Official Title: A Phase II Trial to Evaluate the Safety and Tolerability of Clazakizumab® (Anti IL-6 monoclonal) compared to placebo for the treatment of COVID-19 infection

NCT #: NCT04348500

Document Date: May 05, 2020

PROTOCOL

STUDY TITLE:

A Phase II Trial to Evaluate the Safety and Tolerability of Clazakizumab® (Anti-IL-6 monoclonal) compared to placebo for the treatment of COVID-19 infection

Study Drug

Clazakizumab (Anti-IL-6 monoclonal)

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Version 1.4 May 5, 2020

Abbreviations

ABMR	Antibody-mediated rejection
AE	Adverse Event/Adverse Experience
ARDS	Acute Respiratory Distress Syndrome
BNP	B-type Natriuretic Peptide
CBC with diff	Complete blood count with differential
CLS	Cytokine release syndrome
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRP	C-reactive protein
DSMB	Data and Safety Monitoring Board
ECMO	Extra-corporeal membrane oxygenation
GCP	Good Clinical Practice
GI	Gastrointestinal
GVHD	Graft versus Host Disease
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IL-6	Interleukin-6
IRB	Institutional Review Board
IV	Intravenous
IB	Investigator's Brochure
LDH	Lactate dehydrogenase
PI	Principal Investigator
PsA	Psoriatic arthritis
Q4W	Once every 4 weeks
QA	Quality Assurance
QC	Quality Control
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event/Serious Adverse Experience
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SOC	Standard of care
SOP	Standard Operating Procedure
TB	Tuberculosis
US	United States
WOCP	Women of Child Bearing Potential

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1.0 Background & Rationale

The COVID-19 epidemic is rapidly consuming the world. As of 3/24/20, there are now 414,050 cases worldwide with 18,543 deaths. In the United States, the epidemic is rapidly spreading with increased confirmed cases and deaths. Today, there are 51,134 reported cases with ~ 700 deaths. There have been 7400 new cases in the past 24 hours and 105 deaths. To understand the nature of the pandemic, the graphs below show how rapidly COVID-19 is spreading worldwide.[1]

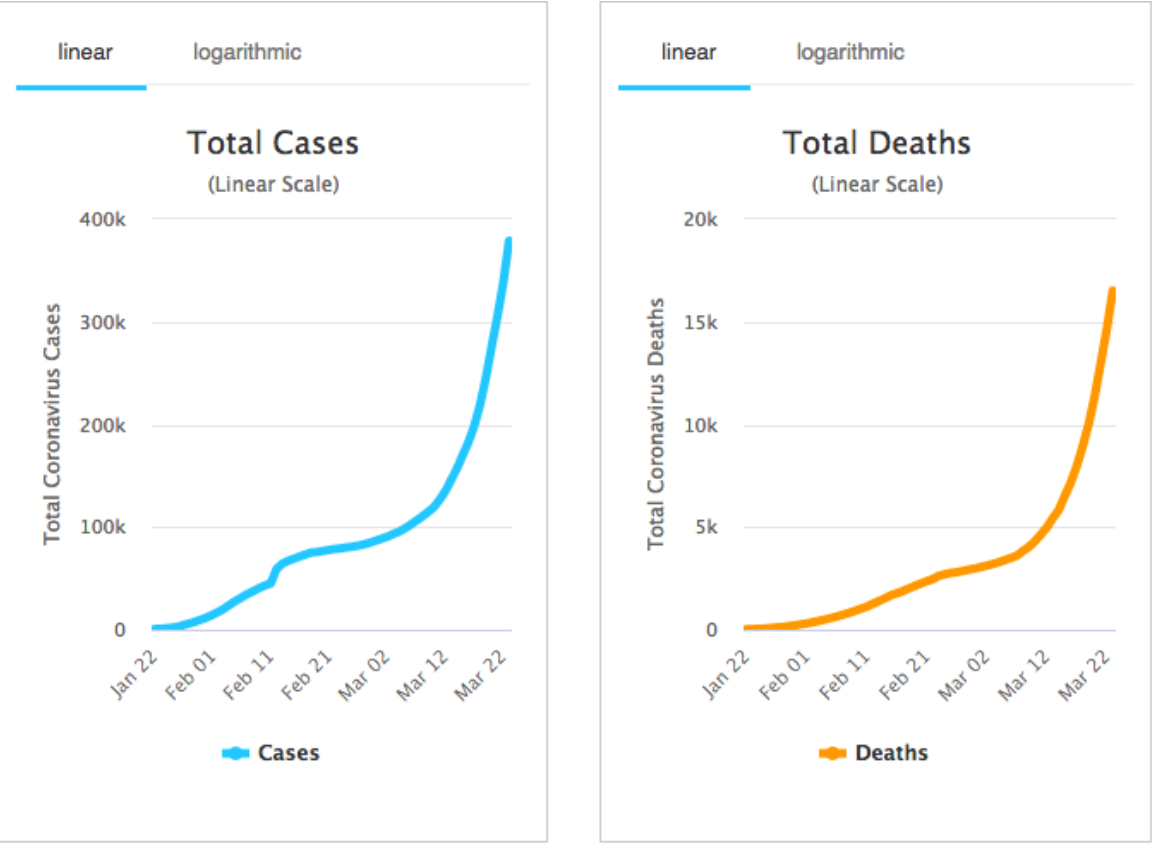

Figure 1 shows the total cases world wide and total deaths. In two days, 3/22/20->3/24/20, the numbers have increased above 414,000 cases and 18,543 deaths.(source: https://www.worldometers.info/coronavirus/)

The COVID-19 epidemic has shut down most of the world and is decimating the world economies with no relief in sighte. Vaccines are being developed but are more than 12-18 months away. There is a clear and prescient need for new drug development to address this deadly epidemic. Drug companies, researchers are trying to move promising agents into clinical trials but most studies to date are anecdotal and of unclear benefit. There is a desperate need for these agents to help save human lives and our economies.

1.1 Interleukin 6 (IL-6) as a Target for Treatment of COVID-19

Interleukin-6 is an important mediator of inflammation and the development, maturation, and activation of T-cells, B-cells and plasma cells.[2] Excessive IL-6 production has been linked to a number of human diseases characterized by excessive and unregulated antibody production and autoimmunity, and recently severe capillary leak or cytokine storm seen in CART-cell therapy.[3]
Recent data has demonstrated the importance of IL-6 in mediating the severity of COVID-19 and SARS-CoV-2 pneumonia. Investigators examined the role of clinical

laboratory data in the differential diagnosis of the severe forms of COVID-19 as they had not been definitely established. They aimed to examine laboratory factors that would distinguish severe from mild cases of COVID-19. They examined forty-three adult patients with COVID-19. The patients were classified into mild group(28 patients)and severe group(15 patients). Here, significant differences in IL-6, D-Dimer, GLU, TT, FIB and CRP (P <0.05)were found. The optimal threshold and area under the ROC curve for IL-6 were 24.3 pg/mL and 0.795 respectively. The area under the ROC curve (AUC) of IL-6 combined with D-Dimer was 0.840. The specificity of predicting the severity of COVID-19 during IL-6 and D-Dimer tandem testing was up to 93.3%, while the sensitivity of IL-6 and D-Dimer by parallel test in the severe COVID-19 was 96.4%. The authors conclude that IL-6 and D-Dimer were closely related to the occurrence of severe COVID-19 and their combined detection had the highest specificity and sensitivity for early prediction of the severity of COVID-19 patients. The authors conclude this is of important clinical value in determining those likely to progress.[4] See Figure 2 below:

