OSPEDALE SAN RAFFAELE

Title:

A randomized, double blind, placebo-**CO**ntrolled trial of **M**avrilimuma**B** for **A**cute respiratory failure due **T**o COVID**-19** pneumonia with hyper-inflammation: the **COMBAT-19** trial

Study code: COMBAT-19
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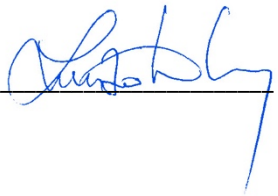
Titolo in italiano: *Studio in doppio cieco randomizzato controllato con placebo con mavrilimumab per trattare l'insufficienza respiratoria acuta nella polmonute COVID-19 con iperinfiammazione: lo studio COMBAT-19*

Firma dello Sperimentatore Principale _____



Data: 23 APR 2020

SUMMARY

1. Protocol Synopsis

Title	*A randomized, double-blind, placebo-**CO**ntrolled trial of **M**avrilimuma**B** for **A**cute respiratory failure due **T**o COVID-**19** pneumonia with hyperinflammation: the **COMBAT-19** trial*
Version	v.3.1; 01/05/2020
Compound	KPL-301 - mavrilimumab
EudraCT number	2020-001795-15
ClinicalTrials.gov	*Not available at this time*
Protocol Code	COMBAT-19
Short title	Mavrilimumab in COVID-19 pneumonia with hyperinflammation
Promoter	IRCCS Hospital San Raffaele – Milan
Coordinator Centre	IRCCS Hospital San Raffaele – Milan
Phase	II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To evaluate the efficacy and safety of mavrilimumab versus placebo on top of best standard of care (SoC) in the treatment of COVID-19 pneumonia. As of April 14 2020, COVID-19 has been confirmed in more than 1.8 million people worldwide. Mortality rate has been reported to be approximately 3.7%, which is nearly 4 times higher than that of influenza: there is an urgent need for effective treatment. Accumulating evidence suggests that patients with severe acute COVID-19 pneumonia have a cytokine storm syndrome, or unbalanced hyper-inflammatory response resulting in markedly elevated cytokine and chemokine production. GM-CSF is a cytokine with dual roles as a critical pulmonary hormone and proinflammatory properties that can exaggerate tissue inflammation. GM-CSF-stimulated macrophages produce proinflammatory cytokines, including tumor necrosis factor (TNF), IL-l , IL-6, IL-23, and IL-12. In addition, GM-CSF receptor activation triggers stimulation of multiple downstream signaling pathways; GM-CSF itself can be induced by inflammatory cytokines and in turn augments production of proinflammatory cytokines, thus functioning as a feed-forward inflammatory

	amplifier. Recent preliminary uncontrolled clinical observations on 13 patients in the promoter institution suggest that GMCSF pathway blockade with mavrilimumab is potentially an effective and well-tolerated treatment for COVID-19 pneumonia.
Primary objective	To evaluate the effect of mavrilimumab versus placebo, added to best SOC, in reducing the dependency on oxygen supplementation in patients with COVID-19 pneumonia and signs of systemic hyperinflammation
Secondary objectives	• To evaluate clinical outcomes using the 7-point ordinal scale in patients with COVID-19 pneumonia and hyper-inflammation - Time to improvement from the worst clinical status to at least one level of improvement on the 7-point ordinal scale - Duration of hospitalization (days) - Need for admission into intensive care unit (ICU) - Incidence and duration of new mechanical ventilation use during the study • To evaluate the time to resolution of fever if present at baseline • To evaluate the improvement in PaO_2/FiO_2 ratio • To demonstrate the potential benefit of mavrilimumab in reducing the case fatality rate over 4 weeks among patients with COVID-19 pneumonia and hyperinflammation regardless of other subsequent clinical interventions • To evaluate the in-hospital outcomes in patients with COVID-19 pneumonia and hyperinflammation • To evaluate the continuous progression of respiratory failure • To evaluate the clinical efficacy of mavrilimumab compared to the placebo by clinical severity stratum (i.e. mild vs moderate subgroup) • To evaluate the proportion of patients requiring rescue medication during the 28-day period • To evaluate change in laboratory parameters through follow up • To evaluate changes in clinical serological measurements related to SARS-CoV-2 infection and to mavrilimumab treatment (i.e.ADA) • To evaluate changes in the National Early Warning Score 2 (NEWS2): - Change from baseline at day 3, 5, 7, 9, 11, 14, 28;

	- Time to clinical improvement defined as a NEWS2 score of 2 or less maintained for at least 24 hours or discharge, whichever comes first • To evaluate the variations in radiological findings in patients that underwent a repeated radiological evaluation, comparing those treated with mavrilimumab to those receiving placebo • To evaluate the safety of mavrilimumab in patients with COVID-19 pneumonia: - Number of participants with treatment-related side effects, serious adverse events, clinically significant changes in laboratory measures and vital signs
Protocol design	This study is a prospective, phase II, multi-center, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of mavrilimumab in hospitalized patients with acute respiratory failure requiring oxygen supplementation in COVID-19 pneumonia and a hyper-inflammatory status. The study will enroll patients to mavrilimumab or placebo, in addition to standard of care per local practice, which may include but not limited to anti-viral treatment, hydroxychloroquine, low-dose corticosteroids (≤ 15 mg of prednisone or equivalent) and/or supportive care. The total trial duration will be 12 weeks after initial mavrilimumab or placebo dose. Safety will be closely monitored by a dedicated external data safety monitoring board (DSMB) at regular intervals during the study.
Study population	Approximately 50 patients with diagnosed COVID-19 pneumonia and hyperinflammation will be randomized to mavrilimumab or placebo in a 1:1 ratio
Inclusion criteria	• Adults (≥ 18 years of age) • Signed informed consent by any patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorized representative or according to local guidelines • Patients clinically diagnosed with SARS-CoV-2 virus by PCR or by other approved diagnostic methodology • Hospitalized with COVID-19-induced pneumonia evidenced by chest x-ray or CT scan with pulmonary infiltrates • Patient requiring oxygen supplementation (i.e. with a SpO2 ≤ 92% while breathing room air) and having a PAO_2/FIO_2 ratio ≤ 300 mmHg

