CRITICAL:
CRIzanlizumab for TreatIng COVID19 vAscuLopathy

Clinical Trial Protocol

Principal Investigator: Charles Lowenstein, MD

Version Number: 30

Date: 14-December-2020

NCT04435184

SIGNATURE PAGE

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in accordance with the design and specific provisions outlined herein; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the study drug and the conduct of the study.

I will use the informed consent form approved by the principal investigator and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board or Ethics Committee responsible for this study.

I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 8 of this protocol.

I also agree to handle all clinical supplies (including study drug) provided by the principal investigator and collect and handle all clinical specimens in accordance with the protocol.

The below signed confirm herewith to have read and understood this trial protocol and/or amendment and appendices; furthermore, to accomplish this study in accordance to the protocol and Good Clinical Practice guidelines, as well as local regulations; and to accept respective revisions conducted by authorized personnel by regulatory authorities.

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LIST OF ABBREVIATIONS

Abbreviation	Abbreviation Term
AE	Adverse Event/Adverse Experience
BID	Twice daily
BP	Blood Pressure
BWH	Brigham and Women's Hospital
BUN	Blood Urea Nitrogen
CC	Coordinating Center
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CTDMS	Clinical Trials Data Management System
CV	Cardiovascular
CVD	Cardiovascular Disease
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EMR	Electronic Medical Record
eSOCDAT	Electronic Source Consultation Data Acquisition Tool
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDS	Investigational Drug Service
IN	Investigator Notification
IND	Investigational New Drug Application

IRB	Institutional Review Board
ITT	Intention-to-Treat
JH	Johns Hopkins
JHH	Johns Hopkins Hospital
JHM	Johns Hopkins Medicine
JHU	Johns Hopkins University
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
PO	“per os” (by mouth, orally)
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SES	Subject Enrollment System
SOCAR	SOcieté CArdiaque Recherche
SOP	Standard Operating Procedure
UP	Unanticipated Problem
UPIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
US	United States
VWF	Von Willebrand Factor

1.0 PROTOCOL SUMMARY

Title	CRITICAL: CRIzanlizumab for TreatIng COVID19 vAscuLopathy
Brief title	Crizanlizumab for Moderate COVID-19
Sponsor and Clinical Phase	Johns Hopkins Medicine
Investigation type	Drug
Study type	Interventional
Purpose	The overall objective of this trial is to determine the therapeutic effect and tolerance of crizanlizumab in patients with coronavirus disease 2019 (COVID-19).
Primary Objective	The primary objective of this study is to compare crizanlizumab to placebo in reducing soluble P-selectin in patients with moderate COVID-19 at day 3 post randomization or hospital discharge day whichever is earlier.
Secondary Objectives	• To compare crizanlizumab to placebo in reducing markers of vascular inflammation and thrombosis including VWF, D-dimer, and CRP at days 3, 7 and 14 after randomization, and soluble P-selectin at day 7 and 14 after randomization. • To compare crizanlizumab to placebo in improving an ordinal severity of illness scale (incorporating O2 requirement, mechanical ventilation, death) measured daily. • To compare crizanlizumab to placebo in time to hospital discharge. • To assess the safety of crizanlizumab compared to placebo in patients with moderate COVID-19.
Exploratory Objectives	• To compare crizanlizumab to placebo in reducing markers of vascular inflammation and thrombosis including fibrinogen, IL-6, PCSK9 at days 3, 7 and 14 after randomization. • To compare crizanlizumab to placebo for time to resolution of fever. • To compare crizanlizumab to placebo for time to liberation from supplemental oxygen. • To compare crizanlizumab to placebo in need for and duration of high flow nasal cannula at FiO2>0.3 and/or flow >30 L/min, • Time to death or mechanical ventilation • To compare crizanlizumab to placebo in need for and duration of mechanical ventilation • To compare crizanlizumab to placebo in time to arterial or venous vascular event, ischemic stroke, or myocardial infarction
Study design	This pilot study is a single-center, randomized, double-blind, parallel group, placebo-controlled, trial.
Population	Approximately 40 male and female patients ≥ 18 years of age who are currently hospitalized with COVID-19 and elevated D-Dimer.

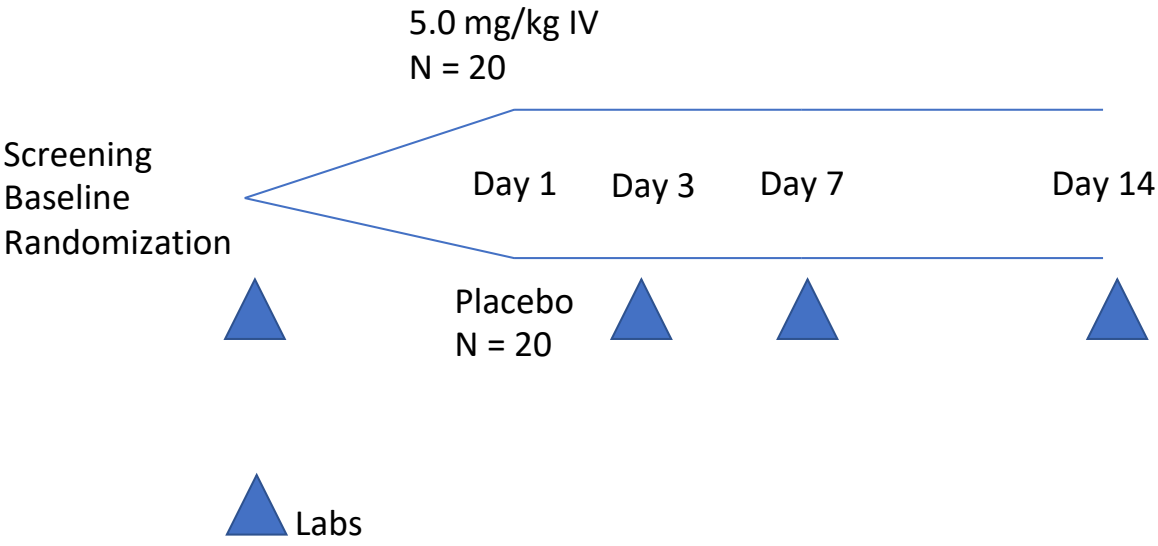
Inclusion criteria	1. Willing to provide written informed consent. 2. Willing to comply with all study procedures and be available for the duration of the study 3. Male or female ≥18 years of age 4. SARS-CoV-2 infection (COVID-19) within the past 10 d documented by laboratory test (NAT or RT-PCR) 5. Currently hospitalized

	6. Symptoms of acute respiratory infection (at least one of the following: cough, fever > 37.5°C, dyspnea, sore throat, anosmia) within past 10 days 7. Radiographic evidence of pulmonary infiltrates 8. Requiring supplemental oxygen or the peripheral capillary oxygenation saturation (SpO2) < 94% on room air at screening. 9. Elevated D-Dimer > 0.49 mg/L 10. Negative pregnancy test for females of childbearing potential
Key Exclusion criteria	1. Use of home oxygen at baseline 2. Current use of mechanical ventilation 3. Inability to provide informed consent 4. Do Not Intubate status 5. Prisoner or incarcerated status 6. Pregnant or nursing (lactating) women. 7. Participation in other interventional drug trials for COVID-19 (emergency use or unblinded use of convalescent plasma is permitted). 8. INR > 3 or aPTT > 60
Investigational and reference therapy	Crizanlizumab 5.0 mg/kg vs. Matching Placebo

Efficacy assessments	• Soluble P-selectin at 7 and 14 days after randomization • D-dimer at 3, 7 and 14 days after randomization • VWF at 3, 7 and 14 days after randomization • CRP at 3, 7 and 14 days after randomization • Fibrinogen at 3, 7 and 14 days after randomization • IL-6 at 3, 7 and 14 days after randomization • PCSK9 at 3, 7 and 14 days after randomization • Liberation from supplemental oxygen at day 3, 7 and day 14, • Need for and duration of high flow nasal cannula at FiO2≥0.3 and/or flow ≥30 L/min, • Need for and duration of mechanical ventilation, • Time to death or mechanical ventilation • Time to hospital discharge • Time to arterial or venous vascular event • Time to ischemic stroke • Time to myocardial infarction • World Health Organization (WHO) Ordinal Scale for COVID-19 Trials measured daily up to 14 days after crizanlizumab.[1] The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. The scale is as follows: (0) Uninfected; no viral RNA detected. (1) Ambulatory; asymptomatic; viral RNA detected. (2) Ambulatory; symptomatic; independent. (3) Ambulatory; symptomatic; assistance needed. (4) Hospitalized: no oxygen therapy. (5) Hospitalized; oxygen by mask or nasal prongs. (6). Hospitalized; oxygen by NIV or high flow. (7) Hospitalized; intubation and mechanical ventilation, pO2/FIO2 ≥ 150 or SpO2/FIO2 ≥ 200. (8). Hospitalized; intubation and mechanical ventilation pO2/FIO2 < 150 or SpO2/FIO2 < 200 or vasopressors. (9) Hospitalized; intubation and mechanical ventilation pO2/FIO2 < 150 or SpO2/FIO2 < 200 and vasopressors, dialysis, or ECMO. (10) Dead.
Safety assessments	• Suspected Unexpected Serious Adverse Reactions • Deaths, requirement for mechanical ventilation, thrombotic events will be assessed as efficacy endpoints • Time to major bleeding event. • Presence of arthralgia, diarrhea, pruritis, vomiting, chest pain
Data analysis	The primary efficacy variable will be assessed as analysis of covariance of a log-transformed P-selectin levels with baseline value and treatment
	allocation as covariates. Secondary biomarker efficacy assessments will be similarly analyzed.

