurement of trough concentrations of GLS-1027. The first 15 subjects are to be enrolled into a sub-study to determine drug elimination of GLS-1027 in SARS-CoV-2 infected patients.

6.6 Serum and PBMCs for immunology assessments

Serum and PBMCs are collected per the Schedule of Events to assess the effect of treatment on cytokine expression and serum levels, and STAT3 activation in PBMCs relative to treatment group.

7. EVALUATION OF SAFTY AND MANAGEMENT OF TOXICITY

7.1 Safety Parameters

7.1.1 Adverse Events (AEs)

An AE (also referred to as an adverse experience) is defined as any unfavorable and unintended sign, symptom, or laboratory abnormality that is temporarily associated with the use of a drug or treatment and does not imply any judgement about causality. An adverse event can arise with any use of a drug or treatment regardless of route of administration, dose, and may be delayed after a drug or treatment has been discontinued. An adverse event is not the same as an "overdose"; an overdose is a dose-related event specifically caused by exposure to an increased amount of drug.

An unexpected AE is:

- Not identified in the Investigator's Brochure (IB) or otherwise not expected from the characteristics of the clinical material
- Not listed at the specificity or severity that has been previously observed
- Not specifically mentioned in the IB as known to occur with the particular drug under investigation, even though the adverse event may be known to occur with other drugs in the same pharmacologic class or with drugs that share pharmacologic properties with the study drug.

Treatment emergent AEs (TEAE) include the following:

- Post-treatment complications that occur as a result of protocol mandated procedure

- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE
- Complications and termination of pregnancy; see Section 7.1.8 for additional information.
- Non-elective medical or surgical procedures

Study related AEs do not include the following:

- Expected complications or clinical consequences due to elective medical or surgical procedures
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before study enrollment or prior to the first administration of study drug that do not worsen
- Overdose of non-study drug
- Incorrect or increased dose administration of study drug without adverse clinical sequelae
- Any laboratory abnormality that is considered as non-significant
- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without medical reason

7.1.2 Serious Adverse Events (SAEs)

A SAE is any AE that meets one of the following conditions:

- Is immediately life-threatening (e.g., participant was, in the view of the Investigator, at immediate risk of death from the event as it occurred).
- Requires or prolongs hospitalization;
- Results in congenital anomaly or birth defect;
- Results in persistent or significant disability/incapacity;
- Is an important medical event that may not result in death or be life threatening, but based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
- Results in death

Important medical events that do not result in death, are life-threatening, or require hospitalization may be considered as an SAE when, in the judgement of the Investigator, potentially jeopardize the study participant and may require medical or surgical intervention.

SAE's occurring up to and including the final study visit will be collected regardless of the Investigator's opinion of causation.

If an Investigator becomes aware of an SAE that has occurred after a participant has completed the study, the Investigator should report the SAE to the sponsor regardless of the Investigator's opinion of causation.

SAEs should be followed until resolution. The reporting period for SAEs is described in Section 9.6.2.

7.1.3 Suspected Unexpected Serious Adverse Drug Reactions (SUSARs)

A SUSAR is a serious adverse event not listed in the IB and that the PI identifies as related to study drug or procedure.

7.1.4 Assessing Severity (Intensity)

The Investigator will grade laboratory AEs and clinical AEs (based on discussions with study participants) using the NCI Common Terminology Criteria for Adverse Events v5.0:

- Mild (Grade 1)
- Moderate (Grade 2)
- Severe (Grade 3)
- Life-threatening consequences (Grade 4)
- Death related to AE (Grade 5)

Adverse events will be recorded on the eCRF at the severity reported by the investigator. If an ongoing AE worsens or increases in its severity or its relationship to the study drug changes, a new AE entry for the event should be entered on the eCRF.
The following is a link to the grading scale:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

7.1.5 Causal Relationship of Investigational Product to Adverse Events

A causally related AE is one judged to have a suspected relationship to the administration of the investigational agent. Conversely, an AE may also be assessed as not related to the investigational product. The Investigator is responsible for reporting adverse events and judging the relationship between the administration of the investigational product and an AE because the investigator is knowledgeable about the participant (e.g., medical history, concomitant medications), administers the investigational product, and monitors the participant's response to the investigational product. The Sponsor will assess the overall safety of the investigational product and determine whether expedited reporting to regulatory agencies is indicated.

