CLINICAL STUDY PROTOCOL

Study Title:	A Pilot, Randomized, Placebo-Controlled Trial of GC4419 (avasopasem manganese) in Patients with Critical Illness Due to SARS-CoV-2 Infection (COVID-19)
Sponsor:	Galera Therapeutics, Inc.
IND Number:	150,065
Protocol ID:	COV-4419-201
Medical Monitor:	Jon T. Holmlund, MD
Protocol Version/Date:	Version 5.0/08 March 2021

STUDY ACKNOWLEDGEMENT

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Protocol No. COV-4419-201 Protocol Date: 08 March 2021

This protocol has been approved by Galera Therapeutics, Inc. The following signature documents this approval.

DocuSigned by:
Jon Holmlund
Signer Name: Jon Holmlund
Signing Reason: I approve this document
Signing Time: March 24, 2021 | 1:48:07 PM EDT
4015E5E16BC84EFBBD0C961CCDA550FB

Jon T. Holmlund, MD
Chief Medical Officer
Galera Therapeutics, Inc.

Investigator Statement

I have read the attached protocol and appendices and agree to abide by all provisions set forth therein. I will provide copies of the protocol and other pertinent information to all individuals responsible to me who will assist with the study.

I agree to comply with the International Conference on Harmonisation, Tripartite Guideline on Good Clinical Practice (ICH, GCP) and applicable global and local government regulations/guidelines including 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312.

I agree to ensure that Financial Disclosure Statements will be completed before study initiation, during the studies if there are changes that affect my financial disclosure status, and one year after study completion by:

- myself (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub-investigators (including, if applicable, their spouses [or legal partners] and dependent children)

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Galera Therapeutics.

The Sponsor or its designee will have access to source documentation from which case report forms have been completed.

_____ _____

Signature of Principal Investigator Date (DD Month YYYY)

_____

Printed Name of Principal Investigator

REVISION HISTORY

Revisions to Version 4.0 dated 08 February 2021

Summary of Change	Rationale	Affected Protocol Sections
Added statement that study drug infusions should not begin if the subject's mean arterial pressure (MAP) is less than 65 mmHg	DMC recommendation	• Synopsis • Section 9.2 • Section 10.2.2 • Appendix 1
Added clarification to SAE reporting	To provide sites with further guidance on SAE reporting for this patient population	• Section 10.5.1

Revisions to Version 3.0 dated 30 June 2020

Summary of Change	Rationale	Affected Protocol Sections
Updated estimated enrollment period and studied period	To be accurate with current study status	• Synopsis
Updated Inclusion Criteria #1 to allow sites to use their standard of care testing method for SARS-CoV-2 Infection	To be consistent with site's standard practice	• Synopsis • Section 7.1
Revised Inclusion Criteria #3 to require FiO_2 of >/= 50% instead of >/= 60%	To allow inclusion of additional subjects who still will fit the critically ill patient population	• Synopsis • Section 7.1
Added clarification to Exclusion Criteria #7 and prohibited medication section regarding subject participation in concurrent clinical trials	To provide additional guidance to sites on subject inclusion	• Synopsis • Section 7.2 • Section 8.2
Added window of +/- 2 hours for study drug dosing	To provide additional guidance for subject dosing	• Synopsis • Section 6.1 • Section 6.2 • Section 10.2.2 • Appendix 1
Revised CYP2D6 requirements and removed from prohibited medications	To allow investigators to use their judgement in the use of these medications	• Synopsis • Section 8.1 • Section 8.2
Revised to require direct bilirubin, CRP, and triglycerides at baseline only unless clinically indicated.	To be consistent with site's standard practice	• Section 10.1.2 • Appendix 1
Revised to require SOFA score only while subjects are in the ICU.	To align with standard practice	• Synopsis • Section 10.2.3 • Appendix 1
Added language around timing of first two doses	To provide additional guidance for subject dosing	• Appendix 1
Revised to require Hematology/Chemistry samples	To be consistent with site's standard practice	• Appendix 1

Summary of Change	Rationale	Affected Protocol Sections
after completion of treatment only if clinically indicated.		
Clarified PK collection timepoints	To emphasize samples only need to be collected pre/post first infusion on Days 1 and 3	• Appendix 1
Added language to allow post-discharge follow-up visits to be done remotely (virtual/phone).	To provide flexibility to study subjects depending on their post discharge status.	• Appendix 1
Updated Schedule of Assessments: - to specify that Apache IV score only needs to be done once at screening/baseline and the worst value in the past 24 hours should be recorded. - to remove the collection of daily fluid balance after treatment discontinuation - to specify that if multiple labs are done in one day, the worst value should be recorded. - to revise requirement of viral load testing to screening/baseline, Day 7, and Day 14 - to revise requirement of cytokine blood draw to screening/baseline, Day 7, and Day 14 - to revise "each additional day in hospital" to "each additional day in ICU" - to revise "after discharge from hospital" to "after discharge from ICU"	To provide additional guidance to sites	• Appendix 1
Other editorial changes have been made throughout	To correct administrative errors and ensure content accuracy and consistency.	• Throughout

1. SYNOPSIS

Name of Sponsor/Company: Galera Therapeutics, Inc.	
Name of Investigational Product: GC4419	
Name of Active Ingredient: avasopasem manganese	
Title of Study: A Pilot, Randomized, Placebo-Controlled Trial of GC4419 (avasopasem manganese) in Patients with Critical Illness Due to SARS-CoV-2 Infection (COVID-19)	
Number of Study Center(s): up to 10	
Estimated Enrollment Period: 9-12 months	
Studied period: First patient enrolled: September 2020 Estimated date last patient completed assessment for primary endpoint: September 2021	**Phase of development:** 2
Background: SARS-CoV-2/COVID-19: Approximately 20% of people with confirmed, symptomatic COVID-19 disease, due to infection with the SARS-CoV-2 virus, will develop viral pneumonia requiring hospitalization. These patients exhibit respiratory compromise that can be characterized as severe (demonstrating dyspnea, hypoxia, and/or extensive lung opacities on chest x-ray); or critical, with respiratory failure, which may be accompanied by shock or multiorgan dysfunction). Approximately 25% of hospitalized patients, comprising approximately 5% of all patients with symptomatic infection, will have critical disease as described herein. Critical disease often manifests as a clinical picture consistent with the acute respiratory distress syndrome (ARDS), although information is still being obtained regarding the pathophysiology and pathophysiology of pulmonary compromise associated with SARS-CoV-2, compared with ARDS related to other causes. Retrospective series suggest that, after a variable initial course of disease, dyspnea begins approximately 6-7 days after the first symptoms of infection, with swift progression to frank respiratory failure/ARDS 2-3 days thereafter. Intensive care is often required for 14 days or more, and more than one attempt at ventilator weaning may be required before eventual extubation. Comorbidity among these critically ill patients includes renal, cardiac, and hepatic damage as well as hypotension requiring vasopressor treatment (Yang et al, 2020). Mortality for critically ill patients, highest among the elderly or those with significant prior concomitant conditions, has been reported to be on the order of 50-60% (Yang et al, 2020; Wu et al 2020). The IHME has recently projected that, assuming full social distancing throughout the United States through May 2020, nationwide needs for hospital beds and ICU beds will exceed national capacity (https://covid19.healthdata.org/projections, accessed 15 April 2020, 12 noon EDT) Further, pending effective treatments or vaccine(s), potential remains for recurrent waves of infection and the attendant needs for hospital resources.	

The proximate cause of ARDS in COVID-19 disease appears to be an inflammatory response, including a cytokine "storm," complicating the initial infection and producing pneumonitis. Such responses are accompanied by production of large amounts of superoxide by activated macrophages and neutrophils. It is this superoxide free radical which both initiates and sustains the inflammation, and which is produced in amounts sufficient to overwhelm the normal capacity of endogenous superoxide dismutase (SOD) enzymes to remove it. Similarly, superoxide is critical to the development of shock characterized by hypotension that is non-responsive to vasopressor (catecholamines such as norepinephrine) therapy. In the latter case, superoxide deactivates endogenous catecholamines, reacting with them via a free radical autoxidation cascade producing toxic products called "adrenochromes" (Macarthur et al, 2000). This process also results in hyporeactivity to exogenously-administered catecholamines, producing hypotension that is refractory to vasopressor treatment.

Avasopasem manganese (avasopasem): Avasopasem manganese is a highly selective, small molecule (MW 483) mimetic of naturally occurring superoxide dismutase (SOD) enzyme, which, like native SOD, converts superoxide to hydrogen peroxide and molecular oxygen specifically and selectively, at an enzymatic rate comparable to that of the native SOD. In disease states characterized by excessive superoxide production, administration of avasopasem replaces or augments deficient or insufficient endogenous SOD capacity. Accordingly, avasopasem and related active dismutase mimetics have demonstrated ability to protect tissues from superoxide-mediated damage in laboratory studies and in the clinic. Results from i*n vivo* models include: reduced zymosan-induced lung neutrophil infiltration, lipid peroxidation and lung injury, and mortality (Cuzzocrea et al, 2004); in the bleomycin intratracheal mouse model, reduced lung inflammatory infiltrates and alveolar epithelial apoptosis (Herzog, 2014); in a chronic asthma guinea pig model, reduced neutrophil infiltrate, lipid peroxidation and alveolar epithelia apoptosis (Masini et al, 2005); and in a lung focal irradiation mouse model, reduced late stage pulmonary fibrosis (Sishc et al, 2018). Results from animal studies also include reduction of *E. coli*-induced hypotension, vascular hyporeactivity to catecholamines, and mortality in septic shock (Macarthur et al, 2003), and decreased levels of proinflammatory cytokines such as TNFα, IL-1β and IL-6 (Cuzzocrea et al 2004; Macarthur et al, 2003), with increase in the anti-inflammatory cytokine IL-10 (Macarthur et al, 2003). In these studies, dismutase mimetic was administered continuously or repeatedly over several hours after challenge with zymosan or *E. coli* (Cuzzocrea et al 2004; Macarthur et al, 2003). In a hamster model, avasopasem reduced severe oral mucositis (Sonis, unpublished data, GC4419 Investigator's Brochure), supporting clinical trials of GC4419 to reduce radiation-induced severe oral mucositis. In Phase 1-2b clinical trials (Anderson et al 2018; Anderson et al 2019), GC4419 reduced the incidence, severity, and duration of severe oral mucositis produced from the superoxide generated due to concurrent chemoradiotherapy for head and neck cancer, with an acceptable safety profile, and a confirmatory Phase 3 trial (NCT03689712) in this indication is underway under Breakthrough Therapy Designation from FDA.

GC4419 has been safely administered to over 300 human subjects, with the Phase 3 oral mucositis trial testing 90 mg by 60-minute IV infusion, repeated each weekday, prior to standard radiotherapy, for 7 weeks—a total of up to 35 doses. Toxicity attributable to GC4419 has been limited to transient, infusion-related mild hypotension and postural symptoms, and mild circumoral paresthesia, attributable to reversible potentiation of nitric

oxide. These effects appear to be related to the C_{max} (which occurs at the end of the IV infusion), and are further limited with lower doses or prolonged infusion time at a given dose, with mild orthostatic lightheadedness reported in 6 of 72 healthy volunteers who have received 27 mg of GC4419 over 60 minutes, and 5 of 34 healthy volunteers who received 30 or 51 mg of GC4419 IV over 15 minutes. Adverse events observed in the oral mucositis trials have been those observed with the underlying standard regimen of radiation therapy plus cisplatin, and in a placebo-controlled randomized Phase 2b trial, the adverse event profiles for subjects receiving GC4419 or placebo were similar.

No effect on the QT interval was found in a precision QT clinical trial of GC4419 at a dose of 51 mg IV over 15 minutes, a dose and schedule at which C_{max} exceeds that produced after a 90 mg/60-minute infusion of GC4419.

Nonclinical GLP toxicology studies of avasopasem in rats and dogs have shown no abnormal histopathologic findings except for injection-site reactions after subcutaneous administration. These studies include 6-month chronic toxicology in rats (final report pending). A 9-month chronic toxicology study in dogs is in progress in the in-life phase. Results of GLP toxicological studies support dosing of GC4419 at a total daily dose of up to 198 mg for up to 14 days.

GC4419 has a plasma half-life of approximately 2 hours, reaching maximum concentration at the end of IV infusion and declining in a bi-exponential fashion thereafter. Plasma exposure is approximately dose-proportional. In past clinical trials, GC4419 has been quantifiable in plasma up to approximately 24 hours after a 60-minute IV infusion, with minimal accumulation in plasma with repeated daily dosing. Non-clinical data indicate a longer half-life of GC4419 in tissues, with rapid entry into cells related to C_{max} and slower release from cells.

GC4419 is eliminated by GI and renal routes. Human volunteer studies of GC4419 in the setting of compromised renal or hepatic function are in progress. There has been no apparent nephrotoxicity or hepatotoxicity of GC4419 in human clinical trials.

Rationale for the present study: The pathogenesis of severe-to-critical pulmonary disease complicating SARS-CoV-2 infection—and, when it occurs, the pathogenesis of attendant shock—along with the mechanism and available nonclinical and clinical data with GC4419, suggest that GC4419 could attenuate or reduce the risk of ARDS and the need for mechanical ventilation, and attenuate shock, in people suffering from them due to SARS-CoV-2.

The present study is intended as an initial assessment to confirm the safety of GC4419 in COVID-19 patients with critical respiratory illness. Hospitalized subjects whose respiratory function has deteriorated to the point where mechanical ventilation is needed will be studied. Subjects will be randomized in a 1:1 ratio to receive either GC4419 or placebo plus standard supportive care.

Upon review of results from this trial, future trials to treat COVID-19 patients with GC4419 earlier in the course of disease—e.g., in the setting of worsening hypoxemia and increasing requirement for supplemental oxygen short of mechanical ventilation—may be considered.