Schematic of Trial Design

Crizanlizumab



2.0 KEY ROLES

2.1 Steering Committee

The Steering Committee is responsible for oversight and management of the conduct of the study at the single study site. Specifics duties include:

- Protocol development
- Ensuring all study staff are trained on the conduct of the protocol and study procedures
- Ensuring adequate resources are available
- Ensuring that the investigation is conducted according to the investigational plan, protocol and applicable regulations
- Ensuring proper monitoring of the investigation
- Ensuring that the reviewing Institutional Review Board(s) (IRB) and regulatory authorities are promptly informed of significant new information or significant new adverse effects/risks
- Public registration of study with ClinicalTrials.gov.

2.2 Clinical Coordinating Center

The Johns Hopkins Medicine Division of Cardiology will serve as the clinical coordinating center (CCC), providing technical and administrative leadership under the authority and direction of the lead Principal Investigator (PI). Responsibilities include working with the lead PI to complete the following:

- Developing and maintaining the protocol and Manual of Procedures (MOP)
- Assisting with the development and design of data collection methods (e.g., case report forms)
  - Assisting with budgets
- Collecting and maintaining critical documents from affiliated investigators (e.g., resume/CV, medical license, certification of completion of training, laboratory certifications and laboratory norms)
- Conducting regular study meetings
- Ensuring the study site has the most current version of the protocol, investigational product information, consent form(s) and other study documents
- Tracking, reporting and maintaining documentation of all serious adverse events and unanticipated problems and disseminating the information to the Sponsor
- Providing periodic updates to affiliated investigators on subject enrollment, general study progress, and relevant scientific advances

2.3 Data Coordinating Center (DCC)

Brigham and Women's Hospital and SOCAR research will serve as the Data Coordinating Center (DCC). The DCC will be responsible for providing expertise and support for data management, quality control and quality assurance, information technology for communication and trial conduct monitoring, and statistical methods for design including randomization, interim monitoring, final analysis and final interpretation of findings from analysis, preparation of results in tabular and graphical formats for presentation and publication of findings from the trial.

2.4 Study Sites

Subjects will be recruited from sites within Johns Hopkins Medicine (Table 1). Roles and responsibilities of the local investigators and study team include: • Compliance with protocol, MOP, IRB, federal and state regulations

- Participation in site initiation visit and study meetings
- Recruitment, screening and enrollment of subjects
- Protection of subjects' rights
- Data collection and subject follow-up through study completion
- Transfer of data to the DCC and resolution of all queries
- Compliance with and accountability of administration of study intervention
- Retention of specific records, (e.g., drug distribution records)
- Communication of questions, concerns, and/or observations to the CCC
- Notifying the CCC of changes in study staff
- Adhering to the CCC's policies and procedures

Table 1: Cli ıical Study Sites

Study Site	Local PI	IRB of Record
Johns Hopkins Hospital 600 N. Wolfe St. Baltimore, MD 21287	Charles J. Lowenstein, MD *clowens1@jhmi.edu* 410-955-3097	JHM IRB 00249874

Johns Hopkins Bayview Medical Center **4940 Eastern Ave** **Baltimore, MD 21224**	Charles J. Lowenstein, MD *clowens1@jhmi.edu* 410-955-3097	JHM IRB 00249874
Howard County General Hospital **5755 Cedar Ln** **Columbia, MD 21044**	Charles J. Lowenstein, MD *clowens1@jhmi.edu* 410-955-3097	JHM IRB 00249874

2.5 Funding Source

Novartis Pharmaceuticals Corporation is providing financial support and study drug for this investigator-initiated clinical trial. Specific responsibilities include:

- Approving protocol changes in writing
- Providing appropriate quantities of investigational product
- Preparing and issuing investigator notifications (INs) for the study drug within 15 calendar days of first notification of the suspected unexpected SAE or subsequent follow-up information
- Incorporating a summary of the institution-generated DSUR for the study into the Novartis DSUR for the product

3.0 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

3.1 Disease Background and Study Rationale

Epidemiology: Infection with severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) causes coronavirus disease 2019 (COVID-19).[2,3] The COVID-19 pandemic has affected over 4,000,000 individuals around the world, and cases continue to accumulate.

Clinical course: The clinical course of COVID-19 is variable. The incubation period of about 5 d is followed by clinical disease that can progress from mild to moderate to severe disease.[4,5] A classification of COVID-19 has been proposed:[6]

I. Stage I: Mild COVID-19 About 80% of infected patients develop mild disease and then recover. This stage involves *viral replication* with non-specific symptoms. Symptoms include fever, malaise and cough; laboratory tests include viral PCR.

II. Stage II: Moderate COVID-19 About 15% of patients progress to moderate disease. This stage is characterized by *pneumonia*. Symptoms can include fever, cough, and dyspnea; laboratory tests show lymphopenia and transaminitis, and imaging tests show bilateral infiltrates in the lung. Hypoxia can occur at this stage.

III. Stage III: Severe COVID-19 develops in about 5% of patients; this stage is characterized by *systemic hyperinflammation*. Severe COVID-19 includes acute respiratory distress syndrome (ARDS), shock, or multiorgan dysfunction leading to death in about 1% of all cases. Abnormal laboratory features include lymphopenia, elevated lactate dehydrogenase, and elevated inflammatory markers. Imaging findings include chest CT with ground-glass opacities in a peripheral distribution. It is likely that the vascular injury is not confined to the pulmonary circulation, but extends to other organs such as the brain, heart, and kidneys. Inflammation in the coronary circulation, as well as the myocardium itself, predispose to cardiac arrhythmias, including atrial fibrillation and malignant ventricular arrhythmias which are often the terminal event in these patients.

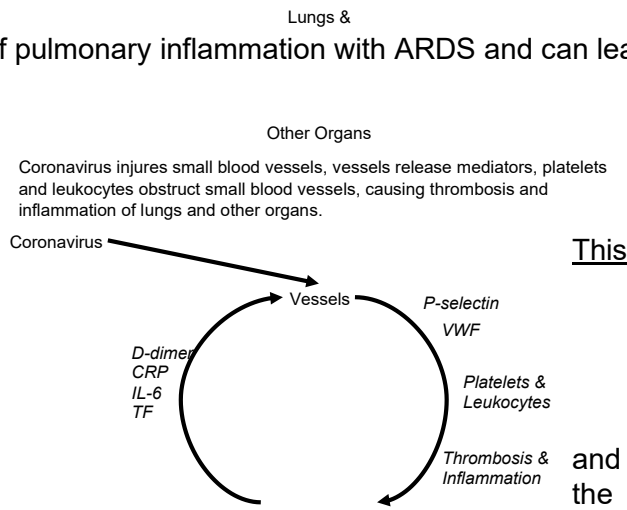
Unique characteristics of COVID-19 suggest microvascular inflammation and thrombosis: We propose that microvascular inflammation and thrombosis plays a central role in the pathophysiology of COVID-19 and its clinical sequela. Our conclusion is based on a combination of clinical and lab findings in patients with moderate and severe stage COVID-19 – including elevated inflammatory biomarkers, elevated thrombotic biomarkers, increased thrombosis,

sequestration of leukocytes, and autopsies of patients dying from COVID-19 – which taken together suggest vascular inflammation and thrombosis.

1. COVID-19 is associated with high levels of biomarkers of systemic inflammation such as IL-6, TNF-a, IL-1ß.
2. COVID-19 is associated with high levels of markers of endothelial activation, such as VWF.[7]
3. COVID-19 is characterized by high levels of biomarkers of thrombosis such as D-Dimer and fibrinogen.[8]
4. The incidence of thrombosis in patients with COVID-19 is unusually high: as many as 25% - 30% of patients with COVID-19 hospitalized in an ICU have venous thromboembolism (VTE) such as deep vein thrombosis (DVT) and pulmonary embolism (PE).[9-11] Physicians at Hopkins and elsewhere have also noted thrombi in the lungs, hearts, liver and kidneys of some patients with COVID-19.
5. The profound lymphopenia seen in COVID-19 suggests that an inflamed vasculature is sequestering lymphocytes in the lung and possibly other organs as well.
6. ARDS associated with COVID-19 is very different from typical ARDS: COVID-19 associated ARDS includes compliant lungs (less stiff than classic ARDS), and a unique pattern of lung injury seen on chest CT with interstitial inflammation and ground-glass opacifications often in the lung periphery (different in appearance and location from typical of classic ARDS). This unique form of COVID-19 associated ARDS could suggest a vascular inflammatory process.
7. Finally, a recent report documents extensive vascular injury and endothelial inflammation in several patients who died from severe COVID-19.[12]

New COVID-19 Paradigm: Vascular Inflammation and Thrombosis: Taken together, these findings suggest a new paradigm for inflammation in COVID-19. The SARS-CoV-2 virus activates endothelial cells in the pulmonary vasculature, and then lung endothelial cells release both pro-thrombotic and pro-inflammatory mediators together, such as VWF and Pselectin. P-selectin activates two parallel pathways: P-selectin mediates leukocyte rolling along the vessel wall, and Pselectin anchors VWF to the vessel wall where VWF interacts with platelets. Leukocytes and platelets adhere to the endothelial cells and obstruct the lung microvasculature, leading to a prothrombotic and pro-inflammatory state. These vascular events cause a unique form of pulmonary inflammation with ARDS and can lead to systemic inflammation.