Investigators should use their knowledge of the Study Participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug by the following criteria:

- Related – the investigator considers that there is a causal relationship between the event and study drug;
  - Probably related – the Investigator considers that there is a probability of a causal relationship of the event to the study drug. Such events should be entered as "related" in the database
  - Possibly related – the investigator considers that there is a possible causal relationship of the event to the study drug. Such events should be entered as "related" in the database
- Not related – the investigator considers that the event has no relationship to administration of the study drug

The following guidance should also be taken into consideration:

- Temporal relationship of event to initiation of study drug;
- Course of the event, discontinuation of study drug, or reintroduction of study drug (when applicable);
- Known association of the event with the study drug or with similar treatments;
- Known association of the event with the disease under study;
- Presence of risk factors in the Study Participant or use of concomitant medications known to increase the occurrence of the event

7.1.6 Abnormal Laboratory Values

Laboratory abnormalities will be classified according to the CTCAE v5:

7.1.7 Pregnancy During Study

Pregnancy is an exclusion criterium for the study. If a participant is found to be pregnant at any time during the study after enrollment, then study medication will be immediately discontinued. Such participants are requested to remain in the study for continued observation and will be analyzed with regard to assigned study treatment. Data on fetal outcome will be collected for regulatory reporting. Pregnant subjects will be assessed for efficacy endpoints in the same manner as all other subjects.

7.1.8 Decreases in renal function during study

Pharmacy will monitor patient's renal function during the study. Study drug will be administered as per the assigned group for a calculated creatinine clearance ≥ 60. If the calculated creatinine clearance decreases below 60 then study drug will be discontinued until the eGFR is ≥ 60. Should study drug administration be interrupted due to a change in renal function, the total length of treatment is determined by the day of enrollment. The primary treatment period is still up to 28 days from enrollment and is not extended for days of interrupted therapy. Subjects with interrupted or discontinued treatment due to renal function, will be assessed for efficacy endpoints in the same manner as all other subjects.

7.1.9 Post-study Reporting Requirements

SAEs, including deaths, regardless of cause or relationship, must be reported to Sponsor at the time that such events become known to the Investigator.

Investigators are not obligated to actively seek AEs or SAEs beyond the follow up period for participants. However, if the Investigator learns of an SAE that occurs within 30 days from completion or termination visit, the Investigator should promptly document and report the event to the study team and medical monitor.

7.2 Methods and Timing for Collection and Recording of Safety Data

Participants will be queried daily as to adverse events that have occurred since the previous day and the current status of any AE that was reported at a prior visit that has not yet resolved. Additionally, labs and ECGs will be reviewed for safety.

All AEs, regardless of severity, seriousness, or presumed relationship to study treatment, must be recorded using medical terminology in source documents and on the eCRF. Whenever possible, a diagnosis will be documented, in lieu of symptoms. The source document and the eCRF must contain the Investigator's opinion concerning the relationship of the AE to study treatment.

AEs should be described with the following attributes:
- Duration (start and end dates)
- Seriousness
- Severity
- Causality
- Action(s) taken
- Outcome

7.3 Safety and Toxicity Management

The Medical Monitor will be responsible for the overall safety monitoring of the study. The site Investigator will be responsible locally for safety.

Safety assessments include the following:
- Incidence of all adverse events classified by system organ class, preferred term, severity, and relationship to study treatment
- Changes in safety laboratory parameters
- Changes in ECGs
- Other clinically significant changes in safety evaluations

7.3.1 Events Requiring Expedited Reporting

Events requiring expedited reporting (ERER) are defined as Adverse Events including:

- Suspected or confirmed anaphylaxis or drug-related allergic reaction

Sites will inform the Sponsor of any ERER within 24 hours to discuss whether dosing to the participant should continue.