Objectives:

Primary:

- To evaluate 28-day all-cause mortality/overall survival

Secondary (all through the same 28 days as for the primary endpoint):

- To evaluate the safety of avasopasem in the study population
- To evaluate the frequency of successful ventilator weaning
- To evaluate the number days alive and intensive care-free
- To evaluate the number of days alive and ventilator-free
- To evaluate the number of days with minimum SpO_2/FIO_2 ratio or $PaO_2/FIO_2 > 300$
- To evaluate the number of days alive without vasopressor/catecholamine support
- To evaluate the incidence of mean arterial pressure < 65 mmHg on optimized vasopressor therapy
- To evaluate the number of days alive with a SOFA score of 6 or less
- To evaluate the percentage of subjects with an increase in mean arterial pressure of 10 mm Hg or more at the end of more than one infusion of GC4419

Exploratory:

- To assess levels of circulating cytokines IL-6, TNF-alpha, IL-1 beta, IL-10
- SARS-CoV-2 viral load by PCR testing for viral RNA
- To assess the plasma exposure to GC4419 in the study subjects

Methodology:

COV-4419-201 will be a randomized study to evaluate GC4419 administered IV to subjects with confirmed SARS-CoV-2 infection and critical pulmonary disease.

To help ensure balanced randomization, subjects will be stratified at randomization for age < 60 years vs >=60 years

All subjects will receive standard supportive care according to the policies of the treating institution.

Subjects will be randomized in a 1:1 ratio to receive either:

- GC4419 by IV infusion q 12 hours (+/- 2 hours) for 7 days, plus standard supportive care, or
- Placebo by IV infusion q 12 hours (+/- 2 hours) for 7 days, plus standard supportive care

Rationale for GC4419 dosing plan:

- Extensive clinical experience in cancer patients supports the safety of 90 mg of GC4419 administered over 60 minutes for 35 doses (M-F, up to 7 weeks) concurrently with chemoradiotherapy.
- C_{max}-related transient mild hypotension and orthostasis has been observed at the current 90 mg/60-minute infusion schedule, but this is less frequent with lower doses.
- Therefore, administering 90 mg of GC4419 IV over 180 minutes (3 hours) is expected to provide an additional margin of safety.
- The plasma half-life of GC4419 is approximately 2 hours.
- Pharmacokinetic results to date do not indicate significant plasma accumulation of GC4419 with repeated dosing.

- Results of GLP animal toxicology studies support a total daily dose of GC4419 up to 198 mg, administered for up to 14 days (compared with planned 7 days in the current study).
- Administration of a related dismutase mimetic to rats in the zymosan and *E. coli* sepsis models was performed over a period of several hours after challenge with zymosan or *E. coli*. Moreover, the persistent superoxide production is expected to be associated with the ongoing COVID-19 disease process. Accordingly, a dosing schedule that maintains extracellular concentrations of GC4419 as much as possible and feasible may be desirable.

In light of the above, subjects will receive, in a blinded fashion, either GC4419, 90 mg intravenously, or placebo, administered over 3 hours (180 minutes), repeated every 12 hours (+/- 2 hours) for 7 consecutive days.

Subjects requiring renal dialysis should not have that procedure performed at any time during GC4419/placebo infusion and until at least 2 hours after infusion. If continuous renal replacement therapy is required for >24 hours, dosing with blinded GC4419/placebo will be discontinued.

Adverse Events and Serious Adverse Events will be assessed daily during dosing of GC4419/placebo, then daily during hospitalization and weekly after hospital discharge, for a total of 30 days after the last dose of GC4419/placebo. Post-dosing AE assessment may be done on an outpatient basis for subjects who are discharged from the hospital.

Ongoing safety results will be monitored by an independent Data Monitoring Committee (DMC) that will operate under a specific DMC charter separate from this protocol document.

Number of patients (planned):

Approximately 50 subjects, 25 receiving GC4419 and 25 receiving placebo.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Laboratory-confirmed SARS-CoV-2 infection as determined by a positive PCR test documented prior to randomization:
    a. Performed on a swab sample from the nasopharynx of a non-intubated subject or pulmonary secretions from an intubated subject per site's standard practice
    b. Analyzed by a commercial, local, or public health laboratory
    c. A duplicate swab will be retained for subsequent confirmation at a Central Laboratory
2. Requirement for intensive inpatient hospital care
3. Acute hypoxemic respiratory failure typifying ARDS, as indicated by:
    a. PaO_2/FiO2 ratio < 300 mm Hg, or SpO_2 < 94% on FiO_2 >/= 50% with bilateral pulmonary infiltrates along with respiratory distress and increased work of breathing requiring intubation and invasive mechanical ventilation, OR
    b. Non-invasive mechanical ventilation with SpO_2 < 94% on FiO_2 >/= 50%
4. Adequate liver function as indicated by:
    a. Total bilirubin ≤ 1.5 x upper-normal limit (ULN)
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
5. Age 18 years or older

6. Serum or urine pregnancy test negative for females of childbearing potential
7. Properly obtained informed consent obtained from subject or legally authorized representative

Exclusion Criteria:

1. Expected survival for less than 48 hours after randomization
2. Child-Pugh stage C hepatic impairment and/or portal hypertension secondary to cirrhosis
3. Stage IV chronic kidney disease or end-stage kidney disease on maintenance hemodialysis
4. Requirement for extra-corporeal membrane oxygenation (ECMO)
5. Acute Myocardial Infarction (AMI)
6. Active bleeding requiring transfusion
7. Concurrent participation in another clinical trial of experimental treatment for SARS-CoV-2
   Note: Concurrent participation in any study of an approved treatment, or a product with Emergency Use Authorization for COVID treatment, is permitted if the Principal Investigator attests that the mechanism of the EUA product is not expected to interfere with the mechanism of GC4419 and that completion of study requirements for this protocol will not be compromised
8. Female patients who are pregnant or breastfeeding
9. Requirement for concurrent treatment with nitrates

Investigational product, dosage and mode of administration:

GC4419 (avasopasem manganese) is formulated as a clear solution at a concentration of 9 mg/mL in 26 mM sodium bicarbonate-buffered 0.9 wt. % saline for parenteral administration (drug product). GC4419 will be presented in single use vials. Vials will be filled with 11 mL of GC4419, of which 10 mL will be added to 170 mL of normal saline, for IV administration over 180 minutes every 12 hours (+/- 2 hours) for 7 consecutive days.

Duration of treatment:

Seven (7) days.

Reference therapy, dosage and mode of administration:

Placebo will be normal saline and will obtained from site stock.

Placebo, 180 mL, will be administered in blinded fashion via IV administration over 180 minutes every 12 hours (+/- 2 hours) for 7 consecutive days.

Clinical Laboratory Assessment: Local clinical laboratories will be used for standard clinical laboratory assessment. A reference laboratory will be designated for exploratory laboratory endpoints.

Criteria for evaluation:

- Adverse Events and Serious Adverse Events—MedDRA classification

- Clinical observation of ON or OFF ventilator
- Clinical observation: IN intensive care unit or NOT
- Minimum SpO_2/FIO_2 ratio or PaO_2/FIO_2—recorded once per 24-hour period (midnight to midnight)
- Clinical observation of ON or OFF vasopressors in any 24-hour period (midnight to midnight)
- Standard clinical evaluations of oxygenation and blood pressure
    - Mean arterial pressure
    - SpO_2/FIO_2 ratio or PaO_2/FIO_2 as clinically applicable
- Standard ventilatory parameters
- Sequential Organ Failure Assessment (SOFA) score (in ICU only)
- Apache IV score (at baseline only)
- Daily fluid balance
- Hematology and serum chemistry per standard of care

The following assessments will be performed specifically for this research:

- Circulating cytokine levels: IL-6, IL-1beta, TNF-alpha, IL-10
- Quantitative PCR for viral load

Safety Monitoring and Toxicity Management:

Adverse/Serious Adverse Event assessments per GCP standards. Severity of events will be graded according to the NCI-CTCAE v 5.0.

For any given subject, study drug infusions should not begin if the subject's mean arterial pressure (MAP) is less than 65 mmHg.

For any given subject, hold blinded GC4419/placebo and reduce by 25% (from the initial dose) for all future infusions if:

- During infusion or within 1 hour of completing infusion, the subject experiences an acute decrease in systolic blood pressure requiring bolus fluid resuscitation OR requiring initiation of vasopressor therapy OR increased vasopressor therapy. Hold GC4419/placebo until the dose of vasopressor therapy is stable and bolus fluid resuscitation is not required.
- The subject develops serum creatinine > 5 mg/dL. Hold GC4419/placebo until the creatinine is =<5 mg/dL.
- The subject develops serum total bilirubin > 6 mg/dL, or AST or ALT >10 times upper limit of normal. Hold GC4419/placebo until the parameters in question are below these levels.
- The subject experiences a serious or severe adverse event considered by the investigator to be related or possibly related to blinded GC4419/placebo. Hold GC4419/placebo until the event is no longer serious or severe.

Up to two such dose reductions for a cumulative 50% from the initial dose of GC4419/placebo will be permitted for a given subject. If a subject cannot tolerate GC4419/placebo infusion after a 50% dose reduction, all dosing with GC4419/placebo for that subject will be discontinued.

Patients unable to tolerate GC4419/placebo must discontinue treatment with GC4419/placebo but should continue with other protocol assessments at the discretion of the treating investigator and with the ongoing consent of the subject.

An independent Data Monitoring Committee (DMC) will monitor ongoing safety results. The DMC will promptly receive all reports of Serious Adverse Events (SAEs). The DMC will also be convened for review of available safety data after 20 subjects have completed blinded dosing of GC4419/placebo, and may convene other meetings at its discretion. If upon review the DMC finds that more than 20% of experimental arm subjects require that GC4419 be discontinued according to the rules in this section, OR if the DMC finds an increase in serious or severe adverse events sufficient to constitute an unacceptable safety risk associated with GC4419, all dosing of GC4419/placebo for subjects on study will be discontinued, enrollment to the study will be terminated, and data reviewed with FDA prior to the sponsor considering additional dosing with GC4419 in this patient population.

Concomitant Medications/Treatments:

Investigators may prescribe any concomitant medication or supportive therapy deemed medically indicated for the care of the subject, with exception of the following prohibited medications/treatments:

- Nitrates, phosphodiesterase type 5 (PDE 5) inhibitors (e.g., sildenafil, tadalafil, or similar agents) or other concomitant drugs that in the judgment of the treating investigator could create a risk of a precipitous decrease in blood pressure are prohibited until at least 24 hours after the last dose of blinded GC4419/placebo.
- Concurrent participation in a clinical trial of investigational therapy for SARS-CoV-2.
    - *Other approved or unapproved agents for SARS-CoV-2, including drug or biologic therapy including immunomodulatory treatments, administered on an expanded access, compassionate care, off-label, or emergency access basis may be administered. Use as part of another, concurrent clinical trial may be considered provided the site principal investigator determines that the mechanism of the other treatment is not expected to interfere with the mechanism of GC4419, and that completion of study requirements for this protocol will not be compromised.*
    - *Examples of acceptable concurrent medications under this provision include remdesivir, hydroxychloroquine (alone or with azithromycin) convalescent plasma, and other drug or biologic treatments for SARS-CoV-2 as long as not part of a clinical trial other than the present trial.*

Statistical considerations:

For this group with critical disease, the null hypothesis is that 50% of subjects will survive for 28 days. The alternative hypothesis is that at least 90% of subjects receiving GC4419 will survive for 28 days compared with the control survival of 50%. A sample size of 50 subjects, 25 in each group, is expected to provide approximately 80% power to detect this difference with a two-sided alpha of 0.05.

Subjects' treatment assignment will be stratified at randomization for age < 60 years vs ≥ 60 years.

The primary endpoint of 28-day mortality will be compared between the GC4419 and control group using an exact Cochran-Mantel-Haenszel (CMH) test stratified by age group (<60 vs ≥60 years) at the two-sided 0.05 Type I error rate. The measure of association will be the CMH stratified relative risk of death by Day 28 along with an asymptotic 95% exact confidence interval. Secondary endpoints will be analyzed descriptively, and results tabulated. As appropriate, percentages and 95% confidence intervals will be calculated.

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

CLINICAL STUDY PROTOCOL 1
1. SYNOPSIS 5
2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 14
3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 17
4. INTRODUCTION 18
4.1. Background 18
4.1.1. COVID-19 and Associated Respiratory Disease 18
4.1.2. Superoxide and Superoxide Dismutase Mimetics in Viral Pneumonia, ARDS and Septic Shock 18
4.1.3 Dismutase Mimetic Nonclinical Pharmacology and Mechanism of Action 20
4.2. Avasopasem Manganese (GC4419) 22
4.3. Rationale for the Present Trial 24
5. TRIAL OBJECTIVES AND PURPOSE 26
5.1. Primary Objective 26
5.1.1. Rationale for Primary Endpoint Selection 26
5.2. Secondary Objectives 26
5.3. Exploratory Objectives 26
6. INVESTIGATIONAL PLAN 27
6.1. Overall Study Design 27
6.2. Treatment Plan and Duration of Therapy 27
7. SELECTION AND WITHDRAWAL OF SUBJECTS 29
7.1. Subject Inclusion Criteria 29
7.2. Subject Exclusion Criteria 29
7.3. Rationale for Patient Population 30
7.4. Screen Failures 30
7.5. Subject Withdrawal Criteria 30
7.6. Study and Site Closure 31
8. INVESTIGATIONAL PRODUCT AND TREATMENT OF SUBJECTS 32
8.1. Concomitant Medications 32
8.1.1. Drug Interactions 32
8.2. Prohibited Medications 32
8.3. Description of Study Drug GC4419 33
8.3.1. GC4419 Drug Packaging and Labeling 33
8.3.2. Placebo Packaging and Labeling 33
8.3.3. Study Drug Storage 34
8.3.4. Study Drug Preparation 34
8.3.5. Administration 34
8.3.6. Accountability and Compliance 34

