Title: Mavrilimumab to reduce progression of acute respiratory failure in patients with severe COVID-19 pneumonia and systemic hyperinflammation

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Table of contents

List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
BMI	Body Mass Index
BUN	blood urea nitrogen
CDS	Core Data Sheet (for marketed drugs)
CFR	Code of Federal Regulation
CK	Creatinine kinase
CK-MB	Creatinine kinase MB
COAR	Clinical Operations, Analytics & Regions
COVID-19	coronavirus disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
CTC	Common Toxicity Criteria
CTRD	Clinical Trial Results Database
CV	coefficient of variation
DMC	Data Monitoring Committee
EC	Ethics committee
Echo	Echocardiogram
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
eSAE	Electronic Serious Adverse Event
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GM-CSF	Granulocyte-macrophage colony stimulating factor
h	hour
HIV	human immunodeficiency virus
IL-6	Interleukin-6
i.v.	intravenous
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LFT	Liver function test

LLN	lower limit of normal
LLQ	lower limit of quantification
MABEL	minimum anticipated biological effect level
MedDRA	Medical dictionary for regulatory activities
MODS	multiple organ dysfunction sydnromes
mg	milligram(s)
MI	myocardial infarction
mL	milliliter(s)
ml	milliliter(s)
MRSD	maximum recommended starting dose
o.d.	once a day
p.o.	oral
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
RBC	red blood cell(s)
RDC	Remote Data Capture
REB	Research Ethics Board
s.c.	subcutaneous
SAE	serious adverse event
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	tuberculosis
TBL	total bilirubin
TNF-α	Tumor necrosis factor alpha
ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)
WHO	World Health Organization

1 Introduction

1.1 Background

The 2019 novel coronavirus (2019-nCoV; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) has spread rapidly since its recent identification in patients with severe pneumonia in Wuhan, China and resulted in a worldwide pandemic (COVID-19). Given the burden of disease, effective treatments are urgently required.

The 2019-nCoV has affinity for cells in the lower respiratory tract and can replicate there, causing radiological evidence of lower respiratory tract lesions in patients who do not present with clinical pneumonia. There seem to be three major patterns of the clinical course of infection: mild illness with upper respiratory tract presenting symptoms; non-life-threatening pneumonia; and severe pneumonia with acute respiratory distress syndrome (ARDS) that begins with mild symptoms for 7–8 days and then progresses to rapid deterioration and ARDS requiring advanced life support.

In clinical and epidemiological data from the Chinese CDC regarding 72,314 case records, providing an important illustration of the epidemiologic curve of the Chinese outbreak, the overall case-fatality rate (on confirmed cases) was 2.3%. Of note, the fatal cases were primarily elderly patients, in particular those aged ≥ 80 years (about 15%) and 70 to 79 years (8.0%). Approximately half (49.0%) of the critical patients were affected by preexisting comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, and oncological diseases died.

In one of the first reports on the disease, Huang et al. illustrated that patients (n = 41) suffered from fever, malaise, dry cough, and dyspnea. Chest computerized tomography (CT) scans showed pneumonia with abnormal findings in all cases. The clinical spectrum of COVID-19 varies from asymptomatic or pauci-symptomatic forms to clinical conditions characterized by respiratory failure that necessitates mechanical ventilation and support in an intensive care unit (ICU), to multi-organ and systemic manifestations in terms of sepsis, septic shock, and multiple organ dysfunction syndromes (MODS). In an initial report, about a third of patients required ICU care and 15% of cases were fatal. Similarly, in a more recent report of 201 hospitalized patient, 41.8% developed acute respiratory distress syndrome (ARDS), and 52.4% of these patients die.

In Italy, the case-fatality rate has been reported at 7.2%. Furthermore, in an initial US experience of 21 critically ill patients, 11 had died at the time of publication, and only 2 survived transfer out of the ICU, highlighting the need for effective treatments before patients become critically ill.

Among the severe clinical manifestations, there are severe pneumonia and ARDS. Although the clinical course of the disease seems to predict a favorable trend in the majority of patients; in a percentage of cases still to be defined, after about a week, there is a sudden worsening of clinical conditions with rapidly worsening respiratory failure and MOD/MOF. Criteria for definition of specific subpopulations are defined:

• *Severe Pneumonia*. Fever is associated with severe dyspnea, respiratory distress, tachypnea (> 30 breaths/min), and hypoxia (SpO2 < 90% on room air). However, the fever symptom must be interpreted carefully as even in severe forms of the disease, it can be moderate or even absent.

• *Acute Respiratory Distress Syndrome (ARDS).* The diagnosis requires clinical and ventilatory criteria. This syndrome is suggestive of a serious new-onset respiratory failure or of worsening of an already-identified respiratory picture. Different forms of ARDS are distinguished based on the degree of hypoxia. The reference parameter is the PaO2/FiO2: a ratio ≤ 315 is suggestive of ARDS.

- Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg. In non-ventilated patients or in those managed through non-invasive ventilation (NIV) by using positive end-expiratory pressure (PEEP) or a continuous positive airway pressure (CPAP) ≥ 5 cmH2O.
- Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg.
- Severe ARDS: PaO2/FiO2 ≤ 100 mmHg.

Unfortunately, no drug or vaccine has yet been approved to treat human coronaviruses. Several options can be envisaged to control or prevent emerging infections of 2019-nCoV, including vaccines, monoclonal antibodies, oligonucleotide-based therapies, peptides, interferon and small-molecule therapies. Although the potential repurposing of existing antiviral agents to treat COVID-19 is already moving into clinical trials, new interventions based on drugs directly active on the virus itself are likely to require months to years to develop.

Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome, leading to pneumonia, respiratory failure, need for mechanical ventilation, and often death. The identification of hyper-inflammation and treatment using existing therapies that are either in clinical development or approved in other indications with understood safety profiles is a relevant option to address the immediate need to reduce the rising mortality and need for ventilatory support.