7.3.2 Reasons to Discontinue Treatment

Discontinuation or interruption of study drug

Study drug will be discontinued with any of the following:

1. Diagnosis of pregnancy.
2. Anaphylaxis or allergic reaction possibly related to study drug

Study drug will be temporarily halted with any of the following:

3. If the eGFR falls below 60 mL/min/1.73 m^2
4. If the patient is intubated and/or ECMO is initiated
5. If oral administration is not possible
6. For those with baseline serum bilirubin in the normal range: a serum bilirubin ≥ 5 times the upper limit of normal (ULN)
7. For those with baseline serum bilirubin above the normal range: a serum bilirubin ≥ 10 times the ULN

8. Transaminase (ALT or AST) elevation of ≥ 20 times the ULN
9. An absolute neutrophil count of < 1000 (Grade 4)
10. Electrocardiographic findings of any of the following: Torsades de Pointes, polymorphic ventricular tachycardia
11. Malignant hypertension characterized by a systolic BP of ≥ 220 mm Hg or a diastolic BP ≥ 110 mm Hg with concomitant neurologic deficit or need for urgent medical intervention
12. Headache with neurologic deficit in a patient without history of migraine or similar syndrome or condition
13. Gastric hemorrhage requiring transfusion or other emergent intervention
14. Uncontrolled emesis for greater than 24 hours, or incident emesis considered to be definitely or probably caused by study drug
15. Occurrence of any opportunistic infection

Study drug should be reinstituted when the event that resulted in temporary interruption of study drug administration has resolved or has improved to a Grade 2 event or lower. In the case that the subject has been intubated or started on ECMO, study drug should be restarted once extubated and/or ECMO discontinued and oral administration of medications is possible. Exceptions are any diagnosis of pregnancy or an opportunistic infection. If a second episode of the same adverse event occurs, study drug will be stopped and not restarted.

If two or more episodes of anaphylaxis possibly related to study drug occur, then the unblinded clinical research coordinator will request that pharmacy provide a report regarding study drug assignments of these participants to the DSMB to determine potential causality. The DSMB will review and determine appropriateness of study continuation.

All episodes of study drug interruption or stoppage should be reported to the Medical Monitor.

Any permanent stoppage of study drug in response to meeting any of the individual stopping rules will be considered as meeting study endpoint for failure except for a diagnosis of pregnancy, or stoppage related to decreased renal function.

Pause in Treatment or Termination of clinical trial

The Medical Monitor or DSMB may recommend global pause of study drug administration to all enrolled subjects if a safety signal is encountered that requires investigation and in the opinion of either the Medical Monitor or DSMB that continuation during the investigation period would present a safety risk to enrolled subjects. The decision to reinstitute study medication may be made at the conclusion of the investigation. The IRB will be informed of all such treatment interruptions and will be provided a report of the investigation.

Except for detection of a safety signal, the study will continue to the target enrollment unless enrollment has been increased to gain additional statistical power for assessing dose dependent response.

7.3.3 Unblinding

This is a double-blind study. Treatment assignments should be maintained as blinded unless such unblinding is considered as critical to the care and well-being of the subject. Unblinding should occur following discussion with the Sponsor Medical Monitor, however, emergency unblinding can occur if the Investigator deems that such a delay would unduly harm the subject and knowledge of the treatment assignment is a critical factor in medical decision making versus a discontinuation of study drug until discussion with the Medical Monitor. In the case of unblinding, the Investigator must record the date, time and reason for unblinding, however, the Investigator is not required to inform the Sponsor of treatment assignment. Unblinded treatment assignment will only be accessible to those who require such information as part of medical decision making and for those involved in Safety reporting to Health Authorities and/or the relevant IRB.

The Investigational Pharmacy will maintain a listing of subject treatment assignments and will provide a mechanism for unblinding in emergency situations.

8. STATISTICAL METHODS and CONSIDERATIONS

Prior to unblinding and analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed for reporting of results from this clinical trial.

8.1 Data Sets to be Analyzed

- The intention to treat population (ITT) includes all participants who are randomized to a treatment allocation. The ITT population will be used for the summary of all demographic and baseline characteristics and for analysis of the primary outcome of treatment failure. Subjects will be grouped in analyses and summaries based on their randomization allocation.
- The modified intention to treatment (mITT) population includes all participants who are randomized to a treatment allocation, and who have received at least one dose of study drug. The mITT population will be used for the summary and analysis of the primary outcome of treatment failure. Participants will be grouped based on the treatment allocation.
- The safety analysis set includes all mITT participants. Participants will be grouped based on the treatment actually received.
- Per-protocol (PP) analysis set includes all Safety subjects who complete the trial by meeting the endpoint or being discharged within 28-days without meeting the endpoint. Participants in this set will be grouped to treatment arms they actually received. This set will be used as a sensitivity analysis to summarize the primary endpoint and for summary of all other efficacy outcomes.

