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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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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 (RRT). 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.

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

Objectives and Purpose

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.

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 kidney injury (AKI) and patient survival in patients who receive IP at two different doses versus placebo.

Study Design and Endpoints

This is a randomized, double-blind, placebo-controlled, design. We propose the administration of an investigational drug in patients with high predicted short-term mortality secondary to COVID-19 disease. 30 Patients will be randomly assigned in a 1:1 ratio to two study arms that will receive clazakizumab at a dose of 25 mg or placebo.

Primary Study Endpoints

The primary endpoint is patient safety assessed by serious adverse events associated with clazakizumab or placebo.

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.

Eligibility

Inclusion Criteria

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

- At least 18 years of age
- Confirmed COVID-19 disease (by Cobas SARS-CoV-2 real time reverse transcription polymerase chain reaction (RT-PCR) using nasopharyngeal swab sample, or equivalent test available to be performed by the Columbia University Irving Medical Center (CUIMC)/New York Presbyterian (NYP) 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.
- Respiratory failure manifesting as: Acute Respiratory Distress Syndrome (defined by a P/F ratio of <200), OR oxygen saturation (SpO2) < 90% on 4 liters (L) (actual or expected given higher O2 requirement) OR increasing O2 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 mcg/L Neutrophil-Lymphocyte Ratio > 4 Lactate dehydrogenase (LDH) > 200 U/L Increase in troponin in patient w/out known cardiac disease
- 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.)
- 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:
    - combined (estrogen and progestogen containing) hormonal contraception combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, or transdermal)
    - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
    - intrauterine device (IUD)
    - intrauterine hormone-releasing system (IUS)
    - vasectomized partner
    - bilateral tubal occlusion
    - 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.
- 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.

Exclusion Criteria

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

- Evidence of irreversible injury deemed non-survivable even if the pulmonary failure recovers (for example severe anoxic brain injury)
- Known active inflammatory bowel disease
- Known active, untreated diverticulitis
- Known untreated bacteremia

- 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).
- Known hypersensitivity to the clazakizumab

Strategies for Recruitment and Retention

The patients enrolled will be identified by the members of the Columbia University Irving Medical Center / New York Presbyterian Hospital (CUIMC/NYPH) COVID-19 inpatient team who have identified the potential subject as critically ill and failing all available medical and supportive therapies. Patient recruitment will begin by direct communication between the COVID-19 inpatient team and the study team. An individual involved in the patient's care must determine and document that the patient or their surrogate (if the patient lacks capacity) has agreed to discuss the study with the researchers.

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.

Total Number of Participants and Sites

The CUIMC/NYP inpatient hospital site is expected to enroll up to30 patients across the 2 arms. NYU will serve as the central data managing site, and will analyze data from patients enrolled at NYU, Columbia, and Johns Hopkins. Total enrollment is expected to be 150 patients across three sites. Expected contribution of patients will be: NYU Langone (New York, NY): 90 total patients (80 already randomized 1:1:1 and 10 to be randomized 1:1 for high-dose clazakizumab 25mg vs placebo) Johns Hopkins Medicine (Baltimore, MD): 30 patients to be randomized 1:1 for high-dose clazakizumab 25mg vs placebo New York-Presbyterian/Columbia University (New York, NY): 30 patients to be randomized 1:1 for high dose clazakizumab 25mg vs placebo Columbia and Johns Hopkins will contribute de-identified data to the central dataset but the conduct of the trial at each site will be overseen by the local IRB the respective sites.

Participant 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.

Randomization

All enrolled subjects will be assigned a unique subject number, and the Investigator will maintain a list of subject numbers and subject names. A total of 30 subjects will be randomized (via an IRT) 1:1 into the 2 treatment arms using a stratified block randomization scheme: 15 subjects in the clazakizumab 25mg group and 15 subjects in the placebo group. In order to randomize the subject, the study coordinator or investigator will enter the unique subject number and data into a centralized database system. Subjects

meeting all clinical, site, and core lab inclusion/exclusion criteria will then be randomized to either the clazakizumab 25mg or placebo groups and will be registered as randomized. 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. Detailed information on enrollment and randomization will be provided in the manual of operations.

Blinding

This study is double-blind and therefore neither the Investigator, the subject, the Sponsor 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 independent study monitor. 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. In the event of suspected unexpected serious adverse event(s), the blinding may be broken in the best interest of and to provide the appropriate care for the affected participant.

Study Procedures

This is a randomized, double-blind, placebo-controlled, adaptive seamless Phase II/III design (ASD). The investigators propose the administration of an investigational drug in patients with high predicted short-term mortality secondary to COVID-19 disease. Patients will be enrolled and randomly assigned in a 1:1 ratio to two study arms that will receive clazakizumab at a dose of 25 mg or placebo.

Experimental: Clazakizumab Group

The first dose will be administered as soon as possible after the patient is enrolled and randomized into the Clazakizumab 25 mg arm. The route of administration will be intravenous. Each dose will be administered as an infusion that is run over 30 minutes. Serum C-reactive protein (CRP) will be evaluated at baseline and on days 1 and 2 following clazakizumab administration. If the CRP does not decrease by 50% within 36-48 hours after the first dose, a second dose of 25 mg clazakizumab will be given no later than day 3.

Placebo Comparator: Placebo Group

The first dose will be administered as soon as possible after the patient is enrolled and randomized into the Placebo arm. The route of administration will be intravenous. Each dose will be administered as an infusion that is run over 30 minutes. Serum CRP will be evaluated at baseline and on days 1 and 2 following clazakizumab administration. If the CRP does not decrease by 50% within 36-48 hours after the first dose, a second dose of placebo will be given no later than day 3.

A detailed Schedule of Events

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)
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, RRT)
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. If discharged, we will collect available data from the medical record)
Day 7 laboratory studies
Collection of clinical data (vital signs, laboratory results, hemodynamic parameters, respiratory parameters, RRT)
Day 14 +/- 2:
(This visit pertains only to subjects who remain inpatient at this time. If discharged, we will collect available data from the medical record.)
Day 14 laboratory studies
Collection of clinical data (vital signs, laboratory results, hemodynamic parameters, respiratory parameters, RRT)
Day 28 +/- 3:
Phone visit for documentation of survival status and assessment of interval AE/SAEs Collection of clinical data (laboratory results indicating kidney function, RRT)
Day 60 +/- 5:
Phone visit for documentation of survival status and assessment of interval AE/SAEs Collection of clinical data (laboratory results indicating kidney function, RRT)
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)
- Dates of initiation/discontinuation and type of renal replacement (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 New York Presbyterian Hospital CUIMC Clinical Laboratory.

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.

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.

Statistical and Analytical Plans (SAP)
Descriptive statistics for the safety endpoints will be used. With 10 patients, the 95% confidence interval (CI) around the rate of SAEs will be no more than 0.62 units wide. With 20 patients (combining the low dose and high-dose groups), the 95% CI will be no more than 0.46 units wide. 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. Data will be analyzed across three sites: NYU, where this protocol originated; Columbia/NYP; and Johns Hopkins.

The first 80 patients at NYU were enrolled in the three-arm study using a 1:1:1 ratio. Following the DSMB's recommendation, additional NYU patients (expected to be 10) will be randomized in a 1:1 ratio to placebo or 25 mg clazakizumab. Columbia/NYP and Johns Hopkins will each enroll 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. The total planned enrollment of 150 subjects across these three sites will considerably increase the power to detect treatment effects. 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.

References

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