	• Lactate dehydrogenase (LDH) > normal range and at least one of the following: fever > 38.0 C; increased levels of C-reactive Protein (CRP) ≥ 10x ULN mg/L (60 mg/l); or increased levels of ferritin ≥ 2.5x ULN (1000 μg/L)
Exclusion criteria	• Onset of COVID-19 pneumonia symptoms (i.e. dyspnea/respiratory insufficiency) ≥14 days • On mechanical ventilation at the time of randomization • A PaO_2/FiO_2 < 100 mmHg • Uncontrolled systemic infection (other than COVID-19) • Hypersensitivity to the active substance or to any of the excipients of the experimental drug • Total neutrophil count < 1500/mm^3 • Severe hepatic cirrhosis • History of chronic HBV or HCV infection • Known or active tuberculosis (TB) or a history of incompletely treated TB; suspected or known extrapulmonary tuberculosis • Moderate/severe heart failure (NYHA Class 3 or 4) • Any prior (within the defined periods below) or concurrent use of immunosuppressive therapies including but not limited to the following: - Anti-IL-6, anti-IL-6R antagonists or Janus kinase inhibitors (JAKi) in the past 30 days or plans to receive during the study period; - Cell-depleting agents (anti CD20) without evidence of recovery of B cells to baseline level; - Anakinra within 1 week of baseline; canakinumab within 8 weeks of baseline; abatacept within 8 weeks of baseline. - Tumor necrosis factor (TNF) inhibitors within 2-8 weeks (etanercept within 2 weeks, infliximab, certolizumab, golimumab, or adalimumab within 8 weeks), or after at least 5 half-lives have elapsed, whichever is longer; - Alkylating agents including cyclophosphamide (CYC) within 6 months of baseline; - Cyclosporine (CsA), azathioprine (AZA) or mycophenolate mofetil (MMF) or leflunomide or methotrexate within 4 weeks of baseline. • Pregnancy or lactation

	• Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study • In the opinion of the investigator, progression to death is imminent and highly likely within the next 24 hours, irrespective of the provision of treatments • Current participation in any other interventional investigational trials
Study treatment	Arm 1: Mavrilimumab 6 mg/kg IV infused over approximately 1 hour Arm 2: Matching placebo infused over approximately 1 hour Mavrilimumab or placebo infusions will be prepared and blinded by an unblinded pharmacist or designated staff member. Patients will be randomized according to their age (<50; 50-69; ≥ 70 yo), and their respiratory stratum (PaO_2/FiO_2 200-300 or 100-199 mmHg) at randomization.
Treatment of interest	Randomized mavrilimumab or placebo as described above. In addition, all patients will receive standard of care per local practice for the treatment of COVID-19-induced pneumonia. The SOC may include but not be limited to anti-viral treatment, low-dose corticosteroids (≤ 15 mg of prednisone or equivalent) and/or hydroxychloroquine or chloroquine and/or supportive care.
Rescue treatment	In worsening patients, treatment with investigational COVID-19 treatments, such as but not limited to antimicrobials, interferon beta, or convalescent serum, is permitted, if approved by the Promoter. Particular attention should be taken when considering rescue treatment with biologic or targeted-synthetic DMARDs/immuno-suppressors due to the risk of potential severe immune-suppression if given in combination with the investigational drug. Systemic corticosteroids (low- or high-dose per medical judgement) could also be used as a rescue medication.
Efficacy assessments	The WHO-adopted 7-point ordinal scale of clinical status will be assessed on a daily basis at baseline and after study treatment during hospitalization as well as at day 7, 14, and 28. NEWS2 score will be assessed on a daily basis at baseline and after study treatment during hospitalization day 7, 14, and 28.

Safety assessments	Adverse event monitoring, physical examinations, and monitoring of laboratory safety values.
Other assessments	Standard safety and laboratory assessment (hematology and clinical chemistry) will be performed during hospital stay and outpatient visits after discharge from hospital (See Schedule of Assessments and Procedures Table). In addition, the following biomarkers will be determined: • hsCRP • Serum ferritin • D-Dimer • IL-6 (if available)
Sample Size Estimation and Statistical design	Up to approximately 50 subjects will be enrolled. Analysis for treatment effect will be based on the evaluable population which includes all subjects who were randomized and received mavrilimumab/placebo treatment.
Safety monitoring	To provide safety surveillance of the patients enrolled in the study, the external Data Safety Monitoring Board (DSMB) will make a blinded monitoring assessment after each increment of 10 evaluable patients has reached 14 days post-dose.
End of the study and timing	The follow-up period according to the protocol is 3 months for each patient enrolled. The end of the study, including statistical analysis and drafting of the final report, is expected at 1 month from the last follow-up of the last patient enrolled. The study will be performed in approximately 3 months, starting from the first patient enrolled.
Keywords	COVID-19, acute respiratory failure, mavrilimumab, SARS-CoV-2