In light of pathological findings of pulmonary edema and hyaline membrane formation, timely and appropriate use of drugs aimed at reducing inflammation in a targeted way, together with ventilator support, should be considered for patients with hyper-inflammation to prevent and treat ARDS development. A cytokine profile resembling secondary hemophagocytic lymphohistiocytosis (sHLH) is associated with COVID-19 disease severity, characterized by increased interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α. Predictors of fatality from a recent retrospective, multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin (mean 1297.6 ng/ml in non-survivors vs 614.0 ng.ml in survivors; $p<0.001$) and IL-6 ($p<0.0001$) suggesting that mortality might be due to a dysfunctional hyper-inflammatory response while clearing the virus (i.e. a hyperinflammatory state driven by the host, not the virus).

In hyper-inflammation, immunosuppression is likely to be beneficial. In fact, in a subgroup analysis of a randomized controlled trial, patients with sepsis and organ dysfunction or hyper-inflammation had improved survival with IL-1 receptor antagonism, and this therapy has not been associated with adverse events, even at high doses. A multicenter, randomized controlled trial of tocilizumab (IL-6 receptor blockade, licensed for cytokine release syndrome), has been approved in China in patients with COVID-19 pneumonia and elevated IL-6 (ChiCTR2000029765).

In our study, we aim to enroll patients with severe COVID-19 pneumonia and hyper-inflammation to identify the subgroup of patients for whom immunosuppression could prevent worsening of pulmonary status, including the need for ventilatory support, with the aim ultimately to improve mortality.

Rationale for mavrilimumab

GM-CSF strongly activates macrophages and is considered to be a pro-inflammatory cytokine. GM- CSF production is associated with tissue inflammation. GM CSF-derived signals are critically involved in the differentiation of macrophages and in the proliferation and activation of other immune cells. GM-CSF-activated macrophages produce pro-inflammatory cytokines, including tumor necrosis factor (TNF), IL-1β, IL-6, IL-23 and IL-12. In addition, GM-CSF receptor activation triggers stimulation of multiple downstream signaling pathways, including Janus kinase 2 (JAK2)/signal transducer and activator of transcription 5 (STAT5), the mitogen-activated protein kinase (MAPK) pathway, and the phosphoinositide 3 kinase (PI3K) pathway, all relevant in activation and differentiation of myeloid cells.

Under physiologic conditions, levels of circulating GM-CSF are low, but levels are elevated in inflammatory conditions. Several cell types can serve as a source of GM-CSF, including fibroblasts, endothelial cells, macrophages, dendritic cells, T cells, neutrophils, eosinophils, and cancer cells, with most production occurring locally at the site of inflammation. This in turn exacerbates the inflammatory reaction via cytokine pathways that have been termed the colony stimulating factor network. GM-CSF can be induced by inflammatory cytokines and in turn increases production of pro-inflammatory cytokines, thus functioning as a feed-forward inflammatory amplifier.

Zhou et al (2020) recently reported elevated levels of GM-CSF in the lungs of patients with COVID-19, specifically showing that, after the 2019-nCoV infection, CD4+T lymphocytes are rapidly activated to become pathogenic T helper (Th) 1 cells and generate GM-CSF, etc. The cytokine environment induces inflammatory CD14+CD16+ monocytes with high expression of IL-6 and accelerates the inflammation. The authors further contend that these aberrant and excessive immune cells may enter the pulmonary circulation in huge numbers and play an immune-mediated damaging role, causing lung dysfunction and rapid mortality.

GM-CSF signals through GM-CSF-R, which consists of a specific ligand-binding α-chain (GM CSF-Rα) and a signal-transducing β-chain (GM CSF-Rβ) that is common to IL-3 and IL-5 receptors. Hence, GMCSF-R signaling can be specifically targeted with antibodies

directed at GM-CSF-Rα. Mavrilimumab is an anti-GM CSF-Rα monoclonal antibody (human isoform IgG4) previously developed by MedImmune and now in development by Kiniksa Pharmaceuticals that has been shown to inhibit the GM-CSF signaling axis in humans and improve clinical outcomes measures in a Phase 2 program in Rheumatoid Arthritis.

1.2 Purpose

The purpose of this prospective, proof-of-concept Phase 2, multicenter, blinded, randomized placebo controlled study is to demonstrate that early treatment with mavrilimumab prevents progression of respiratory failure in patients with severe COVID-19 pneumonia and clinical and biological features of hyper-inflammation. These results will lead to and inform a Phase III randomized placebo-controlled trial.

2 Objectives and endpoints

Primary Objective

To demonstrate that early treatment with mavrilimumab prevents progression of respiratory failure in patients with severe COVID-19 pneumonia and clinical and biological features of hyper-inflammation.

Secondary Objectives

- To evaluate mortality
- To evaluate the duration of hospitalization
- To evaluate safety of mavrilimumab

Primary Endpoint

The primary endpoint is the proportion of subjects alive and off of oxygen at day 14.

When hospitalized patients are off of oxygen, this will be documented as an oxygen saturation >90% for at least 5 minutes at rest. For patients that are discharged before day 14, a telehealth visit will be performed at day 14. For patients discharged **off** of oxygen before day 14, the day 14 visit will assess that they are off of oxygen. For patients who are discharged **on** oxygen before day 14, the decision to discontinue oxygen will be based on standard clinical care according to the health provider who prescribed oxygen therapy. The day 14 telehealth visit will assess whether the patient remains on oxygen, and "off of oxygen" will be defined as no supplemental oxygen use for at least the previous 24 hours.

Secondary Endpoints

The secondary end-points are alive at day 28, and the proportion of subjects alive and without respiratory failure at 28 days. Respiratory failure is defined as needing mechanical ventilation, non-invasive ventilation, or high-flow oxygen.

