Long title: Alpha-1 Adrenergic Receptor Antagonism to Prevent COVID-19 Cytokine Storm Syndrome and Acute Respiratory Distress Syndrome: A Randomized Study Comparing the Efficacy of Prazosin vs. Standard of Care for SARS-CoV-2 infection

Short title: Prazosin to Prevent COVID-19 (PREVENT-COVID Trial)

Johns Hopkins Protocol #: COV2001, IRB00246659

Clinical Phase: 2

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IND Number: IND 149973

Conducted by: Johns Hopkins University

Study Agent: Prazosin (Minipress®)

Version/Date of Issue: Version 2.0, June 12, 2020

PROTOCOL SUMMARY

Sample Size:

As per recommendation of the COVID-19 Review Committee at The Johns Hopkins University School of Medicine, an initial interim analysis will be performed after 30 patients have completed 28 days of follow-up (15 in each arm; 13% of recruitment) to analyze safety endpoints and early signs of efficacy. If the intervention is deemed safe, after discussion with the centralized Data and Safety Monitoring Board (DSMB), recruitment may continue to the next interim analysis (33% and 67% completion of 28 day follow-up) to reach a target enrollment of 220 patients (110 in each arm) based on power analyses for the outlined patient population.

Study Population:

1. Subjects must be 45 years of age or older
2. Provide consent to participate
3. Subjects who tested positive for SARS-CoV-2 AND have clinical symptoms of COVID-19 and have been hospitalized, but are not requiring more than 4 liters/minute of supplemental oxygen by nasal cannula and are not requiring ICU/CCU-level care at time of enrollment

Study Duration:

April 1, 2020 to December 31, 2022. The total duration of treatment with prazosin will be 4 weeks (28 days) from initial dose. Patients will be followed for 60 days.

Study Design:

This randomized phase 2 trial will assess the efficacy of prazosin (Arm 1) vs. standard of care (Arm 2) in patients with positive SARS-CoV-2 testing who are symptomatic and hospitalized, but are not requiring more than 4 liters/minute of supplemental oxygen by nasal cannula. Adults 45 years of age and older may participate. A total of 220 eligible subjects will be randomized in a 1:1 ratio to receive either prazosin 1 mg by mouth every 8 hours (with dose escalation as defined in **Section 4.5**) or standard of care. After 30 patients have completed 28 days of follow-up (15 in each arm; 13% of recruitment), a first interim analysis will be performed to analyze safety endpoints and early signs of efficacy. Enrollment will then depend on the recommendation of the Data and Safety Monitoring Board. Additional interim analyses will occur after 33% and 67% of the patients have completed 28 days of follow-up. Power calculation suggest a target enrollment of 220 patients (110 in each arm).

Randomization:

Randomization will be done by block randomization.

Assessments:

The following will be assessed in all subjects:

- Safety and efficacy: Day 0 (baseline), 1, 3, 7, 14, 21, 28, and 60.

The following laboratory values will be collected based on each participating center's standard of care practice, while the subjects are admitted at inpatient wards:

- Plasma fractionated catecholamines, metanephrines, and other circulating inflammatory and organ damage marker levels: Day 0 (baseline), 1, 3, 7, 14, and 21.
- Blood antibody titer to SARS-CoV-2: Between Day 21 to Day 60

Study Agent:

- Prazosin

Primary Efficacy Objective:

Evaluate the efficacy of treatment with prazosin (given for a total of 28 days) at day 60 to prevent severe COVID-19 (requiring mechanical ventilation *and/or* high flow nasal cannula *and/or* length of ICU/CCU admission *and/or* death) in treated versus untreated subjects who tested positive for SARS-CoV-2 and have clinical symptoms of COVID-19 including being hospitalized, but are not requiring more than supplemental oxygen by nasal cannula and are not requiring ICU or CCU-level care at time of admission.

Primary Endpoint:

Clinical event scale of disease severity (evaluated up to Day 60):

1. Death
2. Hospitalized, requiring mechanical ventilation *and/or* high flow nasal cannula *and/or* ICU/CCU admission (or equivalent setting) *and/or* ECMO
3. Hospitalized, requiring supplemental oxygen, not requiring ICU/CCU level care (or interventions listed under 2)

Primary Safety Objective:

Evaluate the safety of treatment with prazosin in subjects diagnosed with COVID-19

Primary Safety Endpoints:

1. Cumulative incidence of grade 3 and 4 adverse events during the study period
2. Cumulative incidence of serious adverse events during the study period
3. Cumulative incidence of symptomatic hypotension (SBP <90 mmHg) or hypotension requiring cessation of prazosin

Secondary Objectives:

1. Compare rates and duration of laboratory abnormalities in peripheral blood including lymphopenia, leukocytosis, anemia, thrombocytopenia, creatinine, AST/ALT, troponin I, pro-BNP, D-dimer, ferritin, interleukin (IL-)6, soluble IL-2 receptor
2. Compare rates and duration of laboratory abnormalities in peripheral blood including fractionated plasma catecholamines and plasma metanephrines
3. Analyze the interaction between prazosin and D-dimer

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LIST OF ABBREVIATIONS

ADR: Adverse Drug Reaction
AE: Adverse Event/Adverse Experience
ARDS: Acute Respiratory Distress Syndrome
CCU: Cardiac Care Unit
CDC: United States Centers for Disease Control and Prevention
CFR: Code of Federal Regulations
CLIA: Clinical Laboratory Improvement Amendment of 1988
COI: Conflict of Interest
COVID-19: Coronavirus Disease
CRF: Case Report Form
CSS: Cytokine Storm Syndrome
CRS: Cytokine Release Syndrome
DMC: Data Management Center
DSMB: Data and Safety Monitoring Board
ECMO: Extracorporeal Membrane Oxygenation
EUA: Emergency Use Authorization
FDA: Food and Drug Administration
GCP: Good Clinical Practice
ICF: Informed Consent (Informed Consent Form)
ICH: International Conference on Harmonization
ICU: Intensive Care Unit
IEC: Independent ethics committee
IRB: Institutional review board
IWRS: Interactive web response system
MERS: Middle East Respiratory Syndrome
MERS-CoV: Middle East Respiratory Syndrome Coronavirus
RT-PCR: Reverse Transcriptase Polymerase chain reaction
PPE: Personal Protective Equipment
SAE: Serious adverse event
SARS: Severe Acute Respiratory Syndrome
SARS-CoV-1: Severe Acute Respiratory Syndrome Coronavirus 1
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
UP: Unanticipated Problem
UPnonAE: Unanticipated Problem that is not an Adverse Event

1. STUDY OBJECTIVES

1.1. Primary Efficacy Objective

Evaluate the efficacy of treatment with prazosin (given for a total of 28 days) at day 60 to prevent severe COVID-19 (requiring mechanical ventilation *and/or* high flow nasal cannula *and/or* length of ICU/CCU admission *and/or* death) in treated versus untreated subjects who tested positive for SARS-CoV-2, have clinical symptoms of COVID-19, and have been hospitalized, but are not requiring more than supplemental oxygen by nasal cannula and are not requiring ICU or CCU-level care (see inclusion criteria for details).

1.2. Primary Safety Objective

Evaluate the safety of treatment with prazosin in subjects exposed to COVID-19.

1.3. Secondary Objectives

1. Compare rates and duration of laboratory abnormalities in peripheral blood including lymphopenia, leukocytosis, anemia, thrombocytopenia, creatinine, AST/ALT, troponin I, pro-BNP, D-dimer, ferritin, interleukin (IL-)6, soluble IL-2 receptor
2. Compare rates and duration of laboratory abnormalities in peripheral blood including fractionated plasma catecholamines (adrenaline, noradrenaline, dopamine) and fractionated plasma metanephrines (metanephrine, normetanephrine)
3. Analyze the interaction between prazosin and D-dimer

2. BACKGROUND AND SCIENTIFIC RATIONALE

2.1. Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of Coronavirus disease 2019 (COVID-19) and an ongoing pandemic, with a currently estimated case fatality rate of 3.6% in China, and 0.5%-8.8% worldwide[1–7]. Based on experiences in China, about 6% of patients presenting with COVID19 infection will require critical (intensive care unit) level care, with about half surviving to hospital discharge[4]. No proven therapy exists for the treatment or prophylaxis of SARS-CoV-2 infection, particularly those with critical symptoms.