2. Background and rationale

2.1. 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. As of 14 April 2020, coronavirus disease 2019 (COVID-19) has been confirmed in over 1,800,000 people worldwide, with over 117,000 fatal cases, carrying a mortality rate substantially higher than influenza, which is approximately 1%. There is an urgent need for effective treatment. 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 multiorgan and systemic manifestations in terms of sepsis, septic shock, and multiple organ dysfunction syndromes (MODS). 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. About a third of those (13, 32%) required ICU care, and there were 6 (15%) fatal cases. In clinical and epidemiological data from the Chinese Center for Disease Control (CDC) and regarding 72,314 case records (Wu 2020), 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 and affected by preexisting comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, and oncological diseases, died. While 1% of patients were aged 9 years or younger, no fatal cases occurred in this group. 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. Mild disease (non-pneumonia and mild pneumonia) occurred in 81% of cases.

Severe disease (dyspnea, respiratory rate ≥ 30/min, blood oxygen saturation (SpO2) ≤ 93%, PaO2/FiO2 ratio [the ratio between the partial pressure of oxygen (partial pressure of oxygen, PaO2) in the blood and the percentage of oxygen supplied (fraction of inspired oxygen, FiO2)] < 300, and/or lung infiltrates > 50% within 24 to 48 hours, occurred in 14% of cases. Critical disease (respiratory failure, septic shock, and/or multiple organ dysfunction [MOD] or failure [MOF]) occurred in 5% of cases.

Among the severe clinical manifestations 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 SpO2/FiO2 ≤ 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 the severe patients to prevent and treat ARDS development.

A cytokine profile resembling secondary haemophagocytic 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 tumour necrosis factor-α. Predictors of fatality from a recent retrospective, multicentre 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 (Matthay 2020).

In hyperinflammation syndromes with associated tissue injury, targeted immunomodulation is likely to be beneficial. Re-analysis of data from a Phase 3 randomised controlled trial of IL-1 blockade (anakinra) in sepsis showed significant survival benefit in patients with hyper-inflammation, without increased adverse events. Based upon the series of 21 patients treated with tocilizumab reported by Xu, a multicenter, randomized controlled trial of tocilizumab (IL-6 receptor blockade, licensed for cytokine release syndrome), has been authorized in China in patients with COVID-19 pneumonia and elevated IL-6 (ChiCTR2000029765), and tocilizumab has been approved by the SFDA for use in these patients.

In our study, we aim to screen patients with severe COVID-19 pneumonia for hyperinflammation using laboratory trends (e.g., increasing ferritin, or erythrocyte sedimentation rate, C-reactive protein, IL-6 levels) to identify the subgroup of patients for

whomtargeted immunomodulation prevent worsening of pulmonary status, including the need for ventilatory support, with the aim ultimately to improve mortality.

2.2 Rationale for mavrilimumab

GM-CSF strongly activates macrophages and is considered to be a proinflammatory 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 proinflammatory 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 {Hamilton 2002, Shiomi 2015}.

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 {Shiomi 2015}. 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 augments production of proinflammatory cytokines, thus functioning as a feed-forward inflammatory amplifier {Hamilton 2002}.

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 quick 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 {Crotti 2017}. Mavrilimumab is an anti-GM-CSF-Rα monoclonal antibody (human isoform IgG4) previously developed by MedImmune and now in development by Kiniksa 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 {Burmester 2011}.

2.3 Previous clinical experience of mavrilimumab on COVID-19 pneumonia

At the Promoter Institution, thirteen patients (non-mechanically ventilated at baseline) recently received mavrilimumab 6 mg/kg IV in addition to standard of care for severe COVID-19 pneumonia in the context of a compassionate use protocol (Dagna L, *personal observation*). Twenty-six concomitant patients (non-ventilated at baseline) followed at our Institution but not receiving mavrilimumab were considered as comparison group. At day 14, 11 mavrilimumab-treated patients (85%) and 11(42%) untreated patients had an improvement of clinical status and were discharged (p=0.017). Patients treated with mavrilimumab reached the clinical improvement in significantly fewer days compared to comparison patients (8.0[5.0–12.5] vs 14.0[11.0–14.0])(p=0.003)(χ2=11.4, p=0.001). At multivariate analysis, mavrilimumab treatment (RR:6.91,CI:1.1–46.8, p=0.04) emerged as an independent predictor of clinical improvement. None of the patients treated with mavrilimumab, and 7(27%) patients of the comparison group died. Cumulative survival estimated by Kaplan-Meier curve was worse in patients of the comparison group with respect to patient treated with mavrilimumab (χ^2=4.012, p=0.045). Mavrilimumab was well tolerated with no infusion reactions noted. Although the presented data are limited and preliminary, patients treated with mavrilimumab seemed to show greater and faster clinical improvement compared to the comparison cohort.

In addition, the first patient of a separate planned cohort of mechanically ventilated patients received a dose of mavrilimumab 6 mg/kg IV after admission. The patient was subsequently found to have positive blood cultures drawn two days after drug administration. The patient

died of bacterial sepsis despite intervention with antibiotic therapy and best standard of care. The investigator independently assessed the event of bacterial sepsis as not related to mavrilimumab and ascribed the death of the patient to terminal COVID-19 pneumonia

2.4 Purpose of the study

The purpose of this study is to evaluate the efficacy and safety of mavrilimumab in the treatment of hospitalized patients with COVID-19-induced pneumonia and systemic hyperinflammation. The study will also evaluate the morbidity and mortality rate in patients with COVID-19 due to the inflammatory response to SARS-CoV-2 treated with SOC in the control arm.