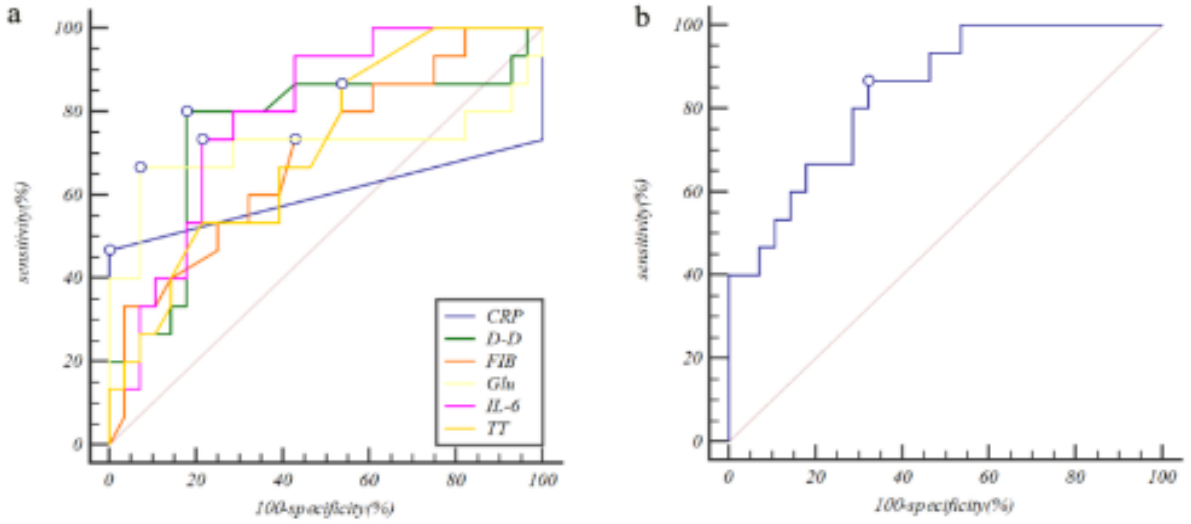

Figure 2

Figure 2: This figure shows the ROC curves for various lab parameters and their predictive value for discriminating severe COVID 19 infections from milder cases. CRP,DD and IL-6 showed significant benefits (a). However, the most robust predictors were IL-6 levels >24 + D-dimer level elevations.[4]

1.2 Tocilizumab (anti-IL-6R) for Treatment of COVID-19

Tocilizumab (Actemra®, Roche/Genentech, CA, USA) is the first in class humanized monoclonal aimed at the IL-6 receptor (IL-6R). Tocilizumab binds to both soluble and membrane bound forms of the IL-6R receptor. Tocilizumab was recently approved by the FDA for treatment of rheumatoid arthritis (RA) and juvenile idiopathic arthritis and cytokine release syndrome (CRS).[5] In patients with CRS after CAR T-cell therapy, elevations of IL-6 and C-reactive protein (CRP) can be seen that have benefit in predicting severity of disease. Tocilizumab has had an important and significant benefit in treating patients with CRS. The question is whether this benefit would translate to other diseases where extreme elevations of IL-6 are seen, such as COVID-19.

Recent data is available to address this. Xu et al recently reported on an open label trial of tocilizumab for treatment of severely ill COVID-19, SARS CoV-2 pneumonia patients.[6] In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China, which spread rapidly and has become a world-wide public epidemic. These investigators aimed to assess the efficacy of tocilizumab (anti-IL-6R) in patients with severe COVID-19. The patients were diagnosed as severe or critical COVID-19 in China. All patients were given tocilizumab (400mg X 1) in addition to standard of care therapy from February 5-February 14, 2020. Assessments included change in clinical manifestations, CT scan image, and laboratory examinations. Analysis of therapeutic efficacy showed that fever returned to normal within 1-2 days and all other symptoms improved rapidly. Fifteen of the 20 patients (75.0%) showed decrements in FiO2 and one patient no longer required oxygen. Sequential CT scans demonstrated an improvement in pulmonary infiltrates in 19 patients (90.5%). Lymphocytes in peripheral blood, were decreased in 85.0% of patients (17/20) before treatment and returned to normal in 52.6% patients (10/19) on day 5 post-tocilizumab treatment. Elevated CRP levels decreased significantly post-tocilizumab in 84.2% patients (16/19). No adverse reactions were observed. Nineteen patients (90.5%) were discharged on average 13.5 days after the tocilizumab. The authors conclude that tocilizumab may represent a novel therapeutic strategy for this often fatal infectious disease. Data from this paper is shown below:

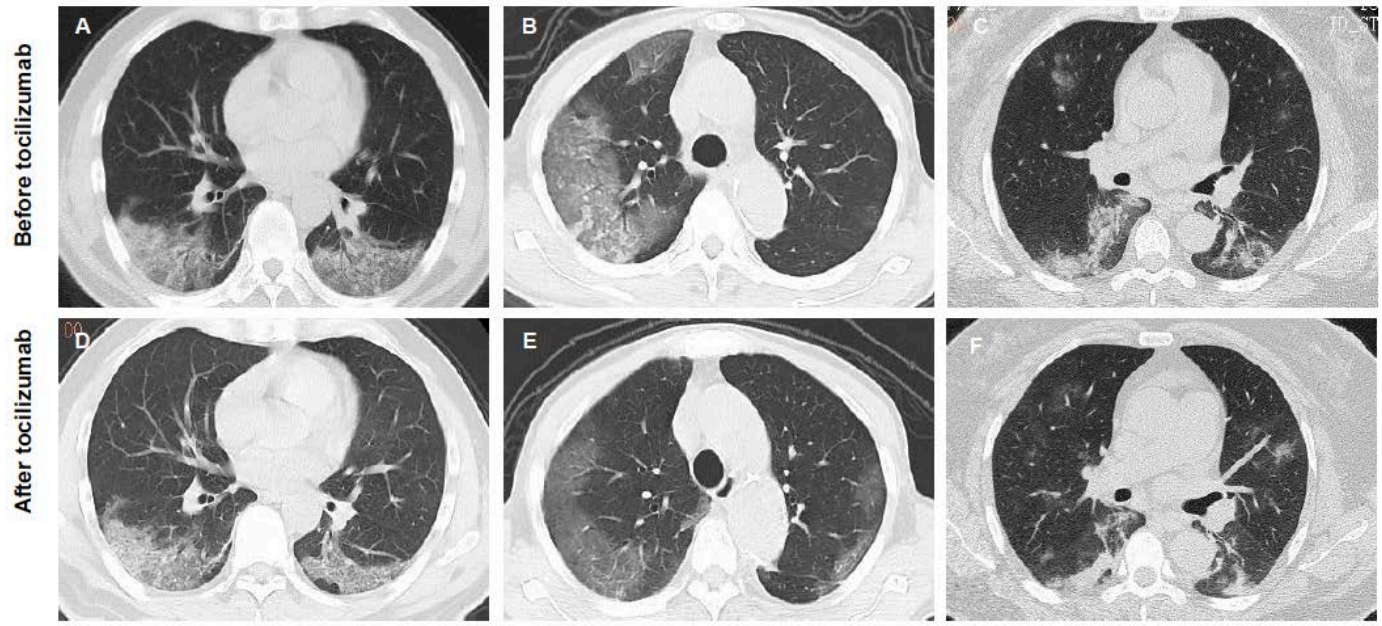

Figure 3: this figure details the improvements in pulmonary infiltrates pre- and post-tocilizumab infusion in 3 patients. These findings correlated with improvements in O2 saturation and decrements in O2 requirements.

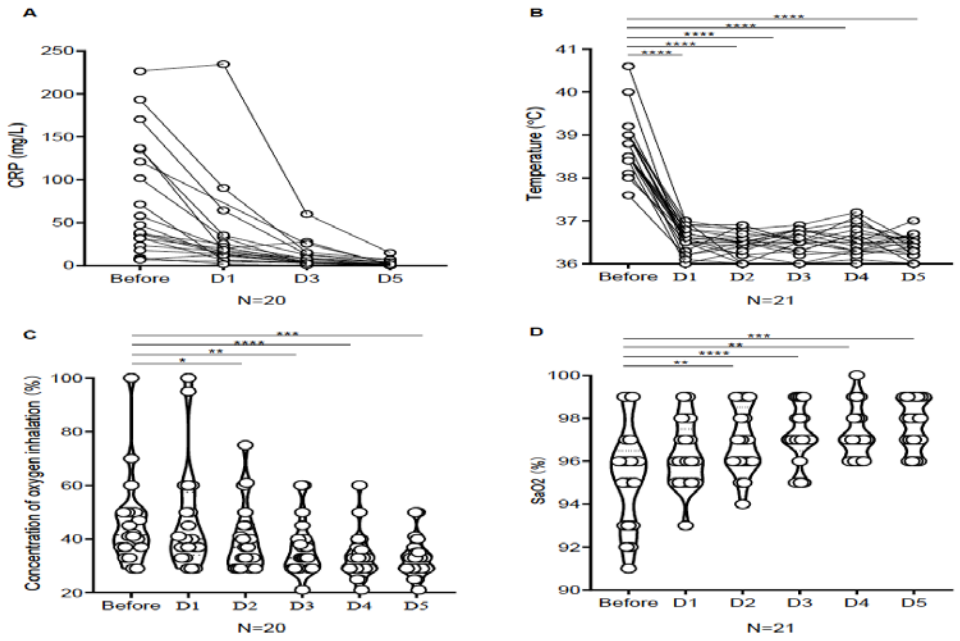

Figure 4: Figure 4 shows the improvements in clinical and laboratory parameters post-tocilizumab therapy. Here rapid improvements in temperature, CRP and oxygen requirements were seen in most patients treated with tocilizumab.