The mortality of COVID-19 appears to be driven by a dysregulated immune response to SARS-CoV-2, resulting in acute respiratory distress syndrome (ARDS), respiratory failure, and multi-organ failure[8,9]. Emerging evidence suggests that a subset of COVID-19 is characterized by the development of a cytokine storm syndrome (CSS) that resembles cytokine release syndrome (CRS)[8,10,11]. COVID-19-CSS is immunologically characterized by the elevation of pro-inflammatory cytokines[11,12]. IL-6 levels diverge profoundly between non-survivors and survivors in the weeks after symptom onset, making them predictors of COVID-19 severity and in-hospital mortality[1,13,14]. Tocilizumab, a monoclonal antibody targeting the IL-6 receptor, is currently being investigated for the treatment of patients with COVID-19-CSS and ARDS[15–18]. To date, it has shown efficacy in a small case series[18], but this strategy is limited to patients who already display severe or critical COVID-19 symptoms. As hospital and critical care capacity during this pandemic is at risk of being exceeded in several nations around the world, preventative approaches that reduce severe complications and hospital admissions are desperately needed.

We recently showed that CRS observed with bacterial infections, chimeric antigen receptor (CAR)-T cell therapy, and other T cell-activating therapies is accompanied by a surge in catecholamines[19]. Catecholamines enhance inflammatory injury by augmenting the production of IL-6 and other cytokines through a self-amplifying feed-forward loop in immune cells that requires alpha-1 adrenergic receptor signaling[19]. Inhibition of catecholamine signaling by treatment with prazosin, a pan-alpha-1 adrenergic receptor antagonist, was effective at preventing cytokine storm and resulted in markedly reduced mortality in multiple animal models. These findings offer a rationale for studying alpha-1 receptor antagonists in the early stages of COVID-19 to prevent progression to severe disease, ARDS, and cytokine storm, thereby reducing necessity and the length of time that critical care management is required.

In this trial, we hypothesize that the treatment of individuals with prazosin who test positive for SARS-CoV-2 AND are (i) asymptomatic or have symptoms that do not require hospitalization OR (ii) have symptoms and warrant inpatient hospital care not to exceed oxygen supplementation by nasal cannula at time of admission could reduce catecholamine surges and secondary cytokine dysregulation. This reduction in disease amplification would directly lead to less severe symptoms and mortality. Preventative strategies to ameliorate COVID-19 severity are critical during the ongoing SARS-CoV-2 pandemic where scarcity of healthcare resources threatens to result in excessive mortality[20].

2.2. Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of Coronavirus disease 2019 (COVID-19) and an ongoing pandemic, with a currently estimated case fatality rate of 3.6% in China, and 0.5%-8.8% worldwide[1–7]. No proven therapy exists for the treatment or prophylaxis of SARS-CoV-2 infection.

In early stages of infection with SARS-CoV-2, an appropriate immune response is initiated against the virus, as occurs against similar coronavirus infections SARS-CoV-1 and MERS-CoV[21,22]. In a subset of patients, the disease course can progress to a dysregulated immune state characterized by systemic hyperinflammation and cytokine storm[10,21,23]. This state manifests as ARDS, shock, and multi-organ failure. Resulting mortality equals or exceeds 50% in this population[24,25]. Interventions that address this subset of patients are critically needed. Current approaches are limited to supportive measures and experimental therapies. Disease-modifying therapies that address the underlying pathophysiology and prevent progression to the hyperinflammatory state will be essential for mitigating morbidity and mortality due to COVID-19.

Biomarkers of advanced stages and poor outcomes of COVID-19 support models of immunopathology and suggest routes of intervention. Absolute counts and relative proportions of immune cell and lymphocyte subsets are aberrant in COVID-19, especially in severe cases[1,6,7,9,25–28]. Inflammatory cytokines, chemokines, and other markers of inflammation including IL-2, IL-6, IL-7, IL-8, soluble IL-2 receptor (CD25), interferon-γ inducible protein 10, monocyte chemoattractant protein 1, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, tumor necrosis factor-α, C-reactive protein, procalcitonin, ferritin, and D-dimer are also increased in severe cases[1,7–14,26–30]. IL-6 specifically diverges between non-survivors and survivors and is predictive of COVID-19 severity and in-hospital mortality[1,13,14]. The levels of these markers mirror those seen in cytokine storm induced by SARS-CoV-1 and MERS-CoV infection[31–35]. Cytokine storm is associated with ARDS, the primary driver of mortality in SARS and MERS[36,37]. COVID-19 cytokine profiles also resemble the hyperinflammation state seen in hemophagocytic lymphohistiocytosis (HLH), a hyperinflammatory syndrome caused by underlying defects in perforin signaling pathways[10,38–41]. Furthermore, the profile of immune

dysregulation of COVID-19 resembles CRS seen as an adverse effect of biologic and cellular immunotherapies, including CAR-T cells[42–44].

Pending data from randomized controlled trials, retrospective data from 21 patients with severe or critical COVID-19 treated with tocilizumab suggests that inhibition of the IL-6 signaling axis is highly effective[18]. However, considerable cost, limited availability, the potential for serious adverse events, and the risk of prolonged immunosuppression limit the application of biological therapies targeting the IL-6 axis in COVID-19.

Tocilizumab is available in only limited quantities, and its use in COVID-19 must be weighed against the competing use for treating patients undergoing CAR-T therapy experiencing CRS. The use of tocilizumab will therefore likely be limited to patients who have progressed to severe or critical COVID-19[21,23,45]. Hospital and critical care capacities have already been exceeded in certain regions and are likely to be exceeded in others[46,47]. Preventative therapies that could reduce the risk of severe COVID-19 prior to disease onset would alleviate both hospital capacity and critical care capacity and need for advanced supportive measures. Furthermore, in those patients who survive COVID-19-associated ARDS, reducing pulmonary inflammation and secondary lung fibrosis may prevent long-term morbidity and functional disability while increasing quality of life[48–50].

Another drawback of biological therapies that target the IL-6 axis is their prolonged immunosuppressive effect. Use could lead to impaired viral clearance or favor secondary bacterial infection and viral co-infection or reactivation[51]. As secondary infections are a predictor of mortality with COVID-19, broadly immunosuppressive therapies such as glucocorticoids, anti-IL-6 receptor antibodies, or Janus kinase (JAK) inhibitors carry not insignificant risk in the critically-ill patient with COVID-19[8,52]. Indeed, use of glucocorticoids in SARS and MERS was associated with delayed viral clearance and did not reduce mortality[53–55].

Considering the pathophysiology of severe COVID-19 and the limitations of current treatments, there is a critical need for other host-directed therapies[48]. Targeting the catecholamine axis is a promising route.

We have recently shown that CRS observed with bacterial infections, CAR-T cells, and other T cell-activating therapies is accompanied by a surge in catecholamines[19]. Catecholamines enhance inflammatory injury by augmenting the production of IL-6 and other cytokines through a self-amplifying feed-forward loop in immune cells (macrophages and T cells) that requires alpha-1 adrenergic receptor signaling. Other studies have demonstrated in animal models that production of catecholamines from immune cells increases downstream cytokine production and enhances inflammatory lung injury whereas blockade of catecholamine signaling decreases lung inflammation[56,57].

Prophylactic inhibition of catecholamine synthesis by treatment with metyrosine, a tyrosine hydroxylase antagonist, reduced levels of catecholamines and cytokine responses and resulted in markedly increased survival following various inflammatory stimuli in mice[19]. Similar protection against a hyper-inflammatory stimulus was observed after prazosin administration, demonstrating that alpha-1 receptor antagonists can also prevent cytokine storms in mice.

Additional studies have explored the effects of alpha-adrenergic blockade with prazosin in prevention or protection of inflammatory cascades and cytokine-induced injuries. In models of pulmonary edema that are characterized by inflammation and neutrophil accumulation, adrenergic blockade with phentolamine or prazosin attenuated the increase of proinflammatory

cytokines in the lung and peripheral blood, and resulted in restoration of normal fluid transport capacity of alveolar epithelium after hemorrhagic shock[58,59]. In a model of brainstem encephalitis, early alpha-1-receptor blockade using prazosin allowed for preservation of cardiac output, reversed neutrophil infiltration in lungs, and prevented hemorrhagic pulmonary edema[60,61]. Prazosin was also found to suppress the clinical and histological expression of experimental autoimmune encephalomyelitis (EAE) in preclinical models[62–64]. In a mouse model of ischemia-reperfusion injury, prazosin administration led to a decrease in the expression levels of IL-6, TNF-α, IL-10, and IL-1, and prevented mortality[65]. In humans, prazosin is a first-line treatment in scorpion envenomation, a process that involves dysregulated inflammatory responses that can progress to ARDS[66]. Expression of alpha-1 adrenergic receptors are increased during sepsis[67], and catecholamine levels are elevated in septic shock[68]. Finally, elevated catecholamines in enterovirus A71-related hand, foot, and mouth disease may contribute to cardiopulmonary failure and mortality[68–71].

