A RANDOMIZED PLACEBO-CONTROLLED SAFETY AND DOSE-FINDING STUDY FOR THE USE OF THE IL-6 INHIBITOR CLAZAKIZUMAB IN PATIENTS WITH LIFE-THREATENING COVID-19 INFECTION

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

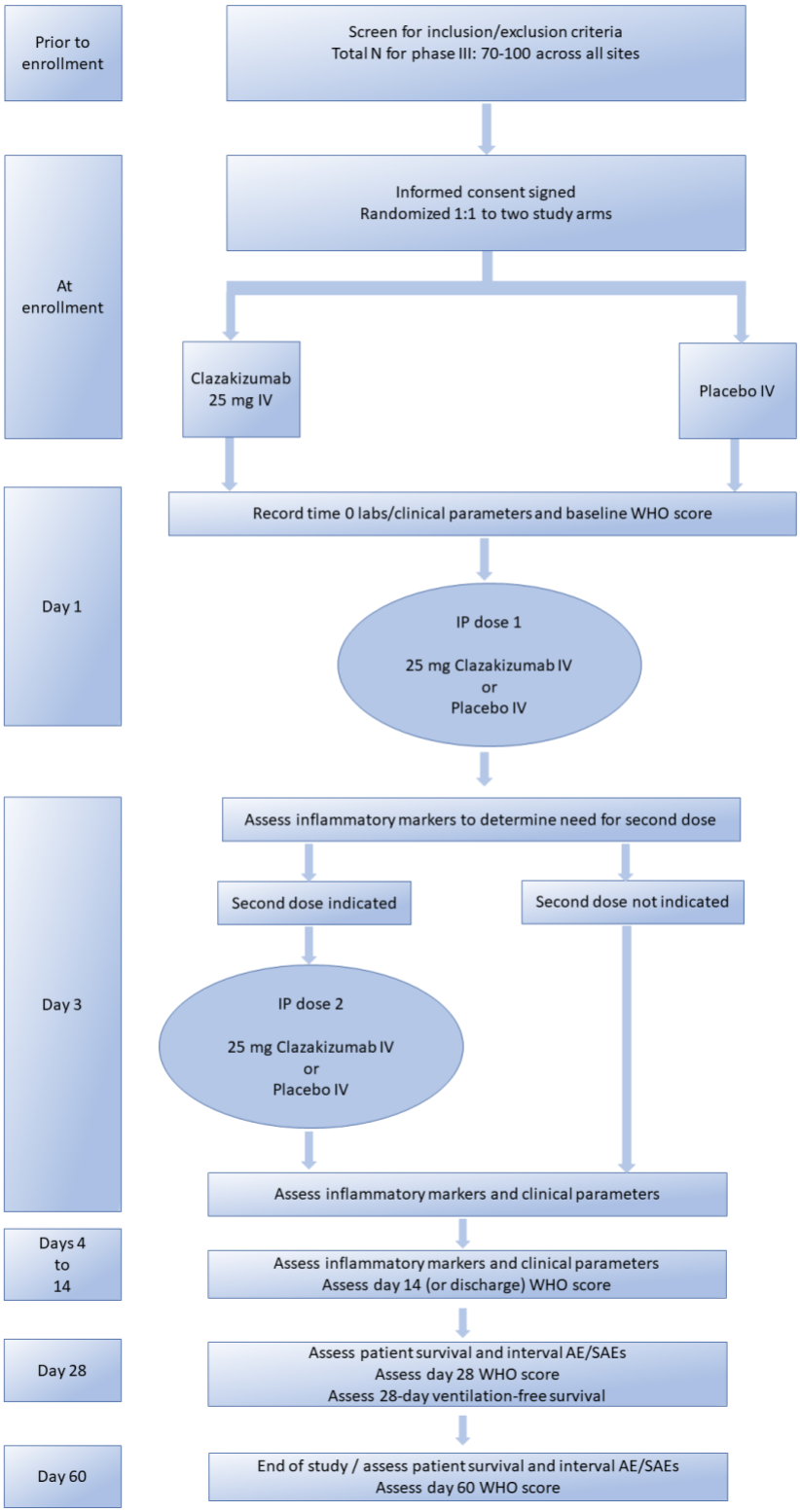
ADL	Activity of daily living
AE	Adverse Event/Adverse Experience
AKI	Acute Kidney Injury
ARDS	Acute Respiratory Distress Syndrome
CFR	Code of Federal Regulations
CRF	Case Report Form
CRP	C-reactive protein
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federal wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IL-6	Interleukin-6
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RRT	Renal Replacement Therapy
sHLH	Secondary hemophagocitic lymphhistiocytosis
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

Protocol Summary

Title	A randomized placebo-controlled safety and dose-finding study for the use of the IL-6 inhibitor clazakizumab in patients with life-threatening COVID-19 infection
Short Title	N/A
Brief Summary	In this study we propose to administer clazakizumab to patients with life-threatening COVID-19 infection manifest by pulmonary failure and a clinical picture consistent with a cytokine storm syndrome. This is a single-center randomized, double-blind, placebo-controlled trial in which 80 patients will be enrolled and randomly assigned in a 1:1:1 ratio to three study arms and received clazakizumab at a dose of 12.5 mg, 25 mg or placebo. Based on interim analysis, all remaining subjects across all sites will be randomly assigned to a 1:1 ratio to two arms that will receive clazakizumab at a dose of 25 mg or placebo. The NYU site will serve as the central data management site for other centers who undertake this protocol. Other sites will enroll patients based on the two arm 1:1 randomization. A minimum of 150 patients across all sites are expected to enroll.
Phase	2-3
Objectives	The primary objective is to assess the safety of clazakizumab treatment in COVID-19 infected patients with respiratory failure due to hyperinflammation related to cytokine storm. The primary outcomes will be to assess the efficacy by evaluating the mechanical ventilation free survival at 28 days, and the rate of WHO 11 points scale status at 14 and 28 days
Methodology	Randomized, double-blind, placebo-controlled, single-center trial
Endpoint	The primary safety endpoint for the Phase II portion is the rate of hypersensitivity reactions in the patients receiving clazakizumab compared to those receiving placebo. The primary efficacy endpoint is the rate of levels 6-10 status on the WHO 11 points scale at day 14. The primary endpoint for the Phase III portion is 28-day survival free from ventilation.
Study Duration	12 Months
Participant Duration	60 Days
Duration of IP administration	Single dose (If second dose is necessary, administered within 2 days)
Population	Patients with known COVID-19 disease, male or female, 18 years of age or older, who are critically ill with respiratory failure and do not have any evidence of irreversible injury deemed non-survivable.
Study Sites	NYU Langone Health, New York, New York, United States External sites to be determined as single center investigator initiated trials with data contribution in a centralized EDC system managed by NYULH
Number of participants	150-180 patients
Description of Study Agent/Procedure	Clazakizumab is a humanized monoclonal antibody that binds to human IL-6. The patients randomized to the investigational arms will be given either a single intravenous dose of clazakizumab 25mg or placebo. Patients who fail to achieve the expected decrease in inflammatory markers following the first dose will have the day 1 dose repeated (clazakizumab 25 mg or placebo) on day 3. Clazakizumab will be administered by intravenous infusion over 30 minutes.
Reference Therapy	Placebo (NS infusion)

Key Procedures	Clazakizumab infusions and blood draws
Statistical Analysis	Estimation of the likelihood of superiority of one or more active treatments over placebo at each interim analysis point on the basis of the Phase III endpoints.

Schematic of Study Design



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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

The limited understanding of the clinical behavior of patients infected with SARS-CoV-2 (the viral organism responsible for COVID-19 disease) is evolving on a daily basis. Reports from China indicate that a subset of patients with the worst clinical outcomes may manifest cytokine storm syndrome. Hypotheses that excess cytokines may trigger a secondary hemophagocytic lymphhistiocytosis (sHLH) have been proposed. Indeed, cytokine profiles consistent with this picture were observed in Chinese patients with severe pulmonary involvement (1). Specifically, elevated ferritin and interleukin-6 (IL-6) were associated with fatalities among the infected patients. A role for targeted anti-inflammatory and anti-cytokine therapies in the treatment of pulmonary hyperinflammation and acute kidney injury has been proposed.

Clazakizumab is a genetically engineered humanized IgG1 monoclonal antibody (mAb) that binds with high affinity to human IL-6. This investigational agent is currently being studied as a treatment for chronic active antibody mediated rejection of renal allografts (2-4). Vitaeris holds INDs 134376 and 108525 for the ongoing clinical investigations of this agent.