COVID-19 causes microvascular obstruction and organ damage.



Auto-Amplifying Inflammatory Loop: This vascular pathway creates an auto-amplifying inflammatory loop: pulmonary vascular inflammation and thrombosis leads to pulmonary injury, which causes more pulmonary vascular inflammation and thrombosis. This process starts in the lung, may expand to an auto-amplifying loop in and then the entire body: systemic vascular inflammation leads to injury in multiple organs which causes further systemic vascular inflammation.

Need for Interventions: New therapies for COVID-19 are urgently needed. Over 1000 trials registered on clinicaltrials.gov study various classes of therapy for COVID-19 including: antiinflammatory drugs (glucocorticoids, NSAIDs, IL-6 pathway inhibitors), anti-viral drugs (remdesivir, hydroxychloroquine), and convalescent plasma. No current or proposed therapy directly targets vascular inflammation in COVID-19. The unique aspect of our proposal is a drug

that targets the vasculature, interrupting the auto-amplifying loop by breaking the link between vascular inflammation and tissue injury.

3.2 Investigational Product Background

Summary: Crizanlizumab is an IgG2 kappa humanized monoclonal antibody that binds to P-selectin with high affinity, blocking the interaction between P-selectin and its ligand.

Mechanism of Action: The interaction between P-selectin and its ligand is the first step in vascular inflammation and thrombosis. Resting endothelial cells and resting platelets do not express P-selectin. Immediately following injury or activation, endothelial cells and platelets display P-selectin on the outer surface of the cell. P-selectin on endothelial cells interacts with leukocytes and begins the process of vascular inflammation. P-selectin on the surface of platelets begins the process of platelet adherence and thrombosis. Crizanlizumab blocks the interaction between P-selectin and its ligand, interfering with leukocyte and platelet adherence to the vessel wall.

Indication: Crizanlizumab is indicated to reduce the frequency of vasoocclusive crisis in patients 16 and older with sickle cell disease (SCD). The SUSTAIN clinical trial showed that crizanlizumab prevents vaso-occlusive events in patients with SCD, a process that involves endothelial release of P-selectin and vaso-occclusion.[13] This trial led to FDA approval of crizanlizumab to reduce the frequency of vaso-occlusive sickle cell crises in 2019.

Pharmacology: Crizanlizumab is administered 5.0 mg/kg intravenously over 30 min in patients with SCD. Crizanlizumab is 100% bioavailable. The median time to reach maximum concentration is 1.6 h. The volume of distribution is 4.3 L after a single dose in healthy volunteers. The half-life is 10.6 d. The route of elimination is not through the liver or kidneys.

Safety: Crizanlizumab has a favorable safety profile. In a randomized double-blindplacebo controlled trial (SUSTAIN) of 198 patients, serious adverse events were reported in 55 patients, including 17 patients in the placebo group, 21 in the low dose crizanlizumab group, and
17 in the high dose crizanlizumab group.[13] There were no significant adverse events in the SUSTAIN trial. “The serious adverse events that occurred in at least 2 patients in either active treatment group and at a higher frequency than in the placebo group were pyrexia and influenza. A total of 5 patients died during the trial, including 2 patients in the high-dose crizanlizumab group (1 patient from the acute chest syndrome, and 1 from endocarditis and sepsis), 1 in the low- dose crizanlizumab group (from the acute chest syndrome, aspiration, respiratory failure, and progressive vascular congestion), and 2 in the placebo group (1 from right ventricular failure, and 1 from vaso-occlusive crisis, ischemic stroke, coma, sepsis, and venous thrombosis of the right lower limb). Three additional single-occurrence adverse events that were considered to be both serious and life-threatening but that did not result in death included sepsis (in the placebo group), anemia (in the low-dose crizanlizumab group), and intracranial hemorrhage (in the low-dose crizanlizumab group). The patient with intracranial hemorrhage was being treated with ketorolac, which is associated with an increased risk of hemorrhagic stroke, at the time of the event. No other clinically significant bleeding events were observed in the trial. Adverse events that occurred in 10% or more of the patients in either active-treatment group were headache, back pain, nausea, arthralgia, pain in upper and lower limbs, urinary tract infection, upper respiratory tract infection, pyrexia, diarrhea, musculoskeletal pain, pruritus, vomiting, and chest pain.”[13] “Adverse events that occurred in 10% or more of the patients in either active treatment group and at a frequency that was at least twice as high as that in the placebo group were arthralgia, diarrhea, pruritus, vomiting, and chest pain.”[13]

Infusion related reactions: Administration of monoclonal antibodies can be associated with infusion related reactions (IRR) In the SUSTAIN trial of crizanlizumab for the prevention of vasoocclusive events in patients with sickle cell disease, , IRRs were more frequent in the 5 mg/kg arm (23 patients, 34.8%) than placebo arm (13 patients, 21.0%). However, only 1 event, nausea, was reported in at least 10% of patients: 10.6% vs. 1.6% patients in 5 mg/kg vs. placebo arm, respectively. Except for nausea, none of the events were reported with an absolute differences of

more than 5% in the crizanlizumab 5 mg/kg arm vs. placebo. A review of potential IRR events revealed few cases supportive of typical IRRs. None of these AEs were suggestive of severe allergic or anaphylactic reactions. Most patients continued their treatments without need for premedication.[13]

Subjects in the current trial protocol will be randomly assigned to crizanlizumab 5.0 mg/kg IV or a matching placebo once. All study drug will be provided free of charge by Novartis during the treatment phase. Additional open label anti-inflammatory and antithrombotic medications and other medications will be permitted for subjects.

3.2.1 Summary of Findings from Relevant Clinical Trials

The SUSTAIN trial (Study to Assess Safety and Efficacy of Crizanlizumab (SelG1) with or without Hydroxyurea Therapy in Sickle Cell Disease Patients with Sickle Cell–Related Pain Crises) was a multicenter, randomized, double-blind, placebo-controlled trial in 198 subjects with sickle cell disease and a history of vaso-occlusive crises.[13] Subjects were randomized to receive crizanlizumab or placebo every 2 weeks and followed for 52 weeks. The primary endpoint was the annual rate of vaso-occlusive pain crises. Secondary endpoints included annual rate hospitalized days, annual rate of uncomplicated crises, annual rate of acute chest syndrome, pain score by questionnaire, time to first and second vaso-occlusive crisis. Crizanlizumab therapy decreased the rate of vaso-occlusive crises (45% lower rate, P = 0.001). “Adverse events that occurred in 10% or more of the patients in either active treatment group and at a frequency that was at least twice as high as that in the placebo group were arthralgia, diarrhea, pruritus, vomiting, and chest pain.”[13]

3.2.2 Summary of the Known and Potential Risks and Benefits to Human Subjects Risks associated with crizanlizumab have been reported in the SUSTAIN trial.[13] Adverse events that occurred in at least 10% of patients receiving crizanlizumab and that occurred more than twice the rate of patient receiving placebo included arthralgia, diarrhea, pruritus, vomiting, and chest pain. Serious adverse reactions to crizanlizumab include pyrexia 2%. A summary of all adverse reactions to crizanlizumab include: nausea 14%, abdominal pain 8%, diarrhea 8%, vomiting 5%, pyrexia 2%.

4.0 OBJECTIVES/ENDPOINTS

4.1 Primary Endpoint

The primary endpoint is the difference in level of soluble P-selectin between the group receiving crizanlizumab and the group receiving placebo at day 3 after randomization or hospital discharge day, whichever is earlier.

4.2 Secondary Endpoints

The secondary objectives are as follows:

- level of soluble P-selectin at day 7 and 14 (+/- 1 d)
- level of D-dimer at day 3, day 7 and 14,
- level of VWF at day 3, day 7 and 14,
- level of CRP at day 3, day 7 and 14;
- World Health Organization (WHO) Ordinal Scale for COVID-19 Trials measured daily up to 14 days after crizanlizumab. The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. The scale is as follows:

0. Uninfected; no viral RNA detected
1. Ambulatory; asymptomatic; viral RNA detected
2. Ambulatory; symptomatic; independent
3. Ambulatory; symptomatic; assistance needed

4. Hospitalized; no oxygen therapy
5. Hospitalized; oxygen by mask or nasal prongs
6. Hospitalized; oxygen by NIV or high flow
7. Hospitalized; intubation and mechanical ventilation, pO2/FIO2 ≥ 150 or SpO2/FIO2 ≥ 200
8. Hospitalized; intubation and mechanical ventilation, pO2/FIO2 < 150 or SpO2/FIO2 < 200 or vasopressors
9. Hospitalized; intubation and mechanical ventilation, pO2/FIO2 < 150 or SpO2/FIO2 < 200 and vasopressors, dialysis, or ECMO
10. Dead

- time to hospital discharge
- safety of crizanlizumab

Note: units for labs include: soluble P-selectin ng/ml, VWF antigen %, CRP mg/dL, D-dimer mg/L FEU, IL-6 pg/mL.

