Title: Safety and Efficacy of the Treatment of Hospitalized Patients with COVID 19 Infection with an Inhibitor of IL-4 and IL-13 Signaling: A Phase IIa Trial

Short Title: Safety and Efficacy of Dupilumab for Treatment of Hospitalized COVID-19 Patients

Phase of Study: Phase IIa
IND Number: 154664

Study Center: University of Virginia

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1.0 SUMMARY

Background: It has been widely recognized that severe disease from SARS-CoV-2 infection has been attributed to a substantial dysregulation of the immune system leading to significant respiratory compromise, end organ damage and death (1). Central to this immune response are certain cytokines, specifically those that activate the Type 2 (Th_2) pathway of inflammation, which have been associated with severe disease in COVID-19 (2,3). Interleukin-13 (IL-13) has been identified as a key driver in respiratory compromise leading to ventilation in patients with COVID-19 and, when neutralized in mice, has shown reduced disease severity. Dupilumab, an inhibitor of IL-13 and IL-4 used currently in treatment of atopic disease, has also been associated with reduced disease severity when observing outcomes of those diagnosed with COVID-19 who are concomitantly prescribed dupilumab (2). This therefore raises the possibility of successful use of dupilumab for treatment of COVID-19 infection and moreover provides an avenue for more targeted anti-inflammatory therapy in these patients.

Clinical Experience: Dupilumab, an anti-interleukin-4 receptor-α monoclonal antibody, leading to blockage of IL-4 and IL-13 signaling, has been FDA approved for treatment of moderate to severe atopic dermatitis since 2017. It has been successfully shown to reduce disease severity in not only those with atopic dermatitis but in other allergic diseases where Th_2 cytokines have been implicated, including asthma and chronic rhinosinusitis (4). Original clinical trials noted excellent safety profiles in addition to favorability in its use when considering the negative impacts of long term steroid use in these patients (5,6).
Dupilumab therapy for asthma is associated with eosinophilia, with the highest incidence at 16-20 weeks after the initiation of therapy, and in approximately 4% of patients, of which only 0.3% were symptomatic (7). Preliminary analysis of COVID-19 hospitalization data at our institution showed an increase in eosinophil counts in patients throughout their admission. Although an overall favorable drug safety profile, the association of eosinophilia with dupilumab use in addition to its association with severe COVID-19 infection raises concern for an additive effect with both exposures and potential subsequent clinical repercussions. It is therefore important that safety is also evaluated in addition to clinical efficacy of dupilumab use in those hospitalized with COVID-19 in this randomized, double-blind, placebo-controlled, superiority phase IIa trial.

Primary Objective:

- Determine the efficacy of dupilumab use plus standard of care management in patients hospitalized with moderate to severe COVID-19 infection compared to placebo plus standard of care management assessed by the proportion of patients alive and free of invasive mechanical ventilation at 28 days.

Primary Endpoint:

- Proportion of patients alive and free of invasive mechanical ventilation at 28 days.

Secondary Objectives:

- Evaluate the safety of dupilumab use in patients hospitalized with moderate to severe COVID-19 infection.
- Evaluate clinical endpoints of dupilumab use in patients with COVID-19.
- Evaluate the immunologic and biologic end points of inhibition of type 2 inflammation.

Secondary Endpoints:

- Percentage of patients with eosinophilia (defined as an absolute eosinophil count > 0.6 k/μl at ≥ 1 measurement throughout the study period) in those receiving dupilumab in addition to standard of care compared to those who receive standard of care management plus placebo. Complete blood counts with differentials and complete metabolic panels will be measured on Day 0, 2, 5, 7, 14, 28 and 60. Day 7, 28 and 60 optional, although recommended, if patient

discharged within the time frame[1].

- Cumulative incidence (defined as number of new events divided by the total number of individuals in the population at risk for the time interval) of adverse events: injection site reactions, eye/eyelid inflammation, conjunctivitis, oropharyngeal pain, insomnia, tooth ache, gastritis, arthralgia, bacterial pneumonia, herpes viral infection, hypereosinophilic syndrome, hypersensitivity reaction.
- Prevalence of B.1.1.7 and B.1.351 and other SARS-CoV-2 lineages in study cohort: Day 0.
- Plasma total Immunoglobulin E (IgE) levels[2]: Day 0 and 14.
- Plasma inflammatory markers (C-reactive protein and ferritin)[3]: Day 0, 7 and 14. Day 7 optional if patient discharged[1].
- Plasma cytokine levels including TARC (CCL17), YKL40, eotaxin 3 (CCL26), IL-13, IL-4, Arg1, Hyaluronan, soluble ST2[4]: Day 0, 2, 5, 7, 14, and 28. Day 7 and 28 optional if patient discharged[1].
- Change in PaO2/SaO2 to FiO2 ratio: Day 0, 2, 5, 7 (if patient remains inpatient throughout)
- All-cause mortality rate at 28 days.
- Hospital length of stay (LOS)
- ICU LOS
- Proportion of patients alive and free of invasive respiratory failure at 28 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 60 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 90 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 120 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 150 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 180 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 270 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 360 days.
- National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale (see Appendix): Day 0, 2, 5, 7, 14, 28, 60, 180 and 360.
- Need for vasopressors
- Need for renal replacement therapy
- Need for extracorporeal membrane oxygenation (ECMO)

Study Design: This is a randomized, double-blind, placebo-controlled, superiority phase IIa trial to assess the safety and efficacy of dupilumab use in hospitalized patients with moderate to severe COVID-19 infection. A total of 40 eligible subject will be enrolled and randomized in a 1:1 ratio to receive either dupilumab or placebo, stratifying on the disease severity measured by the required oxygen ≤ 15L or > 15L by nasal cannula. Both arms will receive standard of care management per current National Institutes of Health (NIH) COVID-19 treatment guidelines (8) in addition to their randomized treatments. Patients will be followed prospectively for up to 360 days after enrollment.

Study Population:

[1] Patient will be required to have mandatory in person follow up 14 days after initial dupilumab dose. Therefore, if patient inpatient through day 14 thus receiving 2nd dupilumab dose, will be required to follow up 14 days after (same for day 28 injection).

[2]Total IgE levels will be analyzed through UVAMC clinical lab.

[3]C-reactive protein and ferritin levels will be analyzed through UVAMC clinical lab.

[4]Plasma cytokines will be measured using the MILLIPLEX® MAP Human Cytokine/Chemokine/Growth 28 Factor Panels, and individual Simplex or ELISA kits.

Inclusion Criteria for Enrollment

- Male or female 18 years of age or older at the time of enrollment.
- Patients hospitalized with a positive RT-PCR for SARS-CoV-2 within the last 14 days, with illness duration within the last 14 days, and evidence of moderate to severe COVID-19 infection as defined by NIH COVID-19 Severity Categorization (8):

  -Moderate illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen SpO2≥ 94% on room air at sea level.

  -Severe illness: Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%.
- Patient and/or legally authorized representative is willing and able to provide written informed consent and comply with all protocol requirements.
- Patients with hematologic malignancies or solid tumors are eligible.
- Patients with autoimmune disorders are eligible.
- Patients with immunodeficiency and organ or stem cell transplant recipients are eligible.
- Patients with acute or chronic renal injury/failure are eligible.
- Patients with neutropenia/lymphopenia are eligible.
- Patients with elevated liver function tests are eligible.
- Women who are not taking contraception are eligible.
- Patients who are currently or have recently received steroids and/or remdesivir are eligible.
- Patient agrees to not participate in another clinical trial for the treatment of COVID-19 through end of study period.

Exclusion Criteria

- Patients who do not require inpatient admission for COVID-19 infection.
- Patients who require invasive mechanical ventilation at time of enrollment.
- A pre-existing condition or use of a medication that, in the opinion of the site investigator, may place the individual at a substantially increased risk due to study participation.
- Pregnancy or breast feeding (lactating women who agree to discard breast milk from day 1 until two weeks after the last study product is given are not excluded).
- Allergy to Dupilumab or its excipients.
- Current acute parasitic helminth infection or history of chronic parasitic infection.
- History of ocular scleritis, uveitis, keratitis or recent (<6 months) eye injury (chemical or traumatic), infection or vascular occlusion.
- Have received any live vaccine (that is, live attenuated) within 4 weeks before screening, or intend to receive a live vaccine (or live attenuated) during the study. *Note: Use of non-live (inactivated) vaccinations is allowed for all subjects*.