In this study we propose to administer clazakizumab to patients with life-threatening pulmonary failure secondary to COVID-19 disease. A new IND request has been submitted and the study team has received safe-to-proceed correspondence from the FDA. The IND assigned to this protocol is 149176.

2.2 Name and Description of the Investigational Agent

Investigational agent: clazakizumab
Supplier of clazakizumab: Vitaeris Inc, Vancouver, BC, Canada
Manufacturer: Ajinomoto Althea Bio-Pharma, Inc, San Diego CA, USA

Clazakizumab is a genetically engineered humanized mAb directed against the human cytokine IL-6. Clazakizumab is a soluble protein consisting of 4 polypeptide chains that include 2 identical heavy chains of 450 amino acids each and 2 identical light chains of 217 amino acids each. Its molecular weight is 145,239 Daltons. It is clear to slightly opaque, colorless to yellow colored in solution. The pH in solution is 5.5-6.5.

This is an investigational drug which is currently under Phase 3 investigations for patients with chronic active antibody mediated rejection after kidney transplantation. Vitaeris holds INDs for these studies but the drug does not currently have an FDA-approved indication. Existing INDs will be cross-referenced for this study.

2.2.1 Preclinical Data

Clazakizumab was shown to be a potent inhibitor of IL-6-induced acute phase proteins. In pharmacokinetic and pharmacodynamic (PD) studies, a single dose of clazakizumab resulted in full inhibition of IL-6 activity as measured by the inhibition of IL-6-induced phosphorylated STAT3 (pSTAT3) activity in whole blood treated ex vivo with IL-6. The results of this functional PD assay correlated with drug exposures where full inhibition of pSTAT3 activity was observed when drug levels exceeded 50 ng/mL (approximately 0.3 nM). In a tissue cross-reactivity study, tissue binding of clazakizumab was observed in multiple tissues in both human and cynomolgus monkey, was generally cytoplasmic in nature, and was consistent with the known expression of IL-6 by cells and tissues. Results from both single- and repeat-dose nonclinical toxicology studies of up to 6 months in cynomolgus monkeys demonstrated an acceptable safety profile for clazakizumab. In a preliminary enhanced pre- and post-natal development study conducted in cynomolgus monkeys, an increase in the number of monkeys with retention of the placenta at parturition was observed at clazakizumab doses of 3 mg/kg (n=2) and 30

mg/kg (n=3), corresponding to doses 34 and 340 a human dose of 12.5 mg once every 4 weeks (Q4W). There were no other safety findings of clinical concern. Preclinical data are described in detail in the Investigator's Brochure (5).

2.2.2 Clinical Data to Date

Clinical studies have been conducted in healthy subjects and in the following patient populations: rheumatoid arthritis, psoriatic arthritis, Crohn's disease, graft-versus-host disease, and oncology. These completed clinical studies include a total of 1,223 subjects, of which 1,056 subjects were exposed to clazakizumab for up to 175 weeks (including open-label, long-term extension phases) with doses ranging from 1 mg to 640 mg, given by either IV or subcutaneous (SC) injection.

In addition, preliminary safety data are available from the ongoing pivotal Study VKTX01 (IMAGINE) in renal transplant recipients with chronic active antibody-mediated rejection and 3 ongoing Investigator-initiated trials (IITs) in the kidney transplant setting including highly-human leukocyte antigen (HLA)-sensitized subjects awaiting a kidney transplant; subjects with CABMR; and subjects with late, active ABMR.

Further details of these clinical trials are described in detail in the Investigator's Brochure (5).

2.2.3 Dose Rationale

The proposed doses of 25 mg and 12.5 mg IV in the planned COVID-19 infection trial are based on a rational dose justification taking into account the results of the clazakizumab nonclinical program, the safety and efficacy data from completed clinical trials where repeat dosing was studied, preliminary safety results from the ongoing pivotal study VKTX01 and 3 ongoing IITs in the kidney transplant setting, and comparison with the experience with tocilizumab, an anti-IL-6R mAb, approved for use in rheumatoid arthritis and recently investigated with promising results in a small observational study of severe/critical Chinese COVID-19 patients. The completed clinical trials provide an extensive drug exposure experience to define the safety profile of clazakizumab, which is primarily associated with its IL-6 blocking effects. The AEs observed with clazakizumab have been described with other mAbs that block IL-6 signaling, such as tocilizumab and sarilumab. Further details can be found in the dose selection rationale document (in Attachments).

An intravenous route of administration is proposed for this study. Apart from the bioavailability being about 40% less by the subcutaneous route compared to intravenous, the most notable difference between the two routes is the median time to Tmax. Tmax was achieved after 1 week in patients receiving a subcutaneous dose, compared to at the end of infusion for patients receiving an intravenous dose. Given that the study subject enrolled here is critically ill, any beneficial effect of the IP will need to be imparted immediately. The patient may not survive long enough to see the effect of a drug that achieves Tmax at one week. For this reason, the route of administration will be intravenous.

Eighty subjects were enrolled with the aforementioned dose rationale. Based on interim analysis the DSMB has recommended discontinuing the low-dose 12.5 mg clazakizumab arm. They have advised that all subsequent enrollments should be carried out based on a 1:1 randomization for high-dose 25 mg of clazakizumab versus placebo.

2.3 Rationale

As of March 20, 2020, the novel 2019-coronavirus has infected nearly 250,000 people resulting in over 10,000 deaths. There is no known treatment for this disease. Among the subset of patients who develop critical illness, evidence points towards the development of a cytokine storm syndrome that is similar to what is observed in secondary hemophagocytic lymphhistiocytosis (sHLH). Clinical and laboratory features of sHLH include high fevers, elevated ferritin, elevated triglycerides, low fibrinogen, and cytopenias. About half of the patients with sHLH develop ARDS which carries a high mortality (1). In China, hypercytokinemia was observed in patients with severe COVID disease and one study published online associated elevations

in ferritin and IL-6 with greater mortality risk in these patients (6). It is reasonable to postulate that the pulmonary involvement may be the result of unchecked hyperinflammation, and that there may be a benefit to immunosuppressive, specifically, anti-cytokine therapies. Currently a multicenter randomized trial to evaluate the IL-6 receptor blocker tocilizumab is rolling out in China. Vitaeris Inc manufactures a direct IL-6 inhibitor, clazakizumab, which is currently under phase 3 investigations for patients with chronic active antibody mediated rejection after kidney transplantation. Recognizing, based on its mechanism of action, clazakizumab is hypothesized to have benefit for patients with life-threatening COVID-disease, Vitaeris is willing to provide drug for this investigator initiated trial for use in patients who are at greatest risk of dying from COVID-19 disease. This study is a prospective, randomized, double-blind, placebo-controlled trial of clazakizumab to prevent death from respiratory and multi-organ failure in COVID-19 disease. An under-recognized co-morbidity in SARS-CoV-2 infected patients is acute kidney injury (AKI) occurring in up to 30% of critically ill patients, and contributing to fluid retention, worsening oxygenation, and the need for renal replacement therapy. While multiple etiologies may be at play, the effects of systemic and possibly local inflammation are highly likely to be significant contributing factors. Improving renal function via IL-6 inhibition would be a substantial clinical benefit.

2.4 Potential Risks & Benefits

2.4.1 Known Risks

Identified risks associated with clazakizumab based on experience in Phase 1-3 clinical trials include: infections, liver function test abnormalities, hematologic derangements (neutropenia and thrombocytopenia), dyslipidemia, gastrointestinal perforations, injection site reactions.

Infections: as IL-6 is a component of innate and adaptive immunity, IL-6 blockade can potentially promote infections. Since this study does not propose longitudinal administration of clazakizumab, the likelihood of prolonged immune compromise related to IL-6 inhibition is low.

Liver function tests: treatment with clazakizumab is associated with transaminitis. Liver function tests will be monitored in the study subject as outlined in the study procedures below. Transaminitis may be confounded by liver insults that occur as a result of hypotension and hypoperfusion in critically ill patients such as the study subject enrolled.

Gastrointestinal perforations: Three cases of bowel perforations were seen in patents with Crohn's disease. Cases of perforated diverticulitis were also observed in one patient with head and neck cancer and in two patients with antibody mediated rejection of kidney transplants. Patients with active inflammatory bowel disease or active untreated diverticulitis will be excluded from participation in this study.

Hematologic derangements: clazakizumab is associated with the development of neutropenia and thrombocytopenia. Cytopenias are known to be associated with severe COVID-19 infections and therefore the etiology of hematologic derangements may be difficult to discern. Blood cell counts will be monitored as outlined in the study procedures below and supportive maneuvers instituted as deemed clinically appropriate.