8.2 Sample Size

Based on the initial data obtained to date and data in the literature [1], it is anticipated that approximately 50% of subjects hospitalized with PCR-positive SARS-CoV-2 infections

(WHO COVID-19 Classification level 3 or 4) will progress to WHO COVID-19 classification level of 6 or greater as defined by one or more of the following: the need for intubation or mechanical ventilation (level 6), the need for ECMO (level 7), or any cause death (level 8). The sample size estimate for this proof of concept is based on Fisher's Exact two-sided test for 2 proportions using NQuery 8 (www.statsols.com). Estimates of admitted patients requiring salvage therapy is unknown, however, the clinical data set who require intubation is a likely subset of those whose condition worsens but do not progress to respiratory compromise.

Although the interim analysis will utilize masked treatment assignments, the O'Brien Fleming group sequential sample size estimation confirms that a single interim look would retain a cumulative exit probability of 70% with a cumulative alpha =0.05 after the final analysis using the target enrollment of 132 (44 per group) to detect a reduction of those reaching the endpoint of treatment failure, which includes advancing to WHO COVID-19 Classification level ≥6 from 50% (SOC treated) to 25% in either treatment group of SOC plus GLS-1027. Other conditions also qualify a subject as treatment failure include: need for salvage therapy with IL-6 monoclonal antibody; or institution of salvage therapy with dexamethasone (≥ 6 mg/day), withdrawing consent from the study, becoming lost to follow-up, or discontinuation of treatment for any reason other than renal function or pregnancy. This study is not powered to assess statistically significant differences between GLS-1027 doses.

8.3 Randomization

Randomization to treatments will occurred using a centralized randomization system. Randomization will be stratified by site to ensure equal distribution of treatments within each site. Subjects within each site will be randomly assigned in a 1:1:1 ratio to receive placebo, 120 mg GLS1027 or 360 mg GLS1027 daily for their duration of hospitalization or until intubation or mechanical ventilation constrains oral medication.

8.4 Demographic and Other Baseline Characteristics

Demographic and baseline data, vital signs, medical history, concomitant illnesses, and current medications/treatments will be summarized by means of descriptive statistics: continuous variables as mean, median, standard deviation, minimum and maximum values and categorical variables as frequencies and percentages, grouped by treatment arm based on the ITT population and overall.

8.5 Safety Analysis

All safety and tolerability summaries will be performed on the safety analysis population.

8.5.1 Adverse events

Treatment emergent AEs will be summarized by frequencies and will be presented by system organ class and preferred term with the number and percentage of participants affected. Frequencies will be presented with respect to maximum severity. Multiple occurrences of the same AE will be counted only once following a worst-case approach with respect to severity and relationship to Study Treatment.

8.5.2 Laboratory Data

Continuous response variables per time point will be summarized with mean, median, minimum, and maximum values. Categorical response variables will be summarized per

time point with percentages. In addition, each laboratory parameter will be summarized as a shift from baseline based to the last lab assessments prior to meeting the primary endpoint or 28 days, whichever comes last.

8.6 Efficacy Analysis

The primary endpoint is treatment failure which is defined as any subject who achieved WHO level ≥ 6 (intubation and mechanical ventilation, requirement for ECMO, or death) within 28 days of initiating treatment or who meet the following reasons for treatment failure:

- Receiving salvage therapy with either an IL-6 monoclonal antibody or for those who are prescribed daily dexamethasone starting 72 hours or later after the 1st dose of study drug within the 28-day primary treatment period.
- Lost to follow-up through hospital transfer, within the 28-day primary treatment period.
- Discontinuation of study drug for any cause prior to discharge will be considered as a treatment failure, except for those for whom study drug was suspended due to a decrease in renal function (creatinine clearance of < 60 mL/min), and those become pregnant during treatment. These subjects will be followed for the primary endpoint for up to 28 days post enrollment, and for up to 56 days for safety.

Subjects who complete 28 days of treatment but remain hospitalized without increase in WHO COVID-19 Classification level to ≥6, will not considered be as treatment failures with respect to the primary endpoint.