Exploratory Endpoints

- Mortality at day 14
- Mortality at day 60
- Proportion of patients in each category according to the following ordinal scale at day 7, 14, 21, and 28:
    1. Not hospitalized
    2. Hospitalized, no supplemental oxygen
    3. Hospitalized, on supplemental oxygen
    4. Hospitalized, requiring nasal high-flow oxygen or non-invasive ventilation
    5. Hospitalized, requiring ECMO, invasive mechanical ventilation or both
    6. Death
- Freedom from mechanical ventilation
- Duration of hospitalization
- Change in SOFA score at day 7, day 14, day 21, and day 28, or until discharge
- Reduction in CRP at day 7 and day 14 (understanding that labs may be obtained until patient discharge)
- Time to negative SARS-CoV2 RNA levels in oropharyngeal or nasopharyngeal swabs
- Worst value for PaO2/FiO2 (or SaO2/FiO2 if PaO2 not available) at day 3, day 5, day 7, day 14, day 21 and day 28, or until discharge
- Safety including number of adverse events and serious adverse events

3 Study design

This prospective, proof-of-concept Phase 2, multi-center, blinded randomized placebo-controlled study is designed to demonstrate that early treatment with mavrilimumab prevents progression of respiratory failure in patients with severe COVID-19 pneumonia and clinical and biological features of hyper-inflammation while gathering data to support a larger Phase III randomized controlled trial.

The study population includes patients who meet criteria of impending mechanical ventilation.

Enrollment: The study will be performed in approximately 4 months total, starting from the first patient enrolled with enrollment expected to complete within 2 months.

Follow-up period: The follow-up period is 60 days for each patient enrolled.

A total of 60 patients will be randomized using a 1:1 allocation ratio: 30 subjects will receive mavrilimumab at 6mg/kg IV, and 30 subjects will receive placebo infusion. The investigator, clinical team, and subject will be blinded to treatment assignment.

Participants will be identified by regular review of hospitalized COVID19 patients to evaluate for inclusion and exclusion criteria. Participants will then be approached in the standard manner by study investigator and coordinator/research nurse.

Research interventions will take place in the hospital in accordance with privacy standards.

The study team is informed on all study procedures and requirements with daily meetings and the opportunity to continuously update through secure channels.

In this multicenter consortium, each participating site will have their own IND for patients enrolled at their site. However, data collection, data analysis, and randomization scheme will be performed at one site, Cleveland Clinic C5 Research.

4 Rationale

4.1 Rationale for study design

We aim to enroll patients with severe COVID-19 pneumonia and hyper-inflammation to identify the subgroup of patients for whom immunosuppression could prevent worsening of pulmonary status, including the need for ventilatory support, with the aim ultimately to improve mortality.

4.1.1 Rationale for choice of background therapy

Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome. The identification and treatment of hyper-inflammation using existing therapies with understood safety profiles that are either in clinical development or approved in other indications is a relevant option to address the immediate need to reduce the rising mortality.

Mavrilimumab is an anti-GM CSF-Rα monoclonal antibody (human isoform IgG4) previously developed by MedImmune and now in development by Kiniksa Pharmaceuticals that has been shown to inhibit the GM-CSF signaling axis in humans and improve clinical outcomes measures in a Phase 2 program in Rheumatoid Arthritis.

4.2 Rationale for dose/regimen and duration of treatment

Preliminary, publicly available data suggest efficacy of mavrilimumab at a dose of 6 mg/kg IV. However, these results are from an open-label study, and the results from our Phase II randomized, placebo controlled trial may inform the design and dose for larger studies.

In a Phase 1 single-ascending-dose (SAD) study, the pharmacokinetics (PK) of mavrilimumab were tested at doses of 0.01-10 mg/kg in patients with mild-to-moderate RA. Mavrilimumab was well-tolerated in a single IV injection up to 10 mg/kg in subjects with mild to moderate RA at all dose levels. Pharmacokinetic and pharmacodynamic simulations from studies in subjects with RA, coupled with the PK data form the Phase 1 study, indicate that a single dose of ≥3 mg/kg will provide EC90 (the concentration that leads to 90% maximal response) for the RA endpoint ACR50 (American College of Rheumatology 50% response criteria; data on file) for up to 22 days. Therefore, at doses ≥3 mg/kg, the pharmacologic profiles indicated sustained peripheral inhibition of the GM-CSF-Rα signaling axis for at least three weeks.

In preclinical studies, the potential systemic effects of mavrilimumab (CAM-3001) have been investigated in a 4-week and an 11-week repeat dose cynomolgus monkey study. There were no effects attributable to intravenous (IV) administration of CAM-3001 (mavrilimumab) in doses up to 100 mg/kg/week for 4 weeks in a study conducted in accordance with Good Laboratory Practice (GLP). In an 11-week exploratory (non-GLP) study, there were no effects attributable to IV administration of CAM-3001 (mavrilimumab) following 10 mg/kg/week, and the no observed adverse event level (NOAEL) was 100 mg/kg/week. An immunocytochemistry screen to test in vitro binding of CAM-3001 (mavrilimumab) to a panel of normal human tissues revealed no non-specific or unanticipated binding of the antibody. Reference for further details on safety studies in animals and humans is made to the investigator brochure.