Dyslipidemia: Moderate increases in total cholesterol and triglyceride levels have been observed in patients receiving serial doses of clazakizumab. As these were observed to occur early (after the first dose) lipid panels will be measured as outlined in the study procedures below.

Injection site reactions: These occurred most commonly with subcutaneous injection and the route of administration in this study will be intravenous.

There is a risk that administration of the investigational product may afford the patient no benefit, and that the patient may continue to clinically deteriorate and may expire. This may be either because there is no

therapeutic effect of the investigational product, or that the investigational product may have been administered too late in the patient's course to enable clinical recovery.

There are no known active metabolites of clazakizumab. Metabolism studies have not been performed for clazakizumab, which is a mAb. Metabolism studies are generally not performed for therapeutic proteins, such as mAbs, which are degraded to their component amino acids which are then recycled into other proteins. Since it is an immunoglobulin, no formal drug-drug interaction studies have been performed (5).

2.4.2 Potential Risks

Infusion reactions including hypersensitivity type reactions: This type of reaction has not been observed with clazakizumab to date, however has the potential to occur with IV administration of antibody products. These can manifest as fevers, tachycardia, shortness of breath/tachypnea, hemodynamic derangements such as hypotension or hypertension. Cardiopulmonary and hemodynamic monitoring will be continuous in the critically ill patients who will be enrolled in this study. Suspected infusion reaction will be managed by pausing or discontinuing the infusion, and supportive therapy with corticosteroid and/or epinephrine as appropriate.

2.4.3 Known Potential Benefits

There are no certain benefits to this study. We are proposing an experimental use of an agent with a similar mechanism to a drug that showed promise in a small cohort of Chinese patients who developed life-threatening pulmonary failure after acquiring COVID-19 disease. On that basis, there is potential that receiving clazakizumab could rapidly abrogate the hyperinflammatory syndrome that may otherwise lead to respiratory failure and death in COVID-19 disease. Extremely limited literature exists on this topic. A recent correspondence in the Lancet summarizes the experience to date (1).

3 Objectives and Purpose

3.1 Primary Objective

The primary objective is to assess the safety of clazakizumab treatment in COVID-19 infected patients with respiratory failure due to hyperinflammation related to cytokine storm

3.2 Secondary Objectives

The secondary objectives are to assess efficacy by evaluating the incidence and duration of mechanical ventilation, the length of ICU stay, severity and duration of acute renal failure and patient survival in patients who receive IP at two different doses versus placebo.

4 Study Design and Endpoints

4.1 Description of Study Design

This is a randomized, double-blind, placebo-controlled, adaptive seamless Phase II/III design (ASD). We propose the administration of an investigational drug in patients with high predicted short-term mortality secondary to COVID-19 disease. 80 patients were randomly assigned in a 1:1:1 ratio to three study arms that will receive clazakizumab at a dose of 12.5 mg, 25 mg or placebo. Interim analyses have occurred every 7 days since the enrollment of the first 30 patients. Based on week 4 interim analysis the DSMB has recommendation discontinuing the low-dose 12.5 mg of clazakizumab arm. The DSMB has advised continuing enrollment in the placebo and high-dose 25 mg of clazakizumab arms in a 1:1 randomization.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

The primary Phase II endpoint is patient safety as determined by freedom from Category A adverse events, defined as death, intubation, need for pressors, and need for mechanical ventilation. The primary Phase III endpoint is survival, free from mechanical ventilation, at 28 days.

4.2.2 Secondary Study Endpoints

The secondary endpoints are: incidence of intubation, time to extubation, length of ICU stay, trend in C-reactive protein, severity of AKI, need for RRT, duration of RRT and patient survival at 28 and 60 days.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, the patients must meet all of the following criteria:

1. At least 18 years of age
2. Confirmed COVID-19 disease (by Cobas SARS-CoV-2 real time RT-PCR using nasopharyngeal swab sample, or equivalent test available to be performed by the NYU Langone clinical laboratory). Effort will be made to have the confirmatory test result <72 hours prior to enrollment however given overall clinical demand this may not be feasible in all cases.
3. Respiratory failure manifesting as: Acute Respiratory Distress Syndrome (defined by a P/F ratio of <200), OR SpO_2 < 90% on 4L (actual or expected given higher O2 requirement) OR increasing O_2 requirements over 24 hours, **PLUS** 2 or more of the following predictors for severe disease:
    - CRP > 35 mg/L
    - Ferritin > 500 ng/mL
    - D-dimer > 1 mg/L
    - Neutrophil-Lymphocyte Ratio > 4
    - LDH > 200 U/L
    - Increase in troponin in patient w/out known cardiac disease
4. Has a consent designee willing to provide informed consent on behalf of the patient (this assumes that a mechanically ventilated patients lacks capacity to consent on his/her own behalf. Should it be deemed that the patient has capacity to consent, consent may be obtained from the patient.)
5. Women of childbearing potential must be willing and able to use at least one highly effective contraceptive method for a period of 5 months following the study drug administration. In the context of this study, an effective method is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly such as:
    a. combined (estrogen and progestogen containing) hormonal contraception combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, or transdermal)
    b. progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
    c. intrauterine device (IUD)
    d. intrauterine hormone-releasing system (IUS)
    e. vasectomized partner
    f. bilateral tubal occlusion
    g. true abstinence. when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence, such as calendar, ovulation, symptothermal, postovulation methods, and withdrawal are not acceptable methods of contraception.
6. Men must be willing to use a double-barrier contraception from enrollment until at 5 months after the last dose of study drug, if not abstinent.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Evidence of irreversible injury deemed non-survivable even if the pulmonary failure recovers (for example severe anoxic brain injury)
2. Known active inflammatory bowel disease
3. Known active, untreated diverticulitis
4. Known untreated bacteremia
5. Pregnancy. (The protocol will exclude pregnant subjects given the lack of overall data on use of clazakizumab in pregnancy however the study team would consider a protocol revision should more than 3 potential pregnant study subjects be excluded on this basis).
6. Known hypersensitivity to the clazakizumab

5.3 Vulnerable Subjects

Vulnerable subjects will not be excluded. This study is designed to include any patients deemed at risk for imminent death, and the opportunity to enroll will not be withheld provided the subject meets the above inclusion and exclusion criteria.

5.4 Strategies for Recruitment and Retention

The patients enrolled have been identified by the members of the NYULH COVID-19 inpatient team who have identified the potential subject as critically ill and failing all available medical and supportive therapies.

Patient recruitment will be by direct communication between the COVID-19 inpatient team and the study team.

5.5 Duration of Study Participation

The entire duration of study participation is 60 days. Study specific laboratory tests will be performed within the first 14 days of study initiation. Beyond 14 days, all data collected will be that which is acquired for purposes of clinical care. Patients will be followed for the survival endpoint for 60 days.

5.6 Total Number of Participants and Sites

80 patients were enrolled in the phase II study and randomized 1:1:1 between placebo, low-dose 12.5mg and high-dose 25mg clazakizumab. Based on DSMB recommendations, all subsequent subjects enrolled will be randomized 1:1 to receive placebo or high dose 25mg clazakizumab.

NYU will serve as the central data managing site for additional external sites where this protocol will be implemented. Total enrollment is expected to be a minimum of 150 patients across three sites. This includes the 80 patients enrolled at NYU in the former three-arm randomization scheme. At least 70 and up to 100 additional patients are expected to be enrolled and randomized 1:1. A maximum of 180 patients will be enrolled.

The external sites will contribute de-identified data to a central dataset but the conduct of their trials will be overseen by local IRB at their respective sites.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

The predicted mortality rate for patients with COVID-19 and ARDS is in excess of 50% (7). As such we anticipate there will be mortality amongst some of the participants. Death will constitute withdrawal from the trial. Otherwise we would not anticipate premature withdrawal from the study as the patients are expected to remain hospitalized (likely in an ICU setting) for the entire duration of the 14-day period where study specific data are collected. If the patient is discharged before day 28 survival status will be obtained by patient lookup in the electronic medical record. For discharged patients in whom there is no definitive record documenting patient status (alive or dead) after 28 days have elapsed, the study team

will contact the patient or patient's family by phone to assess patient survival and to assess for the occurrence of any interim AEs/SAEs. At end of study (day 60), a phone call will also take place to assess patient survival and again asses for interim AEs/SAEs. The IP administration will occur over a maximum of 3 days following enrollment. Study specific laboratory tests will be performed in the first two weeks and if a patient (or consent designee should the patient lack capacity) wishes to withdraw from participation and refuse these laboratory studies, they will be free to do so.