The proportion of subjects in each treatment group who reach the study endpoint of treatment failure by 28 days will be compared to placebo using Fisher's Exact 2-sided test of proportions. Additionally, the frequency for each outcome (intubation, ECMO, death) will be determined within each group. The ITT, mITT and PP analysis populations will be used to analyze the primary endpoint.

8.7 Other Analysis

Exploratory endpoints include the following which will be summarized using the PP populations by treatment group received:

- Assess the number of days requiring ICU care relative to treatment group. If a subject does not require ICU care, the number of days will be set to zero for the group summary. The number of ICU days will be summarized for all subjects in each group and for the proportion of those who are actually in ICU.
- Assess the number of days of mechanical ventilation relative to treatment group. If a subject does not require mechanical ventilation, the number of days will be set to zero for the group summary. The number of mechanical ventilation days will be summarized for all subjects in each group and for the proportion of those who are actually on mechanical ventilation.

- Assess incidence of WHO COVID-19 Classification levels relative to baseline serum IL-6 level
- Assess incidence of WHO COVID-19 Classification levels relative to baseline serum ferritin level
- Assess incidence of WHO COVID-19 Classification levels relative to baseline CRP
- Assess trough level of GLS-1027 relative to serum creatinine
- Assess the maximal level of Positive End-Expiratory Pressure (PEEP) for subjects who are intubated relative to treatment group.
- Assess the number of days of PEEP > 5 cm H_2O for subjects who are intubated relative to treatment group
- Incidence of progression to WHO COVID-19 Classification level 6, or 7, or 8 (individually)
- Assess SARS-CoV-2 IgM antibody responses relative to treatment group

No adjustments or imputations will be made for deaths or other forms of missingness except those already described above.

8.8 Interim Analysis

A masked interim analysis will be performed when 22 subjects in each group have been assessed for the primary endpoint of treatment failure. Unless safety is of concern, the study will not be stopped for futility and enrollment will continue to at least the targeted sample size of 132.

8.9 Missing Values

Subjects may have a missing endpoint for the following reasons:

- Lost to follow up due to transfer to another hospital
- Remains in the hospital for >28 days without ever achieving WHO COVID-19 Classification level ≥ 6.
- Withdrawal of consent prior to meeting endpoint

If a subject is lost to follow-up due to transfer to another hospital, the subject will be considered a treatment failure per the ITT and mITT populations and will be excluded from the analysis per the PP population. Missing primary endpoint assessment because of continued hospitalization beyond 28 days will be counted as treatment success if the subject has not met the criteria for WHO COVID-19 Classification level ≥ 6 at any time up to 28 days. Subject who withdraw consent without being assessed for the primary endpoint will be considered treatment failure. To minimize missing values, enrolled participants will be followed through to the end of the primary study period (through to hospital discharge, death, or 28 days from treatment initiation) for safety and efficacy assessment. Additionally, safety and clinical status will be monitored through to Day 56 as per the schedule of events.

9. DATA COLLECTION, MONITORING, AND AE REPORTING

9.1 Confidentiality

Information about study participants will be kept confidential to the best of the study site's ability.

In the event that a participant revokes authorization to collect or use personal health information (PHI), the sponsor retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the participant is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in original source documents. Examples of these original documents and data records include (as applicable): hospital records, clinical and office charts, laboratory notes, memoranda, participant's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, pharmacy records, laboratory records, medical records (including electronic records) relative to the clinical trial.

9.3 Data Collection

Data will be collected using Electronic Data Capture (EDC). Participants will be identified by PID#. Initial data collection may utilize a paper form of the EDC. Any such records will be maintained as source data.

9.4 Record Retention

It is the Investigator's responsibility to retain study essential documents as per country regulations: in the US for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained.

9.5 Safety and Quality Monitoring and Record Availability

Monitoring

Monitoring of the clinical trial will be performed by experienced monitors, who will report to the Sponsor as outlined in the Monitoring Plan.

Record availability and auditing

The investigator will make study documents (e.g., ICFs, drug accountability forms) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, regulatory agencies, GeneOne Life Science, Inc. or its designee for confirmation of the study data.

Participation as an investigator in this study implies acceptance of potential inspection by regulatory authorities and applicable compliance and quality assurance offices.