Together, these findings offer a rationale for studying alpha-1 receptor antagonists in the prophylaxis of patients with COVID-19. Prospective, randomized clinical trials of alpha-1 receptor antagonists administered prior to the onset of severe symptoms, as proposed herein, are needed to assess their utility in preventing CSS and reducing mortality in patients with COVID-19.

2.3. Known potential risks

Prazosin is a quinazoline derivative and commonly used drug in the long-term treatment of patients with benign prostatic hyperplasia, arterial hypertension, post-traumatic stress disorder (PTSD) and other conditions[72]. Similar to other alpha-1 receptor antagonists, prazosin is inexpensive and relatively safe. Given the role of alpha-adrenergic signaling on vascular tone and blood pressure regulation, adverse reactions related to a decrease in total peripheral resistance and hypotension are predicted to be most common. Thus, the administration of prazosin requires careful dose escalation.

Although the safety profile of prazosin for the modulation of hyperinflammation is unknown, its common use for hypertension and psychiatric disorders has been well-documented, particularly in the older age cohort that COVID-19 has impacted most seriously. More recently, prazosin was used for treatment of post-traumatic stress disorder (PTSD) in a cohort of 304 military veterans (96% male, mean age 52 years) for 26 weeks[73]. For dosing in men and women, prazosin was safely escalated up to 20 mg and 12 mg, respectively. Of importance, the number of serious adverse events did not differ significantly between prazosin and placebo. As expected, only dizziness, lightheadedness, and urinary incontinence occurred significantly more often in the prazosin group (34% vs 21%, 34% vs 20%, and 12% vs 4% respectively).

In a double-blind randomized clinical trial for alcohol use disorder, prazosin in a cohort of 44 individuals (mean age 49.1 years) was escalated to three doses daily (4 mg, 4 mg, and 8 mg per day) for 10 weeks[74]. A greater proportion of participants with prazosin experienced drowsiness and edema than those with placebo. Five serious adverse events occurred; however, none of which were determined by the institutional review board to be related to participation in the study. In a pilot study with Alzheimer's disease, prazosin (up to 6 mg) was well-tolerated in twenty-two nursing home participants (mean age 80.6 years) with no significant differences in adverse effects between prazosin and placebo groups[75]. Early reports of prazosin use in patients with prostate obstruction also indicated oral prazosin to be safe and effective in long-term treatment[76]. The reported side effects of prazosin and other alpha-blockers by manufacturers are summarized in **Table 1**. Prazosin has a similar side effect profile to other alpha-blockers. Due to the lack of

reported serious adverse events such as stroke and myocardial infarctions in current published trials, we believe prazosin will be well-tolerated within our cohort.

Table 1. Reported adverse events for different alpha-1 receptor antagonists[77]

	Prazosin	Terazosin	Doxazosin	Tamsulosin	Alfuzosin
Dizziness	10.3%	9.1%	15.6%	14.9%	5.7%
Somnolence	7.6%	3.6%			
Fatigue	6.5%	7.4%	8.0%	7.8%	2.7%
Postural Hypotension	1-4%	3.9%	1.7%		
Edema	1-4%		2.7%		
Dyspnea	1-4%		2.6%		
Rash	1-4%				
Syncope	1.0%				
Tachycardia/Bradycardia	<1%				
Rhinitis	<1%	1.9%			3.0%
Erectile Dysfunction	<1%	1.6%		1.0%	
Allergic Reaction	<1%				
Headache					3.0%

2.4. Known potential benefits

2.4.1. Potential benefits of treatment

The potential benefits of treatment with prazosin in patients at risk for developing severe COVID-19 are unknown. To date, no controlled trials have examined the role of alpha-1 adrenergic receptor antagonists for the prevention of cytokine storm syndromes and ARDS in human subjects.

To investigate a potential role for alpha-1 adrenergic receptor antagonists in preventing poor outcomes in ARDS, we performed a case-control study analyzing the potentially protective effect of alpha-1 receptor antagonists on ventilator dependence in adults with ARDS. Using data from the Truven Health MarketScan Research Database (2010-2017), we conducted a case-control study of 18,964 patients (age 18-65) with a diagnosis of ARDS that was seen in an inpatient setting. ARDS was determined using codes from the International Statistical Classification of Disease and Related Health Problems (ICD), 9th and 10th revision, respectively. Our analysis included 3,087 cases with invasive mechanical ventilation and 15,877 controls nested within a population of ARDS patients. The alpha-1 adrenergic receptor antagonists included were doxazosin, prazosin, silodosin, terazosin, and tamsulosin. Logistic regression models were used to calculate odds ratios (OR) and confidence intervals (CI) correlating any prior use of alpha-1 adrenergic receptor antagonists with the risk of ventilator dependence.

The majority of patients in our cohort were women (53%), with a mean age of 50.7 (SD=11.2). We found that patients with prior use of alpha-1 adrenergic receptor antagonists experienced a 15.8% reduced risk of invasive mechanical ventilation compared to non-users (OR 0.82, 95% CI 0.70-0.94, p=0.0065) (**Figure 1A**). This association remained significant after adjustment for several potential confounders including age, year, sex, hypertension, chronic obstructive pulmonary disease, and diabetes mellitus (adjusted OR 0.83, 95%CI 0.71-0.96). We performed a subsequent analysis investigating the possible association between alpha-1 receptor antagonist use and mortality. This analysis included 4,864 adult inpatients with ARDS between 2010-2015, with an average age of 51.9 (SD=11.2). Strikingly, we found that patients with prior use of alpha-1 adrenergic receptor antagonists experienced a 48.9% reduced risk of mortality compared to non-users (OR 0.49, 95% CI 0.27-0.81, p=0.0098) (**Figure 1B**). This association remained significant after adjustment for the aforementioned list of confounders (OR 0.45, 95%CI 0.25-0.77). Using the same data set, in-hospital mortality in patients with ARDS was 4.75% for individuals treated with alpha-1 adrenergic receptor antagonists vs 9.28% for patients not on this class of drugs (test of proportions: p=0.0114) (**Figure 1C**).

Mirroring findings from pre-clinical models, these data suggest a strong clinical rationale to study alpha-1 adrenergic receptor antagonists in the prophylaxis of ARDS and states of local and systemic immune dysregulation. In patients with COVID-19, we expect that preemptive treatment with prazosin will decrease the risk of developing severe complications of disease (e.g. ARDS, cytokine storm, and death) and reduce morbidity should they develop.

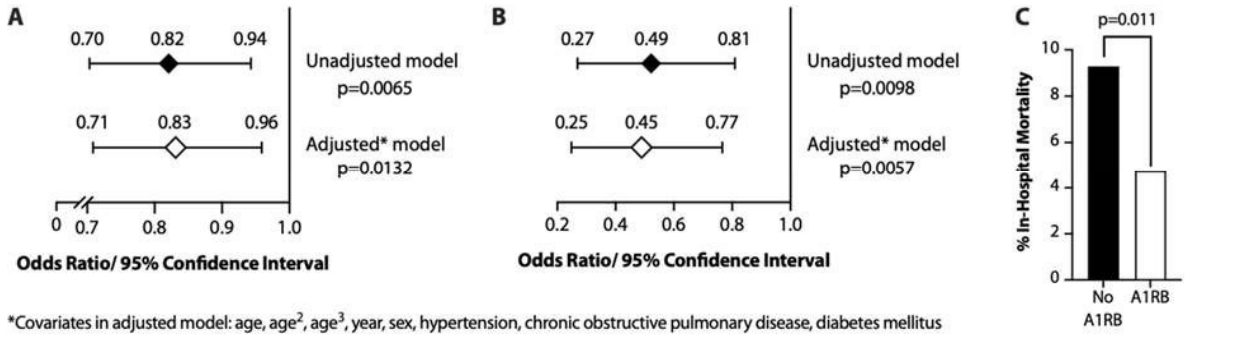


Figure 1. Logistic regression of invasive mechanical ventilation (A) and in-hospital mortality (B) in patients with ARDS who are using alpha-1 adrenergic receptor antagonists in a preliminary case control-study using data from MarketScan Research Database. (C) Percent in-hospital mortality in patients with ARDS who were taking any as compared to no alpha-1 adrenergic receptor antagonists using the same data set.

2.4.2. Potential benefits of clinical monitoring and virologic testing

Subjects enrolled in the study will undergo close clinical and laboratory monitoring that could facilitate improved management of COVID-19 with associated benefit to the individual, their family and the community at large.