Assessment and Data Acquisition:

1. Baseline: Age, sex, symptoms, pertinent comorbidities and medical history, days from symptom onset to initiation of dupilumab treatment, NIAID 8 point ordinal scale, type of admission to the floor or ICU, physical exam, chest xray, chest CT, vital signs including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, oxygen requirement
2. Safety and efficacy: Day 0 (baseline), 2, 5, 7, 14, 28 and day 60. Safety labs and cytokine data may not be obtained if patient has since been discharged and chooses not to follow up in person on optional follow up time points as previously discussed[5].

[5]Patient will be required to have mandatory in person follow up 14 days after initial dupilumab dose. Therefore, if patient inpatient through day 14 thus receiving 2nd dupilumab dose, will be required to follow up 14 days after (same for day 28 injection).

3. Complete blood count with differential and complete metabolic panel: Day 0, 2, 5, 7, 14, 28 and 60. Day 7, 28 and 60 are optional if patient discharged in this time frame[5].
4. Day 0 viral sample collected for SARS-CoV-2 PCR as above will be held for sequencing to determine prevalence of SARS-CoV-2 B.1.1.7 and B.1.351 lineages in study cohort.
5. Plasma total IgE levels[6]: Day 0 and 14.
6. Plasma inflammatory markers (C-reactive protein and ferritin)[7]: Day 0, 7 and 14. Day 7 optional if patient since discharged.
7. Plasma cytokine levels including TARC (CCL17), YKL40, eotaxin 3 (CCL26), IL-13, IL-4, Arg1, Hyaluronan, soluble ST2[8]: Day 0, 2, 5, 7, 14, and 28. Day 7 and 28 optional if patient since discharged[5].
8. Change in PaO2/SaO2 to FiO2 ratio: Day 0, 2, 5, 7 (if remains inpatient throughout).
9. NIAID 8-point ordinal scale (see Appendix): Day 0, 2, 5, 7, 14, 28, 60, 180 and 360.
10. Outcome measures: O_2 requirement (PaO_2/FiO_2 ratio or $SpO2/FiO_2$), supplemental oxygen strategy (nasal cannula, high flow nasal cannula, noninvasive ventilation, intubation and invasive mechanical ventilation, rescue ventilation i.e. neuromuscular blocking agents, prone positioning, ECMO), vasopressors, renal support, ICU LOS, hospital LOS, all-cause mortality at 28 days, proportion of patients alive and free of respiratory failure at 28 days, and proportion of patients alive and free of mechanical ventilation at 28, 60, 90, 120, 150, 180, 270 and 360 days.

Drug: Subjects will receive a loading dose of dupilumab (600 mg, given as two 300 mg subcutaneous injections) on day 0. This dosing regimen was selected to be equivalent to regimen used in the LIBERY ASTHMA VENTURE phase 3 clinical trial and per recommendations for patients with asthma in the dupilumab Food and Drug Administration (FDA) package insert (9,10). Given the suspected longevity of IL-13 elevation in severe COVID-19 disease (documented by Lucas et al.) out to day 25 of illness, additional single doses of 300 mg will be given at 14 days and 28 days (dose spacing as recommended for atopic disease) if the patient remains hospitalized and receiving active care by these days (i.e. NIAID 8 point ordinal scale of 4 and above) (3,9).

Immune Evaluations: Immune evaluations will be performed to assess the extent to which dupilumab administration influences the immune response in COVID-19 disease. Total serum IgE levels will be measured at day 0 and day 14. IL-4, IL-13, TARC (CCL17), YKL40, eotaxin 3 (CCL26), Arg1, Hyaluronan, soluble ST2 and levels of other Th_1/Th_2 serum cytokines will be measured 0, 2, 5, 7, 14, and 28 days after dupilumab injection. Plasma inflammatory markers will be measured at 0, 7 and 14 days after dupilumab injection. Day 7 and 28 optional to patient if has been discharged in time frame[5].

[6]Total IgE levels will be analyzed through UVAMC clinical lab.
[7]C-reactive protein and ferritin levels will be analyzed through UVAMC clinical lab.
[8]Plasma cytokines will be measured using the MILLIPLEX® MAP Human Cytokine/Chemokine/Growth 28 Factor Panels and individual Simplex or ELISA kits.

List of Abbreviations

ADR	Adverse Drug Reaction
ADE	Antibody-mediated enhancement of infection
BP	Blood pressure
CIP	Convalescent Immune Plasma
DAIDS	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DLT	Dose limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECG/EKG	Electrocardiogram
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HTLV	Human T-cell lymphotropic virus
IB	Investigator's Brochure
ICF	Informed Consent (Informed Consent Form)
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEs	Immune Evaluations
IEC	Independent ethics committee
IFN-γ	Interferon-gamma
IND	Investigational New Drug Application
IRB	Institutional review board
ISBT	International Society of Blood Transfusion
LOS	Length of Stay
LVEF	Left Ventricular Ejection Fraction
MAS	Macrophage Activation Syndrome
MNC	Mononuclear Cells
MERS	Middle East Respiratory Syndrome
NA	Nuclear antibody
NP	Nasopharyngeal
OP	Oropharyngeal
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PI	Principal Investigator
Pts	Patients
RT-PCR	Reverse Transcriptase Real-Time Polymerase chain reaction
PK	Pharmacokinetic
SAE	Serious adverse event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SBP	Systolic Blood Pressure
SOC	Standard of Care
TACO	Transfusion-associated circulatory overload
T. cruzi	*Trypanosoma cruzi*
TRALI	Transfusion-related acute lung injury
UP	Unanticipated Problem
UPnonAE	Unanticipated Problem that is not an Adverse Event

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2.0 OBJECTIVES

2.1 Primary Objective

- Determine the efficacy of dupilumab use plus standard of care management in patients hospitalized with moderate to severe COVID-19 infection compared to placebo plus standard of care management assessed by the proportion of patients alive and free of invasive mechanical ventilation at 28 days.

2.2 Secondary Objectives

- Evaluate the safety of dupilumab use in patients hospitalized with moderate to severe COVID-19 infection.
- Evaluate clinical endpoints of dupilumab use in patients with COVID-19.
- Evaluate the immunologic and biologic end points of inhibition of type 2 inflammation.

2.3 Study Design

This is a randomized, double-blind, placebo-controlled, superiority phase IIa trial to assess the safety and efficacy of dupilumab use in hospitalized patients with moderate to severe COVID-19 infection. A total of 40 eligible subjects will be enrolled and randomized in a 1:1 ratio to receive either dupilumab or placebo, stratifying on the disease severity measured by the required oxygen ≤ 15L or > 15L by nasal cannula. Both arms will receive standard of care management per current National Institutes of Health (NIH) COVID-19 treatment guidelines (8) in addition to their randomized treatments. Patients will be followed prospectively for up to 360 days after enrollment.

3.0 BACKGROUND AND SIGNIFICANCE

3.1 Background and Scientific Rationale

It has been widely recognized that severe disease from SARS-CoV-2 infection has been attributed to a substantial dysregulation of the immune system leading to significant respiratory compromise, end organ damage and death (1). This has been further exemplified through finding a reduction in mortality of COVID-19 patients requiring oxygen with use of dexamethasone when compared to patients not receiving steroids (11). Central to this inflammatory process are cytokines, including interleukin-6 (IL-6), which have led to clinical trials investigating their blockade in severe COVID-19 infection (12). However, due to the significant heterogeneity of cytokine elevations seen in SARS-CoV-2 infection, it has been difficult to identify specific targets for intervention that are associated with and can provide clinical benefit for patients with COVID-19 (12–14). Nevertheless some studies have implicated type 2 (Th_2) cytokines in severe disease (3).

Elevated interleukin-13 (IL-13), a Th_2 cytokine, has been shown to be a central component of the immune response leading to ventilation in patients with SARS-CoV-2 infection. This was validated in two separate patient cohorts from University of Virginia and Virginia Commonwealth University Medical Center, and is consistent with findings of Lucas et al. in demonstrating an association of IL-13 with severe COVID-19 disease (2,3). Furthermore, Lucas et al. show increasing levels of IL-13 through the course of disease, with elevations out to day 25 of illness (3). IL-13 is known to be involved in eosinophilic inflammation, mucous secretion, goblet cell metaplasia and fibrosis, and has been regularly implicated in airway hyperresponsiveness and atopic disease (15). Inhibition of IL-13 in a K18- hACE2 transgenic mouse model led to improved clinical scores and reduced weight loss when infected with SARS-CoV-2. RNAseq analysis of mice infected with SARS-CoV-2 further found elevations in type 2 associated genes (2). Hyaluronan, a pulmonary glycosaminoglycan whose low molecular weight form is proinflammatory and implicated in numerous other lung pathologies, was identified as a driver of pulmonary disease in COVID-19 patients and, additionally, as a downstream effector of IL-13 (2,16).