4.3 Exploratory Endpoints

The exploratory endpoints are as follows:

- levels of fibrinogen at day 3, day 7 and day 14,
- levels of IL-6 at day 3, day 7 and day 14,
- level of TNF-alpha at day 3, day 7 and day 14
- level of factor 8 at day 3, day 7 and day 14
- levels of soluble ICAM-1 at day 3, day 7 and day 14
- levels of soluble VCAM-1 at day 3, day 7 and day 14
- levels of CCL2 at day 3, day 7 and day 14
- level of troponin isoform T or I at day 3, day 7 and day 14
- level of NT-pro-BNP at day 3, day 7 and day 14
- levels of PCSK9 at day 3, day 7 and day 14,
- time to resolution of fever,
- time to liberation from supplemental oxygen,
- time to mechanical ventilation,
- time to hospital death,
- time to arterial or venous vascular event
- time to ischemic stroke,
- time to myocardial infarction
- time to hospital discharge.

4.4 Safety Assessments

Standard laboratories will be collected at days 3, 7, and 14 including: basic metabolic panel (Na, K, HCO2, Cl, BUN, Cr) and complete blood count (WBC, Hct, Hgb, Plt) with differential.

4.5 Correlative Objective

None.

5.0 STUDY DESIGN

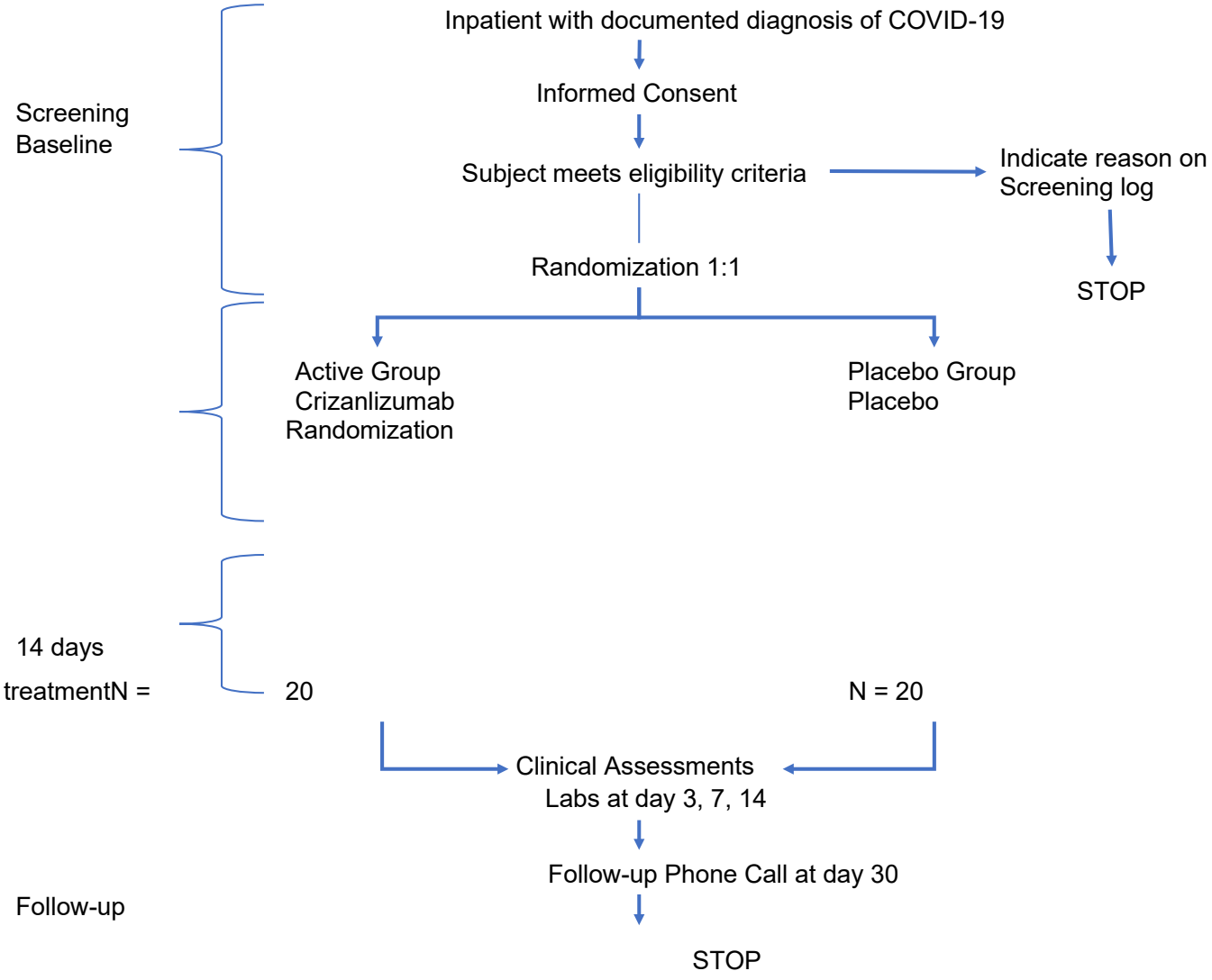
CRIzanlizumab for TreatIng COVID19 vAscuLopathy (CRITICAL) is a prospective, single center, doubleblind, placebo-controlled, randomized, phase II trial to compare the effects of crizanlizumab to placebo in patients with moderate severity COVID-19. A total of 40 subjects will be enrolled at a single

center. Subject accrual will occur over 6 months with the total duration of the trial expected to be 8 months.

Following the completion of screening and baseline procedures, eligible subjects will be randomized to a single dose of crizanlizumab 5.0 mg/kg IV or placebo. Subjects will be followed as inpatients for 14 d or until discharge. Subjects discharged before 14 d will be called at home. Clinical labs will be assessed at baseline (visit 1) and 7 and 14 d post randomization and hospital discharge day.

Figure 2: Study Flow Diagram

Study Flow Diagram



6.0 STUDY POPULATION

6.1 Eligibility Criteria

Eligibility will be determined by the below inclusion and exclusion criteria and confirmed by medical record review as necessary.

Inclusion Criteria
1. Willing to provide written informed consent
2. Willing to comply with all study procedures and be available for the duration of the study
3. Male or female ≥ 18 years of age
4. SARS-CoV-2 infection (COVID-19) within the past 10 d documented by laboratory test (NAT or RT-PCR)
5. Currently hospitalized
6. Symptoms of acute respiratory infection (at least one of the following: cough, fever > 37.5°C, dyspnea, sore throat, anosmia),
7. Radiographic evidence of pulmonary infiltrates

8. Requiring supplemental oxygen or the peripheral capillary oxygenation saturation (SpO2) < 94% on room air at screening
9. Elevated D-Dimer > 0.49 mg/dL
10. Negative pregnancy test for females of childbearing potential
Exclusion Criteria
1. Use of home oxygen at baseline
2. Current use of mechanical ventilation
3. Inability to provide consent
4. Do not intubate status
5. Prisoner or incarcerated
6. Pregnancy or Breast Feeding
7. Participation in other interventional drug trials for COVID-19 (emergency use or unblinded use of convalescent plasma is permitted).
8. INR > 3 or aPTT > 60

6.2 Accrual Goal

A total of 40 subjects will be enrolled from clinical sites within Johns Hopkins Medicine.

6.3 Subject Identification and Recruitment

Several recruitment strategies will be employed. Specific recruitment strategies are as follows (non-comprehensive list):

6.3.1 Inpatient Visits

Potential subjects may be identified by visits to the hospital inpatient floors in the recruiting site, review of Emergency Department admission logs, or notification by treating physicians. A member of the clinical team will inform patients of the research opportunity and ask if they would like more information. If the patient is agreeable, the research team will initiate contact or the potential subject may also directly contact the study team. Potential subjects will be pre-screened through medical record review and conversation with the subject using an IRB-approved script with appropriate protection for study personnel. Information collected from patients who fail pre-screening will be destroyed. Patients who meet all prescreening criteria will be invited to participate as an inpatient in a formal screening/baseline visit.

6.3.2 Electronic Medical Record (EMR) Query

Potential subjects may also be identified via EMR query using diagnostic codes for COVID-19 or viral infection or coronavirus and other eligibility criteria. The research team will conduct further prescreening of individual records to further refine the list of potential subjects. The treating physician of potentially eligible subjects will be notified prior to approaching their patient about the research study. If the treating physician does not object, the study team will contact the patient in the hospital and offered the chance to opt out. Patients who do not opt-out will be contacted by a member of the study team to discuss the project using an IRB-approved script. Information collected from patients who fail pre-screening will be destroyed. Patients who meet all pre-screening criteria will be invited to participate as an inpatient in a formal screening/baseline visit.

7.0 STUDY DRUGS

7.1 Crizanlizumab

Crizanlizumab is a monoclonal IgG2 kappa humanized antibody to P-selectin. The FDA approved the use of crizanlizumab 5.0 mg/kg every two weeks to prevent vaso-occlusive disease in patients with sickle cell anemia.