3. PATIENT POPULATION

3.1. Inclusion Criteria for Enrollment

1. Subjects must be 45 years of age or older

2. Provide consent to participate
3. Subjects who tested positive for SARS-CoV-2 AND have clinical symptoms of COVID-19[1] AND have been hospitalized, but are not requiring more than 4 liters/minute of supplemental oxygen by nasal cannula and are not requiring ICU/CCU-level care at time of enrollment

3.2. Exclusion Criteria for Enrollment

1. Female subjects who identify as pregnant, self-reported positive pregnancy testing, or who are breastfeeding during the study period
2. Age >85 years
3. Subjects whose primary reason for hospitalization was not for clinical symptoms of COVID-19 although tested positive for SARS-CoV-2.
4. Known history of known orthostatic hypotension, unexplained history of syncope, postural orthostatic tachycardia syndrome (POTS), neurally-mediated hypotension, heart failure, myocardial infarction, stable or unstable angina, history of coronary artery bypass surgery, stroke, carotid artery disease, or moderate to severe mitral or aortic stenosis
5. Currently enrolled in another clinical trial for COVID-19
6. Need for vasopressors, inotropes, or intra-aortic balloon pump at time of enrollment
7. Allergy or intolerance to quinazolines (including prazosin)
8. Requires oxygen supplementation beyond 4 liters of oxygen/minute per nasal cannula at time of enrollment (i.e. not requiring oxygenation by non-rebreather, high-flow nasal cannula, CPAP/BiPAP, or invasive mechanical ventilation)
9. Patients who are in the custody of state or federal entities (prisoners)

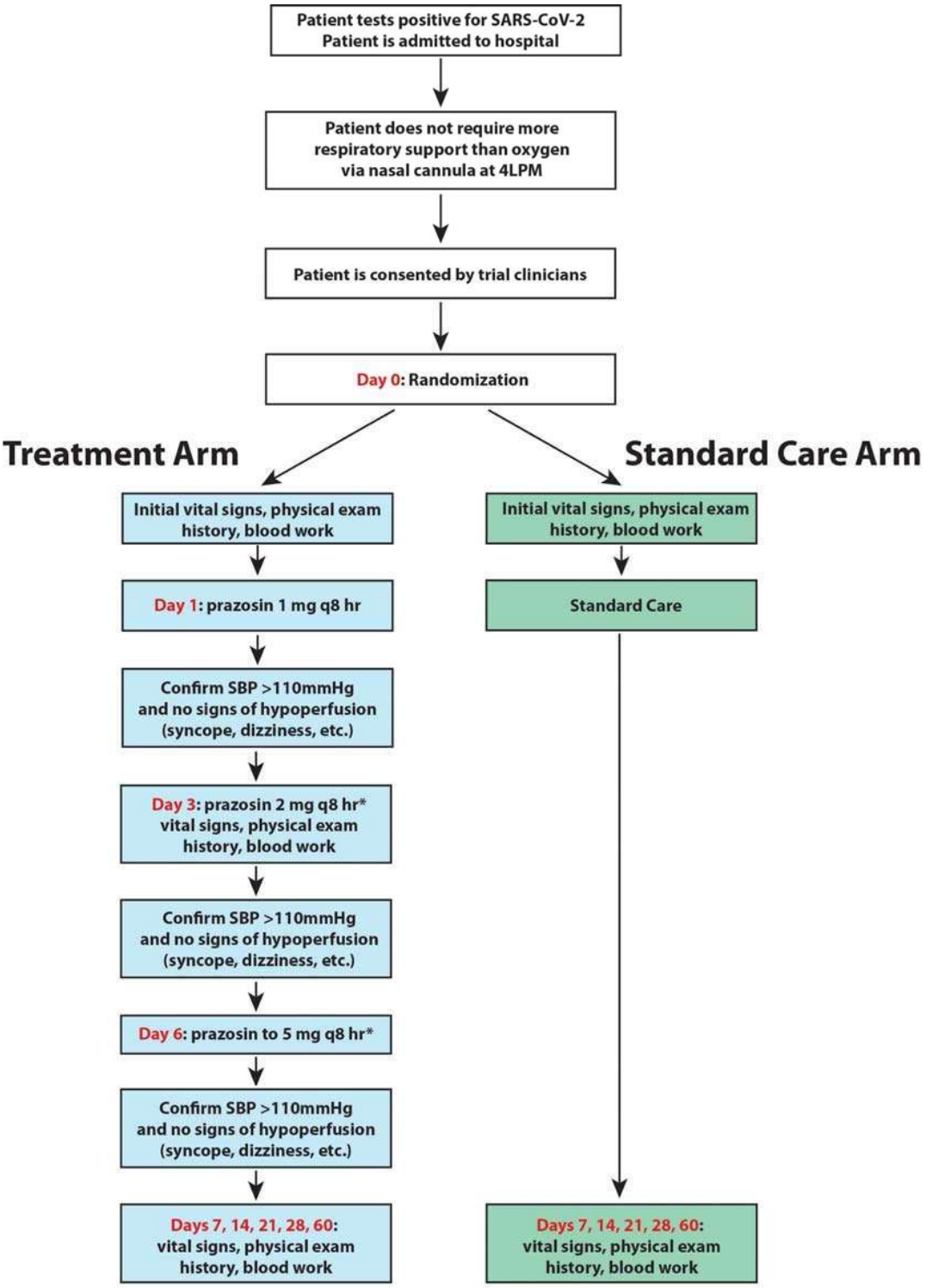
4. INVESTIGATIONAL PLAN

4.1. Definitions

I. Enrolled: From time consented to initiation of study therapy until designated as off study either through discontinuation or completion of the study.
II. Randomized: when a subject ID number is assigned through randomization.
III. Screen Failures: signed informed consent, but then determined to be ineligible or withdraws before initiation of study therapy.
IV. Discontinued: randomized, but then withdrawn by investigator or withdraws consent. A subject may be discontinued from treatment but continue to be monitored in the post-treatment follow-up portion of the trial, or discontinued from the trial.
V. Completed: Subjects are considered completed when they are followed through to Day 60 or died before that.

[1] *Acute respiratory tract infection (sudden onset of at least one of the following: fever, chills, sore throat, myalgia, diarrhea, cough, or shortness of breath) AND with no other etiology that fully explains the clinical presentation*

Figure 2: Summary of Investigational Plan



*Patients who do not tolerate escalation due to dizziness or syncope may be escalated on a modified schedule or maintained at maximum asymptomatic dose (see trial submission for details)

4.2. Randomization

Randomization will be done by block randomization.

4.3. Intervention

I. Subjects will be randomized in a 1:1 ratio to receive treatment vs standard of care
II. Study drug: Prazosin
III. Active arm will receive prazosin given by mouth three times a day with dose escalation over 6 days to target dose of 5 mg or as tolerated
IV. Control arm will receive standard of care
V. Once the patient is discharged, they should be instructed to complete the **Study Drug and Blood Pressure Patient Diary**.

4.4. Rationale for medication dosing

Prazosin is FDA-approved for the treatment of arterial hypertension, either alone or in combination with other antihypertensive drugs. The initial dose of prazosin is 1 mg two or three times a day, with therapeutic dosages most commonly employed ranging from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy. Effective therapeutic doses of prazosin for the treatment of benign prostatic hyperplasia and arterial hypertension commonly range from 1 mg by mouth every 8 hours to 5 mg by mouth every 8 hours. At these doses, the medication is typically well tolerated. Clinical trials were conducted on more than 900 patients. During these trials and subsequent marketing experience, the most frequent reactions associated with prazosin therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances, side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

Less frequent adverse reactions which are reported to occur in 1-4% of patients are:

- Gastrointestinal: vomiting, diarrhea, constipation.
- Cardiovascular: edema, orthostatic hypotension, dyspnea, syncope.
- Central Nervous System: vertigo, depression, nervousness.
- Dermatologic: rash.
- Genitourinary: urinary frequency.
- EENT: blurred vision, reddened sclera, epistaxis, dry mouth, nasal congestion.

In addition, fewer than 1% of patients have reported the following (in some instances, exact causal relationships have not been established):

- Gastrointestinal: abdominal discomfort and/or pain, liver function abnormalities, pancreatitis.
- Cardiovascular: tachycardia.
- Central Nervous System: paresthesia, hallucinations.
- Dermatologic: pruritus, alopecia, lichen planus.
- Genitourinary: incontinence, impotence, priapism.
- EENT: tinnitus.
- Other: diaphoresis, fever, arthralgia

Based on a pre-clinical model of treating hyperinflammation, we estimate the required total daily dose of prazosin to be less than 15 mg daily. This dosing range is further supported by data from a cohort study of patients with ARDS which showed that use of alpha-1 adrenergic receptor antagonists at commonly prescribed doses was indeed associated with a reduction of outcome severity.