This has led to consideration of dupilumab, an anti-interleukoin-4 receptor-α monoclonal antibody which blocks signaling by both IL-4 and IL-13, as a treatment for moderate to severe COVID-19 infection. In a large

retrospective analysis of an international cohort of 350,004 patients with COVID-19, those on dupilumab prior to infection with SARS-CoV-2 were shown to have a lower risk of ventilation and death when matched to with patients of similar comorbidities (2).

Dupilumab has been FDA approved for treatment of moderate to severe atopic dermatitis since 2017. It has been successfully shown to reduce disease severity in not only those with atopic dermatitis but in other allergic diseases where Th_2 cytokines have been implicated, including asthma and chronic rhinosinusitis (4). Original clinical trials noted limited adverse events in addition to its favorability in use for treatment of atopic patients as a steroid sparing regimen (5,6). Overall, dupilumab's excellent safety profile, its demonstrated ability in reduce other Th_2 pathologic processes and its targeted approach to therapy which limits harmful effects of steroid use makes it an exciting prospective candidate for successful treatment of COVID-19 infection.

3.2 Experience with the use of dupilumab in allergic disease

Dupilumab was first FDA approved in the United States for treatment of moderate to severe atopic dermatitis in adults uncontrolled with topical medications. In 2018, it was approved in patients with moderated to severe asthma aged 12 years or older with eosinophilic phenotypes or with oral steroid dependent asthma (4). In 2019, the FDA approved its use in adults with nasal polyps accompanied by chronic rhinosinusitis (17). Its use in atopic dermatitis was extended to children aged 6-11 years old in 2020 for those with moderate to severe disease not adequately controlled with topical prescription therapies (18). Studies of dupilumab use in these patients demonstrates its ability to reduce Th_2 associated biomarkers in addition to reduction in expression of genes involved in Th_2 inflammation including IL-13 (4,19). Dupilumab is supplied as a single-dose pre filled syringe of either 300 mg per 2mL solution or 200 mg per 1.14 mL solution, which are administered subcutaneously. For atopic dermatitis, a 600 mg initial dose followed by maintenance dose of 300 mg injected every other week is recommended (4). A peak mean concentration of drug is reached within one week of initial dosing. Although trough concentrations were noted to be lower in adult patients with higher body weights, no dose adjustments are recommended. In addition, while there have not been any studies on the pharmacokinetics of dupilumab in hepatic or renal impairment, no dose adjustments are recommended in these patients (4).

Adverse events (AEs) identified through clinical trials with dupilumab in atopic dermatitis include eczema herpeticum and herpes zoster although these have not been consistently validated in subsequent meta-analysis studies (4). Dupilumab has additionally been found to result in a lower risk of skin infections which is suspected to be due to its normalization of the skin barrier (4,9). Prescribing information additionally lists conjunctivitis as an AE with dupilumab use in those with atopic dermatitis, although this increased risk was not seen in asthma and chronic sinusitis trials. Conjunctivitis episodes are listed as mild to moderate in severity with rare need for drug discontinuation (4). Additional prescribing information for dupilumab lists additional AEs as hypersensitivity reactions and cardiovascular events (9). Although no trials to date have been devoted to dupilumab use in pregnancy, there are trials ongoing in this patient population (20).

Clinical trials in asthma patients revealed similar rates of AEs across study groups. Common AEs from these trials included injection site reactions, nasopharyngitis, nausea, conjunctivitis, headache, upper respiratory tract infections, bronchitis, and sinusitis. Transient eosinophilia (>500 cells/ μL) was noted in both phase 2 and phase 3 asthma clinical trials (4). In the LIBERTY ASTHMA VENTURE phase 3 international, randomized, double-blind, placebo-controlled trial enrolling 210 asthma patients found asymptomatic eosinophilia in 14% of dupilumab treated patients compared to 1% of placebo patients. Per the trial authors, eosinophilia was of no clinical consequence in these patients (10). In LIBERTY ASTHMA QUEST phase 3 randomized, double-blind-placebo-controlled, parallel group enrolling 1,902 asthma patients, eosinophilia was seen in 4.1% of the dupilumab treated patients compared to 0.6% of the placebo treated patients, with 1.2% of dupilumab-treated with eosinophil counts of greater than 3,000 cells/μL. Eosinophilia in this trial resulted in eight patients to be discontinued from the trial (7 in the dupilumab group and 1 in the control group) (7). In a multicenter retrospective cohort enrolling 214 patients with atopic dermatitis found higher rates of eosinophilia than in the clinical trials, reporting 57% had eosinophilia out of 177 patients who had at least 1 eosinophil count measured

with 29.8% with hypereosinophilia (>1500 cells/ μL) and a maximum count of 7800 cells/μL. A total of five of these patients discontinued the drug due to persistent hypereosinophilia (21).

4.0 ELIGIBILITY

4.1 Inclusion Criteria for Enrollment

- Male or female 18 years of age or older at the time of enrollment.
- Patients hospitalized with a positive RT-PCR for SARS-CoV-2 within the last 14 days, with illness duration within the last 14 days, and evidence of moderate to severe COVID-19 infection as defined by NIH COVID-19 Severity Categorization (8):

  -Moderate illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen SpO2≥ 94% on room air at sea level.
  -Severe illness: Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%.
- Patient and/or legally authorized representative is willing and able to provide written informed consent and comply with all protocol requirements.
- Patients with hematologic malignancies or solid tumors are eligible.
- Patients with autoimmune disorders are eligible.
- Patients with immunodeficiency and organ or stem cell transplant recipients are eligible.
- Patients with acute or chronic renal injury/failure are eligible.
- Patients with neutropenia/lymphopenia are eligible.
- Patients with elevated liver function tests are eligible.
- Women who are not taking contraception are eligible.
- Patients who are currently or have recently received steroids and/or remdesivir are eligible.
- Patient agrees to not participate in another clinical trial for the treatment of COVID-19 through end of study period.

4.2 Exclusion Criteria

- Patients who do not require inpatient admission for COVID-19 infection.
- Patients who require invasive mechanical ventilation at time of enrollment.
- A pre-existing condition or use of a medication that, in the opinion of the site investigator, may place the individual at a substantially increased risk due to study participation.
- Pregnancy or breast feeding (lactating women who agree to discard breast milk from day 1 until two weeks after the last study product is given are not excluded).
- Allergy to Dupilumab or its excipients.
- Received any of the following in the two weeks prior to screening as treatment of COVID-19:
  - small molecule tyrosine kinase inhibitors (e.g. imatinib, gefitinib, acalabrutinib, etc.);
  - monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [or sarilumab], etc.);
  - monoclonal antibodies targeting T-cells or B-cells as treatment for COVID-19;
  - Any other immunomodulatory (other than steroids) medications within 5 half-lives or 30 days prior to randomization.
  -
- Current acute parasitic helminth infection or history of chronic parasitic infection.
- History of ocular scleritis, uveitis, keratitis or recent (<6 months) eye injury (chemical or traumatic), infection or vascular occlusion.

- Have received any live vaccine (that is, live attenuated) within 4 weeks before screening, or intend to receive a live vaccine (or live attenuated) during the study. *Note: Use of non-live (inactivated) vaccinations is allowed for all subjects*.

4.3 Strategies to Maintain Diversity of Enrollment

Subjects will be enrolled at the University of Virginia Medical Center, a tertiary care center with over 600 beds and a large catchment area including areas in Tennessee, West Virginia and North Carolina. UVA Health provides services to a wide variety of patients including racial and ethnic minorities, which have been disproportionately affected by COVID-19. Each patient admitted to UVA hospital for management of COVID-19 infection will be assessed for possible enrollment. If eligibility criteria are met, patients will be approached with special care taken to provide clear language and open communication about trial goals and design, particularly when discussing with minority populations. Every effort will be made to encourage patient trust and maintain study transparency.