However, with regards to mitigation of the aberrant immune response in the setting of COVID-19, it is unclear whether blockade of GM-CSF in the lung is required in addition to abolition of signaling in the periphery. Studies with the mavrilimumab surrogate anti-mouse GM-CSF-Rα antagonistic antibody, CAM-3003, were performed to interrogate the pulmonary vs peripheral pharmacodynamics of ascending single and repeat doses. Single doses of 3-30 mg/kg delivered intra-peritoneally showed no pharmacodynamic effects in the lungs (as assessed by bronchoalveolar lavage (BAL) fluid assay), despite the 3 mg/kg dose demonstrating complete receptor occupancy (RO) in the periphery. Pharmacodynamic effects in the lungs, measured by IL-6 induction from BAL cells (72% ± 11% inhibition), were seen following only repeated daily doses of 30mg/kg. In contrast, daily administration of 3 mg/kg did not affect IL-6 induction of BAL cells. This indicates repeated, very high doses (≥10x required to completely block the signaling axis in the periphery) are required for the anti-GM-CSF-Rα antibody to have an inhibitory effect on alveolar macrophages. Interestingly, Campbell et al also indicate that significant pharmacodynamic effects of the antibody on the lung cells could be observed after 5 daily doses of 30mg/kg CAM-3003 (53%±23% inhibition). The authors also indicate that PK studies using BAL measurements to quantify portioning in the lung lumen underestimate the partitioning due to dilution with the lavage fluid.

Of further note, these studies were done in mice without underlying lung pathology, and the translatability of these studies in normal mice to humans with COVID-19 pneumonia is unclear. Nevertheless, these data suggest that a dose higher than that needed to achieve 100% RO in circulation may be required in order to achieve therapeutic concentrations in the lung. In current COVID-19 patients, it is likely that the inflammatory process afflicting the lung of severe

pneumonia patients with hyper-inflammation may lead to a higher ratio of penetration than observed in animal studies, thus allowing for potentially direct inhibitory effects on macrophages which have already migrated in the lungs.

Taken together, a dose of up to 10 mg/kg (the highest tested in humans) may be required to confer significant pharmacodynamic effects in the lung to inhibit cytokine storm and prevent further lung damage. Supported by the safety data provided by the Phase 1 study, it would be reasonable to administer a single dose of mavrilimumab at levels up to 10 mg/kg in an attempt to provide desired pharmacodynamics in COVID-19 patients, where direct inhibition of GM-CSF in the lung may be a requirement. Hypothetically, a dose of 3 mg/kg may be sufficient and reasonable to be tested, but only if higher proposed dosages in the study are found not to be safe (very close safety monitoring is proposed). Given the lethality of pulmonary complications from COVID-19, the Sponsor/Investigator, with input from COVID-19 treating physicians, is proposing that, in Phase 2, higher doses (higher than 3 mg/kg, given that this dose is apparently sufficient to completely block the signaling axis only in the periphery) be tested first. The IV route of administration is supported by Phase 1 (Burmester 2011) safety of SAD study in RA patients. As a precaution, the IV infusion of mavrilimumab in the COVID-19 Phase 2 study will be administered at slower rates than those applied in the SAD study.

4.3 Risks and benefits

To date, there are no adverse events with a recognized causal relationship to exposure to mavrilimumab. However, there are a number of hypothetical risks that can be extrapolated from the mechanism of action. In particular, GM-CSF antagonism may interfere with immune response to infections. It is unknown how likely these effects are to occur, but their frequency may be lower with a one-time dose as compared to a longer duration to treat a chronic disease.

Frequent side effects:

- Nausea (approximately 1 in 10 subjects, self-limiting)
- Nasopharyngitis (approximately 1 in 10 subjects, self-limiting)
- Headache (approximately 1 in 10 subjects, self-limiting)

Rare but potentially life-threatening adverse reaction:

- Severe hypersensitivity reactions: While these have not been reported with Mavrilimumab, such reactions (including anaphylaxis, anaphylactoid reactions, cytokine release, and endotoxemia) have been observed after administration of other monoclonal antibodies. These reactions may be severe and may result in death.
- Leukopenia resulting in an increased risk of opportunistic infections. Mavrilimumab reduces the number of neutrophils. In some patients the reduction may be such to expose to additional (opportunistic) infection.

Additional potential side effects (of unknown frequency):

- Pulmonary alveolar proteinosis (PAP): studies have linked blockage of GM-CSF, the target of Mavrilimumab, with PAP. While the use of Mavrilimumab has not been

associated with the development of PAP in patients, a potential risk for this complication with Mavrilimumab use may exist.

- While the use of Mavrilimumab has not been associated with the development of cancer, drugs that modulate the immune response may increase the risk of cancer.
- Impaired response to vaccines. Drugs that reduce the immune response, like Mavrilimumab can impair the immune response to vaccine.
- Antibodies that inactivate the study drug thus losing its efficacy

In general, the risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, as well as periodic review of all safety data by an independent data monitoring committee (DMC).

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

The benefit a patient might have by participating in the study is the close monitoring of their condition and optimization of treatment of known risk factors during the full duration of the study.

There may be unknown or unforeseen risks associated with study participation.

5 Population

The study will enroll patients identified by regular review of hospitalized COVID-19 patients to evaluate for inclusion and exclusion criteria. The study population includes patients who meet criteria of impending mechanical ventilation. Specifically, these patients will have severe pneumonia, defined as hospitalization due to COVID-19 with abnormal chest imaging, hyper-inflammation and SpO2 <92% on room air or requirement for supplemental oxygen.

5.1 Inclusion criteria

The eligibility criteria, including the inclusion and exclusion criteria, will be verified both by a study investigator and a research nurse using checklists.