Given the role of alpha-adrenergic signaling on vascular tone and blood pressure regulation, adverse reactions related to a decrease in total peripheral resistance and hypotension are most common. Careful dose escalation of prazosin over a period of 6 days will therefore be employed to achieve a target total daily treatment dose of 15 mg daily, given in divided doses of 5 mg daily, as outlined below. The protocol further allows for individualized dosing based on the highest tolerated daily dose of prazosin identified following the dose escalation protocol outlined below.

We are aware that the titration of most anti-hypertensive agents is often performed during weeks, and not days as proposed in our trial, yet the need for maximizing benefits before week 2 of the disease have made us adopt this more aggressive escalation schema. The fact that patients' blood pressure will be monitored routinely, and a de-escalation schema is also in place, reinforces our decision.

4.5. Specific dosing and dose escalation considerations for prazosin

1. First dose: A single loading dose of prazosin 1 mg by mouth should be given to observe whether the medication is tolerated or whether signs or symptoms of hypotension develop (e.g. dizziness, lightheadedness).

    - Prazosin may cause syncope with sudden loss of consciousness due to an excessive postural hypotensive effect. Syncopal episodes usually occur within 30 to 90 minutes of the initial dose of the drug.
    - It is expected that the arterial blood pressure can decrease by 5-10 mmHg with the first dose of prazosin.
    - The patient should be counseled about possible adverse effects of prazosin and advised what measures to take should they develop symptoms of hypotension, namely, dizziness and lightheadedness. The patient should be counseled that mild lightheadedness with rapid change of position is common. Accordingly, they should be instructed to slowly change position and take 30 seconds to move from supine to a sitting position, from a sitting to standing position, and from standing to ambulation (until they completed the dose escalation protocol and know that their current dose is tolerated). Patients should be counseled that caution should be taken when getting up and walking to the bathroom at night since they are at increased risk of syncope, falling, and injury. Patients should be counseled to sit down to urinate until they have completed the dose escalation protocol and they have tolerated stable doses for several days.

2. The blood pressure (BP) should be measured prior to the next dose: if the patient remains asymptomatic and BP ≥110/60 mmHg, continue prazosin 1 mg by mouth every 8 hours
3. The blood pressure (BP) should be measured prior to the next dose on Day 3: if the patient remains asymptomatic and BP ≥110/60 mmHg, the dose will be increased to 2 mg by mouth every 8 hours

4. Blood pressure measurement on Day 6: if the patient remains asymptomatic and BP ≥110/60 mmHg, the dose will be increased to a target dose of 5 mg by mouth every 8 hours
5. If the **BP is <110/60 mmHg at any time** on spot measurement, the next dose of prazosin should be held, and the patient instructed to continue with the highest previously tolerated dose 8 hours later:
    a. For patients who have received 5 mg dosing, the next dose will be 2 mg TID
    b. For patients who have received 2 mg dosing, the next dose will be 1 mg TID
    c. For patients who are still on 1 mg dosing, the next dose will be 1 mg BID
    d. Patients will be dose de-escalated to 1 mg BID until BP is stable, or be removed from study treatment if not able to tolerate this lowest schedule
    e. There will be no intra-patient re-escalation, excepts scenario described in 6 below
6. If the patient did not tolerate dose escalation to 5 mg by mouth every 8 hours and is persistently hypertensive (BP ≥130/80 mmHg for 2 subsequent days), one attempt can be made to increase the dose of prazosin to 3 mg by mouth every 8 hours. If this is not tolerated, the patient is instructed to continue with the highest previously tolerated dose 8 hours later.
7. The maximum total daily dose of prazosin should not exceed 15 mg by mouth.
8. **If blood pressure monitoring is not available at study onset, repeated occurrences of postural dizziness should trigger drug dose reduction or BP monitoring.**
9. Before the patient is discharged, he/she will receive an automated blood pressure cuff and instructions on how to monitor and record blood pressure at home at least once daily. He/she will remain on the highest tolerated dose at discharge and be instructed to complete the **Study Drug and Blood Pressure Patient Diary** with each dose. There will be no dose titration at home.

4.6. Definition of an Overdose for this Protocol

Overdose of prazosin is defined as:

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Appropriate supportive treatment should be provided if clinically indicated.

All reports of overdose (with and without an AE) must be reported within 24 hours as an SAE per **Section 9**.

Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate prazosin is not dialysable because it is protein bound.

4.7. Prohibited Medications:

Approved or investigational drug with established activity against SARS-CoV-2.

4.8. Subject Withdrawal

The reason for study removal and the date the subject was removed will be documented in the CRF. A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as parent or legal guardian) withdraws consent.

A subject must be discontinued from treatment (but may continue to be monitored in the post-treatment follow-up portion of the trial) for any of the following reasons:

- The subject or legal representative (such as legal guardian) withdraws consent.
- Intercurrent illness that prevents further administration of treatment,
- Severe or life-threatening prazosin-related AE(s), including but limited to:
  Gastrointestinal: Severe persistent (more than 24 hrs) vomiting, diarrhea
  Cardiovascular: Severe orthostatic hypotension, dyspnea, syncope, angina
  Central Nervous System: vertigo
- If in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the patient,
- Noncompliance with trial treatment or procedure requirements,
- Patient is lost to follow-up,
- Patient becomes pregnant

Randomized subjects who withdraw from the study will not be replaced.

5. PHARMACEUTICAL INFORMATION

5.1. Agent Accountability

The IND Sponsor or the IND Sponsor's representative shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

5.2. Mode of Action

Prazosin (MINIPRESS®), a quinazoline derivative, is an oral alpha-blocker; used primarily to treat hypertension. The exact mechanism of the hypotensive action of prazosin is unknown. Recent animal studies, however, have suggested that the vasodilator effect of prazosin is also related to blockade of postsynaptic alpha-adrenoceptors.

5.3. Description

Prazosin is supplied as the following:

Strength	Capsule Color	Package Size
MINIPRESS® 1 mg	White	90's
MINIPRESS® 2 mg	Pink and White	90's

MINIPRESS® 5 mg	Blue and White	90's

5.4. Packaging

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

5.5. Storage

Prazosin should be stored at room temperature (between 68 and 77 degrees F) while protected from light and moisture and in a secure, limited access storage area, accessible only by authorized personnel.

5.6. Route of Administration

Prazosin is administered orally. The dose of prazosin should be adjusted according to the patient's individual blood pressure response. The initial dose will be 1mg TID starting on Day 1 and dose escalated to 2 mg TID on Day 3 and 5 mg TID on Day 6 if tolerated per **Section 4.5**. Once the patient is discharged, he/she will remain on the highest tolerated dose and should be instructed to complete the **Study Drug and Blood Pressure Patient Diary** at home. There will be no dose titration at home.

5.7. Subject Care Implications

As with all alpha-blockers, prazosin may cause syncope with sudden loss of consciousness. In most cases, this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120–160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally, they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of prazosin. The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution. Hypotension may develop in patients given prazosin who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of prazosin. The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of prazosin therapy.

Addition of a diuretic or other antihypertensive agent to prazosin has been shown to cause an additive hypotensive effect. This effect can be minimized by reducing the prazosin dose to 1 to 2 mg three times a day, by introducing additional antihypertensive drugs cautiously, and then by retitrating prazosin based on clinical response.

Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate prazosin is not dialysable because it is protein bound.

If a dose of prazosin is missed for more than 1 hour or if a patient vomits after the dose, the dose should be skipped and dosing should resume at the next scheduled dose.

5.8. Returns and Reconciliations

Each local investigator is responsible for keeping accurate records of the clinical supplies, the amount dispensed to, and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the local site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6. STATISTICAL CONSIDERATIONS

6.1. Sample Size and Power Considerations

As per recommendation of the COVID-19 Review Committee at The Johns Hopkins University School of Medicine, an initial interim analysis will be performed after 30 patients have completed 28 days of follow-up (15 in each arm; 13% of recruitment) to analyze safety endpoints and early signs of efficacy. If the intervention is deemed safe, after discussion with the centralized Data and Safety Monitoring Board (DSMB), recruitment may continue to the next interim analysis (33% and 67% completion of 28 day follow-up) to reach a target enrollment of 220 patients (110 in each arm). The estimated sample size that is required based upon the assumptions below is 202 participants. We have a planned sample size of 220 subjects to allow for losses or withdrawals. Participants will be randomized in a 1:1 ratio to prazosin (Arm 1) vs standard of care (Arm 2).