1.2.1 Tocilizumab (anti-IL-6R) for Treatment of COVID-19 (Cedars-Sinai Experience)

From 3/13/2020-3/22/2020, 9 patients with COVID-19,SARS-CoV-2 pneumonia admitted to Cedars-Sinai Medical Center and intubated due to severe hypoxia and pneumonia were treated with tocilizumab 400 mg X 1. Although early, some important indicators have emerged from this open label trial. To date, all patients are alive with one being extubated and home. The other patients have all shown decreasing FiO2 requirements but are still intubated. Some patients have shown improvements in CXR while others are stable, but all have shown dramatic reductions in CRP values and temperatures similar to that seen in the study of Xu et al.[6] Data are summarized below:

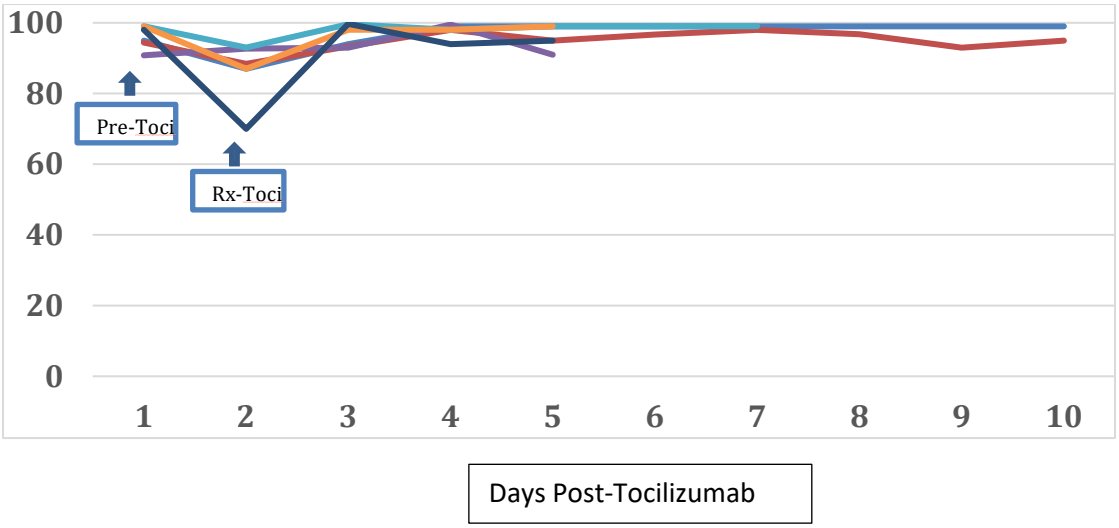

Figure 5: This figure shows the O2 saturation in the patients' blood Pre-, at and Post-Tocilizumab 400mg X 1 dose. All patients have shown reductions in FiO2 requirements, but 8/9 remain intubated.

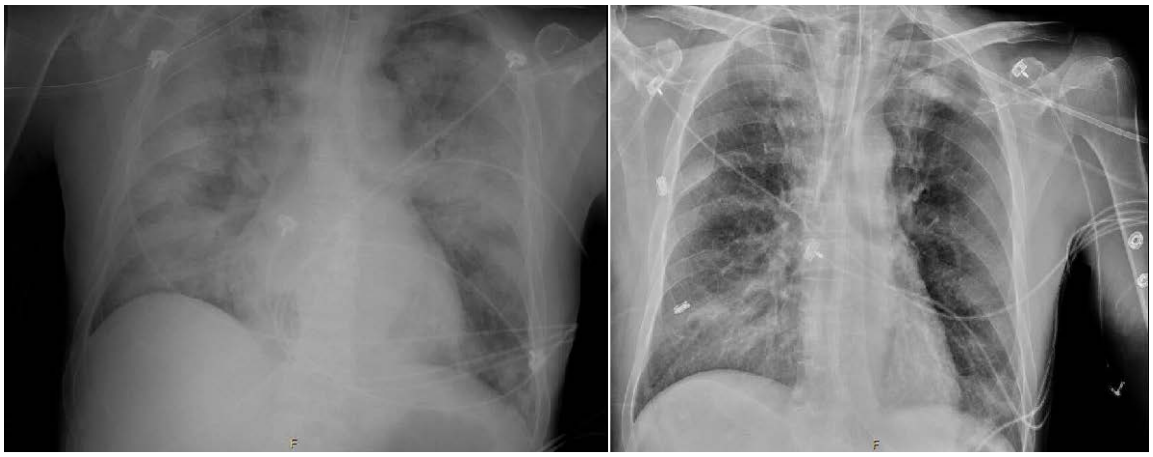

Figure 6: This figure shows pre- & post-tocilizumab CXR in a patient with COVID-19+ with SARS-CoV-2 pneumonia. Patient showed rapid clinic improvement clinically consistent with improvements in his CXR.

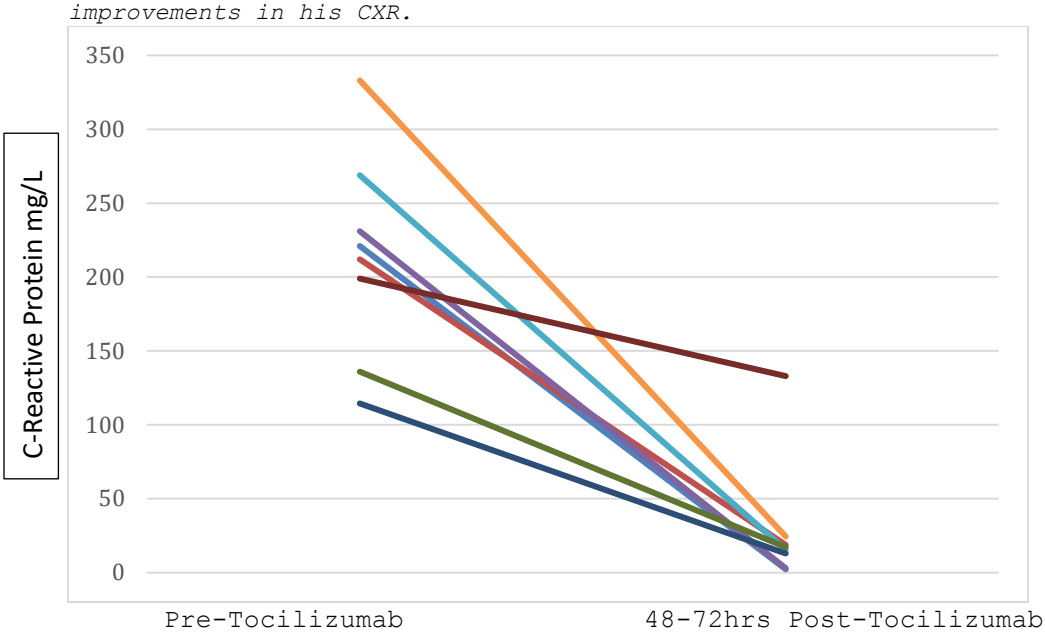

Figure 7: This figure shows rapid improvement in CRP levels in all patients with COVID-19, SARS-CoV-2 pneumonia (NL: 0-5 mg/L). This indicates effective blockade of the IL-6/IL-6R classic and trans signaling pathway, thus reducing inflammation. Mean IL-6 levels in this group were 262.7 pg/ml (NL: 0-5 pg/ml) prior to tocilizumab treatment.