5.0 TREATMENT PLAN

5.1 Treatment Summary

This is a randomized, double-blind, placebo-controlled phase IIa trial to assess the safety of dupilumab use in hospitalized patients with moderate to severe COVID-19 infection. A total of 40 eligible subjects will be enrolled and randomized to receive either dupilumab or placebo at 1:1 ratio. The randomization will be stratified based on disease severity: patients who are on 15L or less of oxygen by nasal cannula (severity group A) and those requiring more than 15L of oxygen by nasal cannula including any noninvasive ventilation measures (severity group B). Both arms will receive standard of care management per current National Institutes of Health (NIH) COVID-19 Treatment Guidelines (8) in addition to their randomized treatments. Patients will be followed prospectively for up to 360 days after enrollment. We will document adverse events related to respiratory or clinical status with injection of dupilumab and adverse events duringthe first 60 days of the study period: injection site reactions, eye/eyelid inflammation, conjunctivitis, oropharyngeal pain, insomnia, tooth ache, gastritis, arthralgia, bacterial pneumonia, herpes viral infection, hypereosinophilic syndrome, hypersensitivity reaction. Immune testing will be performed to sequentially profile the immune responses of the patients after they receive dupilumab. Patients ≥ 18 years of age, hospitalized with a positive RT-PCR for SARS-CoV-2 within the last 14 days, with illness duration within the last 14 days, and evidence of moderate to severe COVID-19 infection will be enrolled in the study. Subjects will receive a loading dose of dupilumab (600 mg, given as two 300 mg subcutaneous injections) on day 0. This dosing regimen was selected to be equivalent to regimen used in the LIBERY ASTHMA VENTURE phase 3 clinical trial and per recommendations for patients with asthma in the dupilumab Food and Drug Administration (FDA) package insert (9,10). Given the suspected longevity of IL-13 elevation in severe COVID-19 disease out to day 25 of illness, additional single doses of 300 mg will be given at 14 days and 28 days (dose spacing as recommended for atopic disease) only if the patient remains hospitalized and receiving active care by these days (i.e. NIAID 8 point ordinal scale of 4 and above) (3,9).

5.2 Study drug administration

- Subcutaneous administration will be done in the hospital.
- If an AE develops directly after injection, management will occur per investigator and clinical care team discretion (i.e. if perceived as allergic reaction, will treat with epinephrine, steroids, diphenhydramine as dictated per guidelines for anaphylaxis).
- Subjects will be removed from the trial if anaphylaxis or other severe, life threatening AE occurs and is deemed to have developed due to first or any subsequent dupilumab injections.

5.3 Concomitant medications

Concomitant medications will be documented on the Case Report Form (CRF). Concomitant medications will be assessed from 7 days prior to enrollment to Day 60 for all medications with the exceptions listed in the bullets below. All medications, except biologics and corticosteroids, can be recorded once regardless of the number of

times it was given during the time period. For example, vasopressors should be recorded when first dose given (as the start date) and the last dose given (as the end date) during the period of assessment.

The following medications will not be recorded in the concomitant medications list:

- All topical medications: ointments, creams, and lotions;
- All intranasal medications: nasal decongestants, nasal allergy medications, nasal steroids, and nasal saline drops/sprays;
- All ophthalmic medications: ophthalmic allergy medication, ophthalmic medications for infection, and ophthalmic medications for eye dryness (e.g., saline eye drops);
- Antiseptic mouth wash, lozenges;
- Cough medication: mucolytics, cough suppressants, and expectorates;
- GI medications: H2 blockers, proton pump inhibitors, GI stimulants, prokinetics, laxatives, stool softeners, antacids, anti-diarrheal and anti-nausea medications;
- Symptomatic care medications: antipyretics, antihistamines, decongestants, and NSAIDs;
- Mineral or herbal supplements, dietary supplements, iron/ferrous sulfate, magnesium, calcium, electrolyte replacement;
- Albumin infusions;
- Melatonin;
- Nicotine patch, lozenge, gum, or nasal spray, or other product to treat tobacco dependence;
- Dyes: contrast media, iodine – based dye, barium sulfate, and diatrizoate sodium.

5.3.1 Acceptable Concomitant Medications
All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator. This includes antimicrobial therapies, steroids, insulin, acetaminophen, ibuprofen, anticoagulants, and any other therapies that are considered standard of care, are recommended in the National Institutes of Health (NIH) COVID-19 Treatment Guidelines, and are not listed in the exclusion criteria. Overlapping toxicities of dupilumab with standard of care treatment including off-label use of other drugs will be monitored.

5.3.2 Prohibited Concomitant Medications
Subjects are prohibited from receiving medications or vaccinations that are specified in the exclusion criteria during study period.

5.4 Subject Removal
Subjects will not receive any further study treatments if life threatening or severe AEs are deemed to have developed due to first or any subsequent injections of dupilumab. Discontinuation of study drug will not mean withdrawal from the study. All remaining study procedures should be completed as indicated by protocol.

Subjects are free to withdraw from participation in the study at any time upon request without prejudice.

5.5 Enrollment, Screen Failures, and Study Completion
Patients are considered enrolled from time consented to participate until designated as a screen failure, or have revoked consent and have been withdrawn from the study, or have completed the study. A screen failure is a patient who signed informed consent, but then was determined to be ineligible or withdraws from the study prior to any study interventions. Subjects are considered to have completed the study when they are followed through day 360 or death occurred prior to day 360.

5.6 Study Timeline

Day 0 Baseline:

A. Subject informed consent (obtained before performing study related activities)'
B. Baseline Screening:
    1. Medical history as it pertains to inclusion/exclusion criteria
    2. Demographics (age)
    3. Determination of RT-PCR for SARS-CoV-2 within the last 14 days, with illness duration within the last 14 days

DAY 0 Baseline Enrollment, Randomization and Administration:

1. Additional demographics (sex, ethnicity, race), height and weight
2. COVID-19 onset of symptoms, source of contagion (if known) and symptom screen (fevers, cough, shortness of breath, diarrhea, anosmia)
3. Assessment of clinical status (8-point ordinal scale)
4. Medical history and medication use
5. Physical examination
6. COVID-19 testing (RT-PCR) from nasopharyngeal or throat if not already obtained on admission
7. CBC with differential, comprehensive metabolic panel, C-reactive protein and ferritin
8. Blood for immune evaluation of cytokine levels (1 light green top, 2 mL/draw)
9. Randomization and dupilumab administration: subcutaneous injection into the upper arm, thigh or lower abdomen, avoiding areas within 2 inches of navel, avoiding areas where skin is damaged or tender.

Day 1-6 (data collected through electronic medical record and/or documentation per primary team)

1. Vital signs daily (including supplemental oxygen requirements)
2. COVID-19 symptom screen (fevers, cough, shortness of breath)
3. Assessment of clinical status (8-point ordinal scale)
4. New medical conditions, AE evaluation
5. PaO2/SaO2 to FiO2 ratio at days 0, 2, 5, 7 days (if patient remains hospitalized).

Days 0, 2, 5, 7 (± 1 day), 14 (± 2 days), 28 (± 2 days), 60 (± 7 days):

1. Complete blood count with differential (lavender top tube, ~3mL) and comprehensive metabolic panel (light green top tube, ~2mL) on days 0, 2, 5, 7, 14, 28 and 60 days. Day 7, 28 and 60 labs are optional if patient has been discharged in the time frame[9].
2. SARS-CoV-2 PCR from oropharyngeal or nasopharyngeal swabs: Day 0 (if not already obtained on admission).
3. Day 0 viral sample collected for SARS-CoV-2 PCR as above will be held for sequencing to determine prevalence of SARS-CoV-2 B.1.1.7 and B.1.351 lineage in study cohort.
4. Blood for immune evaluation of cytokines including TARC (CCL17), YKL40, eotaxin 3 (CCL26), IL-13, IL-4, Arg 1, Hyaluronan, soluble ST2[10]: before dupilumab administration (day 0) and 2, 5, 7, 14, and 28 days after dupilumab administration (light green top tube, ~2mL). Day 7 and 28 are optional if patient has been discharged[9].
5. Blood for total IgE levels[11]: Day 0 and 14 (gold top tube, ~2mL).

[9]Patient will be required to have mandatory in person follow up 14 days after initial dupilumab dose. Therefore, if patient inpatient through day 14 thus receiving 2nd dupilumab dose, will be required to follow up 14 days after (same for day 28 injection).

[10]Plasma cytokines will be measured using the MILLIPLEX® MAP Human Cytokine/Chemokine/Growth 28 Factor Panels, and individual Simplex or ELISA kits.

[11]Total IgE levels will be analyzed through UVAMC clinical lab.

6. Blood for inflammatory markers (C-reactive protein and ferritin)[12]: Day 0, 7 and 14 (light green top tube as CMP above). Day 7 labs are optional if patient has been discharged[13].
7. Physical examination: Day 28 (optional in person attendance, otherwise will be done via telephone call without exam)[13].
8. Vital signs, assessment of clinical status (8-point ordinal scale – see Appendix), symptom screen, concomitant medications and AE evaluation: Day 0, 2, 5, 7, 14, 28 and 60. Mandatory in person assessment at day 14 if previously discharged, otherwise optional in person attendance with information obtained via telephone call if preferred[13].
9. Status of alive and free of mechanical ventilation and proportion of patients alive and free of respiratory failure at Day 28 and proportion of patients alive and free of invasive mechanical ventilation at day 60 derived from the 8-point ordinal scale clinical status.