8.3.7. Study Drug Handling and Disposal 35
9. TOXICITY MANAGEMENT 36
9.1. Anticipated toxicities of GC4419 36
9.2. Dose Delays and Dose Modifications for Toxicity 36
9.3. Supportive Care Guidelines 36
10. ASSESSMENTS 38
10.1. Safety Assessments 38
10.1.1. Clinical Assessments 38
10.1.2. Laboratory Assessments 38
10.2. Schedule of Time and Events 39
10.2.1. Screening Phase 39
10.2.2. Hospitalization/Treatment Phase 39
10.2.3. Post ICU Discharge 40
10.3. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS 40
10.4. Definitions 40
10.4.1. Adverse Event (AE) 41
10.4.2. Serious Adverse Event (SAE) 41
10.5. Adverse Event Reporting Requirements 42
10.5.1. Serious Adverse Events 42
10.5.2. All Adverse Events (AEs) Regardless of Seriousness 42
10.5.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs 42
10.5.4. Grading of Adverse Events 43
10.6. Relationship to Study Drug 43
10.7. Recording Adverse Events 44
10.8. Follow-up of AEs and SAEs 45
10.9. Post-Study Reporting Requirements 45
10.10. Pregnancy 45
10.10.1. Time Period for Collecting Pregnancy Information 46
10.10.2. Action to be Taken if Pregnancy Occurs in a Female Partner of a Male Patient 46
10.11. Regulatory Reporting of Adverse Events 46
11. STATISTICS 48
11.1. General Considerations 48
11.2. Sample Size 48
11.3. Randomization and Stratification 48
11.4. Analysis Populations 48
11.5. Definition of Endpoints 48
11.5.1. Primary Endpoint 48
11.5.2. Secondary Efficacy Endpoints 48
11.5.3. Exploratory Endpoints 49
11.6. Safety Analysis 49

11.6.1. Interim Safety Analysis....49
11.7. Primary Efficacy Analysis....49
11.7.1. Primary Analysis....49
11.7.2. Secondary and Exploratory Analyses....49
12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS....50
12.1. Study Monitoring....50
12.2. Audits and Inspections....50
12.3. Protocol Compliance....51
12.4. Protocol Modifications....51
12.5. Information Disclosure....51
12.5.1. Ownership....51
12.5.2. Confidentiality....51
12.5.3. Publication....52
13. QUALITY CONTROL AND QUALITY ASSURANCE....53
14. ETHICS....54
14.1. Ethical Conduct of the Study....54
14.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Board (REB) Approval....54
14.3. Written Informed Consent....54
14.4. Data Monitoring Committee....54
15. DATA HANDLING AND RECORDKEEPING....56
15.1. Case Report Forms....56
15.2. Retention/Inspection of Records....56
16. LIST OF REFERENCES....57
APPENDIX 1. SCHEDULE OF ASSESSMENTS....58
APPENDIX 2. SEQUENTIAL ORGAN FAILURE ASSESSMENT....60
APPENDIX 3. GLASOW COMA SCALE SCORE CRITERIA....61
APPENDIX 4. EXAMPLES OF CYP2D6-SUBSTRATE DRUGS....62

LIST OF TABLES

Table 1. Abbreviations and Specialist Terms....17
Table 2 Comparison of PK/TK Results Among Human Volunteers, Rat and Dog Studies....23
Table 3: Adverse Event Severity....43

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1. Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Definition
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
APACHE	Acute Physiology and Chronic Health Evaluation
BED	biologically equivalent dose
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CRF	case report form
Dmax	maximum dose
Dmean	mean dose
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
MAP	Mean arterial (blood) pressure
SOFA	Sequential organ failure assessment score
OM	oral mucositis
PDE	phosphodiesterase type 5
PK	Pharmacokinetic
REB	Research Ethics Board
SAE	serious adverse event
SOD	superoxide dismutase
SOM	severe oral mucositis

4. INTRODUCTION

4.1. Background

4.1.1. COVID-19 and Associated Respiratory Disease

Approximately 20% of people with confirmed, symptomatic COVID-19 disease, due to infection with the SARS-CoV-2 virus, will develop viral pneumonia requiring hospitalization. These patients exhibit respiratory compromise that can be characterized as severe (demonstrating dyspnea, hypoxia, and/or extensive lung opacities on chest x-ray); or critical, with respiratory failure, which may be accompanied by shock or multiorgan dysfunction). Approximately 25% of hospitalized patients, comprising approximately 5% of all patients with symptomatic infection, will have critical disease as described herein. Critical disease often manifests as a clinical picture consistent with the acute respiratory distress syndrome (ARDS), although information is still being obtained regarding the pathophysiology and pathophysiology of pulmonary compromise associated with SARS-CoV-2, compared with ARDS related to other causes. Retrospective series suggest that, after a variable initial course of disease, dyspnea begins approximately 6-7 days after the first symptoms of infection, with swift progression to frank respiratory failure/ARDS 2-3 days thereafter. Intensive care is often required for 14 days or more, and more than one attempt at ventilator weaning may be required before eventual extubation. Comorbidity among these critically ill patients includes renal, cardiac, and hepatic damage as well as hypotension requiring vasopressor treatment (Yang et al, 2020). Mortality for critically ill patients, highest among the elderly or those with significant prior concomitant conditions, has been reported to be on the order of 50-60% (Yang et al, 2020; Wu et al 2020). The IHME has recently projected that, assuming full social distancing throughout the United States through May 2020, nationwide needs for hospital beds and ICU beds will exceed national capacity (https://covid19.healthdata.org/projections, accessed 15 April 2020, 12 noon EDT) Further, pending effective treatments or vaccine(s), potential remains for recurrent waves of infection and the attendant needs for hospital resources.

4.1.2. Superoxide and Superoxide Dismutase Mimetics in Viral Pneumonia, ARDS and Septic Shock

Superoxide (O_2•-) plays a central role in initiation of numerous pathologic processes. Under normal circumstances O_2•- is a by-product of mitochondrial cellular respiration and is also produced by activated phagocytes. Since O_2•- is extremely reactive with biological molecules, it is quite toxic to cells. In all studied species, this potentially toxic O_2•- burden is normally contained by a complement of superoxide dismutase (SOD) enzymes. In vertebrates, SOD enzymes are present in the cytoplasm (SOD1 Cu/Zn based), mitochondria (SOD2, Mn based) and extracellular spaces (SOD3, Cu/Zn based). Superoxide dismutases are a class of oxidoreductase enzymes that convert superoxide into molecular oxygen and hydrogen peroxide.

The control of the free radical flux derived from oxygen is jeopardized in many circumstances in which superoxide production is excessive or if the breakdown of superoxide is compromised. This over-production of superoxide can overwhelm the body's ability to eliminate it via catalytic dismutation and lead to a variety of superoxide initiated or mediated disease states, including mucositis.

Normal cells counter the damaging effects of O_2•- by detoxifying ROS via their intact redox protective enzyme systems (SOD, catalase, glutathione peroxidase), converting hydrogen peroxide into water and molecular oxygen, and by the activation of DNA repair mechanisms.

Extensive literature suggests that O_2•- may play multiple roles in viral infection and related pulmonary pathologies, including for the respiratory influenza and coronaviruses. The exact mechanisms involved are still debated. For example, does the virus elevate O_2•- levels to aid virus proliferation, does O_2•- via a hyperactivated immune response drive airway damage, is it both or are there other mechanisms also involved? At the same time, it can be hypothesized that other non-pulmonary inflammatory pathologies in severe respiratory viral disease are similarly driven or exacerbated by O_2•-. Not surprisingly then, overexpression of superoxide dismutases (SOD), the enzymes which remove O_2•- by converting it to hydrogen peroxide (H_2O_2) have also been shown in several studies to inhibit viral infection and pulmonary damage.

A number of researchers have reported various ways that O_2•- can play one or more roles in viral infections including HIV [1-5], HCV [6-10], hemorrhagic fevers [11], influenza [12-25] and coronaviruses [25-26]. For some virus classes O_2•- may play a direct role in virus proliferation, aiding replication [2,15-18,23-24,26] or cell to cell spread [4]. And there is evidence that virus proteins may directly increase O_2•- levels in infected or bystander cells to enlist these pathways [1,3-4,6-10,13-14,17-19].

For all these classes, host response to infection and organ damage clearly involves O_2•-. Researchers report that viral infection appears to elevate intracellular O_2•-, perhaps as part of a proliferative role, directly driving host cell apoptosis [1,7-8.11,19]. In fact, the production of substantial amounts of O_2•- by influenza infection is so well-known that it has been demonstrated as a robust way to assay infection in egg-based avian flu vaccine production [21]. Incidentally, this intracellular elevation might explain part of the reason older patients, without other underlying co-morbidities, disproportionately suffer more severe disease, as recent research has shown that accumulating mitochondrial dysfunction with age renders cells from older humans more susceptible to damage by intracellular O_2•- [27].

Most significantly, especially in respiratory viral disease, the immune response to extensive infection produces massive O_2•- bursts from various monocytic and polymorphonuclear leukocytes. These O_2•- bursts may be an essential part of the immune response to viral infection, either for immune cell recruitment or, when further converted to H_2O_2 and hypochlorous acid (HOCl), for direct action against the virus [28,29]. However, when this inflammatory production of O_2•- is excessive and prolonged it leads to host cell death and tissue damage [20,23,28,29]. This excessive and prolonged production of O_2•- then can become part of a vicious cycle sometimes referred to as cytokine storm, as superoxide not only damages host tissue, but also drives release of pro-inflammatory cytokines such as TNFα, IL-1β & IL-6 [16,18,20,23] and other chemotractants at the site. In the process membrane lipid oxidation also occurs, leading to activation of TLR4 and via that of NADPH oxidase (NOX) enzymes which produce even more O_2•- [25,28-29]. In turn this exacerbates the hyperactive immune response leading to increased generation of O_2•- [28]. For respiratory-targeting viruses this leads to and exacerbates acute lung injury and ARDS.

As O_2•- has been shown to drive similar tissue injury and inflammatory damage patterns in other organs [6,30-35] it is possible that similar biology is involved in viral pathologies in these other sites, such as kidney or heart.

By a somewhat different mechanism, O_2•- has also been shown to be at least partially responsible for the inability to maintain blood pressure and adequate perfusion in so-called (bacterial) "septic shock" [36-38]. In this situation, O_2•- generated by the hyperinflammatory response to septicemia initiates the auto-oxidation of catecholamines such as epinephrine, norepinephrine & dopamine, leading to self-perpetuating refractory hypotension. In animal models of LPS and live bacteria-induced refractory hypotension, the oxidation of the catecholamines produces a characteristic set of toxic end-products, adrenochromes [36], which a clinical observation study also strongly correlated to the presence of septic shock [39]. While some case reports suggest a similar refractory hypotension, it is unclear whether this is an issue for many critically ill COVID-19 patients.

Given the role of O_2•-, it is not surprising that superoxide dismutases (SOD), enzymes which remove O_2•- by converting it to H_2O_2, inhibit the viral infection roles attributed to O_2•-. Via overexpression, exogenous administration and knock-down, the SOD enzymes have been shown to inhibit viral infection [2,4,15,17-18,24], and even more so to robustly decrease inflammatory cell infiltration, pro-inflammatory cytokine release, lung damage and related pulmonary pathologies in response to viral infection [18,22-24]. Much of this work has been done with Influenza A, though parallel results have been shown in avian flu and even coronaviruses. Using exogenous or recombinant SOD enzymes, however, is limited by the challenges facing pharmacologic use of large, multi-subunit proteins as therapeutics, as well as the fact that they can be inactivated under the very conditions they may be intended to treat.

Interestingly, the product of O_2•- dismutation, H_2O_2, is well established as a very effective viral disinfectant and even antiviral [40-45]. In fact, it was first reportedly used successfully against influenza in patients in 1920 [40], and subsequent studies suggest that both influenza and coronaviruses may be particularly susceptible to it [41-42,44]. As a result, the conversion O_2•- to H_2O_2 in a patient with advanced viral pulmonary involvement should not interfere with controlling their infection. It should be noted, however, that its use directly has been thwarted by the portfolio of enzymes, particularly abundant catalase that make it difficult to maintain a therapeutic systemic concentration [45].

4.1.3 Dismutase Mimetic Nonclinical Pharmacology and Mechanism of Action

Galera's manganese pentaaza-macrocycles (MnPAMs) are small molecule dismutase mimetics that can overcome the limitations to using SOD enzymes. They have a similar ability to rapidly convert O_2•- to H_2O_2 as MnSOD [46], on the order of 10^7 molecules of O_2•- per second per dismutase molecule, which is essential to dispose of superoxide before it can initiate tissue damage. Just like the SOD enzymes, they only dismutate O_2•- to H_2O_2, a feature critical to avoiding off-target activity of the dismutase mimetics [47]. As such, they may offer an attractive option to pharmacologically curb O_2•- and treat the severe consequences of SARS-CoV2 pneumonia.

Consistent with the biology described above for O_2•- and SODs, the MnPAM dismutase mimetics have shown potent protective activity in multiple acute lung injury models. In the zymosan i.p. rat model, Galera's MnPAM dismutase mimetic GC4401 reduced zymosan-induced lung neutrophil infiltration, lipid peroxidation and lung injury, TNFa and IL-1b plasma levels, and mortality [34]. Similarly, in the bleomycin i.t. mouse model, another dismutase mimetic, avasopasem, reduced lung inflammatory infiltrates and alveolar epithelial apoptosis [48]. In other lung inflammatory injury models, GC4403 (the enantiomer of avasopasem) reduced neutrophil infiltrate, lipid peroxidation and alveolar epithelia apoptosis in a chronic asthma guinea pig model [49], and also reduced neutrophil infiltrate and lipid peroxidation in a splanchnic artery reperfusion inflammatory shock model [50] while GC4419 blocked late stage pulmonary fibrosis in a lung focal radiation mouse model [51]. Intriguingly, GC4419 worked in this model both when given around the time of the irradiation or starting after the injury, suggesting that it can inhibit an ongoing inflammatory damage cycle. In a related model oral mucosa focal radiation hamster model, both GC4403 & GC4419 reduced tissue damage in the form of severe oral mucositis (OM) [35, 52]. Importantly this OM result has now been reproduced in clinical studies, which likely involves reducing both the initial tissue insult and resulting inflammatory response [53,54].