An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.7.2 Handling of Participant Withdrawals or Termination

Should a patient (or consent designee) withdraw from the study by choice, no further study specific laboratory tests will be drawn. The study team would continue to follow the patient for the primary outcome of patient survival and for secondary outcomes that would be measurable by tests and assessments done for routine clinical care. The overall clinical care of this patient will not change as a result of participation in this study nor will it change should the patient be withdrawn for any reason.

5.8 Premature Termination or Suspension of Study

Patient deaths are expected among study subjects given that the expected mortality of the enrolling patient population exceeds 50%. All deaths and related SAEs within the study period will be reviewed by the DSMB (see section 9.8, Safety Monitoring). The DSMB will determine whether unblinding of the deceased subject is warranted. The decision to stop or suspend the study will be made the DSMB after considering the totality of the data and the benefit-risk of continuing the study.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

Clazakizumab is provided as a preservative-free solution for IV administration, contained in a single-dose 2-cc Type I flint glass vial that is stoppered with a 13-mm stopper and sealed with an aluminum seal. Each vial contains clazakizumab Drug Substance (25 mg/mL), 25 mM histidine buffer (L-histidine, L-histidine monohydrochloride), 250 mM sorbitol, and 0.015% (w/w) polysorbate-80 at pH 6.0. An overfill is included to ensure a 1.0 mL (25 mg) withdrawable volume. In these vials, clazakizumab has a clear, colorless appearance.

Placebo will be sourced locally at the study site from commercially available saline. The placebo will contain 0.9% sodium chloride as a sterile solution. There are no excipients.

6.1.1 Acquisition

Vitaeris, Inc. will ship investigational product directly to the NYU Langone Investigational Pharmacy. The study team will enter an order for the IP in the Epic system. Once the order is received, the medication will be prepared by the pharmacy and delivered to the patient's bedside.
Placebo (normal saline) will be sourced locally at the study site from commercially available saline.

6.1.2 Formulation, Appearance, Packaging, and Labeling

Clazakizumab is manufactured by Ajinomoto Althea Bio-Pharma, Inc., San Diego, CA, USA. The product will be provided a cartons containing single-use glass vials of clazakizumab (25 mg/mL). Vials are 2 mL, containing a minimum of 1.1 mL clazakizumab. The kits will be labeled with an Annex 13 compliant label.

This product is not commercially available and will be shipped directly from the manufacturer to the NYU Langone Investigational Pharmacy for purposes of this study only.

The placebo will contain 0.9% sodium chloride as a sterile solution and will be sourced locally by the study site.

6.1.3 Product Storage and Stability

Clazakizumab vials should be stored at ≤–20°C ± 5°C (≤–4°F ± 9°F) with protection from light.
Prepared infusion bags may be stored for up to 12 hours in a refrigerator, 2°C to 8°C (36°F to 46°F), or at controlled room temperature, 15°C to 25°C (59°F to 77°F) and should be protected from light.

The placebo should be stored at conditions specified in the product labeling.

6.1.4 Preparation

Investigational drug (clazakizumab or placebo) will be prepared and dispensed in identical infusion bags by an unblinded pharmacist/qualified personnel at the investigational site. Each infusion bag will contain a label with details including protocol number, subject ID, and date dispensed. The pharmacist will record the vial number dispensed for each subject, including the date and time of dispensing on an accountability log.

Preparation of 25 mg dose from 25 mg/mL vials:
To prepare the clazakizumab IP solution for infusion, remove one 25 mg/mL vial from the freezer and allow the vial to thaw at ambient temperature, protected from light, until all vial contents have liquefied (this should take approximately 15–20 minutes). During the thaw process, occasionally, gently swirl the vial. Do not attempt to speed up the warming process in any way such as using a microwave or placing the vial in warm water. Once the clazakizumab vial is at ambient temperature, remove the plastic cap on the vial and wipe the septum as well as the minibag port with the alcohol swab. Remove and discard overfill (5 mL) + volume of IP dose from the 50 mL 0.9% sodium chloride bag. Using a single use, sterile needle and syringe, draw up 1 mL of the contents from the vial. Inject into the minibag containing 50mL sterile injectable 0.9% sodium chloride. Apply investigational study label. Transport in a light protected bag to the patient's bedside for administration.

Preparation of Placebo:
To prepare the placebo solution for infusion, remove one vial of 0.9% sodium chloride sterile solution from local supply at the study site. In order to be consistent with preparation of the IP solution, wait 15-20 minutes before preparing. Then remove the plastic cap on the vial and wipe the septum as well as the minibag port with the alcohol swab. Remove and discard overfill (5 mL) + volume of IP dose from the 50 mL 0.9% sodium chloride bag. Using a single use, sterile needle and syringe, draw up 1 mL of the contents from the vial. Inject into the minibag containing 50mL sterile injectable 0.9% sodium chloride. Apply investigational study label. Transport in a light protected bag to the patient's bedside for administration.

6.1.5 Dosing and Administration

Once the patient is consented and enrolled in the trial, the first dose of 25 mg of clazakizumab or placebo will be given as soon as possible thereafter. No premedications will be given prior to the investigational product. Serum CRP will be evaluated at baseline and on days 1 and 2 following clazakizumab or placebo administration to assess response. If the CRP does not decrease by 50% by day 3, a second dose of 25mg clazakizumab or placebo (an identical dose to the day 1 dose) will be given no later than day 3. All doses will be administered in a blinded fashion.

6.1.6 Route of Administration

The route of administration will be intravenous. Each dose will be administered as an infusion that is run over 30 minutes.

6.1.7 Dosing schedule

Patients will be dosed according to the randomization schedule with 25mg of clazakizumab or placebo. Should the patient fail to demonstrate a 50% decrease in CRP by day 3, a second dose will be given. Patients whose CRP decreases by 50% or more by day 3 will not be redosed. Patients with CRP failing to decrease 50% or more will receive a second dose, identical to the first dose (25mg clazakizumab or placebo) on day 3. All doses will be administered in a blinded fashion.

6.1.8 Dose Adjustments/Modifications/Delays

Changes in timing between dose 1 and dose 2 (if dose 2 is determined to be indicated) might occur based on the laboratory turnaround time for the CRP test. We expect that this test will result within 24 hours of being sent. Lab reporting delays could potentially result in a delay in the administration of the second dose. In the event that the CRP lab test is delayed due to laboratory backlog, then clinical judgment of the investigators will be used to determine if a second dose is to be given. Lack of clinical improvement, in the absence of a resulted CRP test, will prompt a second dose.

A second dose, even if deemed indicated, would be held if there was suspicion of any serious adverse reaction deemed likely related to the first dose.

6.1.9 Duration of Therapy

All IP administration is expected to be completed within 2 days of the first dose. It may be the case that only a single dose of clazakizumab is given, in which case all IP administration will be complete after the first infusion.

6.1.10 Tracking of Dose

All doses will be administered in the acute care or intensive care unit. Patients will not have any responsibility for medication self-administration. Standard of care medication administration charting will be performed to ensure that the medication is administered.

6.2 Study Agent Accountability Procedures

Once the site has been approved to receive investigational drug, Vitaeris Inc. will ship clazakizumab directly to the NYU Langone Investigational Pharmacy. Clazakizumab will then immediately be stored in a secured area, accessible only to authorized site personnel. Clazakizumab will be stored, handled, and prepared according to the instructions specified in the Pharmacy Manual.

The Investigator is ultimately responsible for accountability of investigational drug supplies. The Investigational/designee will ensure that an accurate and current accounting of the dispensing of investigational drug for each participant is maintained on an ongoing basis by the study site unblinded pharmacist/designee. The Investigator is ultimately responsible for ensuring that only study participants receive investigational drug.

The amount of investigational drug received, dispensed, and returned/destroyed by the Investigator (or designated site staff) will be recorded on an IP Accountability Log.

The IP accountability records will be made available, upon request, for inspection by the designated representatives of Vitaeris, Inc., representatives of the US Food and Drug Administration (FDA), or other governing regulatory authorities.

6.2.1 Initial Shipment of Products

Once regulatory approval to the study site has been given, the initial shipment of clazakizumab investigational product will be shipped by Vitaeris, Inc. to the NYU Langone Health Investigational Pharmacy. Placebo (normal saline) will be sourced locally by the study site using commercially available saline.

6.2.2 Re-supply

The need for drug resupply will be assessed on a regular basis taking into account the number of subjects enrolled and the number of subjects in screening.