Days 180 (±90 days) and 360 (±30 days) (via telephone call):

1. Patient status on day 90, 120, 150, 180, 270 and 360 as it pertains to end points of alive and free of mechanical ventilation at days 90, 120, 150, 180, 27, 360. This will be assessed via telephone call from study team on days 180 and 360.
2. 8 point ordinal score assessment on day 180 and 360 assessed via telephone call.

5.7 Known potential benefits

This trial is being conducted to test efficacy and ensure safety of dupilumab use in patients hospitalized with moderate to severe COVID-19. If successful, a key potential benefit to dupilumab use in those with clinical disease of COVID-19 is prevention of disease progression than current standard of care for hospitalized patients with COVID-19. Given its favorable safety profile, promising previous observation studies coupled with the high mortality of COVID-19, particularly in elderly and vulnerable persons, suggests that the benefits of its use outweigh the risks. However, for all cases where dupilumab administration is considered, a risk-benefit assessment must be conducted to assess individual variables.

5.8 Known potential risks

5.8.1 Conjunctivitis

Prescribing information for dupilumab lists conjunctivitis as an AE with use in those with atopic dermatitis, although this increased risk was not seen in asthma and chronic sinusitis trials (4). A meta-analysis done with clinical trials for use of dupilumab in atopic dermatitis found a reported conjunctivitis rate of 8% in those treated with dupilumab compared to 3.6% receiving placebo (18). Another meta-analysis comparing twenty-two unique studies involving dupilumab use in atopic dermatitis reported a pooled proportion of 26.1% in those receiving dupilumab. In most studies, details of conjunctivitis episodes were not described in detail but were considered treatable without discontinuation of dupilumab therapy (19). Regardless, given the high occurrence of ocular disease in these patients, and in some circumstance's severe disease, we will exclude patients with history of certain ocular diseases as listed in our exclusion criteria. Occurrence of ocular symptoms will be assessed and managed per the investigator team with consultation of Ophthalmology depending on clinical severity.

5.8.2 Herpes Reactivation

Prescribing information for dupilumab lists herpes infection and eczema herpeticum as an AE with dupilumab use (4). Initial clinical trials for dupilumab use in atopic dermatitis reported herpes infection in 6.1% of participants treated with dupilumab and 5.2% in those treated with placebo (18). Subsequent meta-analysis of dupilumab clinical trials in atopic dermatitis found no association between dupilumab

[12]C-reactive protein and ferritin levels will be analyzed through UVAMC clinical lab.

[13]Patient will be required to have mandatory in person follow up 14 days after initial dupilumab dose. Therefore, if patient inpatient through day 14 thus receiving 2nd dupilumab dose, will be required to follow up 14 days after (same for day 28 injection).

and herpes infections, with a decrease odds of eczema herpeticum. They additionally found no association between dupilumab and overall infection risk (20). Another meta-analysis comparing twenty-two unique studies involving dupilumab use in atopic dermatitis found a pooled proportion of 5.8% of herpes simplex virus (19). Given this, any concern for herpes infection will be assessed and managed per investigator team. Severe manifestation of herpes virus including ocular herpes infection or herpes eczema herpeticum will involve prompt consultation of appropriate subspecialty teams and initiation of treatment therapies as needed.

5.8.3 Injection site reaction

The most common adverse reaction found with dupilumab use in initial trials was injection site reactions, which according to a meta-analysis of clinical trials for use in atopic dermatitis, occurred in 13.2% of those receiving dupilumab compared to 6.5% in those receiving placebo (18). Bothersome injection site reactions will be assessed and managed with appropriate symptomatic therapies.

5.8.4 Hypersensitivity reaction

Hypersensitivity reaction is listed as a potential AE of dupilumab use. There have been case reports of patients developing these reactions with their second dose of dupilumab (21). Response to initial and second injection of dupilumab will be monitored closely with vital sign assessments. Any concern for acute hypersensitivity reaction will involve prompt assessment from the investigator or primary team and, if warranted, treatment with appropriate therapies (i.e. epinephrine, steroids, diphenhydramine etc.).

5.8.5 Hypereosinophilic Syndrome

Hypereosinophilia (HE) is defined as an eosinophil count >1.5 k/µl on peripheral laboratory measurement and/or pathologic evaluation via tissue staining with evidence of: eosinophils exceeding 20% of all nucleated cells in a bone marrow section and/or pathologist opinion of extensive eosinophil tissue infiltration and/or marked deposition of eosinophil granules. Hypereosinophilic syndrome (HES) is defined as meeting criteria for HE plus organ damage and/or dysfunction attributable to HE, and exclusion of other disorders as a major reason for organ damage (22). While eosinophilia and HE were reported in dupilumab clinical trials in asthma patients as previously discussed, most of these instances were considered asymptomatic with no subsequent clinical consequences. In the phase 2b trial assessing efficacy and safety of dupilumab use in 300 asthma patients with a baseline blood eosinophil count >0.3 k/µl, one subject discontinued study treatment due to HES, which was noted to resolve with subsequent steroid treatment (5). Patients will be monitored via lab work for eosinophilia, hypereosinophilia and HES as laid out in the treatment plan with frequent assessments of symptoms. Subjects will be discontinued from study treatment and managed with appropriate therapies (i.e. high dose glucocorticoids etc.) with any evidence of or concern for HES as deemed by the investigator team.

6.0 PREPARATION AND ADMINISTRATION OF DUPILUMAB

Dupilumab and placebo (normal saline) will be maintained in prefilled syringes as prepared by the investigational pharmacy at the University of Virginia. Dupilumab will be sourced commercially and repackaged into syringes that are identical to the placebo to maintain blinding. Per package insert, dupilumab is stored refrigerated at 36°F to 46°F in original carton to protect from light. If necessary pre-filled syringes can be kept at room temperature up to 77°F for a maximum of 14 days. Pre filled syringes should not be exposed to heat or direct sunlight (9). Subcutaneous injection will occur in the hospital in the upper arm, thigh or lower abdomen (avoiding areas within 2 inches of navel) and avoiding areas where skin is damaged or tender. If an AE develops directly after injection, management will occur per investigator and clinical care team discretion (i.e. if perceived as allergic reaction, will treat with epinephrine, steroids, diphenhydramine as dictated per guidelines for anaphylaxis). Subjects should be removed from the trial if life threatening or severe AEs are deemed to have developed due to first or any subsequent dupilumab injections.

Table I: Schedule	Screen	Baseline	Randomiz./ Admin.	Follow-up							
Day (d)	0d	0d	0d	2±1d	5±1d	7±1d	14±2d	28±2d	60±7d	180±90d	360±30d
Informed consent	x										
Demographic and Medical history	x	X									
COVID-19 symptom screen		x									
SARS-CoV-2 RT-PCR[7,9]	x						x				
Drug administration[1]			X				X[1]	X[1]			
Study Procedures											
Vital signs[2,3,4]		X	X[2]	x	x	X[5,6]	X[5]	X[5,6]			
Physical exam[4]		x[5]						x[5,6]			
Symptom screen[3,4]		x		x	x	X[5]	X[5]	X[5]	X[5]		
Concomitant medications[3,4]		x		x	x	X[5]	X[5]	X[5]	X[5]		
Assessment with 8-point ordinal scale[3,4]		x		x	x	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Adverse event monitoring[3,4]			x	x	x	X	x[5]	X[5]	X[5]		
Study Labs											
Blood for total IgE levels[7]		x					x				
Blood for cytokine testing[8]		x		x	x	X[6]	x	X[6]			
SARS-CoV-2 NP or OP PCR[9]		x									
Blood for inflammatory markers[7,10]		x				X[6]	x				

CBC with differential and CMP[7]		x		x	x	X[6]	x	X[6]	X[6]		

[1]Drug to be administered on subsequent days if remains hospitalized and undergoing active medical therapy (i.e. at least ordinal score 4).
[2]Vital signs will be performed pre-administration.
[3]Done daily through hospitalization by primary team or until patient is discharged from the hospital, whichever comes first.
[4]Data to be collected through electronic medical record and/or documentation per primary team unless otherwise stated.
[5]Data to be collected via team investigators directly via in person (mandatory on day 14) or via telephone (day 7, 28, 60, 180 and 360).
[6]Optional lab work/in person assessment unless patient had remained inpatient through day 14 or day 28 and thus received subsequent dupilumab injections on those days then will be required to have a 14 day follow up after the last injection received.
[7]To be analyzed through UVAMC clinical lab.
[8]Cytokine analysis to be done using MILLIPLEX SARS-CoV-2 MAP Human Cytokine/Chemokine/Growth Factor Panels, and individual Simplex or ELISA kits.
[9]Sample collected for SARS-CoV-2 PCR will be held for sequencing to determine prevalence of SARS-CoV-2 B.1.1.7 lineage in study cohort. If SARS-CoV-2 NP PCR not previously collected during current admission, will be collected for sequencing prior to treatment administration.
[10]Includes serum CRP and ferritin.

