Title: Impact of dupilumab use for treatment of acute moderate to severe COVID-19 on post recovery long haul syndrome

Study Center: University of Virginia

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1.0 SUMMARY

Background: Our research group has shown that high interleukin (IL)-13 is associated with respiratory failure in COVID-19 and that IL-13 inhibition protects in a mouse model of SARS-CoV-2 infection[1]. IL-13 is a known cause of pulmonary inflammation in asthma and interstitial lung disease[2]. We have discovered that IL-13 neutralization lessens the severity of COVID-19 and reduces hyaluronan (HA), an extracellular matrix polysaccharide previously implicated in other inflammatory pulmonary diseases, deposition in mouse lung parenchyma[1,3]. It is therefore biologically plausible that IL-13 contributes to the long-haul pulmonary compromise seen in patients with severe COVID-19, potentially through promotion of HA synthesis. We hypothesize that neutralization of IL-13 will protect from acute and chronic pulmonary damage by blocking acute HA synthesis and inflammation downstream of IL-13.

Clinical Experience: We have conducted a phase IIa randomized double-blind placebo-controlled trial to assess the safety and efficacy of dupilumab plus standard of care versus placebo plus standard of care in mitigating respiratory failure and death in those hospitalized with COVID-19 (HSR 210184, enrollment completed/closed November 2021). Through this trial we found that dupilumab was safe for use in this population and that there was a reduced 60-day mortality in those who received dupilumab plus standard of care regimens versus placebo plus standard of care regimens[4]. These findings implicate dupilumab as a promising and novel treatment for those hospitalized with COVID-19. Given this, along with our pre clinical data showing IL-13 influence on pulmonary injury, we plan to determine differences in post recovery pulmonary function between those who were randomized to the dupilumab arm versus placebo during acute COVID-19 infection in the HSR 210184 study cohort 1 year after enrollment.

Primary Objective:

- Determine the difference in post recovery pulmonary function between those randomized to dupilumab arm versus placebo for acute moderate to severe COVID-19.

Primary Endpoint:

- Proportion of patients with abnormal diffusing capacity for carbon monoxide (DLCO) and/or 6 minute walk testing 1 year after acute COVID-19 infection.

Secondary Objectives:

- Evaluate the immunologic and biologic end points of inhibition of type 2 inflammation post recovery from COVID-19 in the dupilumab arm compared to placebo.
- Evaluate imaging abnormalities post recovery from COVID-19 in the dupilumab arm compared to placebo.
- Evaluate long haul symptom incidence post COVID-19 recovery in the dupilumab arm compared to

placebo.

Secondary Endpoints:

- Proportion of patients with new systemic, respiratory, musculoskeletal, neuropsychiatric and/or cardiac symptoms post COVID-19 consistent with long haul syndrome (fatigue, poor concentration, daily activity restriction, chronic malaise, asthenia, dyspnea, persistent cough, pleurisy, sleep abnormalities, chronic headache, olfactory impairments, gustatory impairments, brain fog, memory defects, depression, anxiety, dizziness, myalgias, joint pain, chest pain, palpitations[5]): 1 year after HSR 210184 enrollment
- Proportion of patients with reduce neurocognitive function: 1 year after HSR 210184 enrollment
- Proportion of abnormal predicted forced expiratory volume (FEV1), forced vital capacity (FVC) and/or total lung capacity (TLC): 1 year after HSR 210184 enrollment
- Proportion of patients with new oxygen requirnment after COVID-19 hospitalization: 1 year after initial enrollment
- Proportion of patients with greater than 3% oxygen desaturation during 6 minute walk testing: 1 year after HSR 210184 enrollment
- Plasma cytokine levels including TARC (CCL17), YKL40, eotaxin 3 (CCL26), IL-13, IL-4, Arg1, Hyaluronan, soluble ST2[1]: 1 year after HSR 210184 enrollment
- Differences in high resolution computed tomography (HRCT) chest scan appearance post recovery: 1 year after HSR 210184 enrollment

Study Design: As an extension to the randomized double-blind placebo-controlled trial assessing dupilumab for treatment of those hospitalized with acute moderate to severe COVID-19, this is a follow up assessment of this study cohort post recovery from COVID-19 for evaluation of pulmonary function testing (PFT), pulmonary imaging, immune biomarkers and symptoms. All data will be collected at a single follow up visit 1 year after initial enrollment in the parent study HSR 210184 .

Study Population:

Inclusion Criteria:

- Subjects that were enrolled in study protocol HSR 210184 per inclusion criteria below:
    - 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.