1.3 Clazakizumab (anti-IL-6) as a Potential Agent to Treat COVID-19

Clazakizumab (Vitaeris Inc., Vancouver, BC Canada) is a humanized monoclonal antibody aimed at the cytokine IL-6 ligand. Clazakizumab has been evaluated extensively in patients with RA, but has not yet been approved by the FDA for any condition. Since the introduction of IL-6/IL-6R blocking drugs, reports indicate that inhibition of the IL-6/IL-6R pathway may have significant benefits in Systemic Lupus Erythematosus and other vasculitic disorders and reduces antibody producing cells in treated patients.

Clazakizumab is a genetically engineered humanized immunoglobulin G1 (IgG1) antibody that binds to human IL-6 with an affinity of 4 pM. Using multiple assays

for signaling and cellular functions in response to IL-6 alone (to measure classical signaling) and a combination of IL-6 and sIL-6R (to measure trans-signaling), it was demonstrated that clazakizumab is a potent and full antagonist of IL-6-induced signaling as measured by phosphorylation of signal transducer and activator of transcription 3 (STAT3), as well as cellular functions such as cell proliferation, differentiation, activation, B-cell production of immunoglobulins, and hepatocyte production of acute phase proteins (CRP and fibrinogen). In addition, clazakizumab is shown to be a competitive antagonist of IL-6-induced cell proliferation. This in vitro pharmacological profile supports the potential of clazakizumab to impact multiple immune and non-immune cellular processes that are central to disease pathogenesis, and thus, to offer a new therapeutic modality in the treatment of autoimmune diseases and other IL-6 mediated diseases.

The clazakizumab development program includes a comprehensive nonclinical development program and completed clinical studies conducted in healthy subjects and in subjects with RA, psoriatic arthritis (PsA), Crohn's disease, graft-versus-host disease (GVHD), and oncology. Ongoing studies include a pivotal Phase 3 study in kidney transplant recipients with chronic active antibody-mediated rejection (CABMR)(Study VKTX01) and 3 Investigator-initiated trials (IITs) in the kidney transplant setting including highly- sensitized subjects awaiting a kidney transplant, subjects with CABMR, and subjects with late, active antibody-mediated rejection (ABMR).

Nonclinical Studies

A comprehensive nonclinical development program has been completed. Clazakizumab was shown to be a potent inhibitor of IL-6-induced acute phase proteins. In pharmacokinetic (PK)/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 (ePPND) 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 17 and 170 times a human dose of 25 mg (based on a 70 kg adult). These doses are expected to generate exposures (AUCs) approximately 24 and 240 times higher, respectively, than a human dose of 25 mg once every 4 weeks (Q4W). There were no other safety findings of clinical concern.

Clinical studies

Clinical studies have been conducted in healthy subjects and in the following patient populations: RA, PsA, Crohn's Disease, GVHD, and oncology. These clinical studies include a total of 1,223 subjects, of which 1,056 subjects were exposed to clazakizumab with doses ranging from 1 mg to 640 mg given by either intravenous (IV) or subcutaneous (SC) injection for up to 175 weeks.

Clinical Pharmacology

Following the administration of clazakizumab as a 1-hour IV infusion, the PK of clazakizumab were linear over the dose ranges of 30 mg to 640 mg in healthy subjects and 80 mg to 320 mg in subjects with RA as indicated by consistent clearance at these dose levels. The T-half of clazakizumab at all doses was very similar in healthy male subjects and in subjects with RA and was consistent with

that expected for a humanized IgG1 antibody. Across the doses studied, the mean T-half of clazakizumab ranged from 19.5 to 31.0 days in healthy male subjects and from 26.4 to 30.9 days in subjects with RA. The T-half of clazakizumab after SC administration in healthy male subjects was similar to the IV administration. In a Phase 1 study comparing IV and SC dosing in healthy male subjects, the mean T-half of clazakizumab was 30.7 days after a single IV dose and, 31.1 to 33.6 days after SC administration. The bioavailability of clazakizumab after SC administration was 60% of the IV formulation. As expected, Cmax was lower and Tmax was longer for the SC administration relative to IV administration.

Population PK analysis of the data from clinical studies in RA, PsA and healthy subjects have indicated that body weight affects the PK of clazakizumab such that both clearance and central volume of distribution increase with increasing body weight. Therefore, heavier subjects will have lower drug exposure compared with less heavy subjects.

Clinical Efficacy and Safety Studies

Efficacy and safety data for clazakizumab is available from clinical studies conducted in RA, PsA, and oncology. Preliminary safety data are also available from the ongoing Study VKTX01 and IITs in the kidney transplant setting. Studies conducted in GVRD and Crohn's disease were prematurely terminated due to safety concerns and therefore no efficacy conclusions are available for these studies. In Phase 2 studies in RA and PsA, doses from 5 mg SC Q4W up to 320 mg IV once every 8 weeks were significantly effective with clinical response evident as early as 12 weeks post treatment. One study in RA also demonstrated that the efficacy of clazakizumab is comparable or may be better than the standard of care treatment (adalimumab + methotrexate (MTX)) in RA.

Efficacy with clazakizumab was not shown in the 2 Phase 2 studies in oncology (head and neck cancer and non-small cell lung cancer).

Two studies were terminated prematurely due to safety concerns. A Phase 2 study in Crohn's was terminated early because of gastrointestinal (GI) perforation in 3 subjects who had received clazakizumab and this indication is no longer being studied. Although these subjects had multiple confounding medical issues, and the disease itself has an inherent risk of mucosal perforation, cases of perforated diverticulitis were also observed in 1 patient with head and neck cancer and in 2 kidney transplant patients with antibody-mediated rejection. Gastrointestinal perforations were also observed during the clinical studies with tocilizumab in patients with RA. Gastrointestinal perforation is a recognized risk of anti-IL-6 mAbs. After only 3 subjects were enrolled, a study in subjects with GVHD was also prematurely terminated due to 2 subjects experiencing similar serious adverse events (SAEs) (i.e., acute renal failure) which led to death. Both subjects had severe GVHD disease at the time of death.

Overall, the safety findings from the clinical studies conducted with clazakizumab to date are consistent with the known effects of blocking the IL-6 pathway (see Actemra® prescribing information). Identified risks associated with clazakizumab administration include the following: infections, liver function test abnormalities, changes in hematology parameters (i.e., neutropenia and thrombocytopenia), dyslipidemia (i.e., hypercholesterolemia and hypertriglyceridemia), and GI perforations. Mild or moderate injection site reactions have been reported with SC administration. Infusion reactions including hypersensitivity type reactions have the potential to occur with IV administration of antibody products, although this type of reaction has not been observed to date with clazakizumab.

For further details regarding clinical studies with clazakizumab, please consult the Investigator's Brochure.

Rationale for Dosing

The dose chosen for this study (25 mg IV)is based on the results of nonclinical studies, and the pharmacodynamic efficacy and safety profile seen in repeat-dose clinical studies conducted with clazakizumab in RA and PsA, as well as preliminary safety data from the ongoing pivotal study (VKTX01) and IITs in which clazakizumab is being investigated in the kidney transplant setting at doses of up to 25 mg SC Q4W. Selection of the proposed dose also takes into consideration the comparability of doses of clazakizumab and tocilizumab used in RA, as well as preliminary evidence of the efficacy of IL-6R blockade and acceptable toxicity of tocilizumab in the treatment of patients with severe COVID-19 infections (see Sections 1.2 and 1.2.1, respectively).

In RA, PsA, and in healthy subjects, rapid and durable suppression of CRP has been demonstrated at clazakizumab doses bracketing the proposed investigational dose of 25 mg. In RA studies, the observed level of CRP suppression at clazakizumab doses ≥5 mg SC Q4W was similar to that seen for tocilizumab 8 mg/kg IV injection Q4W +methotrexate. In efficacy analyses in RA, clazakizumab doses of 5 mg, 25 mg, and 100 mg SC injection Q4W were comparable to tocilizumab doses of 4 mg/kg and 8 mg/kg IV Q4W. In Chinese patients(Xu et al) and in Cedars-Sinai patients with severe/critical COVID-19 infection, rapid suppression of CRP was observed with a tocilizumab dose of 400 mg IV (corresponding to 5.6 mg/kg for a 70 kg adult). Based on the data from the aforementioned clinical trials, a 25 mg dose of clazakizumab would be expected to show similar suppression of CRP in this patient population.