3. Study objectives and endpoints

3.1 Primary objective and primary endpoint

Primary objective	Primary endpoint
To demonstrate the benefit of mavrilimumab vs placebo added to best SOC in reducing the dependency on oxygen supplementation in patients with COVID-19 pneumonia and signs of systemic hyperinflammation	Time to the absence of need for oxygen supplementation (time to first period of 24 hrs with a SpO_2 of 94%) within day 14 of treatment, stated as Kaplan-Mayer estimates of the proportion of patients on room air at day 14 and median time to room air attainment in each arm.

3.2 Secondary objectives and secondary endpoints

Secondary objective	Secondary endpoints
To evaluate clinical outcomes using the 7-point ordinal scale (APPENDIX 1) in patients with COVID-19	- Proportion of responders at day 7, 14, and 28 based on the 7-point ordinal scale. Response is defined as a 7-point ordinal scale of 3 or less, i.e. no supplemental oxygen - Time to response, defined as time from date of randomization to the date with a 7-point ordinal scale of 3 or less, i.e. no supplemental oxygen - Proportion of patients with at least two-level improvement in clinical status at day 7, 14, and 28 - Baseline change of clinical status to day 7, 14, and 28
To evaluate the time to disappearance of fever if present at baseline	Time to resolution of fever (for at least 48 hours) in absence of antipyretics, or discharge, whichever is sooner in the 4-week period after

	study treatment. Resolution of fever is defined as body temperature: - ≤36.6°C (axilla) or - ≤37.2 °C (oral), or - ≤37.8 °C (rectal or tympanic) Note: Fever is defined as defined as body temperature > 37.4°C [axilla], or > 38.0 °C [oral], or >38.4°C [rectal or tympanic].
To demonstrate the potential benefit of mavrilimumab in reducing the case fatality rate over 4 weeks among patients with COVID-19 pneumonia and hyperinflammation regardless of other subsequent clinical interventions	COVID-19-related death during the 4-week period after study treatment (in hospital and overall)
To evaluate the in-hospital outcomes in patients with COVID-19 pneumonia and hyperinflammation	Proportion of hospitalized patients who died or required mechanical ventilations (WHO Categories 6 or 7) by day 14
To evaluate change in laboratory parameters through follow up	Variations of the following serological markers over follow-up: - C-reactive protein - Ferritin - D-Dimer
To evaluate changes in the National Early Warning Score 2 (NEWS2, Appendix 2)	- Median changes of NEWS2 score from baseline at day 7, 14, 28 (or discharge, whichever comes first) - Time to clinical improvement (as defined as a NEWS2 score of 2 or less maintained for at least 24 hours or discharge, whichever comes first)
To evaluate the variations in radiological findings in patients that underwent a repeated radiological evaluation, comparing those treated	Variations from baseline to subsequent timepoints (when available) in terms of percentage of lung involvement, modifications in

with mavrilimumab to those receiving placebo	the normal parenchyma, ground glass opacities (GGO), crazy paving pattern, parenchymal consolidations, and evolution towards fibrosis. Analysis will be centralized and performed by at least two independent radiologists, also by means of the IntelliSpace Portal, version 7 (Philips Medical Systems).
To evaluate safety of mavrilimumab in patients with COVID-19-induced pneumonia and systemic hyperinflammation	Number of patients with treatment-related side effects (as assessed by Common Terminology Criteria for Adverse Event (CTCAE) v.5.0), serious adverse events, adverse events of special interest, clinically significant changes in laboratory measurements and vital signs
To evaluate additional outcomes in patients with COVID-19 pneumonia associated with systemic hyperinflammation	To evaluate additional outcomes in patients with COVID-19 pneumonia associated with systemic hyperinflammation such as: - the duration of hospitalization (days); - the need for admission into intensive care unit (ICU) and it median duration, if applicable; - the incidence and median duration of new mechanical ventilation use during the study, if applicable; - the continuous progression of respiratory failure as evaluated by the PaO_2/FiO_2 ratio in the 28-day period or until discharge, whichever comes first; - the proportion of patients requiring rescue medication during the 28-day period, if applicable.

3.3 Exploratory objectives and endpoints

Exploratory objectives	Exploratory endpoints
To evaluate the clinical efficacy of mavrilimumab compared to the control arm by clinical severity (i.e. mild vs moderate subgroup)	To evaluate the primary and secondary endpoints in different subgroups of patients: - mild respiratory failure: PaO_2/FiO_2 ≤ 300 and > 200 mmHg; - moderate respiratory failure: PaO_2/FiO_2 ≤ 200 and > 100 mmHg
To measure the time course of the effects of mavrilimumab on biomarkers associated with but not restricted to those possibly linked to inflammation and disease	Changes in exploratory biomarkers: - Inflammatory biomarkers (i.e. IL-6, IL-1RA, TNF-alpha, CBC and differential) - Levels of antibodies to SARS-CoV-2 / SARS-Cov-2 positivity by PCR Levels of anti-drug antibiodies (ADA)

4. Study design

This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of mavrilimumab plus standard-of-care (SOC) compared with placebo plus SOC in adult patients with COVID-19-induced pneumonia and systemic hyperinflammation.

The study aims to randomize approximately 50 patients throughout the participating centers. Enrollment will stop as soon as the target number of randomized subjects is reached.