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

- 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:

- Subjects enrolled in study protocol HSR 210184 no longer alive, able or willing to complete follow up visit at 1 year after enrollment.
- Any woman who is currently pregnant, or who could be pregnant due to menses history/positive pregnancy test

Assessment and Data Acquisition (1 year after HSR 210184 enrollment):

1. Pulmonary function testing: diffusing capacity for carbon monoxide (DLCO), 6 minute walk testing (6MWT), predicted forced expiratory volume (FEV1), predicted forced vital capacity (FVC) and predicted total lung capacity (TLC)
2. High resolution computed tomography (HRCT) imaging of chest
3. Symptom assessment via questionnaire: fatigue, poor concentration, daily activity restriction, chronic malaiase, asthenia, dyspnea, persistent cough, pleurisy, sleep abnormalities, chronic headache, olfactory impairmenets, gustatory impairments, brain fog, memory defects, depression, anxiety, dizziness, myalgias, joint pain, chest pain, palpitations
4. Neurocognitive testing via questionaire
5. Plasma cytokine levels including TARC (CCL17), YKL40, eotaxin 3 (CCL26), IL-13, IL-4, Arg1, Hyaluronan, soluble ST2[2]

Immune Evaluations: Immune evaluations will be performed to assess the extent to which dupilumab administration influences immune markers post recovery from their COVID-19 hospitalization. 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 1 year after HSR 210184 enrollment.

[2]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
CT	Computed Tomography
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
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
IL	Interleukin
IND	Investigational New Drug Application
IRB	Institutional review board
LOS	Length of Stay
LVEF	Left Ventricular Ejection Fraction
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
PFT	Pulmonary Function Testing
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
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 difference in post recovery pulmonary function between those randomized to dupilumab arm versus placebo for acute moderate to severe COVID-19.

2.2 Secondary Objectives

- Evaluate the immunologic and biologic end points of inhibition of type 2 inflammation post recovery from COVID-19 in the dupilumab arm compared to placebo.
- Evaluate imaging abnormalities post recovery from COVID-19 in the dupilumab arm compared to placebo.
- Evaluate long haul symptom incidence post COVID-19 recovery in the dupilumab arm compared to placebo.

2.3 Study Design

As an extension to the randomized double-blind placebo-controlled trial assessing dupilumab for treatment of those hospitalized with acute moderate to severe COVID-19, this is a follow up assessment of this study cohort post recovery from COVID-19 for evaluation of pulmonary function testing (PFT), pulmonary imaging, immune biomarkers and symptoms. All data will be collected at a single follow up visit 1 year after initial enrollment.

3.0 BACKGROUND AND SIGNIFICANCE

3.1 Background and Scientific Rationale

We have discovered that COVID-19 patients with high plasma interleukin (IL)-13 levels have a significantly greater risk of needing mechanical ventilation[1]. IL-13, which signals through the receptor IL-4Rα along with the closely related cytokine IL-4, is involved in eosinophilic inflammation, mucous secretion, goblet cell metaplasia and fibrosis, and has been regularly implicated in airway hyperresponsiveness and atopic disease[7]. We additionally found that neutralization of IL-13 in K18-hACE2 C57Bl/6J mice protected the animals from severe infection with SARS-CoV-2, as evidenced by reduced clinical score, weight loss and mortality[1]. The association of IL-13 along with other effectors of type 2 immunity with respiratory failure from COVID-19 has also been demonstrated in other observation studies[8]. These findings established mechanistic and biologic plausibility for IL-13 as a driver of pulmonary injury in COVID-19.

RNA-seq analysis of whole lung tissue taken from infected mice who underwent IL-13 neutralization revealed the most downregulated gene to be Has1, which encodes a synthase responsible for hyaluronan (HA) production, a polysaccharide apart of the extracellular matrix that has previously been implicated in other inflammatory pulmonary diseases[1,3]. This was mechanistically further supported by an increase in HA deposition in human and mouse lung with SARS-CoV-2 infection. Additionally, neutralization of the HA receptor, CD44, led to improved survival[1]. As HA has been proposed previously in asthma as a potential culprit in airway remodeling, this led to the hypothesis that HA, as a downstream effector of IL-13, may be involved in pulmonary dysfunction post recovery from COVID-19[9].