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed
2. Documented COVID19 pneumonia defined as positive SARS-CoV2 test **AND** abnormalities/ infiltrates on chest x-ray or computed tomography **AND** active fever or documented fever within 24-48 hours or ongoing anti-pyretic use to suppress fever
3. Hypoxia (Room air SpO2 <92% or requirement for supplemental oxygen)
4. Increased serum inflammatory marker (CRP > 5 mg/dL)
5. Severity of disease warrants inpatient hospitalization

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study:

1. Onset of COVID-19 symptoms >14 days
2. Age < 18 years-old
3. Hospitalized >7 days
4. Mechanically ventilated
5. Serious concomitant illness which in the opinion of the investigator precludes the patient from enrolling in the trial, including (but not limited to):
    - History of immunodeficiency (congenital or acquired)
    - Neutropenia (absolute neutrophil count <1,500/mm3)
    - History of solid-organ or bone marrow transplant
    - History of current systemic autoimmune or autoinflammatory disease(s) requiring systemic immune-modulating drugs
    - History of myeloproliferative disorder or active malignancy receiving cytotoxic chemotherapy
    - Pre-existing severe pulmonary disease (i.e. steroid dependent asthma, COPD on home oxygen, or other restrictive/obstructive lung disease requiring home oxygen)
    - Pre-existing severe left ventricular systolic dysfunction (i.e. LVEF <35%)
    - Known or suspected active tuberculosis (TB), latent TB, or history of incompletely treated TB or at high risk for latent TB (from exposure or prior incarceration)
    - History of active or latent viral hepatitis (i.e. Hepatitis B or C)
    - Concomitant uncontrolled systemic bacterial or fungal infection
    - Concomitant viral infection other than COVID-19 (e.g. Influenza, other respiratory viruses)
    - History of chronic liver disease with portal hypertension
    - History of end-stage renal disease on chronic renal replacement therapy
6. Recent treatment with cell-depleting biological therapies (e.g., anti-CD20) within 12 months, cell-depleting biological therapies (such as anti-tumor necrosis factor [TNF], anakinra, anti-Interleukin [IL]-6 receptor [e.g. tocilizumab], or abatacept) within 8 weeks (or 5 half-lives, whichever is longer), treatment with alkylating agents within 12 weeks, treatment with cyclosporine A, azathioprine, cyclophosphamide, or mycophenolate mofetil (MMF) within 4 weeks
7. Recent treatment with intramuscular live (attenuated) vaccine within 4 weeks
8. Chronic or recent corticosteroid use > 10 mg/day
9. Pregnant and breast-feeding women
10. Enrolled in another investigational study using immunosuppressive therapy
11. Known hypersensitivity to mavrilimumab or any of its excipients

12. In the opinion of the investigator, unable to comply with the requirements to participate in the study
13. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of investigational drug. Such methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - If male and sexually active, must have documented vasectomy or must practice birth control and not donate sperm during the study and for 3 months after study drug administration.
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

6 Treatment

A total of 60 patients will be enrolled across all sites: 30 subjects will receive mavrilimumab 6 mg/kg IV, and 30 subjects will receive placebo infusion. No patient will receive more than one dose. Additional patients may be enrolled upon agreement of the investigators depending on speed of enrollment and availability of study drug.

6.1 Study treatment

6.1.1 Investigational drug

Dosing will be based on actual body weight and is administered IV via a syringe infusion pump.

For investigation: 6 mg/kg mavrilimumab will be infused on a pump.

For placebo: A similar infusion of the provided diluent will be used as placebo.

In preliminary experience with mavrilimumab in COVID-19, no infusion reactions have been reported, and pre-medication will not be required. In the event of an infusion reaction, the following interventions can be considered if needed: NaCl 0.9% IV infusion at 500 mL/hr, diphenhydramine 50 mg IV, hydrocortisone sodium succinate 100 mg IV, epinephrine 1mg/mL 0.3 mg intramuscular.

6.1.2 Additional study treatments

No additional treatment beyond investigational drug are included in this trial.

6.1.3 Treatment group

Eligible subjects will be assigned at the baseline visit to the treatment group in a consecutive fashion.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

No formal drug-drug interaction studies have been conducted with mavrilimumab.

Medication classification used by the subject prior to randomization will be recorded in the eCRF pages.

Concomitant medications to track include: antipyretics, antibiotics related to secondary infections, and all investigational off-label therapies for COVID-19 for each subject (e.g. chloroquine, hydroxychloroquine, anti-IL-6, corticosteroids, remdesivir, lopinavir/ritonavir) along with time, dose, and duration of their administration. Other concomitant medications will be recorded at baseline and daily thereafter while patient is hospitalized until Day 7, at Day 14, Day 21 and Day 28. This information will be included in the final study report.

6.2.2 Prohibited medication

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving mavrilimumab. Therefore, live vaccines should not be given concurrently.

Treatment with cell-depleting biological therapies (e.g., anti-CD20), cell-depleting biological therapies (such as anti-tumor necrosis factor [TNF], anakinra, treatment with alkylating agents, treatment with cyclosporine A, azathioprine, cyclophosphamide, or mycophenolate mofetil (MMF). If a patient is on anti-Interleukin [IL]-6 [e.g. tocilizumab], or abatacept] prior to enrollment they are excluded, however it may be permitted after enrollment if the investigator deems it clinically necessary.

6.2.3 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.) based on central randomization, that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. Upon

signing the informed consent form, the patient is assigned to the next sequential Subject No. available.

6.2.4 Treatment assignment, randomization

After meeting all inclusion/exclusion criteria and obtaining informed consent, patients will be randomized using a 1:1 allocation ratio to one of the two study arms. Randomization will be centralized through REDcap Cloud at C5 research at the Cleveland Clinic. Randomization will be stratified by site.

6.3 Treatment blinding

Subjects, investigator staff, persons performing the assessments, and the clinical trial team will be blinded to treatment. Only the Research Pharmacist and members of the Data Monitoring Committee will have access to the treatment assignments. If the clinical team decides that unblinding the patient is essential for subsequent significant clinical management, then the patient may be unblinded after discussion between the clinical team and the Principal Investigator.

6.4 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described in the pharmacy manual.

A unique medication number is printed on the study medication label.

Each study site will be supplied with study drug and corresponding diluent/placebo. Clinical lots of KPL-301 drug product and corresponding diluent/placebo have been manufactured in different container formats; KPL-301: accessorized pre- filled syringes [APFS] and Diluent/Placebo: vials. The drug product is supplied with a diluent; the diluent will be used as the matching placebo. The deliverable or extractable volume for APFS and the vials is 1.0 mL, each. The Pharmacy Manual contains all the information about drug preparation.