To evaluate the power of the study, the following assumptions were made:

1. The primary analysis will compare the prazosin and standard of care using the formula presented by Palta and Amini for survival analysis[84] and a one-sided Type I error rate (alpha) of 0.025 and Type II error rate (beta) of 0.2. Therefore, we have power of 80%. A one-sided test was chosen as we hypothesize that prazosin will be beneficial and are not interested in whether prazosin is worse than standard of care. That is, the null hypothesis is: There is no significant difference between prazosin and standard of care in the prevention of severe COVID-19. The alternative hypothesis is: Prazosin use is superior to standard of care in the prevention of severe COVID-19.

2. It is anticipated that very few of these subjects will be randomized and not start the study (and so be excluded from the primary analysis) or be lost to follow-up prior to Day 28 (and so have missing data for the primary endpoint) as they are all hospitalized patients.

3. Among those randomized to receive standard of care, by day 28, 34.5% incidence of severe symptomatic disease[2] among individuals that were symptomatic at time of randomization. This results in an overall hazard rate of 0.0151.

4. Among those randomized to receive prazosin, by day 28, 17.3% incidence of severe symptomatic disease, a 50% reduction in risk of progressing to severe disease. This results in an overall hazard rate of 0.0068.

6.2. Statistical Analysis

Analysis of AE data

Analysis of AE data will primarily be descriptive based on CTCAE version 5.0 coding of events. The proportion of subjects experiencing an SAE and the proportion experiencing a Grade 3 or higher. AE will be compared between randomized arms using Fisher's Exact Test.

6.3. Endpoints

Primary Endpoint: Clinical event scale of disease severity (evaluated up to Day 60):

1. Death
2. Hospitalized, requiring mechanical ventilation *and/or* high flow nasal cannula *and/or* ICU/CCU admission (or equivalent setting) *and/or* ECMO

Primary Safety Endpoints:

1. Cumulative incidence of grade 3 and 4 adverse events during the study period
2. Cumulative incidence of serious adverse events during the study period
3. Cumulative incidence of symptomatic hypotension (SBP <90 mmHg) or hypotension requiring cessation of prazosin

The primary endpoint is progression of disease from being hospitalized with no more than 4 liters/minute of supplemental oxygen to either requiring mechanical ventilation, high flow nasal cannula, ICU/CCU admission, or ECMO, or death. Our primary hypothesis that the COVID-19 disease severity will be mitigated among participants taking prazosin. Specifically, we hypothesize that prazosin will mitigate the more severe levels of disease outcomes including the requirement of mechanical ventilation *and/or* high flow nasal cannula *and/or* ICU/CCU admission, and death. These outcomes will be captured in continuous time (i.e. day of requiring mechanical ventilation, day of death) from randomization. Our main analysis will be the cumulative incidence of these severe outcomes from the point of randomization to standard of care or prazosin treatment arms. Our primary approach for estimating the overall cumulative incidence function is a non-parametric Kaplan-Meier estimator that is unadjusted as well as an adjusted analysis using inverse probability of treatment weights. The risk

[2] *requiring oxygen by high-flow nasal cannula, requiring intubation, requiring mechanical ventilation, requiring ICU/CCU-level or equivalent care, requiring tocilizumab/ sarilumab/ siltuximab, or death*

difference of severe disease progression to hospitalization, mechanical ventilation/ICU/CCU, or death, will be estimated at day 28 from the cumulative incidence curve as well as along the entire cumulative incidence curve. Furthermore, we can obtain the restricted mean survival time from the non-parametric survival curves, which provides the expected time to severe disease within a limited period of follow-up time from randomization (e.g., at 28 days)[85]. To obtain the confidence interval on the risk scale, we will bootstrap the survival curves especially as we will be adjusting for the variables that are related to the outcome but would estimate the marginal survival curve[79,80].

As exploratory analysis, we will then move to a flexible Weibull parametric model that allows for a variety of curvature to the hazard function and thus reduce the required distributional assumptions for parametric time-to-event models[78] but yet still increase efficiency and precision by the fact that some distributional assumption is being made. Furthermore, we will allow for interaction between covariates and time to allow for non-proportionality. In order to check the fit of the parametric model, we will graphically assess the parametric cumulative incidence curves to that of the non-parametric estimator. If a good fit is not achieved, we will add additional splines to the flexible Weibull parametric model and/or modify the interaction between covariates and time to allow for additional flexibility in the model over follow-up time.

Additionally, to increase power in a clinical trial, we can adjust for baseline covariates that are related to the outcome[79,80]. Therefore, we will adjust for factors that likely contribute to more severe disease such as age, immune compromised, and whether an individual has comorbidities. Comorbidities may be summarized using an index such as the Charlson Comorbidity Index if deemed appropriate. Depending on the amount of losses-to-follow-up, we will use inverse probability of censoring weights to mitigate the potential for informative censoring[81-83].

Furthermore, in addition to calculating the overall cumulative incidence curves, as a further exploratory analysis, we will examine moving from being hospitalized without the more severe disease to the more severe outcomes as a multistate model, if the study goes to completion and is not stopped early by the DSMB. That is each individual starts in the initial state of being symptomatic and hospitalized but not requiring more than 4 liters/minute of supplemental oxygen by nasal cannula. Participants may then move from being symptomatic and hospitalized to mechanical ventilation/HFNC/ICU/CCU care/ECMO, discharged from hospital alive, and finally they may then transition to death which is an absorbing state. Therefore, we have the following states that individuals may be in: i) hospitalization with or without supplemental oxygen by nasal cannula (but not high flow nasal cannula, non-rebreather, CPAP/BiPAP), ii) mechanical ventilation and/or high flow nasal cannula and/or ICU/CCU admission and/or ECMO, iii) discharged alive, and iv) death. We will allow transition from states i or ii to any of the other states. We will estimate the transition probability given the treatment arm and therefore be able to estimate the probability of transitioning to a more severe state as well as whether individuals transition to a less severe state by study arm.

All analyses will be conducted with a modified intention-to-treat approach, which excludes randomized subjects who do not begin prazosin treatment.

Finally, statistical inference will use a one-sided Type 1 error rate of 0.025 and 95% confidence intervals (note that we will use an O'Brien and Flemming type spending function to preserve the Type 1 error for interim analyses see below under **Section 9.3** Halting Criteria for Study). Because the analysis requires multiple steps to properly study the multiple levels

of the outcome, we will use bootstrap methods to estimate the p-value and 95% confidence intervals.

Secondary Objectives:

1. Compare rates and duration of laboratory abnormalities in peripheral blood including lymphopenia, leukocytosis, anemia, thrombocytopenia, creatinine, AST/ALT, troponin I, pro-BNP, D-dimer, ferritin, interleukin (IL-)6, soluble IL-2 receptor
2. Compare rates and duration of laboratory abnormalities in peripheral blood including fractionated plasma catecholamines (adrenaline, noradrenaline, dopamine) and fractionated plasma metanephrines (metanephrine, normetanephrine)
3. Analyze the interaction between prazosin and D-dimer

The analysis of secondary endpoints will be descriptive. Specifically, we will look for laboratory abnormalities and compare the prevalence between the treatment arms using a logistic model and adjusting for factors related to these outcomes. In order to determine the duration of abnormalities, we will use a discrete time to event model to examine how long participants remain at abnormal levels. A discrete time to event model will be used due to the discrete time points at which laboratory markers will be measured. These models will be adjusted for factors such as age, race, and sex, as well as additional factors that may be related to laboratory abnormalities. While we are not powered to find an interaction between disease severity, as a secondary outcome, we will examine the potential for treatment effect heterogeneity by COVID-19 disease severity at time of randomization D-dimer has been indicated to be a marker for COVID-19 disease progression[1]. Therefore, we will assess whether the treatment effect of prazosin is different by level of D-dimer. This will be done by allowing for D-dimer to be a continuous variable and include interaction term(s) in the model. To allow for non-linearity between D-dimer and disease progression, we will allow for cubic splines for the main effect of D-dimer as well as for the interaction terms with the treatment arm indicator variable.

Analysis of Primary Safety Endpoints

We will track the primary safety endpoints that occur during follow-up by treatment arms. Of particular interest is the cumulative incidence of hypotension (SBP<90 mmHg) or hypotension requiring cessation of prazosin among those in the treatment arm. For the interim analyses of safety endpoints, we will provide the DSMB with the cumulative incidence of each type of primary safety endpoints by treatment arms as well as the risk difference and the 95% confidence interval for the difference between treatment arms.