6.2.3 Destruction of Investigational Product

Every vial must be clearly accounted for in writing from receipt through return/destruction. For this study, partially or fully used clazakizumab vials will be destroyed on-site per site standard destruction practices for hazardous biologics. Any unused clazakizumab vials will be accounted for and destroyed as outlined in the Pharmacy Manual.

7 Randomization, Blinding and Unblinding Procedures

7.1 Randomization

All enrolled subjects will be assigned a unique subject number, and the Investigator will maintain a list of subject numbers and subject names.

Eighty subjects have been randomized (via an IRT) 1:1:1 into the 3 treatment arms using a stratified block randomization scheme: 20-50 subjects in the clazakizumab 12.5mg group, 20-50 subjects in the clazakizumab 25mg group, and 20-50 subjects in the placebo group.

All subsequent enrolled patients will be randomized 1:1 into the placebo arm or the high-dose 25mg clazakizumab arm.

The randomization schema will be pre-prepared by a blinded statistician and will be made available only to the investigational pharmacy. All study investigators and clinical staff administering study drug will be blinded to the content of the dose.

As the study transitions to Phase III, randomization in Phase III will follow the same 1:1 format.

7.2 Blinding

This study is double-blind and therefore neither the Investigator, the subject and its representatives, nor other designated study site personnel involved in running of the study will be aware of the identification of the investigational drug administered to each subject. To maintain blinding, interim analyses will be conducted by the designated Data Safety Monitoring Board. Detailed procedures for maintaining the blind are specified below.

Given that clazakizumab and placebo are packaged differently, investigational drug will be prepared and dispensed by an unblinded pharmacist/qualified personnel at each investigational site. To maintain blinding during the study, the pharmacist/designated staff will dispense either clazakizumab or placebo into identical infusion bags, according to each subject's randomized treatment allocation, and all subjects will receive each dose of investigational drug (clazakizumab or placebo) as an intravenous infusion.

The pharmacist/designated staff will ensure that blinded personnel will not have access to drug supply records.

7.3 Unblinding

In the event that an AE occurs for which knowledge of the identity of the investigational drug administered is necessary to manage the subject's condition and/or for regulatory reporting of a suspected unexpected serious adverse reaction (SUSAR), the blinding code for that subject may be broken by the Investigator and the treatment identified.

Should emergency unblinding be required, the Investigator should call and discuss the patient with the DSMB chair before unblinding wherever possible; however, the Investigator is responsible for the medical care of the individual trial subject and does not require the agreement of the DSMB Chair before unblinding. The reason for unblinding must be documented. The information on investigational drug should only be used for decision making in the subject's further treatment. Details on unblinded treatment assignments should not be shared with the site personnel, or project team unless necessary for care of the subjects.

In case of an emergency, the following process will occur after the DSMB Chair is made aware, if time permits. The Investigator will notify the unblinded Investigational Pharmacist who will serve as the source for emergent unblinding information. The Investigational Pharmacist will be responsible for the following: 1) providing unblinding information to the Investigator only for the specific Subject affected, 2) documenting the provision of unblinding information in the pharmacy records and 3) confirming with the DSMB Chair of the unblinding occurrence and rationale for unblinding.

8 Study Procedures and Schedule

8.1 Study Procedures/Evaluations

8.1.1 Study Specific Procedures

8.1.2 Standard of Care Study Procedures

All critical care interventions will be performed by the clinical care team independent of the study team.

These include but are not limited to:

- Ventilator management and determination of when to extubate (or perform tracheostomy)
- Hemodynamic support (fluid and vasoactive drug administration)
- Mechanical circulatory support if needed (e.g. ECMO)
- Renal replacement therapy
- Enteral or parenteral nutrition
- Surveillance for and management of infections

8.2 Laboratory Procedures/Evaluations

8.2.1 Clinical Laboratory Evaluations

- ***Complete blood count with differential:*** *hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.*
- ***Complete metabolic panel:*** *creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate*
- *aminotransferase (AST)*
- ***C-reactive protein (CRP)***
- ***Interleukin 6 (IL-6)***
- ***Lipid panel:*** *total cholesterol, triglycerides*
- ***Ferritin***
- ***Fibrinogen***
- ***Pregnancy test (only for women of childbearing potential)****, to be done at screening 24 hours prior to study intervention and results must be available prior to administration of study product.*
- ***D-Dimer***
- ***LDH***
- ***Troponin***

8.2.2 Specimen Preparation, Handling, and Storage

No specimens will be collected or maintained for purposes of this study.

8.3 Study Schedule

A detailed Schedule of Events is outlined in Section 20.

Screening (Days -5 to 1):

- Inclusion and exclusion criteria verified
- Informed consent signed
- Medical history and physical exam documented (physical examination as conducted by subject's clinical care team)
- Concomitant medications documented
- Calculation of baseline H-score (see attached documents) for scoring sheet
- Baseline study labs drawn (CRP must be drawn on same day as infusion of Investigational Product; prior to infusion of Investigational Product)
- Collection of clinical data (vital signs, respiratory and hemodynamic support parameters)

Day 1:

- Day 1 laboratory studies (CRP, if screening and Day 1 are not performed on the same day)
- Physical examination (as conducted by subject's clinical care team)
- Infusion of clazakizumab 25mg or placebo IV
- Collection of clinical data (vital signs, respiratory and hemodynamic support parameters)
- Record baseline (at time of first infusion) WHO clinical outcome score

Day 2 No window:

- Day 2 laboratory studies
- Physical examination (as conducted by subject's clinical care team)
- Collection of clinical data (vital signs, respiratory and hemodynamic support parameters)

Day 3 No window:

- Day 3 laboratory studies
- Physical examination (as conducted by subject's clinical care team)
- Assessment of eligibility for repeated clazakizumab dose
- Infusion of clazakizumab 25mg or placebo IV if criteria met
- Collection of clinical data (vital signs, respiratory and hemodynamic support parameters)

Day 4 No window:

- Day 4 laboratory studies

Day 5 No window:

- Day 5 laboratory studies

Day 6 No window:

- Day 6 laboratory studies

Day 7 +/-1: (this visit pertains only to subjects who remain inpatient at this time)

- Day 7 laboratory studies
- Collection of clinical data (vital signs, hemodynamic parameters, respiratory parameters)

Day 14 +/- 2:

- Day 14 laboratory studies – only for those who remain inpatient
- Collection of clinical data (vital signs, hemodynamic parameters, respiratory parameters) – only for those who remain inpatient
- Assess WHO clinical outcome score - for patients discharged prior to this day, WHO score will be recorded as the score at the time of discharge, with patients considered to be Ambulatory.
- Documentation of WHO score will constitute the visit.

Day 28 +/- 3:

If outpatient: phone visit for documentation of survival status and assessment of interval AE/SAEs
Assess WHO clinical outcome score
If inpatient: WHO score will be extracted by review of patient electronic medical record and this will constitute the visit.

Day 60 +/- 5:

If outpatient: phone visit for documentation of survival status and assessment of interval AE/SAEs
Assess WHO clinical outcome score
If inpatient: WHO score will be extracted by review of patient electronic medical record and this will constitute the visit.

Additional clinical data to be collected:

Date of symptom onset
Date of intubation (if performed)
Date of extubation (if performed)
Date of tracheostomy (if performed)
Use and duration of prone positioning (if performed)
Date of ICU discharge (if occurs)
Date of hospital discharge (if occurs)
Date of death (if occurs)

Additional data to be collected if testing becomes available during the conduct of this trial:
Assessment of SARS-CoV-2 viral load by quantitative RT-PCR in blood. This would be tested at enrollment and on day7 if this assay becomes available and able to be performed in the NYU clinical laboratory.

8.3.1 Withdrawal/Early Termination Visit

Should the patient choose to withdraw from the study before the 60 day study duration has elapsed, the patient's choice to withdraw will be documented. The patient will be followed by the medical record to collect clinical data obtained for standard clinical care as pertains to the study outcomes, but no further study-specific blood draws will take place.

8.4 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications being administered at enrollment and during the inpatient stay up to the first 28 days of study participation will be recorded. This will include any investigational drugs (such as antivirals) the patient may have received. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

9 Assessment of Safety

9.1 Specification of Safety Parameters

Patients will be monitored for the manifestations of adverse events related to clazakizumab infusion. Both the nature of the event and the timing related to infusion will be considered. Given the baseline laboratory and physiologic abnormalities of the patient being enrolled in this study, assessments of clinical deterioration will be difficult to attribute with certainty to the underlying disease versus the study drug infusion. The known risks associated with clazakizumab will be considered in determining likelihood of association of AEs with the drug. We will only report adverse events which are deemed more than

probably related or related to the clazakizumab infusion by the Principal Investigator. Any new infection that occurs in a study subject once dosing has commenced, regardless of the infecting agent will be captured as either an AE or an SAE as appropriate. The site of infection and source of the culture (BAL, tracheal aspirate, sputum, blood, urine, etc) will also be recorded. AEs and SAEs will be captured and graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0) scale.