Galera's MnPAM dismutase mimetics have also demonstrated the ability to reduce key pro-inflammatory cytokines in ARDS including TNFa, IL-1b & IL-6. In addition to suppressing zymosan-induced increases in TNFa and IL-1b plasma levels [34], they blocked production of TNFa and IL-6 in LPS-stimulated rat alveolar macrophages while also suppressing NF-kB activation [55]. Similar results have been demonstrated in live E. coli-induced refractory hypotension with plasma TNFa, IL-1b & IL-6 being reduced while the anti-inflammatory cytokine IL-10 was increased [37], collagen-induced arthritis with TNFa & IL-1b being reduced [56], splanchnic artery occlusion/reperfusion with TNFa & IL-1b being reduced [56], and in several other models of inflammatory disease and tissue damage. Whatever the initiating insult or target organ, these inflammatory models consistently show that Galera's dismutase mimetics, reduce inflammatory cell infiltration (including lung, even if not the target organ), lipid peroxidation, key cytokines, cell apoptosis and organ injury, and where appropriate increase survival.

Based on case reports from the current COVID-19 outbreak, three additional nonclinical findings may also be important in subsets of patients. First, based on the understanding that in the hyperinflammatory state, O_2•- can initiate the auto-oxidation of catecholamines, leading to self-perpetuating refractory hypotension, the MnPAM dismutase mimetics have been shown in multiple models to restore response to vasopressor therapy and maintain mean arterial blood pressure [36-38]. It is unclear how broadly refractory hypotension is an issue for critically ill COVID-19 patients, however renal failure does seem to be a substantial issue. While renal failure may be due to compromised circulation (perhaps stemming from refractory hypotension), acute kidney injury has also been linked directly to O_2•- and such injury is reduced by the MnPAM dismutase mimetics in models of direct injury by cisplatin and of the zymosan-induced inflammatory response [30,34]. In addition, in a randomized Phase 2 setting, post hoc analysis suggests that GC4419 reduces chronic kidney disease in cisplatin-treated patients [57]. Finally, analogous to lung injury models discussed above, in myocardial injury models, GC4403 reduced O_2•-, neutrophil infiltrate, lipid peroxidation and myocardial damage, while significantly improving cardiac function post-ischemia/reperfusion, transplant or hyperglycemia [58-61], suggesting that a MnPAM dismutase mimetic might also reduce cardiac myopathy seen in some

critically ill COVID-19 patients. Further, MnSOD overexpression reverses pulmonary hypertension (PAH) in the fawn-hooded rat [62]. In alignment with that MnPAM dismutase mimetics have been shown to reduce PAH in hypoxic piglet and bleomycin rat models [63-66], which could also be a beneficial activity in patients with myocardial injury. Thus, beyond treating or preventing ARDS, in critically ill COVID-19 patients may offer help with refractory hypertension, renal impairment and heart failure co-morbidities.

While it can be debated what the best animal models of ARDS or of critically ill COVID-19 patients are, the nonclinical data above argue strongly for assessing the MnPAM dismutase mimetics in this indication, as well as for protection of other organs targeted by cytokine storm.

Since viral disease has not previously been a development focus for the MnPAM dismutase mimetics, there has been very little prior testing in viral disease models, either for host tissue protection or for anti-viral activity. In the one exception, GC4403 was shown to protect astrocytes from HIV-driven apoptosis, and reported to demonstrate potent antiviral activity [33,67].

Testing in SARS-CoV2-specific *in vitro* and *in vivo* models is now being planned or underway. Until such model results are available, interpolation must be made between O_2^-/SOD viral model and MnPAM dismutase mimetic non-viral model experimental data.

4.2. Avasopasem Manganese (GC4419)

Avasopasem manganese (avasopasem) is a highly-selective, small molecule (MW 483) mimetic of naturally occurring superoxide dismutase (SOD) enzyme, which, like native SOD, converts superoxide to hydrogen peroxide and molecular oxygen specifically and selectively, at an enzymatic rate comparable to that of the native SOD. It is being developed for reduction of the incidence and severity of SOM (severe oral mucositis) induced by RT, without systemic therapy, in patients with head and neck malignancies, under IND 111,539 with the Division of Dermatology and Dental Products, United States Food and Drug Administration (FDA).

In disease states characterized by excessive superoxide production, administration of avasopasem replaces or augments deficient or insufficient endogenous SOD capacity. Accordingly, avasopasem and related active dismutase mimetics have demonstrated ability to protect tissues from superoxide-mediated damage in laboratory studies and in the clinic. As noted in Section 4.1.3, relevant non-clinical studies include: reduced zymosan-induced lung neutrophil infiltration, lipid peroxidation and lung injury, and mortality (Cuzzocrea et al, 2004); in the bleomycin intratracheal mouse model, reduced lung inflammatory infiltrates and alveolar epithelial apoptosis (Herzog, 2014); in a chronic asthma guinea pig model, reduced neutrophil infiltrate, lipid peroxidation and alveolar epithelia apoptosis (Masini et al, 2005); and in a lung focal irradiation mouse model, reduced late stage pulmonary fibrosis (Sishc et al, 2018). Results from animal studies also include reduction of *E. coli*-induced hypotension, vascular hyporeactivity to catecholamines, and mortality in septic shock (Macarthur et al, 2003), and decreased levels of proinflammatory cytokines such as TNFα, IL-1β and IL-6 (Cuzzocrea et al 2004; Macarthur et al, 2003), with increase in the anti-inflammatory cytokine IL-10 (Macarthur et al, 2003). In these studies, dismutase mimetic was administered continuously or repeatedly over several hours after challenge with zymosan or *E. coli* (Cuzzocrea et al 2004; Macarthur et al, 2003). In a hamster model, avasopasem reduced severe oral mucositis (Sonis, unpublished

data, GC4419 Investigator's Brochure), supporting clinical trials of avasopasem to reduce radiation-induced severe oral mucositis. In Phase 1-2b clinical trials (Anderson et al 2018; Anderson et al 2019), GC4419 reduced the incidence, severity, and duration of severe oral mucositis produced from the superoxide generated due to concurrent chemoradiotherapy for head and neck cancer, with an acceptable safety profile, and a confirmatory Phase 3 trial (NCT03689712) in this indication is underway under Breakthrough Therapy Designation from FDA.

GC4419 has been safely administered to over 300 human subjects, with the Phase 3 oral mucositis trial testing 90 mg by 60-minute IV infusion, repeated each weekday, prior to standard radiotherapy, for 7 weeks—a total of up to 35 doses. Toxicity attributable to GC4419 has been limited to transient, infusion-related mild hypotension and postural symptoms, and mild circumoral paresthesia, attributable to reversible potentiation of nitric oxide. These effects appear to be related to the C_{max} (which occurs at the end of the IV infusion), and are further limited with lower doses or prolonged infusion time at a given dose, with mild orthostatic lightheadedness reported in 6 of 72 healthy volunteers who have received 27 mg of GC4419 over 60 minutes, and 5 of 34 healthy volunteers who received 30 or 51 mg of GC4419 IV over 15 minutes. Adverse events observed in the oral mucositis trials have been those observed with the underlying standard regimen of radiation therapy plus cisplatin, and in a placebo-controlled randomized Phase 2b trial, the adverse event profiles for subjects receiving GC4419 or placebo were similar.

No effect on the QT interval was found in a precision QT clinical trial of GC4419 at a dose of 51 mg IV over 15 minutes, a dose and schedule at which C_{max} exceeds that produced after a 90 mg/60-minute infusion of GC4419.

Nonclinical GLP toxicology studies of avasopasem in rats and dogs have shown no abnormal histopathologic findings except for injection-site reactions after subcutaneous administration. These studies include 6-month chronic toxicology in rats (final report pending). A 9-month chronic toxicology study in dogs is in progress in the in-life phase.

A 14-day repeat dose GLP toxicology study in Sprague-Dawley rats with GC4419 administered as a 15-minute intravenous infusion resulted in a bi observed adverse effect level (NOAEL) of 15 mg/kg/day and a calculated HED of 145 mg/day [(15 mg/kg/ 6.2) x 60 kg]. A similarly designed study in beagle dogs resulted in a NOAEL of 5 mg/kg/day and a calculated HED of 167 mg/day [(5 mg/kg/1.8) x 60 kg].

Additionally, toxicokinetic results from the 14-day rat study resulted in GC4419 plasma exposures (C_{max} and AUC_{last}) that when compared to the GC4419 plasma exposures from the Sponsor clinical study GT-001 (90 mg /day), resulted in a AUC-based safety margin of 2.2, further supporting an HED of 198 mg/day (Table 2).

Table 2 Comparison of PK/TK Results Among Human Volunteers, Rat and Dog Studies

Species	Dose	HED (mg/kg)	HED (mg)	C_{max} (ng/mL)	AUC_{last} (ng*hr/mL)	AUC vs AUC Margin	HED (mg)
[1]**Human**	90 mg	-		3650	7160	-	-
[2]**Rat**	15 mg/kg	2.4	145	17,100	15,980	2.2	198

[1]Human data from: Phase 1b/2a trial GT-001, Week 3, Day 3

[2]Rat data from 14d repeat dose (15 min infusion): Day 1 (M + F). Dose reported was the NOAEL.

The Sponsor has also conducted 60-day GLP repeat dose toxicology studies (60-minute infusions) in rat and dog which yield HED of 77 mg/day and 333 mg/day, respectively, based on preliminary assessment of NOAELs based on in-life reports of reduced weight gain and food consumption (full reports pending).

Avasopasem has a plasma half-life of approximately 2 hours, reaching maximum concentration at the end of IV infusion and declining in a bi-exponential fashion thereafter. Plasma exposure is approximately dose-proportional. In past clinical trials, has been quantifiable in plasma up to approximately 24 hours after a 60-minute IV infusion, with minimal accumulation in plasma with repeated daily dosing. Non-clinical data indicate a longer half-life of avasopasem in tissues, with rapid entry into cells related to C_{max} and slower release from cells.

Pharmacokinetic modeling based on human data for a 60-minute IV infusion of 90 mg of GC4419 predicts no increase in C_{max} provided the second dose in a day occurs at least four hours after the first dose, important since the primary acute toxicity associated with GC4419 appears to be related to C_{max} related hypotension.

Avasopasem is eliminated by GI and renal routes. Human volunteer studies of GC4419 in the setting of compromised renal or hepatic function are in progress. There has been no apparent nephrotoxicity or hepatotoxicity of avasopasem in human clinical trials.

See the Investigator's Brochure for additional background information about GC4419.

4.3. Rationale for the Present Trial

The pathogenesis of severe-to-critical pulmonary disease complicating SARS-CoV-2 infection—and, when it occurs, the pathogenesis of attendant shock—along with the mechanism and available nonclinical and clinical data with avasopasem, suggest that GC4419 could attenuate or reduce the risk of ARDS and the need for mechanical ventilation, and attenuate shock, in people suffering from them due to SARS-CoV-2.

With the same extraordinarily fast and specific activity in converting O_2- to H_2O_2 as the SOD enzymes, avasopasem and other manganese pentaaza-macrocycles (MnPAMs) being developed by Galera are true small molecule dismutase mimetics. As such, they may offer an attractive option to pharmacologically harness this biology and treat the severe consequences of viral pneumonia, such as in the current COVID-19 pandemic. Aligned with the O_2- and SOD experimental reports, nonclinical models with the MnPAM dismutase mimetics demonstrate potent protective activity in acute lung injury models perhaps representative of acute respiratory distress syndrome (ARDS). Nonclinical data and mechanism also support a potential role for these candidates in addressing other co-morbidities such as kidney injury and cardiac myopathy, and the refractory hypotension and hemodynamic instability that present in some late-stage patients.

The MnPAM dismutase mimetics have seen only limited testing in viral disease models, either for host tissue protection or for anti-viral activity. Such testing is now being planned or underway. Until such model results are available, interpolation must be made between O_2-/SOD viral model and MnPAM dismutase mimetic non-viral model experimental data.

Galera has identified several potential clinical applications of GC4419 in the setting of SARS-CoV2 infection/COVID-19 in hospitalized patients. First among these is the prevention/reduction of ARDS and long-term related lung pathologies, based on protection of airway tissue from inflammatory injury demonstrated in multiple models (along with reduction

in inflammatory cytokines including TNFa, IL-1b & IL-6), as well as SOD data in influenza pulmonary models. The second application is in an overlapping population displaying hemodynamic instability for the treatment of hypotension refractory to vasopressor therapy, based on LPS and live E. coli challenge models. Third, emerging reports of significant kidney injury and cardiac myopathy among critically ill COVID-19 patients suggest further potential roles for GC4419 in preventing inflammatory damage to these organs, based on the known action of O_2- in driving myocardial ischemia/reperfusion injury and doxorubicin cardiotoxicity, as well as cisplatin kidney injury.

For the oral mucositis indication, at the intended dose and schedule of 90 mg by 60-minute IV infusion M-F for 7 weeks, GC4419 demonstrated efficacy in the proposed indication in a randomized, double-blind, three-arm Phase 2b trial in which patients receiving standard chemoradiotherapy for locally advanced head and neck cancer received either 90 mg or 30 mg of GC4419 or placebo. GC4419 did not increase the known adverse effects of the chemoradiotherapy in this trial; the adverse event profiles for each active arm and the placebo control arm were similar.

Adverse effects attributable to GC4419 in clinical development are limited, with the principal adverse effect being mild, transient postural symptoms or hypotension at the end of the one-hour infusion, and to mild circumoral paresthesia, both attributable to transient potentiation of nitric oxide (NO). Data in humans and animals have demonstrated that these effects, which are related to C_{max}, are further limited by lowering the dose or prolonging the infusion time of GC4419.

In the present trial, fifty (50) subjects with respiratory failure and documented SARS-CoV-2 infection will be randomized, 1:1, to receive either GC4419 or placebo plus standard supportive care or standard supportive care alone. The 90 mg dose currently being tested in the Phase 3 OM trial will be used, but with GC4419/placebo infused over 180 minutes rather than 60 minutes to limit the potential for NO-related adverse events. Twice daily (q12 hour) infusion is proposed for a duration of 7 days, supported by results from animal toxicology, human pharmacokinetic data indicating little if any potential for drug accumulation in plasma, and relevant animal pharmacology studies employing drug administration over a several hour period to maintain extracellular exposure. A double-blind design will be employed.