Patients who meet the inclusion/exclusion criteria will be randomized in a 1:1 ratio to either mavrilimumab + SOC or placebo + SOC and can be dosed immediately after ensuring that the patient has met all eligibility criteria. Randomization will be balanced according to the following strata (in descending order of priority):

- Age (<50; 50-69; ≥ 70 yo);
- Mild respiratory insufficiency (as defined by a PaO_2/FiO_2 ≥ 200 and < 300 mmHg) vs. moderate respiratory insufficiency (as defined by a PaO_2/FiO_2 ≥ 100 and < 200 mmHg) at randomization.

Patients in the mavrilimumab arm will be dosed on Day 1 with a dose of 6 mg/kg (using a solution with a final concentration of mavrilimumab of 50 mg/mL) infused IV over approximately 1 hour. Patients in the placebo arm will be treated with an equal amount of placebo infused IV over approximately 1 hour.

An informed consent will be obtained from patients before assessments solely required for the study are performed. Thereafter, eligibility criteria will be reviewed by study personnel. All patients with signed informed consent must be registered in an *ad hoc* prepared Interactive Response Technology (IRT) system.

Eligible patients will have biomarker sampling according to the Assessment and Procedures Schedule (see below). Additional safety assessments will be performed approximately as described in the Assessment and Procedures Schedule. Additional follow-up visits will occur on Days 7, 14, 28, 56 and 84 either by phone if previously discharged or in the hospital if still hospitalized. If a patient is hospitalized for longer than Day 28, all invasive protocol assessments will be discontinued except at week 8 and 12, if still hospitalized. If the patient has been discharged, then patients should be phoned for follow-up and data collected as in the Assessment and Procedures Schedule. In addition, unscheduled visits are permitted at or after discharge, as needed.

Deaths and SAEs will be monitored in real time with routine pharmacovigilance and by an external, independent DSMB in order to detect any unexpected safety signal. The DSMB will function independently of all other individuals associated with the conduct of this clinical trial. Patients who do not meet the criteria for participation in this study (screen failures) may not be re-screened.

4.1 Rationale for study design

This randomized, double-blind, placebo-controlled design supports the assessment of efficacy as well as safety of mavrilimumab plus standard-of-care therapy for patients with COVID-19-induced pneumonia and hyperinflammation.

Currently, no approved treatment for COVID-19 is available. A placebo-controlled study should mitigate the potential biases associated with the clinical setting, the variability of the disease course, and the endpoints related to the study objectives and allow for an objective assessment of mavrilimumab value in this indication. Mavrilimumab and placebo will be blinded by an unblinded pharmacist (or other designated staff member) at each participating Institution.

4.2 Rationale for mavrilimumab dose and administration route

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. (Burmester 2011). Pharmacokinetic and pharmacodynamic simulations from studies in subjects with RA coupled with the PK data from 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 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 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's brochure.

However, with regard 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 intraperitoneally 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 only following repeat 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 (Campbell 2016). Campbell et al also indicate that, interestingly, 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 portioning 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 the one 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 10mg/kg IV (the highest tested in humans), may be required to confer significant pharmacodynamic effects in the lung to inhibit cytokine storm and reduce 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 the higher proposed dosages in the study, i.e. 6 mg/kg is found not to be safe (very close safety monitoring is proposed) for the target population or if efficacy, if observed, is not apparently dose-dependent. 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 our study will be administered at slower rates than those applied in the SAD study.

5. Study population

The study population includes adult male and female patients who are hospitalized and diagnosed with severe COVID-19-induced pneumonia and hyperinflammation.

5.1 Inclusion criteria

Participants eligible for inclusion in this protocol must meet **all** of the following criteria:

1. Adults (≥ 18 years of age)
2. Signed informed consent by any patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorized representative or according to local guidelines
3. Patients clinically diagnosed with SARS-CoV-2 virus by PCR or by other approved diagnostic methodology
4. Hospitalized with COVID-19-induced pneumonia evidenced by chest x-ray or CT scan with pulmonary infiltrates
5. Patient requiring oxygen supplementation (i.e. with a SpO2 ≤ 92% while breathing room air) and having a PAO_2/FIO_2 ratio ≤ 300 mmHg
6. Lactate dehydrogenase (LDH) > normal range and at least one of the following:
   - fever > 38.0 °C;
   - increased levels of C-reactive Protein (CRP) ≥ 10x UNL mg/L (≥ 60 mg/l);
   - increased levels of ferritin ≥ 2.5x UNL (≥ 1000 μg/L)

5.2 Exclusion criteria

Participants meeting **any** of the following criteria are not eligible for inclusion in this protocol:

1. Onset of COVID-19 pneumonia symptoms (i.e. dyspnea/respiratory insufficiency) >14 days
2. On mechanical ventilation at the time of randomization
3. A PaO_2/FiO_2 < 100 mmHg

4. Uncontrolled systemic infection (other than COVID-19)
5. Hypersensitivity to the active substance or to any of the excipients of the experimental drug
6. Total neutrophil count < 1500/mm^3
7. Severe hepatic cirrhosis
8. History of chronic HBV or HCV infection
9. Known or active tuberculosis (TB) or a history of incompletely treated TB; suspected or know extrapulmonary tuberculosis
10. Moderate/severe heart failure (NYHA Class 3 or 4)
11. Any prior (within the defined periods below) or concurrent use of immunosuppressive therapies including but not limited to the following:
    a. Anti-IL-6, anti-IL-6R antagonists or Janus kinase inhibitors (JAKi) in the past 30 days or plans to receive during the study period;
    b. Cell-depleting agents (e.g., anti CD20) without evidence of recovery of B cells to baseline level;
    c. Anakinra within 1 week of baseline; canakinumab within 8 weeks of baseline; abatacept within 8 weeks of baseline.
    d. Tumor necrosis factor (TNF) inhibitors within 2-8 weeks (etanercept within 2 weeks, infliximab, certolizumab, golimumab, or adalimumab within 8 weeks), or after at least 5 half-lives have elapsed, whichever is longer;
    e. Alkylating agents including cyclophosphamide (CYC) within 6 months of baseline;
    f. Cyclosporine (CsA), azathioprine (AZA) or mycophenolate mofetil (MMF) or leflunomide or methotrexate within 4 weeks of baseline.
12. Pregnancy or lactation (*Note: Women of childbearing age should use effective contraception/abstinence after treatment with mavrilimumab and for 3 months after the dosing)*
13. Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
14. In the opinion of the investigator, progression to death is imminent and highly likely within the next 24 hours, irrespective of the provision of treatments
15. Current participation in any other interventional investigational trials