APFS and vials are to be stored by the GMP pharmacy facility and investigator at 2-8 degrees Celsius at which temperature the product is viable until its listed expiry date.

Individual patient infusions are to be prepared at the investigational site under the authority of the investigator and in accordance with local regulations. Preparation of the investigational drug must be done in a separate space/room where study personnel have no access during time of preparation.

6.4.1 Handling of study treatment

6.4.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the pharmacy manual. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Kiniksa CPO Quality Assurance.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Kiniksa address provided in the investigator folder at each site.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB -approved informed consent via site-approved procedures.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

A copy of the approved version of all consent forms will be kept by the Sponsor/Investigator.

7.1 Visit schedule and assessments

The assessment schedule lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed.

Clinically significant abnormalities must be recorded on the relevant section of the CRFs capturing medical history/current medical conditions/AE as appropriate.

Table 7-1 Assessment Schedule[π]

Activity	Study Day [a]													
	-3 to 0 [b]	0	1	2	3	4	5	6	7	14	21	28 [c]	60	Unscheduled [d]
Informed consent	X													
Demographics	X													
Reason for hospitalization (COVID-19 pneumonia)	X													
Medical history	X													
Eligibility	X													
Physical exam	X													X
Vital signs	X	X	X		X		X		X	X	X	X		X
Body Temperature (Celsius)	X	X	X	X	X	X	X	X	X	X	X	X		X
Body weight	X													
Height	X													
Electrocardiogram	X													X
Chest imaging (CXR or chest CT)	X													X
Clinical assessment (6 category ordinal scale)[α]	X	X	X	X	X	X	X	X	X	X	X	X		X
SOFA score	X								X	X	X	X		
2019-nCoV test*	X								X	X	X	X		X
Respiratory Virus Panel	X													
CRP	X	X	X	X	X	X	X	X	X	X	X	X		X
LDH [e]	X	X	X	X	X	X	X	X	X	X	X	X		X
D-Dimer [e]	X	X	X	X	X	X	X	X	X	X	X	X		X
Ferritin [e]	X	X	X	X	X	X	X	X	X	X	X	X		X
Troponin	X													
NT-proBNP	X													
Mechanical ventilation assessment	X	X	X		X		X		X	X	X	X		X
Respiratory parameters [g]	X	X	X		X		X		X	X	X	X		X

	Study Day [a]													
Activity	-3 to 0 [b]	0	1	2	3	4	5	6	7	14	21	28 [c]	60	Unscheduled [d]
TB screening [h]	X													
Pregnancy test [i]	X													
Hematology (CBC + diff)	X				X				X			X		X
Coagulation (PT, PTT, INR)	X													
Chemistry (lytes, BUN, glucose, CR)	X				X				X			X		X
Liver profile (AST, ALT, Alb, AlkP, Tbili, Dbili)	X				X				X			X		X
Urinalysis	X											X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications [l]	X	X	X	X	X	X	X	X	X	X	X	X		X
Assessment for “off of oxygen” as defined for the primary endpoint∞										X				
Assessment for “respiratory failure” as defined for the secondary endpoint												X		
Assessment of survival (day of death if occurs)[m]	X											X	X	
Mavrilimumab/placebo administration		X												

[π] **Given resource limitation related to COVID-19, all laboratory testing is considered standard of care, though as possible, certain tests that are not considered standard of care may be obtained for research. If the laboratory tests in the schedule of activities are obtained, they will be documented accordingly. If laboratory tests cannot be obtained for other reasons, such as requiring extra use of personal protective equipment, unnecessary exposure to healthcare personnel, or safety issues related to obtaining and processing samples, these will not be considered a protocol deviation.**

[a] Study visits are planned for hospitalized patients only; planned activities that fall on study days that occur after the patient is discharged will not be done.

[b] Screening activities can occur from -3 and 0 days before enrollment except for 2019-nCoV testing, which can occur between -7 and 0 days before enrollment.

[c] For hospitalized patients, this visit will include the activities listed. For patients who have been discharged before Study Day 28, this visit will be conducted by phone/telehealth but will not include any laboratory tests.

[d] An unscheduled visit is planned to occur on the day of discharge if the patient is discharged before Day 28; in which case this will serve as an early termination visit. If patient is discharged the visit on Study Day 28±3 and Study Day 60±3, will be done by telephone call follow-up and lab tests will not be performed. May also be used for adverse event assessments.

* Nasopharyngeal or oropharyngeal swabs for SARS-CoV2 RNA levels will be performed until negative or discharge. Sampling will include both nostrils, or repeat sampling will include the same nostril if only one nostril is used. A local sample will be used for inclusion criteria, and as possible appreciating the concerns related to extra use of personal protective equipment and exposure to healthcare personnel

[α] For the purposes of the primary end-point and time to freedom from supplemental oxygen, the ordinal scale and presence of supplemental oxygen will be assessed daily thru Day 14 while hospitalized. If patient has been discharged prior to Day 14, it will be assessed onDay 14, 21 and 28.

[e] Collect at least baseline and at least weekly thereafter.

[g] Includes FiO_2, SpO_2, Respiratory rate, note if ventilated or not, if yes collect PEEP; rescue therapy used (e.g., Flolan, proning, NM blockade, ECMO). For FiO_2, SpO_2, and PEEP, best and worst of daily value. Calculate P to F ratio best and worst for each day.

[h] Done at Investigator's discretion; not expected to be used for decision to treat; not a mandatory test.

[i] Females of child-bearing potential only, urine or serum at investigator's discretion.

[J] Includes complete blood count (CBC) and differential at screening and CBC on subsequent indicated days.