7.0 STATISTICAL CONSIDERATIONS

7.1 Randomization and Stratification

The double-blind, placebo-controlled, randomized clinical trial aims to evaluate the safety and efficacy of dupilumab in hospitalized patients with COVID-19 positive. Patients will be enrolled and randomized to either dupilumab or placebo and followed prospectively for 360 days post enrollment. The primary outcome is the proportion of patients alive and free of invasive mechanical ventilation at 28 days. The study will also evaluate the incidence of other serious adverse reactions as the secondary outcome. This study will use an automated central randomization procedure to allocate patients in a 1:1 ratio to each of the two treatment groups. The randomization will be stratified based on disease severity: patients who are on 15L or less of oxygen by nasal cannula (severity group A) and those requiring more than 15L of oxygen by nasal cannula including any noninvasive ventilation measures (severity group B).

7.2 Sample Size Justification and Power Analysis

This trial is intended to be an early stage and proof of concept study with the primary goal to collect reliable data and obtain sufficient evidence for future trials. Thus the emphasis of the study is an exploratory estimation of effect size and incidence of adverse events in terms of eosinophilia; it is not considered as a pivotal trial for efficacy at this time. Therefore, a larger significance level (one-sided alpha=0.1) is used and the sample size is pre-selected based on the feasibility. Given the current decline trend in the incidence of COVID-19 positive cases, we anticipate to enroll 40 patients realistically into this randomized clinical trial, which shall be sufficient for us to collect reliable and interpretable data for proof of concept to inform future trials. The COVID-19 hospitalization data from our University of Virginia Health System between March 2020 and April 6, 2021 showed that 79.5% of COVID-19 inpatients were alive and free of mechanical ventilation at 28 days under the usual care. With 40 patients that are deemed to be feasible, we would expect Dupilumab to improve a margin of 17.7% in the proportion of patients alive and free of mechanical ventilation at 28 days. That is, it is anticipated that 97.2% of patients being alive and free of ventilation at 28 days in the Dupilumab arm. The power analysis is conducted using the one-sided Score test (Farrington & Manning) with 75% power and 10% type I error.

7.3 Expected accrual rate, accrual duration, and study duration

Our anticipated accrual rate is about 5-6 patients per month. Thus, it should take approximately 12-14 months to accrue the 40 patients needed for the trial. Allowing for 360 days of follow-up to obtain the primary endpoints on

the last patient enrolled and 3 months to assemble, analyze and interpret the data the total study duration is projected to be at most 18 months.

7.4 Analysis of AE data

Analysis of AE data will primarily be descriptive based on DAIDS coding of events. The proportion of subjects experiencing an SAE and the proportion experiencing a Grade 3 or higher will be recorded. AE will be compared to published data.

7.5 Endpoints

7.5.1 Primary Endpoint:

- Proportion of patients alive and free of invasive mechanical ventilation at 28 days.

7.5.2 Secondary Endpoints:

- Percentage of patients with eosinophilia (defined as an absolute eosinophil count > 0.6 k/μl at ≥ 1 measurement throughout the study period) in those receiving dupilumab in addition to standard of care compared to those who receive standard of care management plus placebo. Complete blood counts with differentials and complete metabolic panels will be measured on Day 0, 2, 5, 7, 14, 28 and 60. Day 7, 28 and 60 optional, although recommended, if patient discharged within the time frame[14].
- Cumulative incidence (defined as number of new events divided by the total number of individuals in the population at risk for the time interval) of adverse events: injection site reactions, eye/eyelid inflammation, conjunctivitis, oropharyngeal pain, insomnia, tooth ache, gastritis, arthralgia, bacterial pneumonia, herpes viral infection, hypereosinophilic syndrome, hypersensitivity reaction.
- Prevalence of B.1.1.7 and B.1.351 and other SARS-CoV-2 lineages in study cohort: Day 0.
- Plasma total Immunoglobulin E (IgE) levels[15]: Day 0 and 14.
- Plasma inflammatory markers (C-reactive protein and ferritin)[16]: Day 0, 7 and 14. Day 7 optional if patient discharged[1].
- Plasma cytokine levels including TARC (CCL17), YKL40, eotaxin 3 (CCL26), IL-13, IL-4, Arg1, Hyaluronan, soluble ST2[17]: Day 0, 2, 5, 7, 14, and 28. Day 7 and 28 optional if patient discharged[1].
- Change in PaO2/SaO2 to FiO2 ratio: Day 0, 2, 5, 7 (if patient remains inpatient throughout)
- All-cause mortality rate at 28 days.
- Hospital length of stay (LOS)
- ICU LOS
- Proportion of patients alive and free of invasive respiratory failure at 28 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 60 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 90 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 120 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 150 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 180 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 270 days.

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[14] Patient will be required to have mandatory in person follow up 14 days after initial dupilumab dose. Therefore, if patient inpatient through day 14 thus receiving 2nd dupilumab dose, will be required to follow up 14 days after (same for day 28 injection).

[15]Total IgE levels will be analyzed through UVAMC clinical lab.

[16]C-reactive protein and ferritin levels will be analyzed through UVAMC clinical lab.

[17]Plasma cytokines will be measured using the MILLIPLEX® MAP Human Cytokine/Chemokine/Growth 28 Factor Panels, and individual Simplex or ELISA kits.

- Proportion of patients alive and free of invasive mechanical ventilation at 360 days.
- National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale (see Appendix): Day 0, 2, 5, 7, 14, 28, 60, 180 and 360.
- Need for vasopressors
- Need for renal replacement therapy
- Need for extracorporeal membrane oxygenation (ECMO)

7.6 Statistical analysis.
All subjects who received one dose of study drug will be included in the safety analysis. Each primary and secondary efficacy outcome measure will be analyzed for the intent-to-treat (ITT) and evaluable population. The intent-to-treat principle is that participants will be analyzed in the groups to which they were randomized, regardless of whether they received the randomized study medication. Another analysis population of interest is the as-treated population. The as-treated population will consist of only participants who were inducted onto study medication, even one dose of drug. Safety outcome will be primarily analyzed for the as-treated population. Summary statistics for each endpoint will be provided for each relevant comparison group including the results of statistical tests. All subjects who have a result for the baseline and a follow-up and who have received at least one dose of study drug will be included for the analysis of efficacy.

After the 14th day of the 20th patient enrolled, the proportion and rate of change of C- reactive protein and ferritin levels will be calculated from day 0 and day 14 time points to determine efficacy trends between the two treatment groups. Additionally, percentage of eosinophilia will be calculated between the two groups to determine safety trend. We expect greater changes in C- reactive protein and ferritin for patients receiving Dupilumab than those receiving placebo and no significant differences in eosinophilia between the two groups. Data will be analyzed by a third party and remain blinded to the study investigators.

Data will be summarized as frequency, with percentage for categorical clinical variables, and as mean ± standard deviation or median with interquartile range for continuous variables. The difference between dupilumab and placebo arms will be tested with Chi-square for categorical measures (e.g., the primary efficacy endpoint) and two-sample t-test or Wilcoxon rank sum test for continuous measures (e.g., age or biomarkers). Due to the relatively small sample size in the study, the adjusted treatment effect of dupilumab will be estimated exploratively in generalized linear regression for the primary and secondary outcomes to account for the potential impact of patient characteristics (e.g., age, sex, race and co-morbidities). Data transformation will be considered for the outcomes with skewed distribution such as hospital length of stay (LOS) and ICU LOS. The trajectory of each immune biomarker over the follow-up time points will be plotted to characterize the change of immune responses over time, and difference in biomarker (or transformed biomarker to improve normal distribution, if necessary) trajectories between the two study arms will be assessed in the mixed effects model.
Since this is intended to be an early stage, proof of concept study for which the primary goal is to inform future trials rather than to perform formal hypothesis testing, no multiplicity adjustment is planned. In addition, machine learning methods such as random forests algorithm will be applied to fully evaluate the treatment effect and predictability of dupilumab and other important predictors on the outcomes non-parametrically.

8.0 EFFICACY, VIROLOGY AND IMMUNE MEASURES

8.1 Clinical Efficacy

- Proportion of patients alive and free of invasive respiratory failure at 28 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 28 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 60 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 90 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 120 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 150 days.