9.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

9.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above.

It is important to acknowledge that the patient being enrolled in this study has a high risk of mortality at the time of enrollment in the study and there is a chance that the patient may die of COVID-19 disease despite rather than because of the clazakizumab administration. In the event of mortality, every effort will be made on the part of the investigators to assess whether there was any probable association between the study drug and the patient death.

In the event of patient death, the study team will consult with the clinical critical care team in an effort to determine whether the patient death was related to the underlying clinical condition (COVID-19 infection) or whether the death was unexpected given the patient's condition between the time of study drug infusion and the patient's death.

9.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

9.2 Classification of an Adverse Event

9.2.1 Severity of Event

CTCAE (v5.0) definitions will be used to describe severity. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living (ADL).
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

9.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

9.2.3 Expectedness

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information described in the current version of the Investigator Brochure (Section 7.3.3).

9.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits. All AEs including local and systemic reactions not meeting the criteria for SAEs, but deemed to have relation to the Investigational product will be captured on the appropriate CRF. Information to be collected includes event description, date and time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. Unanticipated problems will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events related to the Infusion of the Investigational Product with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs and SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify Vitaeris of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. Vitaeris should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

9.4 Reporting Procedures by the Sponsor – Notifying the IRB by the Investigator

9.4.1 Adverse Event Reporting

The IRB and DSMB will be notified within 24 hours if a patient dies during the 60-day study period.

9.4.2 Serious Adverse Event Reporting

The IRB and DSMB will be notified within 24 hours of any SAEs that are determined by the study team and the patient's clinical providers to be probably or more than probably related to the investigational product.

9.4.3 Unanticipated Problem (UPs) Reporting

It is the site investigator's responsibility to report UPs to their IRB and to the DSMB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the drug manufacturer (Vitaeris) within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the drug manufacturer (Vitaeris) within 72 hours of the investigator becoming aware of the problem.

9.4.4 Reporting of Pregnancy

Should the study subject become pregnant within the study period this will be reported within 72 hours to the IRB and to the drug manufacturer (Vitaeris). Given that the patient at enrollment is critically ill, we anticipate the likelihood of new pregnancy (patient or partner) to be exceptionally low.

Clazakizumab was evaluated in pregnant monkeys. In these animals there was an increase in the number of monkeys with retention of the placenta at parturition observed at clazakizumab doses of 3 mg/kg Q2W (n=2) and 30 mg/kg Q2W (n=3), corresponding to doses 17 and 170 times a human dose of 25 mg Q4W, or 34 and 340 times a human dose of 12.5 mg Q4W (based on a 70 kg adult). These doses far exceed what would be administered in this study. No other pregnancy, parturition, or post-delivery issues in the monkeys were reported in this study, and all 5 infants born from the mothers with retained placentas were normal. No retained placentas were seen in the control group. No adverse effect of clazakizumab was noted on infant post-delivery survival or growth and development assessed by clinical observations, body weights, examination for external abnormalities, morphology measurements, neurobehavioral test battery, grip strength, skeletal examination, clinical chemistry, hematology, and immunology.

9.5 Reporting Procedures – Notifying Vitaeris

Vitaeris Inc. is not the sponsor for this study. Vitaeris is supplying investigational product for this investigator initiated trial. Nonetheless the study team will inform Vitaeris of patient death should it occur. Patient death, whether related or unrelated to clazakizumab will be reported to Vitaeris within 72 hours of the death. SAEs deemed related to clazakizumab will be reported to Vitaeris within 24 hours of the study team being made aware.

The FDA will be notified of patient death, whether deemed related or unrelated to the investigational product, within 72 hours of the patient death.

9.6 Reporting Procedures – Notifying the FDA

The IND holder is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND/IDE safety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days*** *(via notification to IND)*
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening
    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit this criteria for reporting (reporting within 7 calendar days from when event was deemed reportable).

- ***Within 15 calendar days*** *(via notification to IND)*
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening
    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit this criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

Additional reporting requirements
The investigator/designee is also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events may be submitted on FDA Form 3500A (MEDWATCH Form), or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3. The contact information for submitting IND safety reports is noted below:

9.7 Treatment Halting Rules

If a treatment related SAE occurs following the first dose, additional dosing may be halted at the discretion of the DSMB or investigator based on a benefit risk assessment. Data collection for safety would not be affected and would continue provided the patient does not elect to withdraw from the study.

9.8 Safety Oversight

9.8.1 Data Safety Monitoring Board (DSMB)

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Safety oversight will be under the direction of the NYULH COVID-19 DSMB. This DSMB committee for this study will be comprised of individuals with expertise across the broad range of disciplines. The DSMB Charter, which outlines DSMB roles and responsibilities are forthcoming.

The DSMB will be notified of all AEs and SAEs as outlined above in sections 9.4.1 and 9.4.2. It will be the responsibility of the DSMB to evaluate cumulative participant safety data and make recommendations regarding the safe continuation of the study. The DSMB will convene a planned meeting after the first 10 patients have enrolled. Subsequent meetings will be at the discretion of the DSMB chair and the principal investigator.

The DSMB will hold emergency meetings in the event of patient deaths to discuss whether unblinding is warranted. The DSMB will hold emergency meetings if the DSMB chair deems this is warranted based on any reported AE or SAE. Emergency meetings will occur within 2 business days of the precipitating event occurring or being recognized. Any event that prompts an emergency DSMB-study team meeting will be reported to the IRB and to Vitaeris within 24 hours of the event occurring or being recognized.

There are planned interim analyses after every 30 patients have 14-day data available on Category A events. The DSBM will review the data in light of the planned interim analysis procedure and determine whether particular arms should be closed, or whether the study should be stopped for efficacy or futility. The DSMB may request to see safety and/or efficacy data in an unblinded fashion; if this occurs, the DSMB statistician will be provided with the randomization codes in order to effect unblinding for the DSMB only.

10 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

11 Statistical Considerations

11.1 Statistical and Analytical Plans (SAP)

11.1.1 Phase II:

Descriptive statistics for the safety endpoints will be used. With 20 patients, the 95% confidence interval (CI) around the rate of SAEs will be no more than 0. 46 units wide. With 40 patients (combining the low-dose and high-dose groups), the 95% CI will be no more than 0.33 units wide. When 30 patients have been enrolled and treated, the DSMB will conduct a comprehensive analysis of safety and efficacy.

Regarding the secondary outcome of patient survival, too little is known about the expected clinical behavior of these patients to make meaningful projections about expected changes in mortality given drug efficacy. The table below summarizes approximate power for the projected sample size (N=20 in each arm) to detect various reductions in mortality from the expected 50% rate in the placebo group, for various levels of Type I error (alpha) assuming use of a two-sided test. For example, we have approximately 68% power to detect a reduction in the mortality rate of 80%, from 0.5 in the placebo group to 0.1 in the treated group, assuming 20 patients per group, at the usual Type I error rate of 0.05. While power is admittedly low with the planned sample size of 60 patients, the trial's primary outcome is safety and the estimates of mortality will provide an important signal of efficacy for future investigations.

Mortality Rate	Reduction (%)	N=20 per group		
		α=5%	α=10%	α=20%

5%	-90	0.84	0.91	096
10%	-80	0.68	0.80	0.89
15%	-70	0.52	0.65	0.78
20%	-60	0.36	0.49	0.64
25%	-50	0.24	0.35	0.49
30%	-40	0.14	0.23	0.35
35%	-30	0.08	0.14	0.23
40%	-20	--	--	--

In Phase II the safety and efficacy of 12.5mg and 25mg clazakizumab will be monitored. Depending upon the safety and efficacy profiles of the two doses. The DSMAB will recommend one of the following actions:

1. Continue into Phase III with the same study design if there is no evidence for any safety issues with either dose, and compare efficacy of the two doses of clazakizumab.
2. Continue into Phase III with only placebo and 12.5mg dose, if there is evidence of safety issues with 25mg dose.
3. Continue into Phase III with only placebo and 25mg dose, if there is no evidence for any safety issues and there is evidence for higher efficacy with 25mg dose.
4. Stop the study if there is evidence for safety issues with both clazakizumab doses.