[l] Prohibited medications include any cell-depleting biological therapies (e.g., anti-CD20) within 12 months prior to Day 0; or previous treatment with noncell-depleting biological therapies (such as anti-tumor necrosis factor [TNF], anakinra, anti-Interleukin [IL]-6 receptor [e.g. tocilizumab], or abatacept) within 8 weeks (or 5 half-lives, whichever is longer) prior to Screening, treatment with alkylating agents within 12 weeks prior to Screening, intramuscular, receipt of live (attenuated) vaccine within the 4 weeks before Day 0, treatment with cyclosporine A, azathioprine, cyclophosphamide, or mycophenolate mofetil (MMF) within 4 weeks of Screening. **Concomitant medications to track include: antipyretics, antibiotics related to secondary infections, and all investigational off-label therapies for COVID-19 for each subject (e.g. chloroquine, hydroxychloroquine, anti-IL-6, corticosteroids, remdesivir, lopinavir/ritonavir) along with time, dose, and duration of their administration**. Other concomitant medications will be recorded at baseline and daily thereafter while hospitalized until Day 7, at Day 14, Day 21 and Day 28. This information will be included in the final study report.

∞ Assessed daily thru Day 14 if hospitalized. If the patient is discharged, assess at Day 14.

[m] Document whether death occurred after withdrawal of care, and if so, reason for withdrawal of care.

7.2 Subject demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all subjects. The number of days between onset of COVID-19 symptoms and initiation of treatment will be recorded in all patients.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

7.2.1 Laboratory evaluations

Pre-treatment screening will include:

- Complete blood count (CBC), serum biochemical tests (including renal and liver function), troponin, NT-proBNP, albumin, total protein, coagulation profile, D-dimer, fibrinogen, LDH, CRP, serum ferritin, IL-6, quantiferon (optional), serum lipid panel (triglycerides), 2019-nCoV test.

On-treatment measurements (as noted in the schedule of activities):

- Complete blood count (CBC), serum biochemical tests (including renal and liver function), albumin, total protein, coagulation profile, D-dimer, LDH, CRP, serum ferritin, IL-6, 2019-nCoV test

7.2.2 Pregnancy assessments

All pre-menopausal women who are not surgically sterile will have a urine or serum pregnancy test performed at the screening visit, at the investigator's discretion. Pregnancy testing is not required for post-menopausal women.

8 Study discontinuation and completion

8.1 Discontinuation

8.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being. After study treatment discontinuation, patient should remain in the study, unless he/she withdraws consent (Section 9.1.2), preferably in writing.

Study treatment must be discontinued under the following circumstances

- Subject/guardian decision
- Pregnancy
- Use of prohibited treatment
- Any situation in which study participation might result in a safety risk to the subject
- Any laboratory abnormalities that in the judgment of the investigator prevents the subject from continuing study drug administration

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent. Where possible, they should return for the assessments indicated in the assessment schedule**, understanding that this may often not be possible with an ongoing COVID-19 pandemic, and therefore telehealth visits may be performed**. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, and letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule. Patient's vital status can also be verified by the study site upon contact with patient's primary care physician or other sources according to local rules and regulations.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new/concomitant treatments
- adverse events/serious adverse events

8.1.1.1 Replacement policy

Subjects who are enrolled but not randomized will be replaced.

8.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore

And

- Does not allow further collection of personal data

It is encouraged that patient provides withdrawal of consent in writing.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and

record this information. Patient's vital status can be verified upon contact with patient's primary care physician or other sources according to local rules and regulations.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Investigative sites will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law:

All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

8.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until the end of the study while due diligence has been completed.

8.1.4 Early study termination by the sponsor

The study can be terminated by the Sponsor/Investigator at any time. Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data

In making the decision to terminate, the Sponsor/Investigator will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRB of the early termination of the trial.

8.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

9 Safety monitoring and reporting

9.1 Definition of adverse events and reporting requirements

9.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade:
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities
    - severe: prevents normal activities

2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be ‘Not suspected’. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Drug interrupted/withdrawn
- Its outcome
  a. not recovered/not resolved;
  b. recovered/resolved;
  c. recovering/resolving,
  d. recovered/resolved with sequelae;
  e. fatal; or unknown.

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 60 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. Continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values, which are considered to be non-typical in subjects with the underlying disease.

9.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (coronary heart disease, cerebrovascular disease or peripheral vascular disease).
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

9.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until the last study visit must be reported to Sponsor/Investigator **within 24 hours** of learning of its occurrence.

The investigator/sponsor will report all serious, unexpected adverse events as an IND safety report to the FDA no later than 15 calendar days after the investigator/sponsor's initial receipt of this information. **Fatal or life-threatening unexpected experiences for which there is a possibility that the experience may have been caused by the drug will be reported by the investigator/sponsor to the FDA by telephone or facsimile transmission no later than 7 calendar days after receipt of this information.** An annual report which includes summaries of all IND safety reports will be submitted to the FDA each year in the annual report and to

Kiniksa Pharmaceuticals (IMP/Drug Manufacturer) by the investigator/sponsor. Investigator is responsible for evaluating all safety information available, and notify FDA and all investigators in an IND safety report of potentially serious risks from this clinical trial or any other source as soon as possible but no later than 15 calendar days after the sponsor/investigator receives the safety information and determines that the information qualifies for reporting.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Kiniksa may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected and Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to FDA.

Any SAEs experienced after the Completion Study should only be reported to sponsor/investigator

9.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to sponsor/investigator within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Newborn will be followed up just until birth according to guidelines as there was nothing observed in any studies that would suggest a fetal development risk.

Any SAE experienced during pregnancy must be reported.

9.1.5 Reporting of study treatment errors

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE.

9.1.6 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress

of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor/investigator whether to continue, modify or terminate a trial.

Summary reports will be provided to a DMC after the first 5 subjects have been reviewed, after 15 subjects have been reviewed, and after every 10 subsequent patients.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor/investigator and the DMC.