Pharmacology: Crizanlizumab is administered intravenously (IV), and is 100% bioavailable. The median time to reach maximum serum concentration (Tmax) was 1.6 hours at steady state following an IV administration of 5 mg/kg over a period of 30 minutes in SCD patients. Distribution is typical of endogenous human antibodies within the vascular and extracellular spaces. The volume of distribution at steady state (Vz) was 4.3 L after a single 5 mg/kg IV infusion in healthy volunteers. Antibodies are predominately eliminated via proteolysis by lysosomal enzymes into small peptides and amino acids. In healthy volunteers, the mean terminal elimination half-life (T1/2) was 10.6 days, and the mean clearance was 11.7 mL/hr at a dose level 5 mg/kg. In patients with SCD, the mean apparent T1/2 during dosing interval was 7.6 days, and the estimated clearance was 17.2 mL/hr. There was no indication of accelerated clearance or time-dependent change in the PK properties of crizanlizumab following repeated administration. No dedicated studies have been conducted to evaluate specific pathways of crizanlizumab excretion, or to investigate the pharmacokinetics PK of crizanlizumab in patients with renal or hepatic impairment, since antibodies are not metabolized by cytochrome P450 enzymes, and the kidneys/liver are not a major organ for antibody metabolism or excretion.

7.2 Placebo

A matched placebo to crizanlizumab will be prepared by the Investigational Drug Service of The Johns Hopkins Hospital. The placebo will be commercially available sterile normal saline 0.9% 100 mL bags.

7.3 Packaging

Crizanlizumab will be supplied in single use vials containing 10 mL at a concentration of 10 mg/mL for administration by IV infusion.

7.4 Acquisition and Shipping

All study drug will be provided free of charge by Novartis during the treatment phase. The placebo of saline will be supplied by the Johns Hopkins Investigational Drug Service. The Johns Hopkins Investigational Drug Service will be responsible for blinding and labeling the study drug vials and distributing study drug to the inpatient floors. The randomization and the randomization codes will be supplied by SOCAR.

7.5 Storage

Investigational product must be stored at a temperature between 2°C to 8°C (36°F to 46°F) in the original carton. Investigational product must be stored separately from normal hospital stocks and must be stored in a securely locked area accessible only to authorized trial personnel until dispensed. The temperature must be monitored and documented on the appropriate form for the entire time that the investigational product is at the trial site. If the storage temperature deviates from the permitted range, the investigational product must not be administered, and the Site Investigator or responsible person should contact the DCC for further instructions.

7.6 Accountability Procedures

The person in charge of product management at Johns Hopkins Investigational Drug Service will maintain records of product delivery to the trial site, product inventory at the site, the dose given to each subject, and the disposal of or return of unused doses to Johns Hopkins Investigational Drug Service. The DCC will verify the trial site's product accountability records against the record of

administered doses in the eCRFs, the source documents, and the communication from the online randomization program.

In case of any expected or potential shortage of product during the trial, the Investigator or an authorized designee should alert the DCC as soon as possible, so that a shipment can be arranged. In the event of a quality issue, the site should quarantine the investigational product and contact Biologics for further instructions.

7.7 Randomization, Dosage and Administration

Subjects will be randomized (1:1) to receive either crizanlizumab or placebo using a secure web based randomization system – cf. section **Error! Reference source not found.**. When a patient is randomized, the Unblinded Pharmacist will receive an automated e-mail message indicating the study treatment number assigned to each subject. The email notification will also detail the patient's body weight.

Subjects will be randomized to one of the below treatment arms:

- Active Group: crizanlizumab 5.0 mg/kg IV
- Placebo Group: placebo IV

7.7.1 *Crizanlizumab*

For subjects randomized to the crizanlizumab group, using the body weight shown on the email notification received (cf. section **Error! Reference source not found.**), the pharmacist or designated personnel will prepare individual doses of crizanlizumab for subjects on a milligram per kilogram basis in a 100 mL infusion bag in accordance with the Pharmacy Manual. Crizanlizumab will be administered over 30 minutes by IV infusion. To maintain blinding, the 100 ml saline pouch will be placed inside an amber colored outer bag.

7.7.2 *Placebo*

For subjects randomized to the placebo group, the pharmacist or designated personnel will prepare the individual 100 ml infusion bag in accordance with the Pharmacy Manual. The placebo infusion will be administered over 30 minutes by IV infusion. To maintain blinding, the 100 ml saline pouch will be placed inside an amber colored outer bag.

Once prepared by the pharmacist, the 100 ml saline pouches containing the study treatment infusion will be labelled and placed in an amber colored outer bag.

7.8 Duration of Treatment and Follow-up

Subjects will be administered a single dose of study treatment on day 1. The subject will be monitored for one (1) hour after infusion.

7.9 Dose Modifications

Not applicable.

7.10 Assessment of Subject Compliance

Not applicable.

7.11 Concomitant Medications

Use of all concomitant medications are permitted during the study.

Interactions between crizanlizumab and other medicinal products have not been investigated in dedicated studies. Monoclonal antibodies are not metabolized by cytochrome P450 (CYP450) enzymes. Therefore, medicinal products that are inhibitors or inducers of CYP450 are not expected to affect PK of crizanlizumab. Concomitant medications including HU/HC had no effect on crizanlizumab PK in patients with SCD in clinical studies.

Based on the data generated to date, crizanlizumab does not have a clinically relevant effect on the QT interval. The relationship between crizanlizumab exposure and changes in QTc from baseline (ΔQTc) was assessed using a linear mixed effect model in pooled data from 66 healthy subjects for whom at least 1 valid time-matched PK-ECG measurement was available. The model estimated mean ΔQTc at steady state Cmax observed in SCD patients was 0.23 ms (90% CI: 0.72, 1.20 ms). This effect is not clinically relevant since the upper 90% CI is well below the regulatory threshold of change in QTc interval of 10 ms.

7.12 Precautions

None. Crizanlizumab can cause lab testing artifacts in automated platelet counts. Platelet counts in blood drawn from patients can show false low platelet levels due to platelet clumping in the test tube. There is no evidence that crizanlizumab causes a reduction in circulating platelets or has a pro-aggregant effect in vivo.

False low readings of platelet counts are observed in blood collected in lavender top test tubes containing EDTA. False low readings of platelet counts can be avoided by collecting blood in blue top test tubes with sodium citrate. When needed, manual platelet estimation via blood smear to assess adequacy of the platelet count may be considered.

7.13 Criteria for Study Treatment Discontinuation

Subjects may discontinue protocol therapy at any time at their own request or at the discretion of the investigator. The reasons(s) for discontinuation will be documented and may include:

- Subjects withdraws from treatment (follow-up permitted)
- Subject withdraws consent (termination of treatment and follow-up)
- Subject is unable to comply with protocol requirements

8.0 VISIT SCHEDULE AND STUDY PROCEDURES

8.1 Visit 1 (Screening/Baseline)

- Obtain written informed consent
- Obtain contact information, demographic information
- Review and document required past medical history, medication history
- Assess inclusion and exclusion criteria
- Pregnancy testing (urine or blood) in women of childbearing age
- Assess vital signs (BP, HR, RR, Temp), record SpO2%, record weight, assess further inclusion and exclusion criteria
- Draw blood for laboratory tests including: soluble P-selectin, VWF, D-dimer, CRP, fibrinogen, IL-6, TNF-alpha, Factor 8, sICAM-1, sVCAM-1, CCL2, troponin, NT-pro-BNP, PCSK9.
- Contact Johns Hopkins Investigational Drug Service
- Schedule Day 3, 7, and Day 14 Study Visit

8.2 Visit 2 (Randomization and Treatment)

- Randomization
- Treatment with crizanlizumab or placebo

8.3 Visit 3 (Day 3 post randomization)

- Assess the occurrence of (S)AEs of interest
- Document concomitant medicines of interest (anticoagulants, anti-platelets, immunosuppressants, antivirals)
- Obtain vitals (BP, HR, RR, Temp) and SpO2%
- Complete hospital log
- Draw blood for laboratory tests including: soluble P-selectin, VWF, D-dimer, CRP, fibrinogen, IL-6, TNF-alpha, Factor 8, sICAM-1, sVCAM-1, CCL2, troponin, NT-pro-BNP, PCSK9.
- Schedule Day 7 Study Visit

8.4 Visit 4 (Day 7 post randomization)

- Assess the occurrence of (S)AEs of interest
- Document concomitant medicines of interest (anticoagulants, anti-platelets, immunosuppressants, antivirals)
- Obtain vitals (BP, HR, RR, Temp) and SpO2%
- Complete hospital log (if still hospitalized)
- Draw blood for laboratory tests including: soluble P-selectin, VWF, D-dimer, CRP, fibrinogen, IL-6, TNF-alpha, Factor 8, sICAM-1, sVCAM-1, CCL2, troponin, NT-pro-BNP, PCSK9. • Schedule Day 14 Study Visit

8.5 Visit 5 (Day 14 post randomization)

- Assess the occurrence of (S)AEs of interest
- Document concomitant medicines of interest (anticoagulants, anti-platelets, immunosuppressants, antivirals)
- Obtain vitals (BP, HR, RR, Temp) and SpO2%
- Complete hospital log (if still hospitalized)
- Draw blood for laboratory tests including: soluble P-selectin, VWF, D-dimer, CRP, fibrinogen, IL-6, TNF-alpha, Factor 8, sICAM-1, sVCAM-1, CCL2, troponin, NT-pro-BNP, PCSK9.