- Proportion of patients alive and free of invasive mechanical ventilation at 180 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 270 days.
- Proportion of patients alive and free of invasive mechanical ventilation at 360 days.
- Change in PaO2/SaO2 to FiO2 ratio at days 0, 2, 5 and 7 days (if remains hospitalized).
- All-cause mortality rate at 28 days.
- Hospital length of stay (LOS)
- ICU LOS
- National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale: Day 0, 2, 5, 7, 14, 28, 60, 180 and 360.
- Need for vasopressors
- Need for renal replacement therapy
- Need for extracorporeal membrane oxygenation (ECMO)

8.2 Virologic measures

1. Day 0 OP or NP swabs obtained for assessment of SARS-CoV-2 RNA positivity as above will be held for sequencing to determine prevalence of B.1.1.7 and B.1.351 and other SARS-CoV-2 lineages in study population.

8.3 Immune Evaluations

Immune evaluations (IEs) will be conducted as delineated in **Table 1**. Blood draws will occur at each time point. Inflammatory markers, CBC, CMP and IgE levels will be obtained through UVAMC clinical lab. Plasma cytokines including TARC (CCL17), YKL40, eotaxin 3 (CCL26), IL-13, IL-4, Arg 1, Hyaluronan, soluble ST2 will be measured using the MILLIPLEX® MAP Human Cytokine/Chemokine/Growth 28 Factor Panels, and individual Simplex or ELISA kits (1 light green top with approximately 2 mL of anti-coagulated blood will be allotted for cytokine assessment at each time point).

9.0 REGISTRATION AND REQUIRED DATA

9.1 Pre-Study

All patients on-study will be evaluated prior to initiation of therapy. Baseline studies will be completed prior to on-study.

9.2 Protocol Registration

Subject must meet all eligibility requirements listed in Section 4.0 prior to enrollment. Subjects who are consented to the study must be registered in the Clinical Trials Office. All subjects who have signed an informed consent should have demographics and date of signed informed consent entered into the database.

9.3 Evaluations and Assessments

All evaluations and assessments should be completed as described in Table 1. Any assessments not described in detail below should be done according to standard of care practices.

9.4 Medical History/Physical Examination

A complete medical history and physical examination will be obtained prior to dupilumab injection.

The medical history includes clinically significant diseases and all medications (with the exception of medications listed in section 5.3). A physical examination will be performed prior to dupilumab injection for baseline conditions. Physical examinations will include the following body systems: general appearance (including height and body weight), skin, neck, HEENT (head, ears, eyes, nose and throat), heart (auscultation of heart sounds), lungs (auscultation of lung fields), abdomen palpation and auscultation of bowel sounds, lymph nodes and extremities.

9.5 Vital Signs
Vital signs including respiratory rate, pulse rate, systolic blood pressure [SBP], and diastolic blood pressure [DBP] and body temperature, and supplemental oxygen requirements will be recorded at time points listed in Table 1.

9.6 Laboratory Parameters
Blood samples for clinical labs will be obtained as described in the Time and Events table for adverse event determination and clinical decision making.

9.7 Laboratory and Clinical Data Review
The Investigator, or designee, must review all laboratory values and report any clinically significant change compared to the baseline sample as an AE. When reporting such AEs the Investigator will use the appropriate clinical term, rather than the laboratory test result (e.g. anemia versus low hemoglobin).

9.8 Immune Evaluations
Immune evaluations (IEs) will be conducted as delineated in **Table 1**. Blood draws will occur at each time point. Inflammatory markers, CBC, CMP and IgE levels will be obtained through UVAMC clinical lab. Plasma cytokines including TARC (CCL17), YKL40, eotaxin 3 (CCL26), IL-13, IL-4, Arg 1, Hyaluronan, soluble ST2 will be measured using the MILLIPLEX® MAP Human Cytokine/Chemokine/Growth 28 Factor Panels, and individual Simplex or ELISA kits (1 light green top tube containing approximately 2 milliliters of anti-coagulated blood will be allotted for cytokine assessment at each time point).

9.9 Subject Status Definitions
- Enrolled: All subjects who sign an informed consent will be considered enrolled on the study. All subjects consented on the study must be entered into Clinical Trials Office Database.
- Screen Failure: A subject who is withdrawn or discontinues from study screening prior to being on study is considered a screen failure. Screen failures are not considered a study accrual and will be replaced. Note: The IRB defines any individual that has signed an informed consent as an enrollment in this study and so screen failures should be reported to the IRB with enrollment numbers.
- On-Study: A subject is considered on-study on the date when the study team has confirmed the subject has met all of the inclusion and none of the exclusion criteria, and the treating physician/surgeon or study PI has signed off on the confirmation.
- On-Treatment: A subject is considered on-treatment on the date that they receive the first study treatment. A subject who is withdrawn or discontinues from the study after receiving at least 1 infusion is considered a discontinuation and will not be replaced.
- On Follow-up: A subject is considered on follow-up on the date that they have met any of the criteria in section 4.0.
- Off-Study: A subject is considered off-study if they are removed from the study for any of the reasons listed in section 4.0 or if they have completed all study assessments through follow-up.

10.0 RISKS AND BENEFITS

10.1 Potential Benefits of Treatment for the Patient
The benefits of anti-inflammatory therapy with dupilumab in patients with respiratory symptoms consistent with pneumonia due to COVID 19 infection at high risk for requiring ICU admission are not known. It is anticipated that treatment will decrease the time to recovery, risk of disease progression, decrease ICU admissions and decrease aggressive respiratory support including possible mechanical ventilation and other ICU support.

10.3 Potential benefits of clinical monitoring and virologic testing
Subjects enrolled in the study may reduce their chances of disease progression.

10.4 Potential risks

1. Risks of dupilumab: injection site reactions, eye/eyelid inflammation, conjunctivitis, oropharyngeal pain, insomnia, toothache, gastritis, arthralgia, bacterial pneumonia, herpes viral infection, eosinophilia, hyper eosinophilic syndrome, hypersensitivity reaction.
2. Risks of phlebotomy: local discomfort, bruising and/or hematoma, bleeding, fainting, infection.
3. Total blood draws will not exceed 500 mL
4. Risks of oropharyngeal and throat swab: local discomfort, vomiting

10.5 Alternatives

The alternative to participation in this study is routine care.

11.0 ADVERSE EVENTS AND SAFETY EVALUATION

Adverse events will be evaluated and scored using Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1 (DAIDS v2.1).
(https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf)

11.1 Adverse Event (AE)

An adverse event will be considered any undesirable sign, symptom, medical, or psychological condition even if the event is not considered to be related to the investigational drug/intervention. Medical condition/diseases present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment/intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of an investigational drug that adversely affects the rights, safety or welfare of subjects.

11.2 Serious Adverse Event (SAE)

An adverse event (AE) is considered a serious adverse event (SAE) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.3 Unexpected Adverse event: (UAE)

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

11.4 Unanticipated Problem (UP)
The Office for Human Research Protections (OHRP) considers unanticipated problems (UPs) (may include a data breach) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

11.5 Protocol Deviation
A protocol deviation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the institution's IRB prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. Protocol violations may or may not be under the control of the study team or UVA staff. These protocol violations may be major or minor violations.

11.6 Reporting Interval
All AEs and SAEs will be documented from the first administration of study product and for the following 60 days or until un-enrollment from the study, whichever comes sooner. All AEs and SAEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an adverse event is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

11.7 Investigator's Assessment of Adverse Events
The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose adverse event information, provide a medical evaluation of adverse events, and classify adverse events based upon medical judgment. This includes but is not limited to physicians, physician assistants, and nurse practitioners.

11.8 Assessment of Severity
For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

11.9 Assessment of Association
All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result,

occurs in a plausible time relationship to study intervention 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 study intervention, 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 participant's clinical condition, other concomitant events).

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology.

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12.0 REPORTING ADVERSE EVENTS AND PROTOCOL DEVIATIONS

All AEs meeting DAIDS grade 3 severity or above including local and systemic reactions not meeting the criteria for SAEs will be captured. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs meeting DAIDS grade 3 severity or above occurring while on study must be documented appropriately regardless of relationship. All AEs meeting DAIDS grade 3 severity or above will be followed to adequate resolution.

Any medical condition (including a laboratory abnormality) that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.
Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

AEs meeting DAIDS grade 3 severity or above must be recorded into the case report forms and will be reported per the following guidelines (**Error! Reference source not found.**2).

It is the responsibility of the principal investigator to use continuous vigilance to prevent, identify and report protocol deviations. Major protocol deviations must be reported to the UVA IRB-HSR per the following guidelines (Table 2). Minor deviations do not need to be reported to the UVA IRB-HSR. All deviations must be addressed in study source documents.