In our current kidney transplant study for ABMR treatment, clazakizumab has been administered 25 mg SC monthly for the first year, followed by 25 mg SC every other month for years 2 and 3. Our kidney transplant desensitization study uses clazakizumab 25 mg SC monthly x 6 months pre-transplant, followed by 25 mg SC monthly for 1 year post-transplant.

The completed and ongoing 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. Clinically significant AEs were mainly seen at higher clazakizumab doses (i.e., ≥100 mg), whereas doses 25 mg or less were well tolerated.

For the route of administration, trials of both the SC and IV routes have been performed. Apart from the bioavailability being about 40% less by the SC route vs IV, the most notable difference between the two routes is the median time to Tmax. Tmax was achieved after 1 week in patients a receiving SC dose, compared to at the end of infusion for patients receiving an IV dose. Given that the study subjects enrolled here are acutely ill, any beneficial effect of the clazakizumab will need to be seen immediately.

2.0 Study Hypothesis

Based on data of efficacy of tocilizumab in capillary leak syndrome, data obtained from the tocilizumab trial in China and data from our institution, we strongly believe the evidence supports the use of anti-IL-6/IL-6R therapies as possible treatments for prevention and treatment of COVID-19 disease and SARS-CoV-2 pneumonia. Unfortunately, tocilizumab is in short supply and not available for purchase at this time. Due to our experience with clazakizumab (anti-IL-6) which

shows potent efficacy in inhibiting both classic and trans-signaling pathways, we would propose a study to investigate efficacy in COVID-19+ patients who have not yet progressed to SARS-CoV-2 pneumonia in an effort to interrupt the severe pulmonary pathology induced by COVID-19 and high mortality. Thus, we proposed a randomized placebo controlled trial to evaluate the utility of clazakizumab as a treatment that is likely to benefit COVID-19+ patients and will significantly reduce or eliminate their progression to SARS-CoV-2 pneumonia with attendant improvements in mortality and morbidity. This treatment is likely to reduce the numbers of patients needing respiratory therapy, reduce hospital length of stay and costs to the health care system.

3.0 Primary Objectives

The primary objective of the study is to evaluate the safety of clazakizumab for the treatment of patients with COVID-19 disease and signs of pulmonary involvement.

3.1 Major Secondary Objectives

The administration of clazakizumab is hypothesized to reduce the risk of progression of COVID-19 disease to ARDS requiring mechanical ventilation and/or extra-corporeal membrane oxygenation(ECMO). The secondary endpoints will be the need for mechanical ventilation and/or ECMO at 14 days after the first administered dose in comparison to placebo, patient survival at 28 and 60 days, the number of patients requiring the dose of open-label clazakizumab, and the ability of clazakizumab to reduce the duration of intensive care unit stay and hospital stay, in comparison to placebo.

3.2 Inclusion Criteria

- ✓ Age >18 at the time of screening.
- ✓ Subject must be able to understand and provide informed consent or have a surrogate decisions maker available to provide consent
- ✓ Subject must be able to comply with the protocol and willing to fully participate in the requirements of the study
- ✓ Hospitalized with COVID19+ disease (confirmed by PCR assay from any specimen within 72 hours of screening e.g. respiratory, blood, urine, stool, other)
- ✓ Not on mechanical ventilation and/or ECMO
- ✓ Evidence of pulmonary involvement with at least 2 of the following:
  - oxygen saturation at rest in ambient air with SpO2 ≤ 94%
  - tachypnea with resting respiration rate (RR) > 25 breaths/minute
  - PaO_2/FiO_2 ≤ 300 mmHg
  - Chest imaging (radiograph, CT scan, or lung ultrasound) with abnormalities consistent COVID-19 pneumonia
  - CRP >35 mg/L

3.3 Exclusion Criteria

- ✓ Previous hypersensitivity or allergic reactions to clazakizumab
- ✓ Lactating or pregnant females.
- ✓ Known, active: inflammatory bowel disease, untreated diverticulitis or GI perforation
- ✓ Known, active infection
- ✓ Subjects with latent TB and who are not receiving treatment.
- ✓ Subjects with active TB

- ✓ A significantly abnormal screening lab result defined as a WBC < 3.0 X 10^3/ml, a Hgb < 8.0 g/dL, a platelet count < 50 X 10^3/ml, an SGOT or SGPT > 5X upper limit normal
- ✓ Participation in another clinical trial investigating COVID-19 aimed agents

3.4 Subject Screening and Enrollment

The patients eligible for the study and who may benefit from the administration of clazakizumab will be identified by the members of the inpatient team and referred to the study team. A member of the study team will then review the medical record to assess eligibility (minimum 17 variables assessed). If the patient is eligible, the PI or Co-Investigator will discuss the study with the patient.

3.5 Subject Recruitment

Hospital leadership is closely monitoring the COVID-19 cases and are in communication with investigators running COVID-19 trials. Treating physicians of COVID-19 patients will be made aware of the research offering. If they have capacity to consent for themselves, treating physicians will ask patients if they are willing to be approached about research options. Researchers may approach potential subjects who indicate they are interested.

Note: patients may be in isolation units. Therefore, this contact may be made over the phone into the patient's room with visualization from the treating physician and research from the window outside the room to minimize contact

The population of patients being admitted with COVID-19 disease does include a large component of older patients with some degree of diminished cognitive function. If patients do not have the capacity to consent for themselves, treating physicians will work with researchers to identify an appropriate surrogate and connect researchers with surrogate decision makers to determine if a research option is appropriate for the patient.

The research relates to life-threatening diseases and conditions of the participants and holds out the prospect of direct benefit. The consenting co-investigators (MDs) will determine the patient's capacity to provide consent. Subjects who lack capacity will be given the opportunity to dissent where appropriate. An individual who has Power of Attorney or who is otherwise authorized to make health care decisions for a potential research subject may not provide consent on behalf of the potential subject if the potential subject has the cognitive capacity to provide consent for themselves. The research will not enroll persons under psychiatric conservatorship or persons on a voluntary or involuntary psychiatric hold. The surrogates will not be paid for providing informed consent. If a subject should regain capacity during their participation, they will be informed of the nature of their participation and given the opportunity to consent to continue to participate in the research or refuse to continue to take part in the study. The study team will document the surrogate decision makers who are involved and available to provide informed consent for the subject, their relationship to the subject, and their respective decisions.

REDCap or DocuSign may be used for remote consent of surrogate decision makers, as there are restrictions in place that preclude in-person visitors. The remote consent process may take place over the phone or via a video visit to allow the consent conversation and process, and signature may be obtained either through REDCap or DocuSign, or the surrogate may scan/email their signed copy for the

investigator to either print and sign, or add an Adobe digital signature. If need be, the surrogate could fax their signature page instead of scanning/emailing.

3.6 Informed Consent Considerations

Given limited supplies of personal protective equipment and isolation requirements, consent may be provided over the phone and, when feasible, with direct visualization through the patient room window or using a video platform to minimize entry into the room. A picture of the consent form with patient signature may be utilized as documentation of informed consent. The signed consent in these circumstances will be photographed and saved electronically. The consenting physician and witness (when the patient is a non-English speaker) will sign a second full copy of the consent and print/attach the photographed patient's signature page.

Given isolation precaution for this population, potential subjects who have capacity to consent and who have access to a smartphone, tablet, or computer with them in their room may be provided a link to a digital version of the consent form using REDCap or DocuSign to avoid the use of paper, which cannot be removed from the containment unit. If the potential subject does not have access to a smartphone/online consent form, then a paper copy will be used. While patients may be approached soon after their visit and/or admission begins, they can take time to consider and discuss participation with others before deciding. All questions will be answered by an investigator prior to signing the consent form. If the above process to obtain consent with the subject are not possible in an individual case, as a last resort, the study team can treat this as a case where the subject cannot physically sign and have a witness (e.g., clinical nurse) to the consent discussion sign to document that the patient agreed to participate. This will be a last resort option and the study team will make every effort first to get a signature from the patient. The process followed will be fully documented with a consent progress note.

For the enrollment of non-English speaking subjects, certified medical interpreters will be used with the short form consent. A certified medical interpreter will be present (over the phone) to translate the document and interpret the consent discussion following IRB policy. A witness to the consent process must sign the consent form and short form, but the witness does not need to be fluent in both languages. If the interpreter is unable to sign as witness, a chart note should document the identity and involvement of the interpreter.