The primary endpoints will be 28-day all-cause mortality, which is expected to be 50% or more for the control group, and safety of GC4419 in the study population. Secondary endpoints will assess safety of GC4419, ability to wean study subjects from ventilator support, ventilator-free and ICU-free days, days of minimum PaO_2/FiO_2 days < 300, days of vasopressor/catecholamine support, effects on SOFA score, and effects of GC4419 on mean arterial blood pressure. Exploratory endpoints will include SARS-CoV2 viral load, circulating cytokine levels and plasma exposure to GC4419 in study subjects.

Based on initial results from this first study, one or more subsequent trials following a similar design (randomized, double-blind, placebo-controlled) may be considered and separately proposed in the future.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

The primary objective of this study is to evaluate 28-day all-cause mortality/overall survival.

5.1.1. Rationale for Primary Endpoint Selection

Based on available reports, the target study population has a high risk of mortality and other morbidity. 28-day all-cause mortality is a standard and readily assessed primary endpoint in critically ill subjects. Additional, related outcomes (see secondary objectives) are also appropriate for observation but insufficient data exist to base a null hypothesis on those.

GC4419 has not yet been studied in this patient population, so an initial assessment of the safety of GC4419 is required.

5.2. Secondary Objectives

The following secondary objectives will be assessed through a 28-day period to align with the primary objective:

- To assess the safety of avasopasem in the study population
- To evaluate the frequency of successful ventilator weaning
- To evaluate the number of days alive and intensive care-free
- To evaluate the number of days alive and ventilator-free
- To evaluate the number of days of minimum SpO_2/FIO_2 ratio or $PaO_2/FIO_2 > 300$
- To evaluate the number of days alive without vasopressor/catecholamine support
- To evaluate the incidence of mean arterial pressure < 65 mmHg on optimized vasopressor therapy
- To evaluate the number of days alive with a SOFA score of 6 or less
- To evaluate the percentage of subjects with an increase in mean arterial pressure of 10 mm Hg or more at the end of more than one infusion of GC4419

5.3. Exploratory Objectives

- To assess levels of circulating cytokines IL-6, TNF-alpha, IL-1 beta, IL-10 before, during, and after treatment
- To assess SARS-CoV-2 viral load by PCR testing for viral RNA
- To assess the plasma exposure to GC4419 in the study subjects
- Lung compliance to be calculated from clinical data for exploratory purposes

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

COV-4419-201 will be a randomized study to evaluate GC4419 administered IV to subjects with documented SARS-CoV-2 infection and critical pulmonary disease.

Subjects will be randomized in a 1:1 ratio to receive either:

- GC4419 by IV infusion q 12 hours (+/- 2 hours), plus standard supportive care, or
- Placebo by IV infusion q 12 hours (+/- 2 hours), plus standard supportive care

To help ensure balanced randomization at a 1:1 ratio, subjects will be stratified at randomization for age < 60 years vs >=60 years

All subjects will receive standard supportive care according to the policies of the treating institution.

Adverse Events and Serious Adverse Events will be assessed daily during dosing of GC4419/placebo, then daily during hospitalization and weekly after hospital discharge, for a total of 30 days after the end of treatment. Post-treatment AE assessment may be done on an outpatient basis for subjects who are discharged from the hospital.

Ongoing safety results will be monitored by an independent Data Monitoring Committee.

6.2. Treatment Plan and Duration of Therapy

Subjects in the present trial will receive, in a blinded fashion, either GC4419, 90 mg intravenously, or placebo, administered over 3 hours (180 minutes), repeated every 12 hours (+/- 2 hours) for 7 consecutive days.

Rationale for GC4419 dosing plan:

- Extensive clinical experience in cancer patients supports the safety of 90 mg of GC4419 administered over 60 minutes for 35 doses (M-F, up to 7 weeks) concurrently with chemoradiotherapy.
- C_{max}-related transient mild hypotension and orthostasis has been observed at the current 90 mg/60-minute infusion schedule, but this is less frequent with lower doses.
- Therefore, administering 90 mg of GC4419 IV over 180 minutes (3 hours) is expected to provide an additional margin of safety.
- The plasma half-life of GC4419 is approximately 2 hours.
- Pharmacokinetic results to date do not indicate significant plasma accumulation of GC4419 with repeated dosing.
- Results of GLP animal toxicology studies support a total daily dose of GC4419 up to 198 mg, administered for up to 14 days; this is greater than the planned 180 mg per day (90 mg q 12 hours) for 7 days.
- Administration of a related dismutase mimetic to rats in the zymosan and *E. coli* sepsis models was performed over a period of several hours after challenge with zymosan or *E. coli*. Moreover, the persistent superoxide production is expected to be associated with the ongoing COVID-19 disease process. Accordingly, a dosing schedule that maintains

extracellular concentrations of GC4419 as much as possible and feasible may be desirable.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

Approximately 50 total subjects from up to 10 investigational sites in the US will be enrolled.

Subjects appropriate for this trial will be identified by the institutional Principal Investigator (or designee) who will make a preliminary determination of the patient's eligibility for the trial in accordance with the provisions of the study protocol. Once a patient is enrolled to the study, the Sponsor or designee will assign a unique patient identification number that does not contain any Personal Health Information that will be used to reference the patient and corresponding data that is collected.

7.1. Subject Inclusion Criteria

Subjects are required to meet the following inclusion criteria before entering the trial:

1. Laboratory-confirmed SARS-CoV-2 infection as determined by a positive PCR test documented prior to randomization:
    a. Performed on a swab sample from the nasopharynx of a non-intubated subject or pulmonary secretions from an intubated subject per site's standard practice
    b. Analyzed by a commercial, local, or public health laboratory
    c. A duplicate swab will be retained for subsequent confirmation at a Central Laboratory
2. Requirement for intensive inpatient hospital care
3. Acute hypoxemic respiratory failure typifying ARDS, as indicated by:
    a. PaO_2/FiO2 ratio < 300 mm Hg, or SpO_2 < 94% on FiO_2 >/= 50% with bilateral pulmonary infiltrates along with respiratory distress and increased work of breathing requiring intubation and invasive mechanical ventilation, OR
    b. Non-invasive mechanical ventilation with SpO_2 < 94% on FiO_2 >/= 50%
4. Adequate liver function as indicated by:
    a. Total bilirubin ≤ 1.5 x upper-normal limit (ULN)
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
5. Age 18 years or older
6. Serum or urine pregnancy test negative for females of childbearing potential
7. Properly obtained informed consent obtained from subject or legally authorized representative

7.2. Subject Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria:

1. Expected survival for less than 48 hours after randomization
2. Child-Pugh stage C hepatic impairment and/or portal hypertension secondary to cirrhosis
3. Stage IV chronic kidney disease or end-stage kidney disease on maintenance hemodialysis
4. Requirement for extra-corporeal membrane oxygenation (ECMO)
5. Acute Myocardial Infarction (AMI)
6. Active bleeding requiring transfusion
7. Concurrent participation in another clinical trial of experimental treatment for SARS-CoV-2

Note: Concurrent participation in any study of an approved treatment, or a product with Emergency Use Authorization for COVID treatment, is permitted if the Principal Investigator attests that the mechanism of the EUA product is not expected to interfere with the mechanism of GC4419 and that completion of study requirements for this protocol will not be compromised

8. Female patients who are pregnant or breastfeeding
9. Requirement for concurrent treatment with nitrates

7.3. Rationale for Patient Population

COVID-19 is associated with respiratory failure and other organ failure. The mechanism and preclinical data with avasopasem indicate that it may attenuate respiratory failure; severe hypotension requiring vasopressor support; or renal, cardiac, or hepatic damage, all of which are mediated by superoxide. Based on prior clinical data, the risks of a short course of GC4419 to human subjects appears to be low, but for a first clinical trial of GC4419 in COVID-19 patients, the benefit-risk appears to be most appropriate for critically ill patients at high risk of mortality or severe morbidity from COVID-19.

7.4. Screen Failures

A subject is considered to be a screen failure if the subject signs the informed consent form (ICF) but withdraws consent or is deemed ineligible prior to Day 1 investigational product administration. The reason why the subject was precluded from the clinical study will be collected. All subjects who sign the ICF for this study, including screening failures, will be logged into the IRT system.

7.5. Subject Withdrawal Criteria

In accordance with the Declaration of Helsinki, a subject has the right to withdraw from the study at any time for any reason. The Investigator may also, at his/her discretion, discontinue a subject from participating in this study at any time. Additionally, study treatment may be discontinued for any of the following reasons:

- AE
- Medical requirement to administer a contra-indicated medication
- Subject non-compliance
- Subject has a confirmed positive serum pregnancy test
- Discontinuation of the study at the request of the Sponsor

The primary reason for ceasing treatment will be clearly documented in the subject's medical record and recorded on the appropriate CRF page. A subject who permanently discontinues treatment with GC4419/placebo will not be allowed to be retreated.

If a subject discontinues study drug as a result of an AE or serious adverse event (SAE), every attempt should be made to keep the subject in the study and continue to perform the required

study-related follow-up and procedures. If this is not possible or acceptable to the subject, the subject may be withdrawn from the study.

If a subject withdraws consent, additional details about the reasons for that decision will be sought and documented.

Withdrawn subjects will not be replaced.

7.6. Study and Site Closure

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator or site staff, as appropriate:

- Return of all study data to the Sponsor (as applicable)
- Resolution of all data queries
- Accountability, reconciliation, and arrangements for all unused GC4419
- Review of site study records for completeness
- Shipment of laboratory samples (as applicable)

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. If the Sponsor determines such action is needed, the Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, the Sponsor will provide advance notification to the Investigator of the impending action prior to it taking effect.

The Sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator must inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Board (REB) promptly and provide the reason for the suspension or termination. If the study is prematurely discontinued, all study data must be returned to the Sponsor.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the Investigator and the Sponsor.

8. INVESTIGATIONAL PRODUCT AND TREATMENT OF SUBJECTS

8.1. Concomitant Medications

All concomitant therapies (e.g., prescription and over-the-counter medications) taken by subjects from Baseline of Day 1 GC4419/placebo administration until 30 days following the last GC4419/placebo dose will be collected in the CRF. Additionally, any concomitant therapies if used to treat any serious or related AE will be recorded in the CRF.

If a subject withdraws consent for the study or is removed from the study completely (i.e., the subject is no longer participating in any study procedures or follow-up) no further data should be collected after the date of the subject's study discontinuation.

8.1.1. Drug Interactions

GC4419 is a strong inhibitor of CYP2D6.

Concomitant use of GC4419 increases the concentration of drugs that are CYP2D6 substrates, which may increase the risk of toxicities of these drugs. Concomitant use of GC4419 with CYP2D6 substrates where minimal increases in concentration of the CYP2D6 substrate should be avoided if possible in situations where minimal increases may lead to serious or life-threatening toxicities (substrates with a narrow therapeutic range). Such CYP2D6 substrates (Appendix 4) include certain antidepressants (eg, tricyclics), antipsychotics (eg, phenothiazines and most atypicals), and antiarrhythmics (eg, propafenone, flecainide).

Beta blockers that are CYP2D6 substrates (e.g. metoprolol) have been administered, with acceptable safety, concurrently with GC4419 to subjects in other clinical trials and may be administered in this study with careful monitoring of the subject.

In addition, concomitant use of GC4419 may decrease the concentration of active metabolites of prodrugs that require CYP2D6 for activation. Concomitant use of GC4419 with CYP2D6 prodrug substrates requiring functional CYP2D6 activity for their clinical benefit (eg, codeine, tramadol, taxomifen) may decrease their effectiveness.

Subjects should receive concomitant administration of a CYP2D6-substrate drug only if the investigator judges that doing so, and continuing blinded GC4419/placebo, is warranted in an individual subject's case.

See the Investigator's Brochure for additional information.

8.2. Prohibited Medications

Investigators may prescribe any concomitant medication or supportive therapy deemed medically indicated for the care of the subject, with exception of the following prohibited medications/treatments:

- Nitrates, phosphodiesterase type 5 (PDE 5) inhibitors (e.g., sildenafil, tadalafil, or similar agents) or other concomitant drugs that in the judgment of the treating

investigator could create a risk of a precipitous decrease in blood pressure are prohibited until at least 24 hours after the last dose of blinded GC4419/placebo.

- Concurrent participation in a clinical trial of investigational therapy for SARS-CoV-2.
    - *Other approved or unapproved agents for SARS-CoV-2, including drug or biologic therapy including immunomodulatory treatments, administered on an expanded access, compassionate care, off-label, or emergency access basis may be administered. Use as part of another, concurrent clinical trial may be considered provided the site principal investigator determines that the mechanism of the other treatment is not expected to interfere with the mechanism of GC4419, and that completion of study requirements for this protocol will not be compromised.*
    - *Examples of acceptable concurrent medications under this provision include remdesivir, hydroxychloroquine (alone or with azithromycin) or convalescent plasma, and other drug or biologic treatments for SARS-CoV-2 as long as not part of a clinical trial other than the present trial.*

Subjects who receive prohibited medications will not automatically be removed from the study; however, administration of a prohibited medication is a significant deviation from the protocol and must be reported to the Medical Monitor as soon as possible and the presiding IRB/IEC/REB (per institutional guidelines). The decision for study continuation or discontinuation will be made at that time on a case-by-case basis and in consideration of the clinical requirement and circumstances.

8.3. Description of Study Drug GC4419

GC4419 is formulated as a sterile solution at the following concentration:

- 99 mg avasopasem manganese in 11mL: 9 mg/mL in 26 mM sodium bicarbonate-buffered 0.9 wt. percentage saline for parenteral administration .

8.3.1. GC4419 Drug Packaging and Labeling

Open-label GC4419 will be provided as single-use vials for daily doses to be administered IV.

GC4419 is packaged as an 11 mL ± 0.1 mL aliquot in a 10 mL glass vial of which 10 mL be added into 170 mL of normal saline, for daily IV administration over 180 minutes. Each bottle will be labeled with the appropriate language, including information required by local heath authority regulations.

Further label details will be provided in a separate Pharmacy Manual.

8.3.2. Placebo Packaging and Labeling

Placebo will be normal saline for parenteral administration only and is to be provided by investigative site.

8.3.3. Study Drug Storage

GC4419 should be stored in a blinded fashion and refrigerated at 2°C-8°C in a secured and controlled area with restricted access. Temperature excursions above freezing and up to 25°C or down to 0.1°C for four hours are accepted; however, the Sponsor, or its designee must be notified immediately of the temperature excursion to ensure proper oversight.