11.1.2 Phase III:

If after Phase II the DSMB recommends continuation into Phase III, we expect that we will be able to activate additional recruitments sites.If other institutions join the protocol, they will each enroll up to 30 patients in a 1:1 randomization ratio, with 15 patients each on clazakizumab 25mg and placebo. At these other sites, with 15 patients, the 95% confidence interval (CI) around the rate of SAEs will be no more than 0.52 units wide.

If three other institutions join the protocol, for a total planned enrollment of 150 subjects, the power to detect treatment effects will increase considerably. The table below summarizes approximate power for the projected sample size in the placebo and 25 mg clazakizumab groups (N=60 in each arm) to detect various reductions in mortality from the expected 50% rate in the placebo group, for various levels of Type I error (alpha) assuming use of a two-sided test. For example, we have approximately 82% power to detect a reduction in the mortality rate of 50%, from 0.5 in the placebo group to 0.25 in the treated group, assuming 60 patients per group, at the usual Type I error rate of 0.05. If each external site enrolls the full 30 patients, a maximum of 180 patients will be enrolled.

Mortality Rate	Reduction (%)	N=60 per group		
		α=5%	α=10%	α=20%
5%	-90	0.99	0.99	0.99
10%	-80	0.99	0.99	0.99
15%	-70	0.99	0.99	0.99
20%	-60	0.94	0.97	0.99
25%	-50	0.82	0.89	0.95
30%	-40	0.61	0.73	0.84
35%	-30	0.38	0.51	0.65
40%	-20	0.19	0.29	0.43

11.2 Interim Analyses

11.2.1 Phase II

Given the nature of the COVID-19 pandemic and the rapid surges of infections in different locations, the DSMB Chair (EA) and statistician (EP) will make real time decisions about additional interim analyses based on deaths and intubation outcomes. Pairwise treatment groups (1:high dose vs. placebo and 2:low dose vs. placebo and 3:low vs. high does) will be compared with respect to status at levels 6-10 on the 11 points WHO scale at day 14 pot first dose. The following actions can be taken:

a) stopping for safety
b) continue the study as is
c) transition to Phase III of this adaptive seamless Phase 2-3 study
d) eliminating a treatment arm

Efficacy

A "bad event" is defined as having a status of 6-10 on the 11 point WHO scale:

6	Hospitalized; oxygen by NIV or High flow
7	Intubation & mechanical ventilation, pO2/FiO2>/=150 or SpO2/FiO2>/=200
8	Mechanical ventilation pO2/FiO2 <150 (SpO2/FiO2<200) or vasopressors
9	Mechanical ventilation pO2/FiO2 <150 and vasopressors, dialysis, or ECMO
10	Dead

q: probability a patient is at level 6-10 on WHO 11 points scale at day 14.
In this study without treatment (or treatment = placebo) the expected rate is 50%, or $q_{pbo} = 0.5$.

Odds(q): q/(1-q)
The odds ratio for the bad event of a given clazakizumab dose X compared to placebo is denoted by OR(doze x/placebo) = odds(q_{dose} x) / odds(q_{pbo})

Bayesian rules

The Bayesian stopping rules are based on the posterior distribution of OR, given the data. The efficacy rule are as follows:

Dose X will continue into Phase III of this adaptive seamless Phase II/III study, if the Prob{OR(doze x/placebo) < 1} >0.95 using uninformative prior distribution for the parameter of interest (log(OR) will be taken to be $N(0, 10^6)$).

Dose X will be discontinued, if
Prob{OR(doze x/placebo) < 1} < 0.5 using uninformative prior distribution for the parameter of interest (log(OR) will be taken to be $N(0, 10^6)$).

Safety

Safety events are those associated with clazakizumab. A safety event will be considered any that is ruled to be probably related to clazakizumab. Hypersensitivity reactions are expected to be clazakizumab-related. Bayesian stopping guidelines will be applied as follows:

Doze X will be stopped for safety, if the odds ratio associated with safety events
Prob{OR(doze x/placebo) > 1} > 0.75 using uninformative prior distribution for the parameter of interest.

We plan interim analyses for efficacy and futility after every 30 patients have accrued 14-day information on the Phase II outcome, occurrence of Category A adverse events (death, intubation, need for pressors, need for mechanical ventilation). We will follow the approach of Stallard and incorporate information on these shorter-term events into the interim analyses to determine which arm(s) should continue to the Phase III portion of the study. Assuming standardized effect sizes of 0.3 and 0.6 for the low- and high-

dose arms, respectively, compared to placebo, we have more than 95% probability of selecting the higher-performing active arm to continue from Phase II to Phase III. In addition, we have more than 85% power to detect a significant improvement of at least one active arm at the Phase III analysis.

11.2.2 Phase III

The Phase III part of this adaptive seamless Phase II/III study is a double-blind placebo-controlled trial for evaluating the efficacy of 25mg clazakizumab. The primary outcome is mechanical ventilation free survival at day 28. The efficacy will be monitored based on Bayesian logistic regression, modeling the primary outcome (survival free of mechanical ventilation, a good event) as a function of treatment, and controlling for: i) age; ii) sex; iii) duration of symptoms prior to study enrollment; iv) baseline WHO 11 point scale measure; and v) BMI at baseline.

Efficacy

A skeptical prior will be used for the regression coefficient for the treatment effect in the logistic regression β^{trt}:

$Prob\{\beta^{trt} > \ln(2)\} < 0.025$ and $Prob\{\beta^{trt} < \ln(0.5)\} < 0.025$,

where "ln" indicates the natural logarithm with base e=2.718.

The DSMB would consider stopping the study for efficacy if $Prob\{\beta^{trt} > 0\} > 0.95$. This would correspond to Prob(OR(25mg claza/placebo)) > 0.95.

Harm

The DSMB will consider stopping for harm if $Prob\{\beta^{trt} < 0\} > 0.75$, using the same model as described above in section Efficacy. In this case, however, an uninformative prior for the β^{trt} coefficient will be used, i.e.,Normal(mean=0,variance=100).

Safety

Safety events are those associated with clazakizumab. A safety event will be considered any that is ruled to be probably related to clazakizumab. Hypersensitivity reactions are expected to be clazakizumab-related. The DSMB will consider stopping the study for safety, if the odds ratio associated with safety events Prob{OR(25mg claza/placebo) > 1} > 0.75. Uninformative prior will be used for the safety monitoring: the prior distribution for ln(OR) will be taken to be Normal(mean=0,variance=100).

12 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government

regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

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

13 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by Vitaeris, and inspection by local and regulatory authorities.

14 Ethics/Protection of Human Subjects

14.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

14.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

14.3 Informed Consent Process

14.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The informed consent document is submitted with this protocol.

14.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. In order to limit exposure of the study team to potential COVID-19 infection, the consent process may be undertaken by phone or video chat between the study team and the patient. Consent forms will be IRB-approved and the

participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record.

FOR PATIENTS WHO LACK CAPACITY TO CONSENT

Some patients eligible to enroll will not have the capacity to sign consent, due to life-threatening critical illness and respiratory failure requiring mechanical ventilation. A consent designee will be contacted to consent for enrollment on behalf of the patient. Since visitors are currently prohibited in the NYULH system hospitals the consent conversation with the consent designee will be held either by phone or by video chat. Written consent will be obtained either digitally (via RedCAP e-consent process) or by fax, email, or the transmission of a digital image of the signed consent form.

If the consent designee does not speak English, a phone interpreter will be used to read the full consent form, and a short form of the consent will be signed by one of the digital processes outlined above. The interpreter's full name and/or ID number will be documented on a printed copy of the signed consent form by the study team.

A copy of the signed consent form will be retained by the study team. A copy of the signed consent form will be provided to the consent designee by email or postal mail unless obtained in RedCAP. Consents obtained in RedCAP are considered available to the individual signing the consent.