6. Treatment plan

The study will enroll patients who require hospitalization with supportive care for COVID-19 pneumonia, including supplemental oxygen. All patients will receive, in addition to the best available standard of care, mavrilimumab or placebo. One single dose of mavrilimumab or placebo will be given.

6.1 Investigational drug

Mavrilimumab

Mavrilimumab (KPL-301) 6 mg/kg of body weight. The drug product is a sterile solution formulated in 50 mM sodium acetate, 70 mM NaCl, 4% (w/v) trehalose dihydrate, 0.05% (w/v) polysorbate-80, pH 5.8. Mavrilimumab will be diluted to a final concentration of 50 mg/mL, so 0.12 mL/kg of the final dilution will be administered on day 1 over approximately 1 hr with a syringe pump.

Diluent/Placebo

A matching dose (0.12 ml/kg of body weight) of placebo (a sterile solution formulated in 50 mM sodium acetate, 70 mM NaCl, 4% (w/v) trehalose dihydrate, 0.05% (w/v) polysorbate-80, pH 5.8) will be administered on day 1 over approximately 1 hr with a syringe pump.

Mavrilimumab or diluent/placebo will be prepared by the unblinded pharmacist. Details on the requirements for storage and management of study treatment, and instructions to be followed for participant numbering, prescribing/dispensing, and taking study treatment are outlined in the pharmacy manual.

All infusions should be administered in the presence of qualified health care personnel as per local hospital regulations under the supervision of the investigator or designee. Immediate access to an emergency crash cart is required. The infusion should last approximately one hour. Premedication to avoid or treat potential infusion-related reaction is at the discretion of the investigator. It is recommended that in the initial 15 minutes the rate of administration

should allow for delivery of approximately 1/6 of the total volume of the infusion. If no moderate or severe infusion reactions are observed by the Investigator, the rate can be doubled for the next 15 minutes. Adjudication of infusion reaction severity is at the discretion of the investigator. After the first 30 minutes the rate can be increased with another 50% if infusion continues to be well tolerated. An example of infusion rates for this protocol would be: 1ml/min in first 15 minutes, followed by 2ml/min during 16-30min, and 3ml/min for the remaining 30 minutes. At any time during the drug administration, if a moderate reaction occurs, the infusion should be stopped and restarted at the discretion of the investigator only after the events have resolve. The infusion should be stopped permanently if a severe reaction is observed.

6.2 Concomitant treatments

All medications, procedures, and significant non-drug therapies (including but not limited to pronation, physical therapy, and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate CRF.
Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Promoter before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact the Promoter to determine if the participant should continue participation in the study.
The patient must be told to notify the Treating Physician about any new medications that he/she takes after the start of mavrilimumab, also after potential discharge from the hospital.

6.3 Permitted concomitant therapy requiring caution and/or action

Patients in this study will be enrolled to mavrilimumab or placebo/diluent, in addition to standard of care per local practice, which may include anti-viral treatment, antimalarials,

corticosteroids (≤ 15 mg of prednisone or equivalent) and supportive care. Immunomodulator (topical or inhaled) use for asthma and atopic dermatitis are not restricted. Use of oral, injected or implanted hormonal methods of contraception are allowed while on mavrilimumab.

In worsening patients, treatment with investigational COVID-19 treatments, such as but not limited to antimicrobials, interferon beta, or convalescent serum, is permitted, if approved by the Promoter. Particular attention should be taken when considering rescue treatment with biologic or targeted-synthetic DMARDs/immuno-suppressors due to the risk of potential severe immune-suppression if given in combination with the investigational drug. Systemic corticosteroids (low- or high-dose per medical judgement) could also be used as a rescue medication.

Information that should be gathered and recorded on the CRF on these medications include:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

.

6.4 Prohibited medications

Any concurrent use of immunosuppressive therapies including but not limited to the following:

- Anti-IL-6, anti-IL-6R antagonists or Janus kinase inhibitors (JAKi);
- Anakinra; canakinumab; abatacept; tumor necrosis factor (TNF) inhibitors
- Cell-depleting agents (e.g., anti CD20)
- Alkylating agents including cyclophosphamide (CYC);
- Cyclosporine (CsA), azathioprine (AZA) or mycophenolate mofetil (MMF) or leflunomide or methotrexate

6.5 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. The Participant No. consists of the Center Number (Center No.) (as assigned by the Promoter to each of the investigative sites) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent (ICF) form, the participant is assigned to the next sequential Participant No. available.

6.6 Treatment assignment, randomization

At Randomization visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. A designated site staff member other than the investigator or study staff involved in safety and efficacy assessments or eCRF completion will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm.