Once prepared, the IV bags containing GC4419/placebo mixtures must also be stored at 2°C to 8°C until use and must be administered to subjects within 24 hours of preparation. GC4419 dosing solutions must not be frozen at any time. If freezing of the material is evident, that supply must be quarantined per institutional guidelines and Galera Therapeutics, Inc. or its designee must be notified immediately.

8.3.4. Study Drug Preparation

GC4419 will be provided to the study site in single use, sterile, pyrogen-free vials ready for dose preparation. Proper mixing with normal saline is required. Standard aseptic techniques will be used to maintain sterility. Infusions should be prepared using a sterile 0.22 micron syringe filter prior to introduction into the infusion bag.

To prepare IV solutions, investigational pharmacists will extract 10 mL GC4419 from a single vial and add to 170 mL of normal saline. No additional modifications or adjustments are to be made to the infusion solution.

To prepare placebo solution, sites are to prepare 180 mL of normal saline.

IV bags should be prepared and labelled in a blinded manner.

Further information and preparation details will be provided in a separate Pharmacy Manual.

8.3.5. Administration

Prepared GC4419/placebo will be administered intravenously at an infusion rate that totals 180 min (± 6 min to account for saline overfill) for the total dose assigned. Infusions of GC4419/placebo must be administered using an infusion pump (i.e., not by drip rate). Infusion pump models are not specified and may be per institutional preference/standard.

To facilitate administration of GC4419/placebo according to the study schedule, an indwelling venous access device may be used, at the discretion of the treating Investigator. If port is to be used for other medications, a flush is required prior to GC4419/placebo administration, at minimum.

8.3.6. Accountability and Compliance

Compliance with GC4419/placebo dosing, including administration details (e.g., volume, start, stop times, etc.) should be documented in the source documents and recorded on the CRF.

The Investigator is responsible for ensuring adequate accountability of all used and unused GC4419. This includes acknowledgment of receipt of each shipment of GC4419 (quantity and condition), subject dispensing records, and quantity of GC4419 vials returned or destroyed.

Dispensing records will document quantities received from the Sponsor and quantities dispensed to subjects, including container number or lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the medication. Any GC4419 that is prepared but not used must also be recorded in the dispensing records.

All GC4419 supplies and associated documentation will be reviewed and verified by an unblinded study monitor. All GC4419 and used containers are to be retained by the site until notified by the unblinded study monitor, who will instruct the site in the disposal and/or destruction of all used GC4419 supplies. Copies of all forms, documenting drug receipt at the study site, drug transportation to satellite sites, and drug return to the Sponsor, together with drug accountability records, will be retained according to the regulations governing record retention.

The Investigator will not allow GC4419 to be given to any patient not included in the study or to any unauthorized person.

8.3.7. Study Drug Handling and Disposal

After completion of the study, all unused study drug will be inventoried and if possible, destroyed locally at the site. GC4419 should not be returned directly to Galera Therapeutics, Inc. unless specifically requested by Galera Therapeutics, Inc.. The study monitor will instruct the site in the disposal and/or destruction of all used and unused GC4419 supplies. Destruction of any GC4419 should be documented appropriately.

9. TOXICITY MANAGEMENT

9.1. Anticipated toxicities of GC4419

Based on the drug's mechanism of action, adverse effects anticipated with GC4419 are attributable to transient potentiation of nitric oxide. Clinical results with GC4419 to date are consistent with this. These effects have been IV infusion related and transient, typically with onset during or at the end of infusion, resolving within 1-2 hours of cessation of GC4419 administration. At the dose and schedule planned in this trial, these effects may include mild hypotension, postural lightheadedness/presyncope, and perioral/facial tingling or paresthesia. Mild nausea and vomiting have also been observed in human subjects receiving GC4419.

See the investigator's brochure for additional details.

9.2. Dose Delays and Dose Modifications for Toxicity

For any given subject, study drug infusions should not begin if the subject's mean arterial pressure (MAP) is less than 65 mmHg.

For any given subject, hold blinded GC4419/placebo and reduce by 25% (from the initial dose) for all future infusions if:

- During infusion or within 1 hour of completing infusion, the subject experiences an acute decrease in systolic blood pressure requiring bolus fluid resuscitation OR requiring initiation of vasopressor therapy OR increased vasopressor therapy. Hold GC4419/placebo until the dose of vasopressor therapy is stable and bolus fluid resuscitation is not required.
- The subject develops serum creatinine > 5 mg/dL. Hold GC4419/placebo until the creatinine is =<5 mg/dL.
- The subject develops serum total bilirubin > 6 mg/dL, or AST or ALT >10 times upper limit of normal. Hold GC4419/placebo until the parameters in question are below these levels.
- The subject experiences a serious or severe adverse event considered by the investigator to be related or possibly related to blinded GC4419/placebo. Hold GC4419/placebo until the event is no longer serious or severe.

Up to two such dose reductions for a cumulative 50% from the initial dose of GC4419/placebo will be permitted for a given subject. If a subject cannot tolerate GC4419/placebo infusion after a 50% dose reduction, all dosing with GC4419/placebo for that subject will be discontinued.

Patients unable to tolerate GC4419/placebo must discontinue treatment with GC4419/placebo but should continue with other protocol assessments at the discretion of the treating investigator and with the ongoing consent of the subject.

9.3. Supportive Care Guidelines

Necessary supportive measures for optimal medical care will be given throughout the study. Sites should assess and provide prophylaxis for venous thromboembolism per standard of care.

Supportive care medications may be administered at the investigator's discretion and recorded in the CRF. However, medications are subjected to the exclusions listed in Section 8.2.

Supportive care parameters such as ventilator settings will be collected in accordance with the Schedule of Events (Appendix 1).

Supportive care for study subjects will be according to investigative sites' institutional protocols, but in all cases clinical respiratory practices for this critically ill study population with COVID-19-associated ARDS are anticipated to conform to the recommendations and best practice guidelines of the Society of Critical Care Medicine [Surviving Sepsis Campaign; Guidelines on the Management of Critically Ill Patients with Coronavirus 2019 (COVID-19), published 3/20/2020].

10. ASSESSMENTS

The study procedures to be conducted for each patient enrolled in the study are presented in Appendix 1.

Any deviation from protocol procedures should be documented and explained in the source documents. The sponsor (or designee) and the site's IRB (as required by the IRB's policies and procedures) should be notified as soon as possible of any substantial deviations potentially affecting patient safety, study drug administration or the assessment of safety, efficacy, and tolerability parameters.

10.1. Safety Assessments

Safety assessments will consist of monitoring and recording all AEs. Safety will be assessed on the basis of treatment-emergent AEs, physical examination findings, clinical laboratory tests, electrocardiogram (ECG) measurements, and vital sign measurements.

10.1.1. Clinical Assessments

See the following clinical assessments are defined when referenced in the schedule of events (Appendix 1) for a list of clinical assessments.

10.1.2. Laboratory Assessments

Clinical laboratory tests during the study will be performed by local laboratories to facilitate standard care of the study subjects.

A laboratory abnormality reported by the local laboratory may meet the criteria to qualify as an AE or SAE as described in this protocol. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event electronic CRF.

For laboratory abnormalities meeting the criteria of SAEs, the site must fax or email the SAE report including the laboratory report (as regionally required) to the sponsor using the SAE form.

The investigator must assess all abnormal clinical laboratory results for clinical significance in a timely fashion. A notation of clinically significant (CS) or non-clinically significant (NCS) with initials and date will be documented on the respective laboratory report next to any abnormal value. Information on laboratory AE reporting can be found in Section 10.2.3.

The following laboratory assessments are defined as referenced in the schedule of events (Appendix 1) for this study:

- Serum or urine pregnancy
- Hematology/Serum Chemistry performed by local lab: CBC with differential and platelet; sodium, potassium, chloride, CO_2, BUN, creatinine, total protein/albumin, AST/ALT, and total bilirubin. Direct bilirubin, triglycerides, C-reactive protein, and troponin to be assessed at baseline only unless clinically indicated. If baseline troponin is above ULN, the highest post-baseline value during hospitalization and the value closest to the date of discharge will also be recorded.

- Pharmacokinetic sampling for central lab analysis
- Cytokines collected for central lab analysis: IL-1 beta, IL-6, TNF-alpha, IL-10
- Viral load: Testing by qPCR of sample collected by nasopharyngeal swab unless subject is intubated, in which case, pulmonary sample to be used
    - Initial testing by local lab for eligibility
    - Duplicate swab will be collected at enrollment for Central Laboratory analysis
    - All subsequent weekly viral load specimens will be run by the Central Laboratory

10.2. Schedule of Time and Events

A schedule of study assessments table is located in Appendix 1. Minor changes to the assessment schedule may be made to accommodate holidays, administrative closures, etc., which if necessary, are not considered as significant deviations by the Sponsor. Sites should contact the Sponsor (or its representative) prospectively to address rescheduling protocol assessments and data handling.

10.2.1. Screening Phase

The following screening observations and procedures will be completed prior to Day 1:

- Obtain a signed IRB/IEC/REB-approved informed consent
- Confirm patient eligibility by reviewing inclusion/exclusion criteria
- Obtain medical history including comorbid conditions hypertension, diabetes, coronary artery disease, hyperlipidemia, asthma, other notable pre-existing conditions
- Record predicted body weight
- Record supplemental oxygen/ ventilation status and parameters
- Blood Pressure/MAP/vasopressor use
- Collect sample for laboratory assessments per Schedule of Assessments
- 12-lead ECG
- Review of concomitant medications
- Record SOFA and Apache IV score
- Record previous day's Daily Fluid Balance, if available

10.2.2. Hospitalization/Treatment Phase

All subjects will receive standard supportive care according to the policies of the treating institution. Subjects will be randomized in a 1:1 ratio to receive either:

- GC4419 by IV infusion q 12 hours (+/- 2 hours), plus standard supportive care, or
- Placebo by IV infusion q 12 hours (+/- 2 hours), plus standard supportive care only

Subjects will receive, in a blinded fashion, either GC4419, 90 mg intravenously, or placebo, administered over 3 hours (180 minutes), repeated every 12 hours (+/- 2 hours) for 7 consecutive days. *Study drug infusions should not begin if the subject's mean arterial pressure (MAP) is less than 65 mmHg.*

The following observations and procedures will be completed per the schedule of assessments:

- Supplemental oxygen/ventilation status and parameters
- Blood Pressure/MAP
- SaO_2 or PaO_2/FiO_2 ratio
- Collect sample for laboratory assessments per schedule of assessments
- Review of concomitant medications and adverse events
- SOFA scores
- Daily Fluid Balance
- Administer GC4419/placebo

10.2.3. Post ICU Discharge

The following observations and procedures will be completed per the schedule of assessments

- Blood Pressure/MAP
- SaO_2 or PaO_2/FiO_2 ratio
- Collect sample for laboratory assessments per schedule of assessments
- Review of concomitant medications and adverse events

10.3. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse Events and Serious Adverse Events will be assessed daily during hospitalization and weekly after hospital discharge, for a total of 6 weeks after day 1 and encompassing at least 30 days after end of GC4419/placebo dosing (experimental arm subjects). Post-treatment AE assessments may be done on an outpatient basis for subjects who are discharged from the hospital.

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. Throughout the study, AEs will be recorded in the source documents and on the appropriate pages of the CRF regardless of whether the AEs are considered related to GC4419/placebo. To avoid confusion, the AE should be recorded in standard medical terminology.

10.4. Definitions

The following definitions of terms are guided by the International Conference on Harmonization and the U.S. Code of Federal Regulations (CFR) and are included here verbatim.

10.4.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity (grade) of the condition.
- New conditions detected or diagnosed after investigational product administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae associated with a suspected interaction of the investigational product with a concomitant medication.
- Signs, symptoms, or the clinical sequelae associated with a suspected overdose of either investigational product or a concurrent medication.

10.4.2. Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening – *NOTE: The term 'life-threatening' in the definition of 'serious' refers to any adverse drug experience [adverse event] that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction that, had it occurred in a more severe form, might have caused death.*
- Requires inpatient hospitalization or prolongation of hospitalization – NOTE*: In general, hospitalization signifies that the patient or subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE*.
- Results in persistent or significant disability/incapacity – *NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions*.

OR

- Is a congenital abnormality/birth defect.
- Is an other important medical event

10.5. Adverse Event Reporting Requirements

10.5.1. Serious Adverse Events

All events meeting the criteria for SAEs (see Section 10.4.2) must be reported by investigational sites within 24-hours of becoming aware of the event. The investigator may determine that the event is the natural progression of disease and therefore should be reported as an AE, but not a Serious AE. Some examples are as follows:

- Progression of respiratory failure to require artificial ventilation
- Prolongation of hospitalization due to ventilator-associated pneumonia
- Persistent oxygen requirement lasting beyond hospital discharge

In order to determine the sponsor's timeline for notifying regulatory authorities and investigators per Federal Regulations, an event term, serious criteria, and causality is required at the time of the initial report. Specific SAE reporting instructions are provided in a separate manual.

The investigator is responsible for notifying the IRB/IEC/REB in writing of serious events as soon as is practical in accordance with the policy of the IRB/IEC/REB.

10.5.2. All Adverse Events (AEs) Regardless of Seriousness

Any adverse medical condition or laboratory abnormality with an onset date before the date of the baseline visit is considered to be pre-existing in nature, and part of a subject's medical history. Adverse medical conditions that begin on or after date of baseline visit will be considered an AE, including SAEs, and followed for 30 days after end of treatment GC4419/placebo. Similarly, new events will be reported as AEs/SAEs if the start date is within 30 Day Follow-up Period. Increases in toxicity grade of pre-existing conditions that occur on or after the date of the baseline visit are also considered an AE.

All AEs must be recorded in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to study drug.

10.5.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the patient's condition, or that are present or detected at the time of the baseline visit and do not worsen, will not be reported as AEs or SAEs.