9.6 Adverse event (AE) Reporting

AEs will be recorded and forwarded to regulatory agencies as required.

9.6.1 Study Reporting Period of Adverse Events

All AEs will be recorded throughout the study and the 28 day follow-up period.

9.6.2 Study Reporting Period for Serious Adverse Events

SAE's will be recorded throughout the study and the 28-day follow-up period.

Expedited reporting of SAEs will be determined by GeneOne Life Science using reference safety information specified in the Investigator's Brochure. An event may qualify for expedited reporting to regulatory authorities if it is an SAE, SUSAR in line with relevant regulatory requirements.

At any time after completion of the SAE reporting period, if an Investigator becomes aware of an SAE that is suspected by the Investigator to be related to the study drug, the event will be reported to the Sponsor.

SAE TELEPHONE AND CONTACT INFORMATION:

SAE REPORTING	Catalyst Pharmacovigilance	safety@catalystcr.com
MEDICAL MONITOR:	Joel Maslow, MD PhD MBA	MAILING ADDRESS:
PHONE:	(484) 965-9147p; (610) 331-7844 c	GeneOne Life Science, Inc.
MEDICAL LIAISON:	Celine Remigio, RN DPT	1040 DeKalb Pike
CELL:	(914) 606-1199	Suite 200
EMAIL:	cremigio@geneonels-us.com	Blue Bell, PA 19422
24 hr Answering Service	(215) 703-5843	
GeneOne FACSIMILE:	(484) 965-9146	
GeneOne Safety Email	GeneOneSafety@geneonels-us.com	

The report should contain as much clinical safety information as possible, but at minimum, the initial report must include the following information:

- Participant number and Study name
- Date of Onset and Date of Resolution (if applicable)
- Detailed description of event
- Investigational product (if known)
- Causal relationship of event to investigational product
- Reporter name and contact information

Follow-up reports will be sent as soon as more information becomes available. Events for which the study participant seeks medical care, the study site will attempt to obtain relevant medical records to include as source documents. These include but are not limited to discharge summary, results of relevant laboratory tests, and reports of relevant radiographic studies. In the case of death, the investigator will attempt to procure relevant reports (such as autopsy reports, medical examiner report, discharge summary).

Each SAE must be followed by the investigator until resolution, stabilization, or return to baseline, even if this extends beyond the end of the study, with follow-up report filed to provide a summary of the event through resolution.

The electronic data capture (EDC) system is integrated to the safety database (Veeva) vault and all SAE information will be collected electronically. A paper SAE form will be available as a back-up. Copies (or electronic copy) will be provided to GeneOne Life Science or its representative, who will be responsible for reporting to regulatory authorities as indicated, and copy will be forwarded to the study sites IRB/REC.

9.6.3 Notification of Serious Adverse Events

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected (e.g., FDA Form 3500A in the US). SUSARs reports shall be made as soon as possible and in no event later than 15 calendar days after the Sponsor's initial receipt of the information. Written notification may be submitted on the form described above or equivalent or in a narrative format and shall bear prominent identification of its contents. Each written notification to regulatory agencies shall be transmitted to the division that has responsibility for review. In each written safety report, the Sponsor shall identify all safety reports previously filed concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports. The Sponsor shall also notify the relevant regulatory authorities by telephone, facsimile, or email transmission of all deaths and any unexpected fatal or life-threatening experience, regardless of causality, as soon as possible but in no event later than 7 calendar days after the Sponsor's initial receipt of the information. Each telephone call or facsimile transmission to regulatory agencies shall be transmitted to the division that has responsibility for review.

Follow up information to a safety report shall be submitted as soon as the relevant information is available. If the results of a Sponsor's event investigation show that an adverse drug experience not initially determined to be reportable is, in fact, reportable, the Sponsor shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made. Results of investigations of other safety information shall be submitted, as appropriate, in an information amendment or annual report. In the event of death, if an autopsy is performed, a copy of the report, redacted for PHI but labeled with the PID#, should be sent to GeneOne Life Science, Inc.

9.7 Study Termination

GeneOne Life Science reserves the right to terminate the study for safety or administrative reasons, including lack of enrollment, at any time. Investigational product must be returned to GeneOne, unless instructed otherwise. Document retention will follow local regulation.

10. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be allowed. Any proposed presentation, abstract and/or manuscript must be made available to GeneOne at least 60 days prior to submission. GeneOne shall have fifteen (15) days for review. If GeneOne considers that material would reveal protectable intellectual property, GeneOne may request a delay in submission for a maximum of three (3) months from the date of receipt in order for patent application(s) to be filed with the United States Patent and Trademark Office and/or foreign patent office(s).

11. LIST OF ABBREVIATIONS

AE	Adverse event
Alk Phos	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
CMP	Complete Metabolic Profile
CPAP	Continuous positive airway pressure
CPK	Creatinine phosphokinase
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CTCAE	National Cancer Institute Common terminology criteria for adverse events
CXR	Chest X-ray (chest radiograph)
CRS	Cytokine release syndrome
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram (synonymous with EKG)
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate (Cockroft-Gault formula)
ERER	Event requiring expedited reporting
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
HMGB1	High mobility group box protein-1
IB	Investigator’s brochure
ICF	Informed consent form
ICU	Intensive Care Unit
IL	Interleukin

IRB	Investigation review board
ITT	Intention-to-treat
LDH	Lactate dehydrogenase
LPS	Lipopolysaccharide
mAb	Monoclonal antibody
MERS-CoV	Middle East respiratory syndrome coronavirus
NS	Not stated
PBMC	Peripheral blood mononuclear cell
PEEP	Positive end-expiratory pressure
PHI	Personal health information
PID#	Participant identification designation number
PK	Pharmacokinetic
PM	Particulate matter
$PM_{2.5}$	Particulate matter of a size < 2.5 μm
PP	Per-protocol
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus, type 2
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TBI	Traumatic brain injury
ULN	Upper limit of normal

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13. APPENDICES

APPENDIX A: Exclusionary period for anti-cytokine agents

CATEGORY	Generic name	Brand name	Exclusionary period
IL-1 inhibitors	Rilonacept	Arcalyst	35 days
	Canakinumab	Ilaris	30 days
	Anakinra	Kineret	30 days
IL-6 inhibitors	Toclizumab	Actemra	50 days
	SIltuximab	Sylvant	100 days
	Sarilumab	Kevzara	105 days
	Atezolizumab	Tencentriq	135 days
	Clazakizumab		120 days
	Olokizumab		120 days
	Sirukumab		120 days
JAK inhibitors	Ruxolitinib	Jakafi	30 days
	Tofacitinib	Xeljanz	30 days
	Oclacitinib	Apoquel	30 days
	Baricitinib	Olumiant	30 days
	Peficitinib	Smyraf	30 days
	Fedratinib	Inrebic	30 days
	Upadacitinib	Rinvoq	30 days
	Filgotinib		30 days
	Cerdulatinib		30 days
	Gandotinib		30 days
	Lestaurtinib		30 days
	Momelotinib		30 days
	Pacritinib		30 days
	Abrocitinib		30 days
TNFα inhibitors	Infliximab	Remicade	50 days
	Etanercept	Enbrel	30 days
	Adalimumab	Humira	75 days
	Certolizumab	Cimzia	55 days
	Golimumab	Simponi	60 days

Note 1: This appendix may be updated through the clinical trial as new agents are either approved or brought into clinical practice. The time prior to enrollment that each drug is to be excluded is listed, but may be updated if new information is published regarding modifications to drug half-life.
Note 2: The decision to initiate treatment with any of the agents listed below is determined either according to the hospital specific SARS-CoV-2 Treatment Algorithm or per individual physician decision. If any agent is started post-enrollment, use should be documented as a concomitant medication. Other study procedures should continue as per the schedule of events.

APPENDIX B: WHO COVID-19 Classification

PATIENT STATE	DESCRIPTOR	SCORE
Uninfected	No clinical or virologic evidence of infection	0
Ambulatory	Infected, with no limitation of activities	1
	Infected, with limitation of activities	2
Hospitalized	No oxygen therapy	3
Mild disease	Oxygen by mask or nasal canula	4
Hospitalized	Non-invasive ventilation or high-flow oxygen	5
Severe disease	Intubation with mechanical ventilation	6
	Ventilation plus any of vasopressor Rx, RRT, ECMO	7
Death	Death	8