Schedule of Safety Assessments:

Data Collection and Database management

Activity	Study Day													
	-3 to 0	0	1	2	3	4	5	6	7	14	21	28	60	Unscheduled
Vital signs	X	X	X		X		X		X	X	X	X		X
Medications	X	X	X						X	X	X	X	X	
Respiratory parameters	X	X	X						X	X	X	X		X
Hypersensitivity reaction			X	X	X	X	X	X	X					
Anaphylaxis reaction (defined according to Sampson's criteria, Sampson HA et al., J Allergy Clin Immunol. 2006 Feb;117(2):391-7		X	X	X										
Secondary Infections	X	X	X						X	X	X	X	X	X
Hematology (CBC + diff: assessment for leukopenia, neutropenia, and thrombocytopenia)	X				X				X			X		X
Coagulation (PT, PTT, INR)	X													
Chemistry (lytes, BUN, glucose, CR)	X				X				X			X		X
Liver profile (AST, ALT, Alb, AlkP, Tbili, Dbili: assessment for drug-induced liver injury according to Hy's law)	X				X				X			X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X

9.2 Data collection

De-identified data from this study will be shared within an Academic Consortium to enhance the ability to monitor safety and efficacy signals.

Data management will be coordinated by C5Research at the Cleveland Clinic. Data will be entered into a secure dedicated REDcap cloud database, and data analysis will be performed by C5Research.

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs and entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

9.3 Site monitoring

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10 Data analysis and statistical methods

10.1 Analysis sets

All patients who provide informed consent and are randomized will be included in the analysis. Specifically, patients who are randomized and do not receive study medication/placebo and patients who have the study infusion discontinued before completion will remain in the intention-to-treat analysis. However, we may also perform a secondary, exploratory modified intention to treat analysis that would include all patients that actually receive study drug or placebo. As noted above, for patients who are lost to follow-up, due diligence will be performed, and given the importance of reliable estimates of the treatment effect for planning futures, every effort will be made to document respiratory status and survival as outlined in the primary and secondary endpoints.

10.2 Subject demographics and other baseline characteristics

The number and percentage of patients who completed the study, who discontinued the study and the reason for discontinuation will be presented for all patients. The frequency (%) of patients with major protocol deviations as well as the criteria leading to data exclusion from analysis will be presented in separate tables, if applicable. Finally, the number of enrolled patients by site will be presented descriptively.

Baseline value is defined as the last non-missing assessment prior to the first dose of study drug unless specified otherwise.

Demographic and background characteristic variables will be summarized using descriptive summary statistics. Continuous variables will be summarized using n, mean, standard deviation, median, Q1 (25th percentile), Q3 (75th percentile), minimum, and maximum. Categorical variables will be summarized using frequency and percentage.

10.3 Analysis of the primary and secondary endpoints

Based on preliminary case-control data of patients with severe COVID-19 pneumonia treated with mavrilimumab, we estimate that 40% of patients in the placebo group will meet the primary endpoint compared to 80% of treated patients. A sample size of 30 patients per arm (60 total) will provide at least 80% power to detect this difference using a 2-sided alpha of 0.05.

The results of our study will inform treatment effect to aid in the planning of larger studies. The primary efficacy analysis will be on an intention-to-treat basis and include all patients who are randomized. Use of supplemental oxygen and vital status will be assessed daily up to day 14. . Patients will be considered to have met the primary endpoint if the patient is alive at day 14 and has not used supplemental oxygen for at least 24 hours, regardless of whether or not the patient is still in the hospital (i.e. success=1). All other patients will be counted as not meeting the primary endpoint (i.e. success=0), including deaths on or before day 14 and patients for whom information cannot be ascertained (eg.lost to follow-up, withdrew consent, or otherwise missing information on the primary endpoint at day 14). This is analogous to imputing the worst case scenario for missing data.

The primary analysis will report the number and percentage of patients meeting the primary endpoint. The chi-square statistic will be used to test the difference between the two treatment groups. The time to freedom from supplemental oxygen will also be displayed geographically with a Kaplan Meier curve. A two-sided p value of < 0.049 will be considered statistically significant for the primary endpoint, though as noted, an important aspect of this study is to better define the magnitude of the treatment effect of our clinical outcomes to appropriately power larger studies.

The secondary endpoints are ~~is~~ the proportion of patients alive at day 28 (i.e. success=1), and the proportion of patients alive and without respiratory failure at day 28 (i.e. success=1). Similar to the primary analysis, patients not meeting the ~~this~~ criteria in each of the secondary endpoints will be considered a failure (i.e. success=0), including deaths on or before day 28 and patients

for whom information cannot be ascertained (e.g. lost to follow-up, withdrew consent, or otherwise missing information on the secondary endpoint at day 28). This is analogous to imputing the worst case scenario for missing data.

The probability of patients achieving the secondary endpoint successfully will also be estimated using Kaplan-Meier estimates and displayed with survival curves. In addition, we do not plan to adjust for multiple hypothesis testing in our secondary and exploratory endpoints. Therefore, these results will be displayed as point estimates with 95% confidence intervals. These intervals should not be regarded as definitive for treatment effects. Finally, we plan to analyze the comparison between mavrilimumab 6 mg/kg versus placebo after all patients have reached day 14 (or have died or been discharged prior to day 14) to expeditiously inform whether a larger study should be undertaken.

10.3.1 Adverse events

All information obtained on adverse events will be summarized in tabular format.

A subject with multiple adverse events of the same type is only counted once towards the total of that event.

All deaths and serious adverse events will be tabulated.

All AEs, deaths and serious adverse events will be provided in patient listings.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations US CFR 21, and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board (IRB) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures and any other written information to be provided to subjects.

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov. In addition, after study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Investigators will apply due diligence

to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by sponsor/investigator and approved by the FDA and IRB, where required, it cannot be implemented.

12 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Kiniksa and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

12.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Kiniksa, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Kiniksa should be notified of this action and the IRB at the study site should be informed according to local regulations.

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