A laboratory abnormality reported by the local laboratory may meet the criteria to qualify as an AE or SAE as described in this protocol. Laboratory abnormalities should only be recorded in the AE section of the CRF if at least one of the following criteria is met:

- Meets the criteria of an SAE

- Treatment is initiated specifically for the abnormality
- Investigational product was discontinued
- Grade 3 or Grade 4 abnormalities not present at baseline, and more severe than expected for the patient's condition in the judgment of the treating investigator

For laboratory abnormalities meeting the criteria of SAEs, the site must complete and send the SAE report including the laboratory report (as regionally required) to the sponsor using the SAE form.

Abnormal assessments (eg, ECGs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definitions as defined in Section 10.4.

10.5.4. Grading of Adverse Events

The severity of adverse events will be designated as mild, moderate, severe, life threatening, or fatal per NCI CTCAE version 5.0. If not specifically addressed in NCI CTCAE version 5.0, use Table 3 below:

Table 3: Adverse Event Severity

Grade	Criteria[1]
Mild – Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate – Grade 2	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[2]
Severe – Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[3]
Life Threatening – Grade 4	Life-threatening consequences; urgent intervention indicated
Death – Grade 5	Death related to adverse event

[1] A semi-colon indicates 'or' within the description of the grade.
[2] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[3] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.6. Relationship to Study Drug

All AEs will be categorized by the investigator with respect to their relationship to GC4419/placebo. The relationship between GC4419/placebo and the AE may be considered related, possibly related, or unrelated. The criteria for each category are listed below:

- **Related:** It is likely that GC4419/placebo caused or contributed to the cause of the AE or laboratory abnormality, when the temporal sequence from the time of GC4419/placebo administration, the known consequences of the patient's clinical/state condition or study procedures, the effects of discontinuing or re-introducing GC4419/placebo on the AE, and other medically relevant factors are considered.

- **Possibly Related:** There is a reasonable possibility that the AE or laboratory abnormality was caused by GC4419/placebo, when the temporal sequence from the time of GC4419/placebo administration, the known consequences of the patient's clinical state/condition or study procedures, and other medically relevant factors are considered.
- **Unrelated:** The investigator has a high level of certainty that the patient's clinical state/condition, study procedures, or other medically relevant factors other than treatment with GC4419/placebo caused the AE or laboratory abnormality. This relationship category should only be used when a clear precipitating cause exists, and it is not reasonably possible that the event is caused by treatment with GC4419/placebo.

If the relationship between the AE/SAE and the investigational product is determined to be "possibly related" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

10.7. Recording Adverse Events

All AEs must be recorded on the appropriate CRF regardless of the severity or relationship to GC4419/placebo. All AEs that meet the seriousness criteria should also be recorded on the SAE Report Form. All SAEs must be reported to the Sponsor or delegated organization within the timeline stated in Section 10.5.

The recording of AEs will be based on data obtained from the following sources:

- Medical and surgical history
- Physical examinations including vital signs
- Clinical laboratory test results
- Subject verbal reports to the investigational staff and documented in the medical chart

All clinical events, including both observed (such as any reaction at sites of application) and volunteered problems, complaints, or symptoms, are to be recorded. The need to capture this information is not dependent upon whether the clinical event is associated with GC4419/placebo use. AEs resulting from concurrent illnesses, reactions to concurrent medications are also to be recorded.

The information to be recorded for AEs will include:

- The specific type of event in standard medical terminology – diagnosis if known, is preferred over symptoms
- Duration of the clinical event (start and stop dates)
- Severity (Grade 1, 2, 3, 4, or 5) of the clinical event
- Seriousness (SAE) criteria, if applicable
- Relationship of the AE to GC4419/placebo as defined in Section 10.6
- Management of GC4419/placebo administration and other action taken to alleviate the clinical events

- Clinical outcome of the AE

10.8. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient and provide further information on the patient's condition. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, or consultation with other health care professionals.

Non-serious AEs that have not resolved by the end of the prescribed Follow-up Period will be considered ongoing, and marked as such in the CRF. All SAEs will be followed until they resolve, or a new baseline is established, at which point the appropriate CRF page(s) or SAE Report Form(s) will be updated.

Routine collection of AEs will stop 30 days after the end of treatment.

As reasonably requested by the Sponsor, the investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. If a patient dies during participation in the study or during a recognized follow-up period, Galera Therapeutics, Inc. will be provided with a copy of any post-mortem findings, including histopathology.

10.9. Post-Study Reporting Requirements

Although such information may not be routinely sought or collected by Galera Therapeutics, Inc., SAEs that occur after the patient has completed a clinical study may be reported. Such cases will be evaluated for expedited reporting.

10.10. Pregnancy

The risks of treatment with GC4419 during pregnancy have not been evaluated. Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse should use a highly effective method of contraception starting at least on day prior to the first day of treatment and throughout the study and for 30 days (females) or 90 days (males) following the last dose of GC4419/placebo.

All females will be considered to be of childbearing potential unless they are postmenopausal (eg, amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing). Subjects with a vasectomy or a vasectomized partner with confirmed azoospermia are eligible.

Highly effective methods of contraception include any of the following:

- total abstinence from heterosexual intercourse (per circumstances and lifestyle)
- an intrauterine device or intrauterine hormone-releasing system (IUS)

- a contraceptive implant

- an oral contraceptive at a stable dose of the same oral contraceptive product, begun at least 28 days before dosing and throughout the study and continued for 30 days after study drug discontinuation)

Pregnant and/or lactating females are excluded.

A subject who becomes pregnant must be withdrawn from the study.

Pregnancies or exposure to study drug through breastfeeding must be reported as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from the date the investigator becomes aware of the outcome.

10.10.1. Time Period for Collecting Pregnancy Information

As permitted by IRB/EC/REB policies, any pregnancy that occurs from the baseline visit up to 30 days after the last dose of GC4419/placebo should be reported using the appropriate form within 2 weeks of learning of the patient's pregnancy. The patient will be followed throughout the course of the pregnancy. Generally, follow-up will be no longer than six to eight weeks following the estimated delivery date. Any premature termination of the pregnancy should be reported. If a pregnancy is identified outside the 30 days after last dose, the investigator may report using clinical judgment.

10.10.2. Action to be Taken if Pregnancy Occurs in a Female Partner of a Male Patient

The investigator will attempt to collect pregnancy information on any female partner of a male study patient who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to Galera Therapeutics, Inc. within 2 weeks of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Galera Therapeutics, Inc.. Generally, follow-up will be no longer than six to eight weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. If a pregnancy is identified outside the 30 days after end of treatment, the investigator may report using clinical judgment.

10.11. Regulatory Reporting of Adverse Events

Galera Therapeutics, Inc. will have final determination of reportability and is responsible for notifying the relevant regulatory authorities of certain events. The investigator will report all SAEs that occur at his/her site to the IRB per the site's IRB regulations. AEs will be reported to regulatory authorities in compliance with 21 Code of Federal Regulations (CFR) 312.32, local and regional law and established guidance by the Sponsor or its designee. The format of the reports will be dictated by the local and regional requirements.

Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB/IEC/REB of these additional SAEs in accordance with local or central IRB/IEC/REB procedures. Copies of each report will be kept in the investigator's files and adequate documentation will be provided to Galera Therapeutics, Inc. including documentation that the IRB/IEC/REB was notified of each safety report.

11. STATISTICS

11.1. General Considerations

A separate statistical analysis plan will provide technical details of the statistical analyses to be performed, in addition to the specifications in this protocol.

11.2. Sample Size

For this group with critical disease, the null hypothesis is that 50% of subjects will survive for 28 days. The alternative hypothesis is that at least 90% of subjects receiving GC4419 will survive for 28 days compared with the control survival of 50%. A sample size of 50 subjects, 25 in each group, is expected to provide approximately 80% power to detect this difference with a two-sided alpha of 0.05.

11.3. Randomization and Stratification

Eligible subjects will be randomized 1:1 to the two treatment arms using a permuted block randomization schedule. Randomization will be stratified by age (<60 versus ≥60 years).

11.4. Analysis Populations

All randomized subjects who receive at least one dose of blinded GC4419/placebo will be included in the population to be analyzed for safety and efficacy.

11.5. Definition of Endpoints

11.5.1. Primary Endpoint

- The primary endpoint is 28-day mortality

11.5.2. Secondary Efficacy Endpoints

- safety of avasopasem
- frequency of successful ventilator weaning
- days alive and intensive care-free
- days alive and ventilator-free
- days alive with minimum PaO2/FiO2 ≥ 300mmHg
- days alive and without vasopressor/catecholamine support
- incidence of mean arterial pressure < 65 mmHg on optimized vasopressor therapy
- days alive with a SOFA score of 6 or less
- percentage of subjects with an increase in mean arterial pressure of 10 mm Hg or more at the end of more than one infusion of GC4419

11.5.3. Exploratory Endpoints

- Levels of circulating cytokines IL-6, TNF-alpha, IL-1 beta, IL-10
- SARS-CoV-2 viral load
- Plasma exposure to GC4419
- Lung compliance to be calculated from clinical data for exploratory purposes

11.6. Safety Analysis

Adverse events will be grouped by system organ class, high level term, and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Incidence by subject will be tabulated for all treatment emergent, serious, severe, and treatment-related AEs. Detailed listings will be provided for all SAEs, deaths, and withdrawals due to AEs.

Laboratory measurements, vital signs, and ECG parameters will be summarized by treatment group at each of the protocol specified time points.

Further details will be provided in the trial's statistical analysis plan.

11.6.1. Interim Safety Analysis

An independent Data Monitoring Committee (DMC) will perform an unblinded safety review while subjects in the study receive GC4419/Placebo (Section 14.4).

11.7. Primary Efficacy Analysis

11.7.1. Primary Analysis

The primary endpoint of 28-day mortality will be compared between the GC4419 and control group using an exact Cochran-Mantel-Haenszel (CMH) test stratified by age group (<60 vs ≥60 years) at the two-sided 0.05 Type I error rate. The measure of association will be the CMH stratified relative risk of death by Day 28 along with an asymptotic 95% exact confidence interval. For each age stratum, 28-day mortality will be presented descriptively. Should any chance imbalance occur between the groups for important baseline prognostic factors, the effect of these covariates on the inference on treatment may also be examined through logistic regression or similar methods.

11.7.2. Secondary and Exploratory Analyses

Secondary and exploratory endpoints will be analyzed descriptively, and results tabulated. As appropriate, percentages and 95% confidence intervals will be calculated.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1. Study Monitoring

In accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the consistency of the data recorded in the electronic CRFs.

The monitor is responsible for routine review of the electronic CRFs at regular intervals throughout the study, to verify adherence to the protocol, and the completeness, consistency and accuracy of the data being entered on them. The monitor should have full access to any patient records needed to verify the entries on the electronic CRFs. The investigator agrees to cooperate with the monitor to assure that any follow-up items identified in the course of these monitoring visits are resolved.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

Due to the timing of this study, it will be necessary to allow monitor remote access to the electronic medical record in order to perform CRF review against source documents remotely.

During site visits, the monitor will:

- Check the progress of the study;
- Review study data collected;
- Conduct source document verification;
- Identify any issues and address their resolution;
- This will be done in order to verify that the:
    - Data are authentic, consistent, accurate, and complete;
    - Safety and rights of subjects are being protected;
    - Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

12.2. Audits and Inspections

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

12.3. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

In general, major protocol deviations include deviations from inclusion/exclusion criteria, from concomitant medication restrictions, and from any other protocol requirement that could, at least hypothetically, result in significant risk to the subject and/or affect the outcome of the clinical trial. Major protocol deviations will be noted in the final Clinical Summary Report.

A minor deviation is defined as non-adherence to the protocol procedures or schedule as defined by the protocol or the primary endpoint that does not place the subject at any added or significant risk or affect the data quality or the outcome of the clinical trial (eg, a missed procedure, an out-of-window site visit).

Only subjects who meet protocol-defined eligibility criteria may be enrolled in this clinical trial. If any protocol eligibility criteria or procedures are unclear, the investigator or investigational site personnel should contact the Clinical Research Associate. If the question requires medical interpretation, the sponsor's medical monitor should be consulted. All protocol deviations should be reported to the IRB/IEC according to the standard practices of the investigational site and applicable regulatory requirements.

12.4. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Galera Therapeutics, Inc. or its representatives. All protocol modifications must be submitted to the IRB/IEC/REB and regulatory authorities in accordance with local requirements. Approval must be obtained before changes can be implemented.

12.5. Information Disclosure

12.5.1. Ownership

All information provided by Galera Therapeutics, Inc. or its representatives, and all data and information generated by the site as part of the study (other than a subject's medical records), are the sole property of Galera Therapeutics, Inc.

12.5.2. Confidentiality

All information provided by Galera Therapeutics, Inc. or its representatives, and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. Information related to this study is subject to the confidentiality provisions of the Clinical Research Agreement between the investigative site and Galera Therapeutics, Inc.

12.5.3. Publication

All publication or presentation rights for the findings of the clinical investigation under this protocol shall be governed by the appropriate terms of the Clinical Research Agreement between the investigational site and Galera Therapeutics, Inc.

13. QUALITY CONTROL AND QUALITY ASSURANCE

The study will be monitored and managed in accordance with ICH GCP E6.

To ensure compliance with GCPs and all applicable regulatory requirements, Galera Therapeutics, Inc. or its representatives may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

14. ETHICS

14.1. Ethical Conduct of the Study

The investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" (version October 2008), ICH guidelines, in particular ICH GCP E6, or with the laws and regulations of the country in which the research is conducted, whichever affords the greatest protection to the study patient. The investigator will also assure that the basic principles outlined in "ICH Guideline for Good Clinical Practice" as published in the Federal Register May 9, 1997, and all applicable Federal regulations including 21 CFR parts 50, 54, 56, and 312 are adhered to.

14.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Board (REB) Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted, by the investigator, to an IRB/IEC/REB. Approval from the IRB/IEC/REB must be obtained and a copy must be provided to Galera Therapeutics, Inc. or its representatives before initiating the conduct of any study procedures including screening or enrolling any subjects into the trial.

No modifications or deviations from this protocol other than those that are deemed medically necessary by the Principal Investigator or designated sub-investigator are to be made. Any protocol deviations will be reported to Galera Therapeutics, Inc. and to the IRB/IEC/REB in accordance with its reporting policy.

Any modifications made to the protocol by the sponsor after receipt of IRB/IEC/REB approval must be submitted to the committee for approval prior to implementation.