4. Study Design & Methods

This is a single center, randomized, double-blind, placebo-controlled, exploratory phase II study. We propose the administration of a blinded dose of an investigational product (IP) (clazakizumab or placebo[0.9% saline]) in patients with COVID-19 disease and signs of pulmonary involvement who have not yet required mechanical ventilation and/or ECMO. If a patient progresses to mechanical ventilation and/or ECMO or develops clinical signs of deteriorating COVID-19 disease, and there are no treatment related serious adverse events(SAEs), within the initial 14 day period after the first dose of the IP, at the discretion of the investigator or treating physician, open-label clazakizumab 25mg IV X 1 dose may be administered (open label dose may be given within the first 14 days of the initial blinded IP dose). A minimum of 24 hours should elapse between the first dose of IP and this dose of open-label clazakizumab. The patient will remain blinded as to the identity of the IP administered in the first dose.

The trial will primarily examine the safety and tolerability of clazakizumab given to patients with COVID-19 disease. All patients will be recruited at Cedars-Sinai Medical Center, unless otherwise designated by sponsor. The patients eligible for the study and who may benefit from the administration of clazakizumab will be identified by the members of the inpatient team. The study protocol is below:

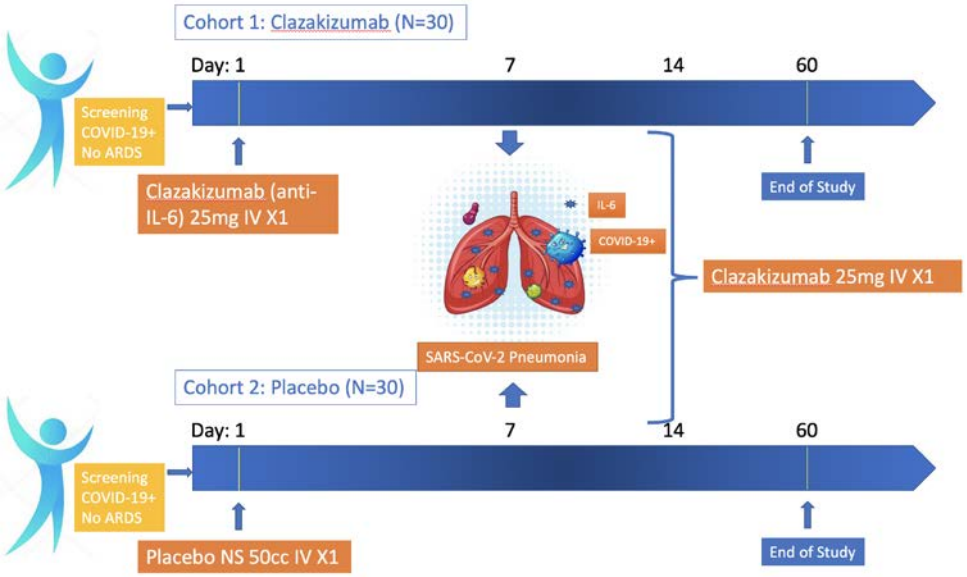

Figure 8 shows the protocol to be followed. Briefly, Patients admitted to hospital with COVID-19 disease with signs of pulmonary involvement will be randomized to receive the anti-IL-6 drug clazakizumab 25mg IV or placebo. Patients will be followed for improvements in clinical symptoms and laboratory parameters which are part of our COVID-19 lab panel described below. Patients will receive SOC supportive treatment and will be followed for 14 days. If a patient from either group progresses to the need for mechanical ventilation and/or ECMO, or develops clinical signs of deteriorating COVID-19 disease, and there are no serious treatment related SAEs, at the discretion of the investigator or treating physician, the patient may receive a single dose of open-label clazakizumab 25mg IV. A minimum of 24 hours should elapse between the first dose of IP and this dose of open-label clazakizumab.

Enrolled patients will receive clazakizumab 25 mg or placebo (0.9% saline) given by IV infusion over 30 minutes. Clazakizumab will be administered in 50 mL of 0.9% saline on Day 1.

COVID19 positivity will be assessed by RT-PCR assay (A*STAR Fortitude 2.0 assay from Singapore) and the Abbott ID NOW rapid PCR assay for detection of COVID-19 RNA in nasopharyngeal samples, as per SOC. COVID-19 lab panel and clinical parameters will be monitored to determine if patients are progressing towards need for ventilation and/or ECMO. The parameters below will be monitored and patient status will be assessed by the clinical team. Signs of ARDS that will be considered include tachypnea, RR>25 breaths/minute **OR** SpO2 < 90% on 4L **OR** increasing O2 requirements over 24 hours, **PLUS** 2 or more of the following predictors for severe disease:

- IL-6 > 10 pg/mL
- CRP > 35 mg/L
- Ferritin > 500-600 ng/mL
- D-dimer > 1 mcg/L
- Neutrophil-Lymphocyte Ratio > 4
- LDH > 200 U/L

- ↑ troponin in patient w/out known cardiac Disease

If patients do develop these criteria, open-label clazakizumab 25 mg IV may be administered as discussed above. A minimum of 24 hours should elapse between the first dose of IP and this dose of open-label clazakizumab. Patients ventilated with or without ECMO will continue to be monitored post-treatment for signs of improvement, (i.e., decreasing FiO2 requirements, CXR improvements, CRP reductions, extubation and discharge home) or death.

4.1 Study Analysis

This single-center, randomized, double-blind, placebo-controlled, Phase II, trial is designed to examine the safety, tolerability and efficacy of clazakizumab vs placebo in subjects with COVID-19 disease, who have not yet progressed to mechanical ventilation and/or ECMO.

4.2 Statistical Considerations

To create a reasonable trial, it is important to understand the risk for progression from COVID-19 disease to ventilation with or without ECMO. In our institution, initial estimates from our infectious disease specialist suggests ~25% will progress to need for ventilation. This is also consistent with unpublished reports from the Chinese experience. Data from a recent report in JAMA indicated that up to 41.8% of patients with COVID-19 disease progressed to ARDS and 33.3% received mechanical ventilation.[7] Based on these observations, we performed the following calculations to estimate the number of patients needed to see a statistical difference between clazakizumab vs. placebo treated patients. Using the Fisher exact test, a significance level of 0.10 α(p-value) and 70% power (rather than 80%), assuming the expected rate of 1/30 (0.033), the SAS power analysis gives an estimated sample size of 30 per group. Estimated sample sizes: N = 60. N per group = 30. (See Appendix D for Statistical Calculations) In summary, when we assume a rate of 25% for placebo treated patients to progress to ARDS with ventilation and/or ECMO, and a 1% rate for clazakizumab, 60 patients are needed to see a statistical difference. Thus we propose to use 30 patients per group to assess this model. Due to the exploratory nature of this study that involves safety endpoints only and the small sample size that is not powered for efficacy end points, our primary objective will be to assess safety.

The statistical analysis for the primary objective of safety will utilize the chi-square test to compare the proportion of severe adverse events (SAE's) between the clazakizumab and placebo groups. The analysis will be performed on an intent-to-treat basis of the entire study population. For analysis of the secondary objective comparing the proportion of patients who required mechanical ventilation in the clazakizumab and placebo groups, statistical comparison will be made with the Fisher's exact test (given a low anticipated event rate in the treatment group).