8.6 Participant Discharge

In the event that a participant discharges before day 14, the study team will draw blood for inflammatory and safety markers on the day of discharge along with obtaining vitals and completing the hospital log.

8.7 Visit 6 Phone Call Follow-up (Day 30 post randomization)

- Assess AEs by querying subjects about new signs and symptoms of acute respiratory infection (cough, fever > 37.5°C, dyspnea, sore throat, anosmia).
- Collect information regarding possible signs or symptoms of venous thromboembolism (new shortness of breath, new swollen leg, new painful leg) and bleeding
- Document subject study completion

8.8 Early Withdrawal Visit

- Collect study medications
- Assess AEs
- Document early withdrawal
- Patients will be encouraged to not withdraw informed consent if they simply do not wish to continue with study procedures. All attempts will be made to follow patients for vital status.

8.9 Schedule of Time and Events Table

Study Procedure	Visit 1 Day 0	Visit 2* Day 1	Daily Day 1-14	Visit 3 Day 3	Visit 4 Day 7	Visit 5 Day 14	Visit 6 Day 30	Unscheduled Visit
Inclusion/Exclusion Criteria	x							
Vital Signs: BP, HR, RR, Temp, SpO2%	x				x	x		x
Pregnancy Test	x							
WHO Clinical Scale, and Fever	x	x	x	x	x	x		
Clinical Labs	x			x	x	x		x
Randomization		x						
Administer study medication		x						
Adverse Event Monitoring		x	x	x	x	x		x
Phone Call							x	

* Visit 2 might be on physical day 3 depending on availability of screening labs

8.10 Study Procedures

8.10.1 Clinical Labs

Approximately 15 ml (about 3 teaspoons) of blood will be collected at four time points (Visits 1, 3, 4, and 5) to assess soluble P-selectin, VWF, D-dimer, CRP, and exploratory endpoint labs (including fibrinogen, IL-6, TNF-alpha, Factor 8, sICAM-1, sVCAM-1, CCL2, troponin, NT-pro-BNP, PCSK9). Samples will be processed by Johns Hopkins Pathology Labs or by the investigator using commercially available ELISA kits. In addition, blood will be drawn by the medical team for standard laboratories for clinical care.

If the study team is unable to obtain a blood sample on a patient who agreed to participant have his or her blood drawn for research purposes (difficult stick, early discharge, hemolyzed sample) we will obtain a remnant blood sample from the waste repository to measure the biomarkers listed above.

8.10.2 Pregnancy Test

Females of childbearing potential must have a negative pregnancy test (urine or blood) prior to randomization. Samples should be processed by the site's clinical laboratory.

9.0 ASSESSMENT OF EFFICACY

9.1 Specification of the Efficacy Parameters for Biomarkers

Standard biomarkers will be measured by the Johns Hopkins Pathology Laboratory. Non-standard biomarkers will be measured in the Principal Investigator's laboratory. The primary efficacy variable will be assessed as analysis of covariance of a log-transformed P-selectin levels with baseline value

and treatment allocation as covariates. The secondary efficacy biomarker variables will be assessed similarly.

9.1 Specification of the Efficacy Parameters for Biomarkers

The secondary efficacy variables that involve clinical variables will be abstracted from the EMR and recorded in eSOCDAT by the investigational team. The WHO composite scale will be calculated by the investigational team based on the EMR.

10.0 ASSESSMENT OF SAFETY

10.1 Specification of Safety Parameters

10.1.1 Definition of Adverse Events (AE)

An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

10.1.2 Definition of Serious Adverse Events (SAE)

A SAE is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

An AE is considered unexpected, when either the type of event or the severity of the event is not listed in the protocol or package insert/product monograph.

10.2 Classification of an Adverse Event

10.2.1 Severity of Event

- Mild: no intervention required; no impact on activities of daily living (ADL)
- Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
- Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

10.2.2 Relationship to Study Agent

- 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.

- 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.

- 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 subject'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 subject'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.

10.2.3 Follow-up of Subjects After a Reportable SAE

SAEs with a causal relationship to trial participation must be followed until the event or its sequelae resolve or stabilize to a level acceptable to the local investigator.

10.2.4 Expectedness

Expected events are those that have been previously identified as resulting from administration of the investigational product. An AE is considered unexpected, when either the type of event or the severity of the event is not listed in the protocol or package insert.

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

All adverse events of interest occurring following administration of the study drug will be collected until 30 d post randomization.

Safety parameters will be assessed at study visits. Safety data will be collected including: vitals (including blood pressure), chemistries and hematology labs. Events of interest include: arthralgia, diarrhea, pruritis, vomiting, chest pain.

All serious adverse events that are possible trial endpoints (including death, rehospitalization, or venous or arterial thromboembolism) within 30 days post randomization, will be collected on the appropriate adverse event collection forms. Serious adverse events that are trial endpoints do not also need to be reported as separate SAEs. All serious adverse events thought to be possibly, probably, or definitely related to study drug or not covered by endpoint collection forms will be collected on appropriate SAE CRFs. CRFs will be completed at the time the event becomes known to study investigators, either by notification by the subject, or during influenza season surveillance, at which time investigators will inquire about the occurrence of events since the last time of contact.

All suspected unexpected serious adverse reactions (SUSARs) will be collected on appropriate CRFs during the course of the trial. All SUSARs will be collected at the time they are

known to study investigators and may be subject to specific reporting requirements by health authorities or local IRBs.

Non-serious adverse events not temporally related to study drug administration and not suspected to be related to study drug administration will not be collected unless required by local GCP guidelines

REPORTING PROCEDURES

Adverse Event Reporting: All adverse events will be reported in the appropriate section of the eCRF.

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Serious Adverse Event Reporting: All reportable serious adverse events must be reported within 24 h of the investigators' awareness of the event.

Reportable serious adverse events and trial endpoints (death or hospitalization) will be collected until 30 days post administration of study drug. Serious, unexpected adverse drug reactions will be reported to FDA and sponsor in an expedited manner as required. SUSAR and SAE not collected as study endpoints will be reported to local IRBs per local IRB requirements.

Unanticipated Problem Reporting: All suspected unexpected serious adverse reactions (SUSARs) will be collected at the time they are known to study investigators. All non-fatal or non-life threatening SUSARs must be filed as soon as possible but no later than 15 calendar days after the event becomes known to study investigators. All SUSARs will be reported to Novartis and to local IRBs as per local IRB requirements.

10.4 Follow-up of Subjects after Adverse Events

SAEs will be followed until 30 d after administration of study drug or until it is judged to be permanent, and an assessment will be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the drug of interest, the interventions required to treat it, and the outcome.

The Steering Committee shall support the site in the following-up of all SAEs so that complete information is available to maintain patient safety and also as part of any commitments by Novartis to any Health authority OR specific Health authority follow-up requests for the product under investigation.

10.5 Unblinding Procedure

In an emergency situation where knowledge of a subject's study treatment allocation must be known in order to determine the further medical management of the subject concerned, or if knowledge of a subject's treatment allocation is required for regulatory reporting purposes, the PI will be able to access to the study treatment code for the subject concerned via the secure, web-based trial-specific treatment allocation system within eSOCDAT. Instructions for access (which is password protected) and use may be found in the respective Manual of Operations. All information (i.e., the name of the person who has accessed the treatment code, the reason, date and time and subject for whom the code was accessed) concerning study treatment code access will be tracked and stored in the web-based system. Further medical management is at the discretion of the Investigator. However, clinical status permitting, all remaining planned outpatient clinic visits and telephone calls must be completed in accordance with the protocol schedule unless the subject refuses further follow-up.

10.6 Safety Oversight

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including cardiovascular disease, pulmonary disease, infectious disease, statistics, and ethics. The DSMB will meet frequently to assess ongoing safety of participants, validity of data, and the integrity of the study. The DSMB will operate under the charter of this trial. The DSMB will provide its input to the study executive committee.

11.0 CORRELATIVE STUDIES

11.1 Correlative Studies

Additional pathways may be involved in the pathogenesis of COVID-19. Potential thrombotic and inflammatory and immune responses may exacerbate COVID19, and potential fibrinolytic or anti-inflammatory pathways may speed recovery form COVID-19.

11.2 Sample Collection Guidelines

Subjects electing to participate in the optional correlatives studies will contribute one blood sample (10 ml).

11.3 Specimen Banking

Subject samples collected for this study will be retained at the Johns Hopkins Hospital. Specimens will be coded and stored until the trial is completed, after which samples will be anonymized and stored until they are used up. If use is denied or withdrawn by the subject during the course of the trial, best efforts will be made to stop any additional studies and to destroy the specimens.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by the Johns Hopkins University, the investigator or a collaborating researcher or entity.

After the study is completed, the Ancillary Studies Committee will be responsible for reviewing and approving requests for de-identified clinical specimens from potential research collaborators outside of the Executive Committee investigators. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research, as well as provide documentation of IRB approval or exemption from their institution for receiving the specimens.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Underlying medical conditions (past medical history)
- Collection time in relation to study treatment
- Results from biomarker studies
- Demographic data

12.0 STATISTICAL CONSIDERATIONS

12.1 Statistical Analysis Plan

All statistical data analyses will be performed using Stata, SAS and R.