7. STUDY PROCEDURES

7.1. Study Calendar

Study Procedures	Screen (Day -2 to 0)	Baseline (Day 0)	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Day 60	Day of Discharge
Visit Window (days)	-	-	-	-	± 1	± 2	± 2	± 2	± 2	-
Informed consent	X									
Demographics & Medical History	X									
Inclusion/Exclusion	X									
Randomization		X								
Prazosin[1]			X Dose escalation up to 5 mg Q8H							
Blood Pressure Monitoring[2]			X							
Vitals signs, height, weight[3]		X	X	X	X	X	X	X	X	X
Physical examination or assessment[4]		X	X	X	X	X	X	X	X	X
COVID-19 Symptom Screen[5]	X	X	X	X	X	X	X	X	X	X
AE Monitoring[5]			X	X	X	X	X	X	X	X
Complete Metabolic Panel[6]		X	X	X	X	X	X			X
Complete Blood Count w/ Differential[6]		X	X	X	X	X	X			X
Pregnancy Test[7]	X									
Serum IL-6[6]		X	X	X	X	X	X			X
Serum soluble IL-2 receptor[6]		X	X	X	X	X	X			X
Fractionated Plasma Catecholamine[6]		X	X	X	X	X	X			X
Fractionated Plasma Metanephrine[6]		X	X	X	X	X	X			X
D-Dimer, Pro-BNP, Troponin-I[6]		X	X	X	X	X	X			X
Ferritin[6]		X	X	X	X	X	X			X
SARS-CoV-2 Antibody[8]							X			
JHH site only: Bank Plasma for Future Testing if co-consented to CCPSEI study[9]		X	X	X	X	X	X			

[1]See Sections 4.5 and 5.6 for details regarding Prazosin dose titration plan.
[2]See Sections 4.5 for details regarding blood pressure monitoring while admitted and after discharge to home.
[3]Blood pressure, pulse, respiratory rate, pulse oximetry, temperature, and weight will be collected per standard of care while patients are admitted. Once discharged, vital signs will be collected if available as part of their regular clinical care. Height will be obtained at or prior to baseline only.
[4]Complete physical examination at baseline; focused physical examinations or assessments thereafter. Physical exams and assessments will be collected per standard of care while the patient is admitted. Once discharged, these will be collected if available as part of their regular clinical care and may be completed remotely via telemedicine, phone, email, or chart review.
[5]Can be completed remotely via telemedicine, phone, email or chart review.
[6]Laboratory values will be collected per standard of care at each participating center while the patient is admitted. Once discharged, labs will be collected if available as part of their regular clinical care.
[7]Women of child bearing potential only
[8]Measured via serum SARS CoV-2 S1 subunit IgG and IgA. Test result will be collected if conducted as part of standard of care on or after day 21.

[9]While inpatient at JHH, sample collection will be conducted per Dr. Lauren Sauer's IRB00245545 "Clinical characterization protocol for severe infectious diseases (CCPSEI)". Research sample collection will be discontinued once the patient is discharged.

7.2. Efficacy And Laboratory Measures

Clinical Efficacy

1. Death
2. Requiring mechanical ventilation and/or in ICU level care
3. Requiring supplemental oxygen more than 4 liters/minute, including non-rebreather, BiPAP/CPAP but not mechanical ventilation.
4. Non-ICU hospitalization, requiring supplemental oxygen no more than 4 liters/minute
5. Non-ICU hospitalization, not requiring supplemental oxygen;

8. ADVERSE EVENTS, RISKS, AND BENEFITS

8.1. Potential Benefits of treatment

The potential benefits of anti-adrenergic treatment with prazosin in patients with COVID-19 are unknown. However, it is anticipated that treatment will decrease the risk of developing severe complications of symptomatic disease (i.e. requiring oxygen by high-flow nasal cannula, respiratory supplementation requiring mechanical ventilation, requiring ICU/CCU-level or equivalent care, ECMO, or death) and decrease the severity of illness should it develop.

8.2. Potential benefits of clinical monitoring

Subjects enrolled in the study will undergo close clinical and laboratory monitoring that could facilitate improved management of COVID-19 with associated benefit to the individual, their family and the community at large.

8.3. Potential risks

1. Risks of prazosin: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%, lightheadedness
2. Risks of phlebotomy: local discomfort, bruising, hematoma, bleeding, fainting
3. Total blood draws will not exceed 500 mL

8.4. Alternatives

The alternative to participation in this study is routine care and monitoring of COVID-19.

8.5. Definitions

8.5.1. Adverse Event (AE)

Adverse event is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy/intervention) even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). Medical conditions/diseases present before starting the study treatment are only considered adverse events if they worsen after starting the study treatment

(any procedures specified in the protocol). Adverse events occurring before starting the study treatment but after signing the informed consent form will not be recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

This study will use the descriptions and grading scales found in the revised CTCAE version 5.0 for AE reporting.

8.5.2. Serious Adverse Event (SAE)

A serious adverse event is an undesirable sign, symptom or medical condition which:

- Results in death
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Supplemental Form)
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Is associated with an overdose
- Is a pregnancy

Events **not** considered to be serious adverse events are hospitalizations for the:

- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).
- Admissions for monitoring of treatment-related infusion reactions that do not otherwise meet the criteria for a SAE.

8.6. Relationship

The relationship of an AE to the administration of the study drug is to be assessed by the investigator according to the following definitions:

- No (unrelated, not related, no relation): The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.
- Yes (related): The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

- The temporal sequence from study drug administration - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication - The other medications the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

Assessment of Grade:

The investigator will make an assessment of grade for each AE and SAE reported during the study, which will be recorded in the CRF. The assessment will be based on the National Cancer Institute's CTCAE (Version 5.0) and graded as shown below:

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

Any AE that changes in grade during its course will be recorded in the CRF at the highest level experience by the subject.

8.7. Expectedness

Unexpected adverse event: An adverse event, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the Investigator's Brochure, package insert or safety reports. Any adverse event that is not included in the informed consent is considered "unexpected".

Expected (known) adverse event: An adverse event, which has been reported in the package insert. An adverse event is considered "expected", only if it is included in the informed consent document as a risk.

8.8. Handling of Expedited Safety Reports

In accordance with local regulations, the IND Sponsor or designee will notify investigators of all SAEs that are unexpected (i.e., not previously described in the IB), and related to prazosin. This notification will be in the form of an expedited safety report (ESR) that is to be emailed to the investigators and the study coordinators. Upon receiving such notices, the investigator must review and retain the notice with the IB and where required by local regulations, the investigator will submit the ESR to the appropriate IRB. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information.

8.9. Reporting

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

All adverse events experienced by subjects will be collected and reported from the first dose of prazosin, throughout the study, and will only be followed for 30 days unless related to the investigational agent.

Subjects who have an ongoing adverse event related to the study procedures and/or medication(s) may continue to be periodically contacted by a member of the study staff until the event is resolved or determined to be irreversible by the investigator.

8.9.1. Routine Adverse Event Reporting

If an ongoing AE changes in its intensity or in its perceived relationship to investigational product, a new AE entry for the event should be completed. Adverse events should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for AEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with AEs at study completion should receive post-treatment follow-up as appropriate.

All identified non-serious AEs must be recorded and described on the appropriate Adverse Event Case Report Form (CRF).

8.9.2. Laboratory Test Abnormalities

Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as adverse events. A grade

1 or 2 clinical laboratory abnormality should be reported as an adverse event only if it is considered clinically significant by the investigator.

In addition, the following laboratory abnormalities should also be captured on the AE CRF page as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have the investigational product discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

8.9.3. Serious Adverse Event Reporting

All SAEs (including deaths) occurring from the first dose of the study drug through 30 days after the last dose of study drug will be collected and recorded on the Adverse Event Case Report Form (CRF).

All SAEs should be reported to the IND Sponsor (cbetteg1@jhmi.edu) within 24 hours of becoming aware of the event occurrence. The SAE Reporting Form should be completed for all SAEs that are deemed related and unexpected. **Section 9.2** outlines reporting requirements for the DSMB.

SAEs will be reported to the Johns Hopkins Medicine IRB per institutional guidelines.

Adverse events that are serious, unexpected, and assessed by the investigator to be related to the study drug will be reported within 24 hours of becoming aware of the event occurrence to the post-marketing departments of the drug manufacturer (Pfizer).

After the initial SAE report, the investigator is required to proactively follow each subject and provide further information in regards to the subject's condition.

All AE(s) and SAE(s) will be followed until:

- Resolution
- The condition stabilizes
- The event is otherwise explained
- The subject is lost to follow-up
- Death

8.9.3.1 Expedited IND Safety Reports to the FDA

All reporting to the FDA will be completed by the IND Sponsor.

7 Calendar-Day Telephone or Fax Report:

The IND Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent.