4.3 Study Schedule

Screening:

- Inclusion and exclusion criteria verified
- Medical history and physical exam documented by a member of the treating team
- Concomitant medications documented
- Quantiferon Gold test prior to administration of clazakizumab (does not have to be resulted prior to dose; can be within the past 30 days)
- Pregnancy test for women of child bearing potential (WOCBP)

Day 1 (may be combined with screening visit)

- Informed consent signed
- Physical examination documented by a member of the treating team
- Baseline COVID-19 panel (See Appendix A for lab list) and Treg profile drawn
- Infusion of IP (25 mg clazakizumab or placebo)

Day 3:

- Collection of information: CMP, COVID-19 panel labs obtained through SOC

Day 7 +/- 1:

- COVID-19 panel and Treg profile drawn

Day 14 +/- 2 (Or at discharge, whichever occurs first)

- Physical examination documented by a member of the treating team
- Collect clinical data (hemodynamic parameters, respiratory parameters)
- Collect information: CMP, COVID-19 panel labs obtained through SOC
- Review of Chest X-ray collected per SOC
- Concomitant medications documented
- If the patient progresses to ventilation, use and duration of proning
- Collect clinical data: Any new infections (infection site, culture source)

Additional clinical data to be collected:

- Date of ICU transfer (if occurs)
- Date of ventilation and/or ECMO (if occurs)
- Date of hospital discharge (if occurs)
- Day 28 and 60 survival status
- Number of days between onset of symptoms and initiation of treatment
- Investigational antiviral agents administered during hospitalization (up to Day 60)

4.4 **Monitoring for AE/SAEs**

Adverse events (AEs) and serious adverse events will be monitored post IP treatment. These include careful attention to infectious complications potentially associated with the IP.

Safety oversight will consist of direct communication between the inpatient team caring for the patient and the PI/Co-Is. Safety concerns raised by the clinical care team or Co-Is of adverse events that are unexpected or unusual, assessed to be connected to the administration of the IP will be directed to the PI.

4.5 Safety Reporting of Adverse Events

Assessment of Safety

Specification of Safety Variables:
Safety assessments will consist of monitoring and reporting all AEs and SAEs, including all life threatening events & events of death, and any study specific issue of concern. We will use the Common Terminology Criteria for Adverse Events (CTCAE) to grade AEs.

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product (IP) or other protocol-imposed intervention, regardless of attribution.
This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with blinded IP infusion or open-label Clazakizumab infusion that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions.
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Methods and Timing for Assessing AND Recording Safety variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, IRB, and Vitaeris Inc. in accordance with CFR 312.32 (IND Safety Reports). Only events that meet the criteria of serious, unexpected, suspected adverse reactions that occur with clazakizumab should be reported to the FDA as an IND safety report

Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained, initiation of study treatment and ends at Day 60.

4.5.1 Reporting of Serious Adverse Events Associated with Clazakizumab

All serious adverse events (SAEs) including follow ups that are unusual and/or unexpected (Version 6.0 of the clazakizumab Investigator's Brochure will be used to assess expectedness of reported SAEs) for which there is a reasonable suspicion the experience may have been caused by clazakizumab should be recorded on a MedWatch 3500A Form and faxed or e-mailed to:

SAE Reporting	**Contact Information**
Vitaeris Drug Safety: Dr Edward Chong This must be reported to Vitaeris within 24 hours. (Please use the safety reporting form attached in Appendix E and also submit to Drug.Safety@bionical-emas.com)	Tel: 604 638 1582 (0ffice), 250 216 6371 (cell) email: eddie.chong@vitaerisbio.com
Study Coordination Center/Principal Investigator: Stanley C. Jordan, M.D.	Tel: 310-423-2641 Fax: 310-423-6369

IRB Contact information. Online submission of MedWatch via Cedars-Sinai IRB portal Keren Dunn Cedars-Sinai Medical Center Executive Director, Research Compliance	Tel: 310-423-4148

AND:
MedWatch 3500A Reporting Guidelines:
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to the IP
- Investigator's assessment of the expectedness of the adverse event as assessed against the current version of IB's Section 7.3.3.

Follow-up information:
Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report; submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form.
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (the patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Vitaeris may contact the reporter for additional information, clarification, or current status of the subject for whom the AE was reported.

Study Drug Relationship:
The investigator will determine which events are associated with the use of the study drugs. The causality assessment is the determination of whether there exists a reasonable possibility that the Study treatment caused or contributed to an adverse event:

- **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.

4.5.2. **Pregnancy Reporting**

Any pregnancy occurring in a female subject during the study will be reported to the FDA and Vitaeris within 72 hours. In the event of a pregnancy, study treatment will be stopped. The outcome of all such pregnancies (including normal births) shall be followed up and documented. Every effort should be made to gather information regarding the pregnancy outcome until 90 days (or otherwise as appropriate) post-partum. It is the responsibility of the Investigator, together with the appropriate support from Vitaeris, to obtain this information.

Pregnancy in and of itself is not an SAE. However, complications of pregnancy such as abortion (spontaneous or induced), premature birth, or congenital abnormality are considered SAEs and will be reported.

4.5.3 **Data Safety Monitoring Board (DSMB)**

Safety oversight will be under the direction of a DSMB. This DSMB committee for this study will be comprised of individuals with expertise across the broad range of disciplines (such as internal medicine, infectious diseases, nephrology). The DSMB Charter is attached in Appendix C.

The DSMB will be notified of all AEs and SAEs. 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 PI.

The DSMB will hold emergency meetings in the event of patient deaths to discuss whether unblinding is warranted or 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 no pre-defined stopping rules for this study. The study team will defer to the judgement of the DSMB whether safety concerns warrant early stopping of the study. There will not be a planned interim unblinded analysis.

5 Dosing of Clazakizumab

Clazakizumab will be administered at a dose of 25mg IV infusion over 30 minutes in 50mL of 0.9% saline.

Product Description, Storage and Administration Instructions

Clazakizumab will be provided by Vitaeris Inc.

Generic name:	Clazakizumab
Active ingredient:	Genetically engineered humanized anti-IL-6 monoclonal antibody
Strength:	25 mg/mL or 12.5 mg/mL
Excipients:	L-histidine, L-histidine monohydrochloride, sorbitol, polysorbate-80, and water for injection
Appearance:	Clear to slightly opaque, colorless to dark yellow-colored solution
Dosage form:	Single-dose vials (25 mg/mL or 12.5 mg/mL) for injection.
Manufacturer:	Ajinomoto Althea, San Diego CA

Clazakizumab vials should be stored at ≤-20°C (-4°F). Protect from light. Prepared infusion may be stored for up to 12 hours in a refrigerator, 2°-8°C (36°-46°F), and at room temperature, 15°-25°C (59°-77°F). The prepared infusion should be protected from light.

5.1 Storage and Handling

Clazakizumab will not be used after the expiry date shown on the kit or vial.

5.1.1 Clazakizumab Overdose

There are no specific antidotes or measures to take in the event of an overdose of clazakizumab. Subjects should be treated with the appropriate supportive care.

5.2 Dose Modification/Toxicity Management

A number of measures will be taken to ensure the safety of patients participating in this study. These measures will be addressed through exclusion criteria (see Section 3.3) and routine monitoring as follows:

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Subjects will be evaluated for AEs (all grades), SAEs, and AEs requiring study drug interruption or discontinuation at each study visit for the duration of study participation.

5.3 Adverse Drug Reactions

Opportunistic Infections and Serious Infections

Physicians should exercise caution when considering the use of clazakizumab in patients with a history of recurring infection or with underlying conditions (eg, diabetes) which may predispose patients to infections.

Vigilance for timely detection of serious infection is recommended for patients receiving biologic agents for treatment of moderate to severe RA as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reaction. Patients must be instructed to contact their physician immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment. If a patient develops a serious infection,

administration of clazakizumab is to be interrupted until the infection is controlled. The clinician should consider the benefit-risk before resuming treatment with clazakizumab.

Gastrointestinal Perforations
Timely diagnosis and appropriate treatment may reduce the potential for complications of diverticulitis and thus reduce the risk of GI perforations. Therefore, patients should be made aware of the symptomatology potentially indicative of diverticular disease, and they should be instructed to alert their healthcare provider as soon as possible if these symptoms arise. In patients with a history of symptomatic diverticulosis, diverticulitis or chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis or other chronic lower GI conditions that might predispose to perforations, the clinician should consider the benefit-risk before using clazakizumab. Discontinuation of clazakizumab is recommended for patients who develop GI perforations.

Demyelinating Disorders
The impact of treatment with clazakizumab on demyelinating disorders is not known; events were rarely reported. Patients should be closely monitored for signs and symptoms potentially indicative of central demyelinating disorders. Physicians should exercise caution in considering the use of clazakizumab in patients with pre-existing or recent onset demyelinating disorders. Treatment with clazakizumab should be interrupted during assessment of a potential demyelination.