12.2 Analysis Population

All randomized subjects regardless of their compliance with the protocol treatment and follow-up will be included in the primary analysis following the intention-to-treat (ITT) principle for the analysis of randomized controlled trials including for the assessment of the balance of baseline

subject characteristics. Reporting of adverse events will be according to the treatment actually received.

12.3 Analysis of Baseline Characteristics

Baseline characteristics between treatment groups will be compared using t-tests for normally distributed continuous variables or Wilcoxon rank-sum tests for non-normally distributed continuous variables, and Chi-Square or Fisher's exact tests, as appropriate, for categorical variables. These comparisons are to evaluate the adequacy of randomization and to identify baseline characteristics that may need to be considered for adjustment in the analysis of the outcome measures.

12.4 Analysis of Primary Endpoint

The primary endpoint of soluble P-selectin at 3 days or hospital discharge day (whichever is earlier) will be summarized for each treatment group with descriptive statistics, including mean, standard deviation, median, and interquartile range. For the assessment of the primary endpoint, change in soluble P-selectin will be assessed in an analysis of covariance, which will be implemented using linear regression with day 3 or hospital discharge day soluble P-selectin as the outcome variable, using baseline soluble P-selectin and treatment group as the covariates. A soluble P-selectin greater than assay will be imputed as 150% of upper limit of assessment.

12.5 Analysis of Secondary Endpoints

The secondary endpoints of other biomarkers (including VWF, D-dimer, CRP) at baseline, day 3, day 7 and day 14, and the secondary endpoint of soluble P-selectin at day 7 and day 14 will be summarized with descriptive statistics. For the assessment of the secondary endpoints, comparison of the changes in biomarkers from baseline to day 14 between the two groups will be made using the similar methods as with the primary endpoint above, after log-transforming baseline and follow-up values of other biomarkers (including VWF, D-dimer, and CRP).

The secondary endpoint of the World Health Organization (WHO) Ordinal Scale for COVID-19 Trials up to day 14 will be summarized by reporting the number and proportion of patients in each treatment group in each WHO category, and analyzed by ordinal logistic regression with patient's baseline score and randomized treatment as the model covariates. Consistency of any detected associations across the range of the ordinal scale will be assessed using the Brant test. Analysis of the repeated measurements of WHO Ordinal Scale (collected daily from day 3 to day 14) will be analyzed using a mixed-effects ordinal logistic regression model with treatment, study day, and baseline score as fixed effects and patient id as a random effect.

12.6 Analysis of Exploratory Endpoints

The secondary endpoints of other biomarkers (IL-6, TNF-alpha, factor 8, soluble ICAM1, soluble VCAM-1, CCL2, troponin isoforms T or I, NT-pro-BNP, PCSK9) at baseline, day 3, day 7, day 14 and hospital discharge day will be summarized with descriptive statistics. For the assessment of the secondary endpoints, comparison of the changes in biomarkers from baseline to day 14 between the two groups will be made using the similar methods as with the primary endpoint above.

The secondary endpoints of individual clinical endpoints (time to resolution of fever, time to liberation from supplemental oxygen, time to mechanical ventilation, time to in hospital death, time to arterial or venous vascular event or ischemic stroke, time to hospital discharge) will be summarized by Kaplan-Meier curves and compared using log-rank tests and univariate Cox models.

12.7 Missing data

This is a well-designed trial with many safeguards in place for assuring complete data, therefore the extent of missing data is expected to be minimal. The primary analysis will use patients with available baseline, day 3 and/or hospital discharge day data. Where data are missing, sensitivity analyses will be done using several assumptions to evaluate the sensitivity of the statistical results to the possible effects on the non-completers. To the extent possible, the reasons for missing data will be documented and evaluated. Using this information, assumptions about the missing data mechanism will be assessed and these assumptions will be used to impute missing values under a variety of scenarios. In multiple imputations, the missing values will be replaced with values consistent with several possible scenarios. If the missing data are extensive, model-based approaches will be considered to estimate effects under various assumptions regarding missing data. Missing data analysis will follow the guideline promulgated in the National Research Council report [National Research Council. The Prevention and Treatment of Missing Data in Clinical Trials. 2010. Washington, DC: The National Academies Press.].

12.8 Interim Analysis

Formal interim analyses for efficacy and futility will not be performed.

12.9 Level of Significance and Sample Size

The primary analysis will focus on between-arm changes in soluble P-selectin. Based on a trial design with two-sided α=0.05, assuming a standard deviation (SD) of 30 ng/ml and a 10% drop out rate, a sample size of 40 subjects (20 per treatment arm) will ensure 83% power to detect a between-group difference of 30 ng/ml and 93% power to detect a between-group difference of 35 ng/ml.

12.10 Stopping Rules for Termination of the Trial

The study will be monitored by the Data and Safety Monitoring Board (DSMB) as described in Section 12.15. However, there will be no formal interim analyses for efficacy or futility and thus no stopping rules for termination of the trial. The DSMB may suggest premature termination of the study based on safety concerns regarding crizanlizumab in patients with thrombosis or bleeding. In addition, early termination of this trial may occur because of a regulatory authority decision, withdrawal of study approval by clinical site IRBs, or investigational product safety problems, or overwhelming efficacy in the opinion of the DSMB. Novartis retains the right to withdraw support of the trial prior to the completion of enrollment of the targeted number of subjects, but will exercise these rights only for valid scientific or administrative reasons.

12.11 Spurious Data Procedures

Consistency checks and range checks will be built into the data management system. This will allow many errors to be identified and corrected at the time of data entry. Queries regarding any problems with data will be sent to site coordinators regularly throughout the course of the trial. The site will also be monitored during the study. Therefore, spurious data are expected to be rare. Any data which are judged by the medical monitors to be definitely incorrect, and which cannot be resolved, will be set to missing.

The study report will indicate the number of subjects who have missing data on each study endpoint. For covariate-adjusted analyses, the number of subjects who have missing data on the covariates will be reported.

Throughout the study, the rate, timing, and reasons for subject withdrawal will be monitored by site and treatment arm.

12.12 Deviation Reporting Procedures

Any modifications or deviations from the statistical plan described in this protocol will be documented in a "Revised Statistical Plan" document.

12.13 Subjects to be Included in Analyses

Data analysis of primary and secondary outcomes will follow an intention-to-treat principle. However, adverse event reporting will include those who have received any dose of treatment according to the treatment actually received. All subjects that are randomized will be included in data analysis.

12.14 Measures to Minimize and Avoid Bias

12.14.1 Randomization

Randomization will be carried out using permuted blocks of size 4. Subjects will be randomized in a 1:1 ratio to crizanlizumab 5.0 mg/kg IV once or placebo IV once.

Subjects will be randomized using a validated Web-based Randomization System (eSOCDAT) only accessible to designated site personnel. eSOCDAT will allocate numbered study treatment pack number(s) which should be used for the subject concerned. Details on how to randomize a subject will be found in the respective user manual. The randomization plan will be kept strictly confidential, accessible only to authorized persons, until the time of unblinding. If a subject discontinues from the study, neither the subject identification number nor the allocated study treatment pack numbers will be reused, and the subject will not be allowed to be re-randomized in the study.

Since the Johns Hopkins Investigational Drug Service will be supplying the placebo, the Johns Hopkins Investigational Drug Service will not be blinded to the identity of the study drug and placebo. Although the Johns Hopkins Investigational Drug Service will know the identity of the vials containing study drug or placebo, it will not be informed of the identity of the patients receiving placebo or study drug, and will not have access to endpoint data.

12.14.2 Masking

Subjects, site investigators and study personnel, and persons performing surveillance will remain blinded to the identity of the treatment from the time of randomization until database lock. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone involved in the study except as required by the Data and Safety Monitoring Board (DSMB), or in the case of subject emergencies, for which unblinding is deemed absolutely necessary. The identity of investigational product will be concealed through over encapsulation by the Johns Hopkins Investigational Drug Service. In addition, the 100 ml saline pouches will be placed in an amber colored outer pouch.

12.15 Data and Safety Monitoring Board (DSMB)

The Data and Safety Monitoring Board (DSMB) will oversee the trial across the single study site. The DSMB is comprised of experienced members (core plus ad hoc) with expertise required to oversee this trial. The DSMB members will review protocol-specific reports created by study statisticians using data pulled from eSOCDAT. These reports summarizing the data by treatment arm, coded as A vs B, will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of subject demographics for balance of randomization, and a summary of the number and seriousness of adverse events. Actual treatment associated with the coded treatment arms will be provided to the DSMB members at the time of each review. These reports will allow the DSMB to independently judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by the study statistician. The DSMB will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination.

In providing oversight for the conduct of this study, the DSMB will meet at a minimum of every week during the six-month study to review all adverse events. Additional meetings may be scheduled as determined by the DSMB or requested by the study team. There will be no prespecified stopping rules either for efficacy, harm or futility. All serious adverse events will be reported to the DSMB and IRB in accordance with their reporting guidelines. We will forward the communication of the DSMB recommended actions and all pertinent regulatory information to the FDA, appropriate Institutional Review Board(s), and the Novartis when applicable.

13.0 ETHICS AND PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

The trial will be conducted in accordance with Good Clinical Practice (GCP) guidelines, the rules and regulations of the Institutional Review Board(s), and applicable state and federal regulatory agency requirements and laws.