6.7 Treatment blinding

This is a randomized double-blind placebo-controlled treatment trial. Participants, all site staff (including study investigator and study nurses) and persons performing the assessments will remain blind to the identity of the treatment from the time of randomization until database lock. Unblinding a single participant at site for safety reasons (necessary for participant management) will occur after discussion with the Promoter.

Drug product will be supplied in bulk, so an unblinded pharmacist/nurse who is independent of the study team will be required in order to maintain the blind. This unblinded pharmacist/nurse will receive the treatment arm assigned by the IRT system during the randomization transaction. Appropriate measures will be taken by the unblinded pharmacist/nurse to ensure that the treatment assignments are concealed from the rest of the site staff.

The independent DSMB will be allowed to access treatment information via a request to the randomization office for the purpose of creating, reviewing and assessing blinded interim results.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure until clinical database lock. Following final database lock all roles may be considered unblinded.

6.8 Additional treatment guidance

Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs) in this patient population. Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

Emergency breaking of assigned treatment code

Emergency code breaks must be undertaken only when it is required to in order to treat the participant safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the promoter. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT after discussing it with the Promoter. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant.

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

6.9 Preparation and dispensation

Each study site will be supplied with study drug. Clinical lots of KPL-301 drug product and corresponding diluent/placebo are manufactured in accessorized pre- filled syringes (APFS). The drug product presentation has a matching placebo. The deliverable or extractable volume for APFS is 1.0 mL. The Pharmacy Manual contains all the information about drug preparation. APFS 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.

The investigational product is to be diluted using the acetate buffer which will be provided. Doses are to be prepared for administration via a syringe driver depending upon the final diluted volume to be administered. Individual dilutions for administration to patients are to be prepared on the day of administration and administered within 4 hours.
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 designated site personnel have access. Upon receipt, all study treatment will be stored according to the instructions specified in the [IB].

Clinical supplies are to be dispensed only in accordance with the protocol. Study treatment will be prepared by an independent pharmacist or qualified site personnel in order to ensure treatment blinding as described above. At the conclusion of the study, and as appropriate during the course of the study, the investigator will return or destroy all unused study treatment, packaging, drug labels. The investigator will retain a copy of the completed drug accountability log.

7. Informed consent procedures

Eligible participants may only be included in the study after providing Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant 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 acquisition of informed consents and information forms should be documented in the patient's medical records, as required by ICH GCP, and the information and informed consent forms should be signed and personally dated by the patient, or a legally acceptable representative, and by the physician who conducted the information and informed consent discussion. The original signed information and informed consent forms should be retained in accordance with institutional policy, and a copy of the signed forms should be provided to the patient or legally acceptable representative.

All patients will be informed of the aims of the study, the potential benefit, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol, whenever he/she wants. This will not prejudice the patient's subsequent care. They will be informed as to the strict confidentiality of their data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. This must be done in accordance with the local regulatory requirement

Regulatory authorities and/or IEC/IRB may request access to all source documents, data capture records, and other study documentation for one-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations (Low n. 675/1996 and amendments)

and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).
The name of the patient will not be asked by the promoter. A identification number will be automatically attributed to each patient enrolled in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, date of birth will also be reported on forms.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information is included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated. New information might require an update to the informed consent and then must be discussed with the participant.
Women of childbearing 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.

8. Visit schedule and assessments

The Assessment & Procedures Schedule (Table 1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen or phoned for all visits/assessments as outlined in the assessment schedule (Table 1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. At the day of discharge from the hospital, all assessments in Table 1 should be conducted. In addition, contact information for the patient and/or legal representatives should be obtained for the follow-up visits.

Screening assessments are to be taken as indicated in Table 1 prior to dosing and are considered baseline measurements. Patients who meet the inclusion/exclusion criteria may be dosed immediately after obtaining the baseline measurements.

8.1 Schedule of Assessment and Procedures (table 1)

Visit Day	-1 (0-24 hrs prior to dose)	0 (investigational drug dosing)	1	every day during hospitalization until day 28 or discharge (whicever is earlier)	7*	14*	28 (or at discharge)*	day 56 +/- 7 days*	day 84 (+- 7 days) End of study*
	S T U D Y P E R I O D							F O L L O W U P	
informed consent	x								
Inclusion/exclusion criteria	x	x(2)							
Demographics / medical history /relevant comorbidities	x								
SarsCoV-2	x(1)	RECORD ALL SARS-CoV-2 DETERMINATIONS AS OBTAINED					x	x (if available)	x (if available)
Vital signs (HR, RR, SpO2 and/or PaO2, BP, body temp)	x	x(2)	x	x	x	x	x		
Oxygen delivery (flow + FiO2)	x	x(2)	x	x	x	x	x	x	x
NIV use (hours/day)	x	x(2)	x	x	x	x	x		
Height, weight	x								
Physical		S(2)	S						
Clinical status with the 7-point ordinal scale		x(2)	x	x	x	x	x	x	x
Vital status (and if applicable, cause of death)			x	x	x	x	x	x	x
Blood cultures (Aer/Anaer)		x(3)							
Hematology (Hb, MCV, WBC, Plt, absolute count of N,L,M,E,B)	x		x	x every other day until discharge	x	x	x	x (if available)	x (if available)
Clinical chemistry (AST, ALT, ALP, LDH, creatine kinase, troponin, UREA/BUN, creatinine, bilirubin, glucose, total protein, CRP, ferritin, D-dimer; IL-6 [if available])	x		x	x every other day until discharge	x	x	x	x (if available)	x (if available)
Pregnancy test (if applicable)	S								
CT scan / chest X-ray	x(1)	RECORD ALL PULMONARY IMAGING AS OBTAINED					x (if available)		
Electrocardiogram	S(1)								
Adverse events	x	x(2)	x	x	x	x	x	x	x
Prior / concomitant medications	x	x(2)	x	x	x	x	x	x	x
Randomization		x(2)							
Study drug administration		x(2)							
In-hospital outcomes:									
Days on non-invasive ventilation		x(2)	x	x		x	x		
Days on mechanical ventilation		x(2)	x	x		x	x		
Days in hospital		x(2)	x	x		x	x		
Days in ICU		x(2)	x	x		x	x		
Days with use of supplemental O2		x(2)	x	x		x	x		
Days on ECMO		x(2)	x	x		x	x		
Blood collection for experimental outcomes		x(2)		x (day 5)	x (if possible)	x (if possible)	x (if possible)	x (if possible)	x (if possible)