Hematologic Abnormalities and Bleeding Events
Decreases in neutrophil and platelet counts have been observed following treatment with clazakizumab in combination with MTX. In addition, there may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist. For patients with concomitant medications associated with hematologic toxicity, the reduction or interruption of the suspected medication is recommended prior to modifying clazakizumab. For Absolute neutrophil count (ANC, cells/mm^3)< 500 or platelet count (cells/mm^3) < 50,000, discontinue clazakizumab

Elevated Liver Enzymes and Hepatic Events
Elevations in ALT and AST have been observed during treatment with the study medications. For ALT or AST > 5n ULN, discontinue clazakizumab

Cardiovascular Events and Elevated Lipids
Patients with RA have an increased risk for cardiovascular disorders, therefore, risk factors for cardiovascular disease (eg, hypertension, hyperlipidemia) should be managed as part of their standard of care. .

Malignancies
The impact of immunosuppression on the development of malignancies is not known, however an increased rate of some malignancies, notably lymphoma, has been observed in RA patients. Although no imbalance of malignancies was observed in clinical trials of clazakizumab, malignancies have been identified as a concern for other biologics. It is recognized that identification of such events in clazakizumab-treated patients may require a longer period of surveillance. Clazakizumab should be discontinued in patients with malignancies (with the exception of local basal or squamous cell carcinoma of the skin that is completely excised with free margins).

Hypersensitivity or Anaphylaxis:
An infusion/dose reaction is defined as an adverse event occurring during and within 24 hours after the infusion or subcutaneous injection of clazakizumab. This may include hypersensitivity reactions or anaphylactic reactions. Signs of a possible hypersensitivity reaction include but are not limited to:

- fever, chills, pruritus, urticaria, angioedema, and skin rash.
- cardiopulmonary reactions, including chest pain, dyspnea, hypotension or hypertension.

Healthcare professionals administering clazakizumab should be trained in the appropriate administrative procedures, be able to recognize the symptoms associated with potential anaphylactic or hypersensitivity reactions, and have the appropriate medication available for immediate use in case of anaphylaxis or hypersensitivity reaction during or after administration of clazakizumab. If a patient has symptoms of anaphylaxis or serious hypersensitivity, or requires an interruption of the study drug because of symptoms of anaphylaxis or hypersensitivity, administration of clazakizumab must be discontinued permanently. The patient should be treated according to the standard of care for management of the hypersensitivity reaction. To date, no infusion reactions have been associated with clazakizumab administered by IV infusion. Injection site reactions have been reported with SC administration. Reactions have been mild or moderate and have resolved without treatment. Both allergic reactions and injection site reactions should be treated with standard of care. Subjects who have developed significant allergic reaction to study drugs should not be re-challenged.

Viral Reactivation
Though rarely reported within the clazakizumab program due to exclusion criteria at study entry, reactivation of viral and other serious infections (e.g. EBV or TB) has been observed with biologic therapies.

Pregnancies and Women of Child Bearing Potential
There are no adequate well-controlled studies in pregnant or lactating women. In nonclinical studies, an increase in the number of monkeys with retention of the placenta at parturition was observed at clazakizumab doses corresponding to 11 and 110 times the planned human dose of 50 mg. In 3 of the 5 monkeys with retained placentas, the resulting excessive uterine hemorrhage led to moribund status in the mothers. Three pregnancies have been reported to date in subjects taking clazakizumab. The outcomes included one spontaneous abortion (outcome unknown for the other 2 pregnancies).

Under no circumstances shall clazakizumab injection be administered to women known to be pregnant or lactating.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise these subjects on the use of highly effective methods of contraception. Subjects must agree to use adequate contraception during the study and for 5 months after the last dose of IP.

5.4 Concomitant Medications
Participation in another study using COVID19 aimed agents will not be permitted during this study. Patients may receive SOC supportive care and off-label COVID19 therapies.

5.5 Latent TB Treatment
If an enrolled patient is found to have latent TB, the treatment for latent TB will not be initiated immediately. Treatment will be initiated 1-2 months after IP administration per the discretion of the investigator and treating team.

5.6 IP Orders

Blinded MD (PI/Co-Is) and pharmacist Co-Is may submit the initial blinded IP order (and if needed, the open-label clazakizumab order) to the unblinded IDS pharmacist. When the pharmacist Co-I submits the order, this order may be placed via scope of practice as allowed by the Pharmacy and Therapeutics Committee.

6 Therapy Stopping Points

As indicated previously, the study will be halted and re-evaluated by the PI along with the IRB if any patient in the study group develops SAEs or evidence of severe infusion related or infectious complications that are deemed to be associated with the clazakizumab. In addition the study will be re-evaluated if a patient develops worsening COVID-19 while on treatment, possibly indicating lack of efficacy of clazakizumab.

7 References

1. Gao Y, Li T, Han M, et al. Diagnostic Utility of Clinical Laboratory Data Determinations for Patients with the Severe COVID-19. J Med Virol 2020.
2. Shirota Y, Yarboro C, Fischer R, Pham TH, Lipsky P, Illei GG. Impact of anti-interleukin-6 receptor blockade on circulating T and B cell subsets in patients with systemic lupus erythematosus. Ann Rheum Dis 2013;72:118-28.
3. Tanaka T, Kishimoto T. Targeting interleukin-6: all the way to treat autoimmune and inflammatory diseases. Int J Biol Sci 2012;8:1227-36.
4. Uciechowski P, Dempke WCM. Interleukin-6: A Masterplayer in the Cytokine Network. Oncology 2020;98:131-7.
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7. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020.

Appendix A Study/Protocol: A Phase II Trial to Evaluate the Safety and Tolerability of Clazakizumab® (Anti-IL-6 monoclonal) As an Agent to Treat COVID-19 Disease

Study visit	Screening[2]	Day 1[2]	Day 3	Day 7± 1 day[3]	Day 14 ± 2 days [3]	Day 28 ± 7 days	Day 60 -7 days, +30 days (EOS)
Medical History	X				X		
Complete Physical Exam	X	X			X		
Hemodynamic and respiratory parameters	X	X	X		X		
Informed Consent		X					
Inclusion/Exclusion criteria review	X						
Randomization		X					
TB testing [Quantiferon TB Gold][1]	X						
COVID-19 PANEL IL-6 CRP Ferritin D-dimer Troponin Procalcitonin LDH BNP CBC with differential		X		X			
Lab test: Treg profile		X		X			
Review Chest X-Ray (collected by SOC)					X		
Concomitant Med Review	X				X		
Clazakizumab or placebo infusion		X					
Adverse Event Monitoring		X			X		X
Assess CMP, COVID-19 panel labs collected by SOC			X		X		
Assess Survival Status						X	X
Open label clazakizumab infusion[4]			X				
Assess use and duration of proning					X		
Pregnancy test for WOCBP (ages 18--55)[6]	X						
Assess new infections					X		
Assess investigational antivirals administered							X[5]

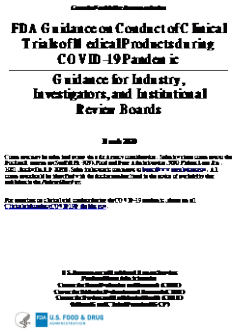
1) At or within one month prior to screening date 2) May be combined (Screening Day and Day 1). Any duplicate items will be collected once. Blood test: comprehensive metabolic panel [CMP] performed per standard of care will be assessed. 3) Or at discharge, whichever occurs first. 4) Patients who decompensate before Day 14 can receive open label clazakizumab (minimum 24 hours from first IP infusion). CBC and CMP will be assessed prior to clazakizumab dose. 5) during hospitalization only; up to study day 60 6) At or within one week of screening

Appendix B: Labs

Lab	Address
Transplant Immunology Lab	Cedars-Sinai Transplant Immunology Lab 8723 Alden Drive, Steven Spielberg Building, Room 336 Los Angeles, CA 90048
Reference Lab	Cedars-Sinai Medical Center Dept of Pathology and Lab Medicine 8700 Beverly Blvd, Room 3719 Los Angeles, CA 90048

Appendix C: FDA Guidance for Clinical Trial Sponsors, FDA Guidance for COVID19 Pandemic, WHO COVID-19 Trial Synopsis

FDA Guidance for Clinical Trial Sponso


FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic

Guidance for Industry, Investigators, and Institutional Review Boards


COVID19 RCT DSMB Charter

Appendix D: Statistical Calculations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Appendix E: Safety Reporting Forms