Such reports are to be submitted to the FDA within 7 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

15 Calendar-Day Written Report:

The IND Sponsor is required to notify the FDA of any SAE that is unexpected and related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

IND Annual Reports:

In accordance with the regulation 21 CFR § 312.33, the IND Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the adverse events and progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.33 for a list of the elements required for the annual report. All IND annual reports will be submitted to the FDA by the IND Sponsor.

9. SAFETY OVERSIGHT

9.1. Monitoring Plan

1. Routine monitoring at both Hopkins and Participating Sites will be conducted quarterly or more as needed. Monitoring will be conducted remotely by a qualified study team member.
2. All AE and grade 1-3 SAE will be reviewed by the protocol team twice monthly, or more if needed. All grade 2-5 SAEs will be reviewed by the protocol team within 24-48 hours of being received.
3. A data safety monitoring board (DSMB), composed of independent experts without conflict of interests, will be established. The Board will review study data to evaluate the safety, efficacy, study progress, and conduct of the study. Additional details can be found in **Section 9.2** and the Data and Safety Monitoring Plan.

9.2. Halting Criteria for the Study

The study enrollment and dosing will be stopped, and an ad hoc review will be performed if any of the specific following events occur or, if in the judgment of the study physician, subject safety is at risk of being compromised:

I. Unexpected death of a dosed subject.
II. Occurrence of a life-threatening allergic/hypersensitivity reaction (anaphylaxis), manifested by bronchospasm with or without urticaria or angioedema requiring hemodynamic support with pressor medications or mechanical ventilation.

III. For a reported unexpected SAE or trend of unexpected SAEs related to the study product.
IV. Two subjects with a Grade 3 or higher lab toxicity for the same parameter associated with the study product.
V. An overall pattern of symptomatic, clinical, or laboratory events that the DSMB consider associated with study product and that may appear minor in terms of individual events but that collectively may represent a serious potential concern for safety.
VI. Any other event(s) which is considered to be a serious adverse event in the good clinical judgment of the responsible physician. This will be appropriately documented.

Upon completion of this review, the DSMB will determine if the study enrollment or study dosing should be interrupted or if study enrollment and study dosing may continue according to the protocol. Should the trial not be stopped at this time point, the final analysis would need to account for the number of interim analyses that were conducted. Therefore, we will use the O'Brien and Flemming type spending function to preserve the overall Type 1 error. This will allow for stopping the trial earlier should the intervention arm be shown to be superior at an interim analysis.

Interim analyses: We plan to provide the number and proportion of the primary outcome of participants who have completed 28 days of follow up from randomization, by masked treatment arms to the DSMB, as well as participant accrual rate, and withdrawals from study at the time of the DSMB meetings. We will ask whether the DSMB would like a formal interim analysis where analysis is done including adjustment for factors related to worse disease outcomes (age, cardiopulmonary comorbidities, gender, etc.) and the results are provided masked to the DSMB. The DSMB may then ask for unmasking of the data and decide whether to halt the trial or not. We plan to do interim analyses at 13%, 33%, and 67% of final sample size reaching day 28. For the primary safety endpoints, we will provide the cumulative incidence of each type of safety endpoint by study arm in addition to the risk difference and 95% confidence interval of the risk difference between study arms.

10. ETHICS/PROTECTION OF HUMAN SUBJECTS

10.1. Ethical Standard

The JHU is committed to the integrity and quality of the clinical studies it coordinates and implements. JHU will ensure that the legal and ethical obligations associated with the conduct of clinical research involving human subjects are met. The information provided in this section relates to all JHU sites participating in this research study.

As the Department of Health and Human Services continues to strengthen procedures for human subjects' protections via new regulations, JHU will review these evolving standards in relation to the proposed activities and will advise the investigators on those that may apply.

In addition, JHU has a Federal wide Assurance (FWA) number on file with the Office for Human Research Protections (OHRP). The FWA number for JHU is FWA00005834.

This assurance commits a research facility to conduct all human subjects' research in accordance with the ethical principles in The Belmont Report and any other ethical standards recognized by OHRP. Finally, per OHRP regulations, the research facility will ensure that the mandatory renewal of this assurance occurs at the times specified in the regulations.

10.2. Institutional Review Board

The JHU IRB will review this protocol and all protocol-related documents and procedures as required by OHRP and local requirements before subject enrollment. The JHU IRB currently holds and will maintain a US FWA issued by OHRP for the entirety of this study.

10.3. Informed Consent Process

The informed consent process will be initiated before a volunteer agrees to participate in the study and should continue throughout the individual's study participation. The subject will sign the informed consent document before any procedures are undertaken for the study. A copy of the signed informed consent document will be given to the subject for their records. The consent will explain that subjects may withdraw consent at any time throughout the course of the trial. Extensive explanation and discussion of risks and possible benefits of this investigation will be provided to the subjects in understandable language. Adequate time will be provided to ensure that the subject has time to consider and discuss participation in the protocol. The consent will describe in detail the study interventions/products and risks/benefits associated with participation in the study. The rights and welfare of the subjects will be protected by emphasizing that their access to and the quality of medical care will not be adversely affected if they decline to participate in this study.

10.4. Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators and their staff. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the IND Sponsor. The results of the research study may be published, but subjects' names or identifiers will not be revealed. Records will remain confidential. To maintain confidentiality, the PI will be responsible for keeping records in a locked area and results of tests coded to prevent association with subjects' names. Data entered into computerized files will be accessible only by authorized personnel directly involved with the study and will be coded. Subjects' records will be available to the FDA, the NIH, the manufacturer of the study product and their representatives, investigators at the site involved with the study, and the IRB.

10.5. Future Use of Stored Specimens

While inpatient at JHH, sample collection will be conducted per Dr. Lauren Sauer's IRB00245545 "Clinical characterization protocol for severe infectious diseases (CCPSEI)". Subjects will be asked to co-consent to CCPSI biorepository study (IRB00245545) when joining this trial. They will consent to use their samples for future testing before any research sample is obtained. The confidentiality of the subject will be maintained. There will be no plans to re-contact them for consent or to inform them of results. The risk of collection of the sample will be the small risk of bruising or fainting associated with phlebotomy. However, these samples will be taken at the same time as other protocol required samples. No human genetic testing will be performed on the samples.

Under this protocol, research samples will be collected at 7 time points (see **Sections 7.1** and **7.2**). Plasma will be frozen in 1-mL aliquots. These samples will be used to answer questions that may arise while the study is underway or after it is completed. If for instance, there were

unanticipated AEs, serum could be used to run tests that might help determine the reason for the AEs. Cytokines of relevance may be measured, for example.

Samples would not be shared with investigators other than investigators at JHU unless outside investigators had relevant assays or expertise not available to the study investigators. The specimens would remain linked and at JHU. Any use of these specimens not specified in the current protocol will be reviewed by the JHU IRB.

Research sample collection will be discontinued once the patient is discharged.

10.6. Data management and monitoring

10.6.1. Source Documents

The primary source documents for this study will be the subjects' medical records. If the investigators maintain separate research records, both the medical record and the research records will be considered the source documents for the purposes of auditing the study. The investigator will retain a copy of source documents. The investigator will permit monitoring and auditing of these data, and will allow the IRB and regulatory authorities access to the original source documents. The investigator is responsible for ensuring that the data collected are complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) should support the data collected and entered into the study database/case report form and must be signed and dated by the person recording and/or reviewing the data. All data submitted should be reviewed by the site investigator and signed as required with written or electronic signature, as appropriate. Data entered into the study database will be collected directly from subjects during study visits or will be abstracted from subjects' medical records. The subjects' medical records must record their participation in the clinical trial and what medications (with doses and frequency) or other medical interventions or treatments were administered, as well as any AEs experienced during the trial.

10.6.2. Data Management Plan

Study data will be collected at the study site(s) and entered into the study database. Data entry is to be completed on an ongoing basis during the study.

10.6.3. Data Capture Methods

The data system includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate.

10.6.4. Study Record Retention

The site investigator is responsible for retaining all essential documents listed in the ICH GCP Guidelines. The FDA requires study records to be retained for up to 2 years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records are also to be maintained in compliance with IRB/IEC, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent provided by federal, state, and local law. It is the site investigator's responsibility to retain copies of source documents.

No study document should be destroyed without prior approval from the Principal Investigator. Should the investigator wish to assign the study records to another party and/or move them to another location, the site investigator must provide written notification of such intent to sponsor with the name of the person who will accept responsibility for the transferred records and/or their new location. The sponsor must be notified in writing and written permission must be received by the site prior to destruction or relocation of research records.

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