13.2 Institutional Review Board (IRB)

The protocol, informed consent form(s), recruitment materials, and all subject 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 subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

13.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the

quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the clinical or research record.

13.4 Exclusion of Women, Minorities and Children (Special Populations)

Crizanlizumab for COVID-19 aims to enroll a representative proportion of minority subjects. Children, pregnant women, prisoners, and institutionalized individuals will not be enrolled. Children are excluded because their phenotype differs from that of an adult, which could confound response results. Pregnant women are excluded because of regulations barring them from this type of research.

14.0 TRIAL MANAGMENT AND COMMUNICATION PLAN

14.1 Monitoring IRB Approvals

The participating institution must provide for the review and approval this protocol and the associated informed consent documents and recruitment material by an appropriate IRB registered with the OHRP. Any amendments to the protocol or consent materials must also be approved before they are placed into use. In the US, only institutions holding a current US Federal-wide Assurance issued by OHRP may participate.

The IRB approval letters will be collected by the CCC and will be required for the study site to be certified as ready to enroll subjects. The date of each IRB approval will be recorded and the single study site will need to inform the CCC about any changes to the IRB approval and all IRB renewals. In the event of a lapse in a site's IRB approval, the site will be responsible to obtain clearance from their IRB to continue to collect follow-up data on subjects enrolled, but no additional subjects can be enrolled from that site until full IRB approval is reinstated.

14.2 Monitoring of Modifications

Modifications to the protocol can only be made by the steering committee. Protocol modifications that affect study design or endpoints in any substantial manner may need to be reviewed by the DSMB.

Modifications to the protocol will be communicated to the study site by the CCC. When modifications of the protocol are made that require the site to resubmit the protocol to a local IRB, the site will be required to provide evidence of IRB re-approval before they can enroll subjects under the new protocol.

14.3 Problem Management

Issues that arise at the study site regarding the conduct of the study must be reported by site personnel to the CCC. The CCC will be responsible for maintaining contact with the single study site.

14.4 Communication

The Steering Committee will meet weekly during the course of the trial. The study site will be updated with study information by means of webinars, conducted prior to study enrollment and on an ad hoc basis as needed.

15.0 DATA COLLECTION AND QUALITY ASSURANCE

15.1 Data Management Responsibilities

The DCC, SOCAR, Dr. Solomon and Dr. Claggett and the staff at the Brigham and Women's Clinical Trials Endpoints Center will be responsible for implementing and maintaining quality control and quality assurance systems with written standard operation procedures (SOPs) to ensure that trial is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice (International Conference on Harmonization E6), and all applicable federal, state, provincial, and local laws, rules, and regulations relating to the conduct of the clinical trial.

The Clinical Site may be subject to review and/or inspection by the Institutional Review Board (IRB), the US Food and Drug Administration (FDA), and/or to quality assurance audits performed by the DCC or CCC.

It is important that the Investigator(s) and the relevant clinical site personnel be available during the monitoring period and possible audits or inspections, and that sufficient time is devoted to the process.

15.2 Clinical Trial Data Management System

eSOCDAT will be the e-clinical solution used to collect and mange subjects and logistic metadata for the current trial. eSOCDAT is a web-based tool and can be accessed worldwide via an internet browser. eSOCDAT is FDA 21 CFR Part 11 compliant and is fully compliant with Good Clinical Practice (GCP) and other applicable rules and regulations for the validation of computerized systems used to collect and manage data for a clinical research study.

The single study site can only access data for their own subjects. All clinical data required by the protocol is entered using a unique subject assigned number and no personal identifying information is entered or stored other than dates of birth and service.

All data entered through eSOCDAT will be stored on servers hosted by SOCAR Research (''SOCAR'') SA. SOCAR Research is fully compliant with ISO/IEC 27002 (previously known as ISO 17799:205) standards. Direct access to SOCAR's servers is restricted to authorized SOCAR personnel only via login credentials. Customers have no access to the server itself. All SOCAR's employees are granted access only to computer and networking areas necessary to perform their duties. Each installation is separate, and cannot be accessed from any other installation. Connection to a hosted instance is encrypted by means of secure socket layer. The application server and database server are secured via firewall, hardened to remove nonessential access credentials, and strong password compliance. Hosted systems are constantly monitored for latencies and intrusion.

15.3 Data Management Procedures

Data will be collected and entered into eSOCDAT at each site participating in the trial. eSOCDAT provides real-time field level validations, context sensitive help and automatic query generation. Data entry forms use browser based logic to enforce proper validations of all data fields and proper skip patterns within study data forms. Interim background data submittals prevent loss of data due to interruption of internet connections.

The CTDMS is programmed to validate data entry fields as the data are entered. Validations are question-by-question checks that give immediate feedback to help catch data entry errors, form completion errors, and out-of-range values. Reports of outstanding edits, generated upon completion of data entry, will enable continuous cleaning of data at each site. Detailed procedures are outlined in the Data Management Plan.

If the DCC observes inconsistent data or patterns of protocol violations or missing data, site staff will be contacted to address the finding.

15.4 Direct Access to Source Data

As noted above, source documents for verification of entry criteria may be queried by the DCC. The investigator will make available to the DCC source documents as requested. The verifications of CRF data will be made by direct review of source documents for a small percentage of subjects as described above. It may be necessary to have access to the complete medical record in some instances.

15.5 Specimen Collection Management

Ensuring the accuracy of blood specimens for this trial is paramount. The Johns Hopkins Hospital has quality control methods in place to ensure this accuracy. Aliquot tubes are linked, and tracked to allow tracing back to the original parent tube. The complete electronic chain of custody in place will allow the data management system to monitor and report on the critical processes involved in specimen collection, shipping and results..

15.5.1 *Data Use and Banking*

During the study, the Ancillary Studies Committee will be responsible for reviewing and approving requests for de-identified data sets from potential research collaborators outside of the Executive Committee investigators. Data will be stripped of all PHI in compliance with the HIPAA Privacy rule. Collaborators will be required to complete an agreement (a Data Transfer Agreement or recharge agreement) that states data will only be released for use in disclosed research, as well as provide documentation of IRB approval or exemption from their institution for receiving the data. Datasets will be provided to researchers by the DCC using SAS transport files and using a secure FTP site. Data use is limited to studying endothelial function and cardiovascular disease. Data must be returned or destroyed when analysis is complete.

After this research study is over and the main results have been published, a complete de-identified data set will be banked at the Brigham and Women's Hospital and at The Johns Hopkins Hospital, including the following data: medical history and medications, vital signs, side effects or other health issues that occurred during the study, health status. Directly identifiable information will be removed and keys linking codes to subject identity will be destroyed, making data withdrawal impossible. The banked data will not be sent to researchers outside of Hopkins or the Brigham. The banked data will be used for future research about COVID-19 and vascular inflammation and thrombosis.

15.6 Confidentiality of Data

By signing this protocol, the Investigator affirms that trail information will be maintained in confidence and such information will be divulged to the IRB or similar expert committee, affiliated institution, and employees only under an appropriate understanding of confidentiality

with such board or committee. Data generated by this clinical trial will be considered confidential by the Investigator, except to the extent that it is included in a publication.

15.7 Confidentiality of Subject Records

By signing the protocol, the Investigator agrees that the IRB, or Regulatory Agency representative may consult and/or copy study documents in order to verify CRF data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying CRF information, the subject will be identified by unique code only and full names and similar identifying information (such as medical record number or social security number) will be masked.

The Clinical Site Investigators will ensure that the identity of subjects will be protected. All study records will be maintained in a secure fashion with access limited to essential study personnel only. All study documents submitted to the Coordinating Center will have identifiers removed other than dates of birth and service and subjects will be identified with a study-specific identification number only. The Clinical Site Investigators will maintain, in a secure location, an enrollment log that includes subject identifying information and links subjects to their studyspecific identification number.

15.8 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the subject, the investigator, or study staff.

Investigators may only implement a deviation from or a change to the protocol to eliminate an immediate hazard(s) to subjects without prior IRB approval.

All deviations from the protocol must be addressed in study subject source documents and promptly reported to Network Study Manager or Clinical Coordinating Center. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

16.0 PUBLICATION POLICY

Publications derived from this study should include input from the Principal Investigator, Steering Committee, and other Investigators in the trial. No results will be released publicly before completion of the final analysis regarding the primary endpoint of this study without the approval of the Steering Committee. The statistical analysis will be performed according to the pre-specified analysis plan. Subsequent to the multi-center publication, or 24-months after completion of the trial, whichever comes first, an Investigator may publish the results of the trial independently, subject to approval of the Steering Committee.

A manuscript of each proposed presentation and publication shall be submitted to Novartis for review prior to submission to anyone who is not employed by the Institution and not under an obligation of nondisclosure and non-use at least substantially identical to that imposed on the Principal Investigator by this Agreement in order to permit Novartis to (1) evaluate the manuscript for accuracy, (2) ascertain whether Confidential Information is being improperly disclosed, (3) provide Confidential Information which may not have yet been made available by Novartis and (4) provide input for consideration regarding the content and/or conclusion(s) of the manuscript. Novartis shall be afforded a review period of fifteen (15)

Working Days for manuscripts not exceeding two (2) double-spaced pages in length (or the equivalent thereof) and forty-five (45) Working Days for all other manuscripts.

17.0 REFERENCES

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