ASSESSMENT AND RE-ASSESSMENT OF CAPACITY TO CONSENT

Any patient who is intubated, mechanically ventilated and/or sedated will automatically be determined to lack capacity to provide consent. Patients who are not intubated, and not on continuous intravenous infusions of sedating medications may have the capacity to provide consent. The study team member will assess consenting capacity by conversing with the patient (by phone or video chat). In the event that the study team member determines that the patient does not have capacity to consent, the study team member will notify the patient that a consent surrogate will be contacted. If a patient is deemed by the study team member to lack capacity to consent, documentation of failure to meet at least one of the following criteria will be made:

- understand the study protocol and why it is being offered
- express a clear choice to agree or decline to participate
- express appreciation of the choice as it pertains to the patient's own situation
- be able to demonstrate reasoning for how they reached their choice

If a subject who has capacity to consent at enrollment loses capacity the following will apply:

- If capacity is lost after all study medication administration is complete (either after day 3 or after day 1 and the patient does not qualify for repeat dosing on day 3) no surrogate consent will be sought. Only laboratory tests as performed for standard of care will be collected. Assessment of survival will be performed at day 60.
- If capacity is lost between days 1 and 3 and the patient qualifies for a repeat dose of the study medication, a surrogate consent will be sought. If the consent surrogate declines further study participation on the patient's behalf, then the repeat dose of study medication on day 3 will not be given and only laboratory tests as performed for standard of care will be collected. Assessment of survival will be performed at day 60.

- Since the study drug will be administered shortly after consent is obtained, we do not envision a scenario where a consenting patient would lose capacity to consent between signing a consent and the time that the study medication is ready to be given, However, in the event this were to occur, the study team would not proceed with administering the study drug. The study team would seek consent from a surrogate before proceeding with study medication administration.

Subjects will be regularly assessed throughout the study with discussions with the clinical care team to determine whether or not they have regained or lost the capacity to consent. If subjects regain the capacity to consent during the study and decline to continue participation, they will be asked if previously collected data can still be used. If they decline, this data will be discarded.

CONSENT SURROGATES
If a study subject candidate lacks consenting capacity the study team would seek to obtain consent from a surrogate. The patient's identified health care proxy will be the default surrogate. If no health care proxy has been designated then the study team will consider the following surrogates in the listed order of priority: spouse, adult child, parent, adult sibling, nearest living relative, close friend. If a surrogate of higher priority wishes to defer surrogacy to a lower priority surrogate, the study team will document that both individuals agree upon the consent designee.

14.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

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

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. Except when required by law, subjects will not be identified by name, personal identification number (e.g. social security number, social insurance number), address, telephone number, or any other direct personal identifier in database records. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Health. This will not include the participant's contact or

identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Health research staff will be secured and password protected and are protected by a firewall. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Health.

14.4.1 Research Use of Stored Human Samples, Specimens, or Data

No specimens will be collected and stored for purposes of this study. Laboratory data collected for purposes of this study will be collected and maintained in the study binders.

15 Data Handling and Record Keeping

15.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant password protected web-based electronic data capture (EDC) system with validated electronic records and electronic signatures provided by the NYULH. All investigational staff authorized to enter study data will receive training on the EDC system. Training records will be retained by the study team.

The EDC includes internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Any out-of-range values or missing key variables will be flagged at the site in real time during the data entry process. When a query is generated on a particular variable, an exclamation point will be present next to the item in the database enabling the system to track the queries and produce reports of outstanding queries. Queries can also be generated from manual review of the data forms. These queries will be entered into the database and tracked in the same manner as the computer-generated queries. Further cross-checking of the data will be performed and discrepant observations flagged will be appropriately resolved through a data query system. The data monitoring group will perform internal database quality-control checks, and data audits throughout the course of the trial. Clinical data will be entered directly from the source documents.

15.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such

indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

15.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents, reported to the NYULH IRB.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

15.4 Publication and Data Sharing Policy

This study will comply with terms outlined in the agreement outlined between NYULH Investigators and Vitaeris Inc.

16 Study Finances

16.1 Funding Source

There is no source of monetary funding associated with this study. Vitaeris, Inc. will supply the investigation product at no cost to the patient, investigators, or institution under an agreement mutually accepted by both Vitaeris Inc. and NYULMH.

16.2 Costs to the Participant

The patient will incur no costs associated with participation in this study.

16.3 Participant Reimbursements or Payments

No payments or reimbursements will be disbursed in exchange for participation in this study.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

18 References

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6. Ruan Q et al (2020) Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020 Mar 3.Epub. doi: 10.1007/s00134-020-05991-x
7. Arentz M (2020) Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA. Published online March 19, 2020. doi:10.1001/jama.2020.4326.
8. Stallard N. A confirmatory seamless phase II/III clinical trial design incorporating short-term endpoint information. Statistics in Medicine 2010, 29 959—971.
9. Nick Parsons a, Tim Friede b, Susan Toddc, Elsa Valdes Marquezd, Jeremy Chataway e,f, Richard Nicholas e, Nigel Stallard. An R package for implementing simulations for seamless phase II/III clinical trials using early outcomes for treatment selection. Computational Statistics and Data Analysis 56 (2012) 1150–1160.

19 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

Attached are:
H-score calculator
Schedule of Events
DSMB Charter
Dose selection rationale
Pharmacy manual
Laboratory manual

H-score calculator

	Number of points
Temperature	
<38·4°C	0
38·4–39·4°C	33
>39·4°C	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenias*	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/L)	
<1·5 mmol/L	0
1·5–4·0 mmol/L	44
>4·0 mmol/L	64
Fibrinogen (g/L)	
>2·5 g/L	0
≤2·5 g/L	30
Ferritin ng/ml	
<2000 ng/ml	0
2000–6000 ng/ml	35
>6000 ng/ml	50
Serum aspartate aminotransferase	
<30 IU/L	0
≥30 IU/L	19
Haemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression†	
No	0
Yes	18

The Hscore[11] generates a probability for the presence of secondary HLH. HScores greater than 169 are 93% sensitive and 86% specific for HLH. Note that bone marrow haemophagocytosis is not mandatory for a diagnosis of HLH. HScores can be calculated using an online HScore calculator.[11] HLH=haemophagocytic lymphohistiocytosis. *Defined as either haemoglobin concentration of 9·2 g/dL or less (≤5·71 mmol/L), a white blood cell count of 5000 white blood cells per mm^3 or less, or platelet count of 110 000 platelets per mm^3 or less, or all of these criteria combined. †HIV positive or receiving long-term immunosuppressive therapy (ie, glucocorticoids, cyclosporine, azathioprine).

Table: **HScore for secondary HLH, by clinical parameter**

The above table was reproduced from Mehta et al (2020). The H-score can also be calculated using an online calculator found at http://saintantoine.aphp.fr/score/

20 Schedule of Events

Activity	Screening (can occur on Day 1)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Windows	**-5 Days**	**No window**	**No window**	**No window**	**No window**	**No window**	**No window**
Study team procedures							
Assess inclusion/exclusion criteria	X						
Consent obtained	X						
Medical History	X						
Physical Exam	X[3]	X[3]	X[3]	X[3]			
Height	X						
Weight	X						
Vitals signs	X	X	X	X			
Document respiratory and hemodynamic support (eg vent settings, vasopressors, circulatory support)	X	X	X	X			
Calculation of enrollment H-score	X						
Dose 1 administered		X					
Dose 2 administered if indicated				X			
Documentation of patient survival status							
Phone visit (AE/SAE/survival assessment) – only if outpatient							
Documentation of WHO score		X (at dose 1)					
Laboratory Assessments							
Comprehensive chemistry panel	X						
CBC with differential	X						
CRP	X	X	X	X	X	X	X
IL-6	X						
Total cholesterol	X						
Triglycerides	X						
Ferritin	X						
Fibrinogen	X						
D-Dimer	X						
LDH	X						
Troponin	X						
Quantitative SARS-CoV-2 viral load[1]	X						
Pregnancy Test[2]	X						

Activity	Day 7 (if still inpatient)	Day 14 (if still inpatient)	Day 28	Day 60
Windows	**+/- 1**	**+/- 2**	**+/- 2**	**+/- 5**
Study team procedures				
Assess inclusion/exclusion criteria				
Consent obtained				
Medical History				
Physical Exam				
Height				
Weight				
Vitals signs	X	X		
Document respiratory and hemodynamic support (eg vent settings, vasopressors, circulatory support)	X	X		
Calculation of enrollment H-score				
Dose 1 administered				
Dose 2 administered if indicated				
Documentation of patient survival status			X	X
Phone visit (AE/SAE/survival assessment) – only if outpatient			X	X
Documentation of WHO score		X	X	X
Laboratory Assessments				
Comprehensive chemistry panel	X	X		
CBC with differential	X	X		
CRP	X	X		
IL-6				
Total cholesterol	X	X		
Triglycerides	X	X		
Ferritin	X	X		
Fibrinogen	X	X		
D-Dimer				
LDH				
Troponin				
Quantitative SARS-CoV-2 viral load[1]				
Pregnancy Test[2]				

1 Only if this testing become available by NYU clinical laboratory over the course of the conduct of this study
2 Only for women of childbearing potential3 Physical examination as conducted by subject's clinical care team