We tested our hypothesis that IL-13 leads to post-recovery pulmonary dysfunction in COVID-19 in a pilot cohort of 55 patients from the UVA Post-COVID-19 clinic who were hospitalized for severe to critical COVID-19 (79% requiring mechanical ventilation). Pulmonary function tests (PFTs) were measured from 1-8 months post recovery, focusing on DLCO (diffusing capacity for carbon monoxide) and 6MWT (six-minute walk test) as prior data in ARDS and COVID-19 implicated these in post recovery pulmonary abnormalities. We discovered that patients with high IL-13 during admission were almost 2.4 times as likely to have an abnormal 6MWT or abnormal DLCO post recovery from COVID-19 when adjusting for race/ethnicity, body mass index, smoking status and days from symptom onset (DFSO) to acute sample collection. Although it is fully recognized that this represents a preliminary exploratory analysis, especially given the small sample size and biomarker heterogeneity in acute disease, this initial

evidence of acute type 2 immune impact on post recovery pulmonary function is an exciting finding and, at the very least, warranting of further investigation.

3.2 Experience with the use of dupilumab in COVID-19

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[10]. 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[11]. 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[11].

We have previously conducted a phase IIa randomized double-blind placebo-controlled trial to assess the safety and efficacy of dupilumab plus standard of care versus placebo plus standard of care in mitigating respiratory failure and death in those hospitalized with COVID-19. Subjects were followed prospectively for 60 days, with collection of clinical outcomes, adverse events and immunologic biomarkers at multiple time points throughout the study period. Through this trial we found that dupilumab was safe to use for this indication, that there was reduced 60-day mortality in those who received dupilumab compared to placebo and that there was a trend toward reduction in ICU admission in the dupilumab group, all of which implicated dupilumab as a promising treatment for those hospitalized with moderate to severe COVID-19[4].

4.0 ELIGIBILITY

4.1 Inclusion Criteria

- Subjects that were enrolled in study protocol HSR 210184.

4.2 Exclusion Criteria

- Subjects enrolled in study protocol HSR 210184 no longer alive, able or willing to complete follow up visit at 1 year after enrollment.
- Any woman who is currently pregnant, or who could be pregnant due to menses history/pregnancy test

5.0 STUDY TIMELINE

Telephone call to discuss follow up visit on Day 365 ± 90 days after enrollment for HSR 210184:

1. Discuss and consent for follow up visit and procedures
2. Schedule follow up visit

Follow Up Visit on Day 365 ± 90 days after enrollment for HSR 210184 to discuss participation in 220171:

1. Urine pregnancy test at the time of consenting to rule out participation
2. Blood for immune evaluation of cytokine levels (1 light green top, 3 mL/draw)
3. CT chest imaging (non-contrast)
4. Pulmonary function testing (spirometry, lung volumes, diffusing capacity for carbon monoxide (DLCO), 6 minute walk testing (6MWT))
5. Symptom screen (fatigue, poor concentration, daily activity restriction, chronic malaiase, asthenia, dyspnea, persistent cough, pleurisy, sleep abnormalities, chronic headache, olfactory impairmenets, gustatory impairments, brain fog, memory defects, depression, anxiety, dizziness, myalgias, joint pain, chest pain, palpitations[5])
6. Neurocognitive testing via questionnaire

5.1 Known potential benefits

Subject recovery from COVID-19 will be assessed by a Pulmonary and Critical Care attending at follow up visit. Subjects will be provided with recommendations based on any abnormalities found.

5.2 Known potential risks

1. PFT: Dizziness, coughing, shortness of breath and/or provocation of asthma attack with deep inhalation during testing.
2. HRCT scan: radiation exposure, harm to unborn children.
3. Phlebotomy: local discomfort, bruising and/or hematoma, bleeding, fainting, infection. Total blood draw not to exceed 5mL.

6.0 STATISTICAL CONSIDERATIONS

6.1 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.

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 endpoint) and two-sample t-test or Wilcoxon rank sum test for continuous measures (e.g., 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) and baseline biomarker measures. Data transformation will be considered for the outcomes with skewed distribution. The difference in the biomarker measures at the follow-up visit and their changes from baseline between dupilumab and placebo groups will also be assessed. 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.

6.2 Sample Size justification

Under the protocol HSR 210184, we conducted a randomized double-blind placebo-controlled trial assessing the safety and efficacy of dupilumab for treating hospitalized patients with acute moderate to severe COVID-19, which was designed as an early stage (Phase IIa) and proof of concept study. A total of 40 patients were enrolled from June 23, 2021 through November 180 11, 2021 in the Phase IIa study, and 7 of them died by Day 60. The sample size of 40 in the original Phase II study were determined largely based on the feasibility with a primary goal to collection reliable data and obtain sufficient evidence for future trials. The current proposed study is an extension of the original Phase IIa study under the HSR 210184, to assess the post recovery of remaining 33 patients from COVID-19 with respect to pulmonary function testing (PFT), pulmonary imaging, immune biomarkers and symptoms at one-year follow-up. All data will be collected at a single visit, 1 year (i.e., 365 ± 90 days) after initial enrollment in the remaining 33 parents from the study HSR 210184. Formal sample size estimation and power analysis is not performed due to the pilot nature of this proposed follow-up study.