14.3. Written Informed Consent

In accordance with regulatory and local IRB/IEC/REB requirements, before study procedures are performed, subjects will be informed about the study and required to sign the IRB/IEC/REB approved ICF. This form will be signed after adequate explanation of the aims, methods, objective and potential hazards of the study and prior to undertaking any study-related procedures. The Sponsor or its designee will provide an ICF template to the investigator. The Sponsor or its designee must approve changes to the ICF template prior to submission to the IRB/IEC/REB. Informed consent will be obtained according to the applicable IRB/IEC/REB requirements. No patient is to be screened or treated until an ICF, written in a language in which the patient or his/her legally authorized representative is fluent, has been obtained. The signed ICF will be retained with the study records. Each patient will also be given a copy of his/her signed ICF.

14.4. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be responsible for safeguarding the interests of the subjects by reviewing study data and providing recommendations about whether

the study is safe to proceed with ongoing enrollment as written and whether a protocol modification is required. The DMC will receive weekly updates on SAEs considered to be at least possibly related to study drug and will make a recommendation based on monthly cumulative summaries of these possibly related SAEs. The DMC will also be convened for review of available unblinded safety data and summaries of clinical data determined by the DMC to be relevant after 20 subjects have completed blinded dosing of GC4419/placebo, and may convene other meetings at its discretion. The DMC may recommend that further dosing of study treatment be discontinued and enrollment be halted pending further review if it finds that either a) more than 20% of GC4419 subjects require treatment discontinuation because of the protocol's criteria for dose reductions and discontinuation or b) the incidence of possibly related serious adverse events in the GC4419 arm constitute an unacceptable safety risk.

15. DATA HANDLING AND RECORDKEEPING

15.1. Case Report Forms

All required study data must be recorded on the electronic CRF provided by Galera Therapeutics, Inc. or its representatives. The data recorded onto the electronic CRF is derived from the source documents. The investigator shall ensure that all data in the electronic CRF is accurate and consistent with the source documents or that any discrepancies of the electronic CRF with source documents are explained (ICH E6 4.9.2).

Electronic CRFs will be accessed by the study center for collection of all study data, and a copy of the electronic CRF will be provided to the site for the investigator files. For each patient who is randomized to the study, the electronic CRF must be completed by site staff and must be signed electronically by the principal investigator in a timely fashion after data collection. If a patient withdraws from the study, the electronic CRFs should be promptly completed and the reason for withdrawal must be noted. If a patient is withdrawn from the study because of a drug-related toxicity, thorough efforts should be made to clearly document the outcome.

The sponsor will ensure that the electronic CRF selected meets the requirements per ICH E6 R2 with regard to data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning.

15.2. Retention/Inspection of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

Records of drug receipt and disposition, electronic file of CRFs, source documents, reports of this investigation and other study documentation must be maintained by the investigator for a period of at least two years following the date on which the investigational drug is approved by FDA or other applicable regulatory agency for marketing for the purposes that were the subject of the clinical investigations. If no application is to be filed, records must be retained until two years following the date that the study is discontinued and the FDA or other applicable regulatory agency is notified. If the application is not approved by the FDA or other applicable regulatory agency for such indication, records must be retained for two years after notification by Galera Therapeutics, Inc. of the FDA or other applicable regulatory agency decision. The records must be available for copying and inspection if requested by regulatory authorities.

Galera Therapeutics, Inc. should be notified in writing at least 30 days prior to the disposal or transfer to another location or party of any study records related to this protocol.

16. LIST OF REFERENCES

Anderson CM, Sonis ST, Lee CM, et al. Phase 1b/2a trial of the superoxide dismutase mimetic GC4419 to reduce chemoradiotherapy-induced oral mucositis in patients with oral cavity or oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys 100:427-435, 2018.

Anderson CM, Lee CM, Saunders DP, et al. Phase IIb randomized, double-blind trial of GC4419 versus placebo to reduce severe oral mucositis due to concurrent radiotherapy and cisplatin for head and neck cancer. J Clin Oncol 37:3256-3265, 2019.

Cuzzocrea S, Mazzon E, Di Paola R, et al. Protective effects of M40401, a selective superoxide dismutase mimetic, on zymosan-induced non-septic shock. Crit Care Med 32:157-167, 2004.

Herzog EL, unpublished data, 2014

Macarthur H, Westfall DC, Riley DP, et al. Inactivation of catecholamines by superoxide gives new insights on the pathogenesis of septic shock. PNAS 97:9753-9758, 2000.

Macarthur H, Couri DM, Wilken GH, et al. Modulation of serum cytokine levels by a novel superoxide dismutase mimetic, M40401, in an *Escherichia coli* model of septic shock: Correlation with preserved circulating catecholamines. Crit Care Med 31:237-245, 2003.

Masini, et al, Free Rad Biol Med, 39:520-31, 2005.

Sishc BJ, Polsdofer E, Bloom DA, et al. The radioprotector GC4419 ameliorates radiation induced lung fibrosis while enhancing the response of non-small cell lung cancer tumors to high dose per fraction radiation exposures. AACR Ann Mtg 2018, abstract 667, 2018.

Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Internal Medicine, published online March 13, 2020, doi.10.1001/jamainternmed.2020, 0994, accessed 8 April 2020

Yang X, Yu U, Xu J et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respiratory, published online February 21, 2020, doi.10.1016/S2213-2600(20)30079-5, accessed 8 April 2020

COVID-19 Projections accessed 15Apr2020 *Health Data*, Institute for Health Metrics and Evaluations, https://covid19.healthdata.org/projections

Galera Therapeutics, Inc. ROMAN: A Study to Investigate the Effects of GC4419 on Radiation Induced Oral Mucositis in Patients with Head/Neck Cancer. Available from https://clinicaltrials.gov/ct2/show/NCT03689712. NLM identifier: NCT03689712.

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessments	Screening/ Baseline	In hospital								After discharge from ICU
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Each additional Day in ICU	Weekly until 30 days after last GC4419/placebo dose[18]
Informed consent	X									
Inclusion/exclusion criteria	X									
Age/Medical history[1]	X									
Predicted Body Weight [2]	X									
Supplemental oxygen/ventilation status and parameters [3]	X	X	X	X	X	X	X	X	X	
Blood pressure/MAP/vasopressor use [4, 5]	X	X	X	X	X	X	X	X	X	X
Serum or urine pregnancy test	X									
12-lead ECG	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X[16]
SaO_2 or PaO_2 /FiO_2 ratio [6]		X	X	X	X	X	X	X	X	X
SOFA score [6]	X	X	X	X	X	X	X	X	X	
Apache IV score [7]	X									
Daily Fluid Balance [8]	X	X	X	X	X	X	X	X		
Hematology, serum chemistry [9]	X	X	X	X	X	X	X	X	X[17]	X[17]
GC4419/placebo administration [10]		X	X	X	X	X	X	X		
Blood for cytokines [11, 12]	X	X						X	X[11]	
Viral load testing [13]	X[14]	X						X	X[13]	
Pharmacokinetic blood testing [15]		X		X						

[1] Include comorbid conditions hypertension, diabetes, coronary artery disease, hyperlipidemia, asthma, other notable pre-existing conditions

[2] Predicted body weight: males—PBW in kg = 50 + 2.3 x (height in inches – 60). Females—45.5 + 2.3 x (height in inches – 60)

[3] Record maximum support needed, once per 24 hour period: ON/OFF mechanical ventilation; high-flow O_2, mask, non-rebreather mask, mechanical ventilation for each 24-hour period; also record the following daily before 10 am (but at least 30 minutes after any sedation vacation): tidal volume, minute ventilation, PEEP, peak inspiratory pressure, plateau pressure, prone positioning yes/no, hours per day of prone positioning. Lung compliance to be calculated from clinical data for exploratory purposes.

[4] Once during screening, then q12 hours and also before each GC4419/placebo infusion, every 30 minutes during each GC4419/placebo infusion, at end of each GC4419/placebo infusion, and 1, 2, and 4 hours post GC4419/placebo

[5] Record vasopressor requirements once at screening and q12 hours while on vasopressors; record specific vasopressor and dose in mcg/minute; not applicable post discharge

[6] Record worst value once a day assessed 8am-6pm

[7] https://intensivecarenetwork.com/Calculators/Files/Apache4.html. Record worst value in past 24 hours at baseline visit only.

[8] Record highest value during any 24-hour period

[9] Performed locally. CBC with differential and platelets; sodium, potassium, chloride, CO_2, BUN, creatinine, total protein/albumin, AST/ALT, and total bilirubin. Include direct bilirubin, triglycerides, C-reactive protein, and troponin at baseline only unless clinically indicated. If baseline troponin is above ULN, the highest post-baseline value during hospitalization and the value closest to date of discharged will also be collected. Record Worst Value for Any Day When Multiple Labs are Drawn.

[10] Administer 90 mg IV over 180 minutes, Q 12 hours (+/- 2 hours) for 7 days. It is acceptable for the timing of the first 2 doses to be modified in order to accommodate subsequent dosing on a Q12 hour schedule that meets institution's standard of care procedures. *Study drug infusions should not begin if the subject's mean arterial pressure (MAP) is less than 65 mmHg.*

[11] Collected once during screening/baseline, at Day 7 and Day 14 (while in the hospital); blood sample to be stored on site for analysis by central lab at end of study

[12] IL-1 beta, IL-6, TNF-alpha, IL-10

[13] Screening sample to be performed by local lab with a duplicate sample collected for central lab analysis. Subsequent samples collected at Day 7 and Day 14 (while in the hospital) for central lab analysis. Nasopharyngeal sample required unless subject is intubated, in which case pulmonary secretion collected.

[14] If viral load test has been performed within 7 days of baseline, no repeat is necessary at baseline

[15] Collected pre and post first infusion on Day 1 and Day 3 for central lab analysis

[16] Adverse Events will be assessed weekly after hospital discharge, for a total of 6 weeks from Day 1 and encompassing at least 30 days after end of GC4419/placebo dosing. Post-treatment AE assessments may be done on an outpatient basis for subjects who are discharged from the hospital.

[17] As Clinically Indicated, Record Worst Value for Any Day When Multiple Labs are Drawn.

[18] If subjects are not able to come into the hospital or clinic for an in-person visit, it is acceptable for a virtual visit or phone call to take place.

APPENDIX 2. SEQUENTIAL ORGAN FAILURE ASSESSMENT

A clinical scoring system, SOFA (Sequential Organ Failure Assessment), is used to assess a patient's mortality risk.

Sequential Organ Failure Assessment (SOFA) Score Scale

Variable	0	1	2	3	4	Score (0-4)
PaO_2/FiO_2 mmHg	> 400	< 400	< 300	< 200	< 100	
Platelets, x $10^3/\mu L$ (x $10^6/L$)	> 150 (> 150)	< 150 (< 150)	< 100 (< 100)	< 50 (< 50)	< 20 (< 20)	
Bilirubin, mg/dL (µmol/L)	< 1.2 (< 20)	1.2 - 1.9 (20 - 32)	2.0 - 5.9 (33 - 100)	6.0 - 11.9 (101 - 203)	> 12 (> 203)	
Hypotension	None	MABP < 70 mmHg	Dop < 5	Dop 6 - 15 or Epi < 0.1 or Norepi < 0.1	Dop > 15 or Epi > 0.1 or Norepi > 0.1	
Glasgow Coma Scale Score (see next page to calculate)	15	13 - 14	10 - 12	6 - 9	< 6	
Creatinine, mg/dL (µmol/L)	< 1.2 (< 106)	1.2 - 1.9 (106 - 168)	2.0 - 3.4 (169 - 300)	3.5 - 4.9 (301 - 433)	> 5 (> 434)	
				TOTAL (0 - 24):		

Dopamine [Dop], epinephrine [Epi], and norepinephrine [Norepi] doses in µg/kg/min (administered for at least one hour). SI units in parentheses ( )

APPENDIX 3. GLASOW COMA SCALE SCORE CRITERIA

Additional Clinical Information regarding SOFA
Glasgow Coma Scale Score Criteria

Criteria	Adults	Score	Criteria Score
Best Eye Response (1 – 4)	No eye opening	1	
	Eye opens to painful stimulus	2	
	Eye opens to verbal command	3	
	Eyes open spontaneously	4	
Best Verbal Response (1 – 5)	No verbal response	1	
	Incomprehensible sounds	2	
	Inappropriate words	3	
	Confused	4	
	Oriented	5	
Best Motor Response (1 – 6)	No motor response	1	
	Extension to painful stimulus	2	
	Flexion to painful stimulus	3	
	Withdraws from painful stimulus	4	
	Localizes to painful stimulus	5	
	Obeys commands	6	
Total Score (add three subscores, range from 3 to 15):			

APPENDIX 4. EXAMPLES OF CYP2D6-SUBSTRATE DRUGS

Beta Blockers and Antiarrhythmics	Antidepressant, Antipsychotics and Other Neurological	Analgesics and Antiemetics	Other
Carvedilol	Haloperidol	Tramadol	**Dextromethorphan**
Metoprolol	**Desipramine**	Codeine	**Eliglustat**
Propafenone	**Nortriptyline**	Oxycodone	**Tolterodine**
Nebivolol	**Perphenazine**	Ondansetron	Tamoxifen
Propranolol	**Atomoxetine**	Metoclopramide	Deutetrabenazine
Timolol	**Venlafaxine**		Valbenazine
Encainide	Amitriptyline		Tetrabenzine
Flecainide	Clomipramine		
Mexilitene	Imipramine		
	Trimipramine		
	Aripiprazole		
	Brexpiprazole		
	Donepezil		
	Doxepin		
	Duloxetine		
	Fluoxetine		
	Fluvoxamine		
	Paroxetine		
	Risperidone		
	Thioridazine		
	Zuclopenthixol		

Red: CYP2D6 substrates commonly prescribed in ICU setting (Zhuo et al Pharmagenomics of Medications Commonly Used in the Intensive Care Unit. Frontiers in Pharmacol, 2018; 9: 1436.)
Bold: Sensitive index substrates that demonstrate an increase in AUC of ≥5-fold with strong CYP2D6 inhibitors in clinical DDI studies.