Table 2

Type of Event	**To whom will it be reported:**	Time Frame for Reporting	How reported?

Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event ***All adverse events deemed to be related to the drug meeting DAIDS severity grade 3 and above will be reported.***	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol deviations This might include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. Unanticipated Problem Report Form
Protocol Deviations/Noncompliance	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Deviation, Noncompliance and Protocol Exception Reporting Form Protocol Deviation Protocol Exception Reporting Form
Data Breach	The UVa Corporate Compliance and Privacy Office ITC: if breach involves electronic data Police if breach includes items that are stolen:	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, https://security.virginia.edu/report-information-security-incident

	Stolen on UVA Grounds OR Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI		UVa Police-Phone- (434) 924-7166
UVA PI HELD IND			
Life-threatening and/or fatal unexpected events related or possibly related to the use of the investigational agent.	FDA	Within 7 calendar days of the study team learning of the event	Form FDA 3500A (MedWatch) or narrative
Serious, unexpected and related or possibly related adverse events	FDA	Within 15 calendar days after the study team receives knowledge of the event	Form FDA 3500A (MedWatch) or narrative
Adverse events meeting DAIDS severity grade 3 and above	FDA	Annually	IND annual report

13.0 SAFETY OVERSIGHT

13.1 Independent Medical Monitor

An independent medical monitor will provide additional safety oversight for this study. The medical monitor will report to the principal investigator and IND sponsor. They will review the following:

- All adverse events
- Audit results
- Application of study designed stopping/decision rules
- Whether the study accrual pattern warrants continuation/action
- Protocol violations

The medical monitor will review the information listed above every two months (or more frequently if needed based on rate of accrual or safety issues) for aggregate review of data. Issues of immediate concern by the medical monitor will be brought to the attention of the Principal Investigator/IND sponsor (and if appropriate to the IRB) and a formal response from the IND-sponsor is requested.

13.2 Study monitoring

The study team will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion according to institutional policies. A safety review and analysis will be conducted after the 10^{th} and 40^{th} participant is enrolled.

Any study under the purview of the University of Virginia IRB-HSR is subject to review of files at the University of Virginia. Studies are chosen for Post-approval Monitoring either a) at random or b) requested by a study team member or any member of the IRB-HSR.

The purpose of Post-approval Monitoring audits is to ensure that documentation of clinical research studies is of the highest quality, verify protocol adherence, and ensure that all Federal and local rules concerning clinical research are being fulfilled. Post-approval monitoring is done by staff within the office of the Vice President for Research (VPR) in accordance with their Standard Operating Procedures. The conduct of an on-site review may include but is not limited to:

- requests for progress reports from investigators,
- examinations of research records, including signed informed consent documents, protocol modifications, and unexpected, serious, and/or related adverse experience reports,
- contacts with research subjects, or
- observation of the consent process and/or research procedures. Examples of when observation of the consent process could occur are:
    - Full board IRB determines during review of a project that a conflict of interest exists such that the informed consent process should be observed by a neutral party;
    - IRB is made aware of a complaint or concern with regard to the informed consent process; or
    - IRB determines as a result of the monitoring process that the consent process is insufficient and education/training is required for conduct of consent.

14.0 STOPPING DECISION RULES

14.1 Study stopping decision rules

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

1. Death within one hour of dupilumab administration
2. 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
3. One subject with a grade 4 or persistent grade 3 (≥72 hours) associated with study product.
4. Two subjects with persistent Grade 3 (≥ 72 hours) or higher lab toxicity for the same parameter associated with study product.
5. An overall pattern of symptomatic, clinical, or laboratory events that the medical monitor, ISM, or SMC 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.
6. Any other event(s) which is considered to be a serious adverse event in the good clinical judgment of the attending physician team. This will be appropriately documented.

Upon completion of this review and receipt of the advice of the independent medical monitor, the PI will determine if study entry or study dosing should be interrupted or if study entry and study dosing may continue according to the protocol.

14.2 Study Drug Stopping Rules Within a Single Subject

Injection of study drug (i.e., patient will not receive any further dupilumab injections if they remain in the hospital during pre-specified time periods) will be halted if any of the following manifestations of anaphylaxis develop and will not be restarted:

1. Skin or mucous membrane manifestations: hives, pruritus, flushing, swollen lips, tongue or uvula
2. Respiratory compromise: dyspnea, wheezing, stridor, hypoxemia

3. A decrease in systolic blood pressure to < 90 mmHg or >30% decrease from baseline or a diastolic drop of >30% from baseline.
4. Tachycardia with an increase in resting heart rate to > 130bpm; or bradycardia <40 that is associated with dizziness, nausea or feeling faint.
5. Any other symptom or sign which in the good clinical judgment of the study clinician or supervising physician warrants halting the infusion. For example, the rapid onset of gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and cramps, for instance, may be manifestations of anaphylaxis and may warrant an immediate halt prior to meeting full SAE criteria.

15.0 STUDY MANAGEMENT

15.1 Institutional Review Board (IRB) Approval

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

15.2 Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. A member of the study team will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. If the participant is deemed incapable of making their own medical decisions (i.e., mechanically ventilated, or otherwise incapacitated), a surrogate decision maker or legally authorized representative will be provided with the study information as detailed above and may consent to enrollment on behalf of the participant. The participant (or surrogate decision maker) will sign the informed consent document prior to any procedures being done specifically for the study.

Results from procedures completed prior to consent for standard of care purposes may be used for research purposes.

Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records.

The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

15.3 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

15.3.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB-HSR approval/favorable opinion.

For any such emergency modification implemented, a UVA IRB modification form must be completed by study personnel within five (5) business days of making the change.

15.3.2 Other Protocol Deviations/Violations

Protocol Deviations: A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

Study personnel will record the deviation, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

Violations should be reported by study personnel to the IRB within one (1) week of the investigator becoming aware of the event (refer to Table 2 in section 13 – Reporting Adverse Events and Protocol Deviations).

15.4 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations, all applicable local regulatory laws and regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study subjects. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion. It is the responsibility of the Principal Investigator to ensure that all study site personnel are aware that the study protocol and all data generated is confidential and should not be disclosed to third parties (with the exception of local and national regulatory bodies which require access for oversight purposes). The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

16.0 DATA HANDLING AND RECORDKEEPING

16.1 Data Collection and Management Responsibilities

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

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into RedCap electronic database. Clinical data will be entered directly from the source documents.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

16.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the IND sponsor, if applicable. It is the responsibility of the IND sponsor to inform the study team when these documents no longer need to be retained. Record retention will be in accord with 21 CFR 312.62 and HIPAA regulations.

16.3 Publication and Data Sharing Policy

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

16.4 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the institution has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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APPENDIX:

NIAID 8-POINT ORDINAL SCALE FOR CLINICAL IMPROVEMENT

- The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. The scale is as follows: 8) Death; 7) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 6) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 5) Hospitalized, requiring supplemental oxygen; 4) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 3) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 1) Not hospitalized, no limitations on activities.

NIH SEVERITY CATEGORIZATION

- *Asymptomatic or Presymptomatic Infection:* Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test or an antigen test) but who have no symptoms that are consistent with COVID-19.
- *Mild Illness:* Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.
- *Moderate Illness:* Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO_2) ≥94% on room air at sea level.
- *Severe Illness:* Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%.
- *Critical Illness:* Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

FDA EXAMPLE OF BASELINE SEVERITY CATEGORIZATION

SARS-CoV-2 infection without symptoms
• Positive testing by virologic test (i.e., a nucleic acid amplification test of an antigen test) • No symptoms
Mild COVID-19
• Positive testing by virologic test (i.e., a nucleic acid amplification test of an antigen test)
• Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, and loss of taste or smell, without shortness of breath or dyspnea
• No clinical signs indicative of Moderate, Severe, or Critical Severity
Moderate COVID-19
• Positive testing by virologic test (i.e., a nucleic acid amplification test of an antigen test) • Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
• Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, heart rate ≥ 90 beats per minute; with saturation of oxygen (SpO2) > 93% on room air at sea level
• No clinical signs indicative of Severe or Critical Illness Severity

Severe COVID-19
• Positive testing by standard RT-PCR assay or an equivalent test
• Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
• Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, $SpO_2 \leq 93\%$ on room air at sea level or $PaO_2/FiO_2 < 300$
• No criteria for Critical Severity
Critical COVID-19
• Positive testing by standard RT-PCR assay or an equivalent test

Respiratory failure defined based on resource utilization requiring at least one of the following:

- Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)
- Endotracheal intubation and mechanical ventilation, oxygen delivered by high- flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
- Multi-organ dysfunction/failure