7.0 CLINICAL EFFICACY AND IMMUNE MEASURES

7.1 Clinical Efficacy

- Proportion of patients with abnormal diffusing capacity for carbon monoxide (DLCO) and/or 6 minute walk testing 1 year after acute COVID-19 infection
- Proportion of patients with new systemic, respiratory, musculoskeletal, neuropsychiatric and/or cardiac symptoms post COVID-19 consistent with long haul syndrome (fatigue, poor concentration, daily activity restriction, chronic malaiase, asthenia, dyspnea, persistent cough, pleurisy, sleep abnormalities, chronic headache, olfactory impairments, gustatory impairments, brain fog, memory defects, depression, anxiety, dizziness, myalgias, joint pain, chest pain, palpitations[5]): 1 year after HSR 210184 enrollment

- Proportion of patients with reduce neurocognitive function: 1 year after HSR 210184 enrollment
- Proportion of abnormal predicted forced expiratory volume (FEV1), forced vital capacity (FVC) and/or total lung capacity (TLC): 1 year after HSR 210184 enrollment
- Proportion of patients with new oxygen requirnment after COVID-19 hospitalization: 1 year after initial enrollment
- Proportion of patients with greater than 3% oxygen desaturation during 6 minute walk testing: 1 year after HSR 210184 enrollment
- Plasma cytokine levels including TARC (CCL17), YKL40, eotaxin 3 (CCL26), IL-13, IL-4, Arg1, Hyaluronan, soluble ST2[3]: 1 year after HSR 210184 enrollment
- Differences in high resolution computed tomography (HRCT) chest scan appearance post recovery: 1 year after HSR 210184 enrollment

7.2 Immune Evaluations
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).

8.0 REGISTRATION AND REQUIRED DATA

8.1 Protocol Registration
Subject must have been enrolled in HSR 210184. 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.

8.2 Evaluations and Assessments
All evaluations and assessments should be completed as described in Study Timeline. Any assessments not described in detail below should be done according to standard of care practices.

8.3 Immune Evaluations
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).

8.4 Subject Status Definitions
- Enrolled: All subjects who sign an informed re-consent will be considered enrolled on the study. All subjects consented on the study must be entered into Clinical Trials Office Database.
- 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~~,~~
- 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

9.0 RISKS AND BENEFITS

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

9.1 Potential Benefits of Follow up with Patient
Subject recovery from COVID-19 is assessed by a Pulmonary and Critical Care attending working in clinic that day and are provided with recommendations based on any abnormalities found.

9.2 Potential risks
1. Risks of PFTs: Dizziness, coughing, shortness of breath and/or provocation of asthma attack with deep inhalation during testing.
2. Risks of HRCT scan: radiation exposure, harm to unborn children
3. Risks of phlebotomy: local discomfort, bruising and/or hematoma, bleeding, fainting, infection.
4. Total blood draws will not exceed 5 mL

9.3 Alternatives
Follow up as needed with primary care physician.

10.0 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)

10.1 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.

10.2 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.

10.3 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.

10.4 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.

10.5 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.

10.6 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.

10.7 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. The study PI will review events that occur at the time of occurrence.

10.8 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".

10.9 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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11.0 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

12.0 SAFETY OVERSIGHT

12.1 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.

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.

13.0 STOPPING DECISION RULES

The study enrollment will be stopped and reviewed by the PI if any of the following specific events occur or, if in the judgement of the study physician, subject safety is at risk of being compromised during the visit:

- Death due to study procedure
- Occurrence of a life threatening allergic/hypersensitivity reaction (analphylaxis), manifested by bronchospasm with or without urticaria or angioedema requiring hemodynamic support with pressor medications or mechanical ventilation due to any of the study procedures performed (pulmonary function testing, blood collection)
- One subject with a grade 4 or persistent grade 3 (≥72 hours) associated with study procedures

- Two subjects with persistent Grade 3 (≥ 72 hours) or higher lab toxicity for the same parameter associated with study procedures
- An overall pattern of symptomatic, clinical, or laboratory events that the study investigators 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.
- 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.

14.0 STUDY MANAGEMENT

14.1 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.

14.2 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, 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. Both paper-based and electronic/e-consent approaches will be utilized as appropriate.

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.

14.3 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.

14.3.1 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.

14.3.2 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).

14.4 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.

15.0 DATA HANDLING AND RECORDKEEPING

15.1 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.

15.2 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.

15.3 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.

15.4 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.

16.0 REFERENCES

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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.