x to be recorded into the eCRF
S to be recorded in the source documentation only

* If patient is discharged prior to Day 28, then all assessments listed for Day 28 should be conducted on the day of discharge. Visits at Days 14, 28, 56, 84 should be conducted via phone for patients who were discharged prior to the visit. These phone visits should only collect Clinical status evaluation with 7-point ordinal scale, Adverse events, Concomitant medications, Additional outcomes; whereas vital signs, physical exam, laboratory tests, NEWS2, and blood collection for biomarkers will not be conducted (but collected if performed for other indications). If the patient remains hospitalized, however, all assessments noted in the table should be conducted on the visit day noted.

(1) Results confirming positive SARS-CoV-2 virus by PCR or by other approved diagnostic methodology available within one week; chest x-ray or CT scan within 4 days prior to randomization may be used for eligibility; ECG in the previous 2 weeks
(2) All assessment at day 0 must be conducted **prior** to mavrilimumab dosing
(3) Blood cultures are acceptable if taken in the 24 hrs before randomization. At day 0 must be they must be taken **prior** to mavrilimumab dosing

8.2 Screening / screening failures

No rescreening will be permitted. Participants who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase.

If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate CRF.

8.3 Participant demographics/other baseline characteristics

Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

8.4 Efficacy

Clinical status (7-point ordinal scale)

Assessment of clinical status using a 7-category ordinal scale (WHO 2020) will be recorded at baseline and then again once daily through Day 28 of the Study Period if hospitalized (Appendix 1). If a patient is discharged from the hospital, the assessment will be made by phone on the visit dates noted in Table 1. Each day, the worse score for the previous day will be recorded. (i.e. on Day 5, Day 4 score is obtained and recorded as Day 4. The scale is as follows:

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities
3. Hospitalized, not requiring supplemental oxygen
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, on non-invasive ventilation or high flow oxygen device
6. Hospitalized, on invasive mechanical ventilation or ECMO
7. Death

Vital signs and oxygen saturation

Vital sign measurements include respiratory rate, pulse rate, systolic and diastolic blood pressure, and body temperature. Peripheral oxygen saturation should also be measured at the same time as the vitals. For patients requiring supplemental oxygen, the oxygen flow rate (L/min) and/or fraction of inspired oxygen (FiO2) should be recorded.

In order to allow assessment of the NEWS2 score (Appendix 2), the vital sign parameters and oxygen saturation should be recorded together once per day, for the duration of the hospitalization during the study.

National Early Warning Score 2 (NEWS2)

In addition to the vital signs, the patient's level of consciousness and the presence/absence of respiratory support must be recorded. The NEWS2 parameter for respiratory support is the selection of either air or "oxygen" can include other forms of ventilation to maintain oxygen saturation (Appendix 2).

These should be recorded at the same time points as the vital sign measurements (Table 1).

NEWS2 values will be calculated electronically based on vital sign parameters and NEWS2 related assessments recorded by the investigator in the appropriate eCRFs.

In-hospital outcomes

In addition to the endpoints mentioned above, the following in-hospital outcomes will be captured on eCRF(s):

- Days on mechanical ventilation
- Days in hospital
- Days in ICU

- Days with use of supplemental oxygen
- Days on ECMO
- Time from intubation for mechanical ventilation to time to extubation

8.5 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

Laboratory evaluations

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

Presence SARS-CoV-2 virus

For the Screening inclusion criterion, SARS-CoV-2 virus should be measured by PCR or by other approved diagnostic methodology ≤ 7days of Screening by local lab. Documentation of the method used should be available in the source notes.

Laboratory evaluations for Safety

Laboratory evaluations will be performed by the local lab.

Hematology

Hemoglobin, mean corpuscular volume (MCV), white blood cell count with differential, and platelet count will be measured according to the assessment schedule in Table 1.

Chemistry

Creatinine, total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase, lactate dehydrogenase, creatine kinase, troponin, total protein, glucose will be measured according to the assessment schedule in Table 1. If a given test is not available locally, this should be documented on the eCRF.

Additional markers of inflammation: high-sensitivity C-reactive protein (hsCRP), ferritin, D-dimer, and IL-6 (if locally available) should be collected in accordance with Table 1.
In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator (in consultation with the Promoter) and shall be based, in part, upon the nature and degree of the observed abnormality. In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the participant to continue in the study.
All patients with laboratory tests containing clinically significant abnormalities should be followed until the values return to within the normal ranges or until a clinical explanation is identified, even after study medication has discontinued.

Physical exam

A complete physical examination will be performed for baseline measurement at the time point defined in Table 1. It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. Then, for remaining timepoints, targeted physical examination, per investigator discretion, may be performed.
Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to informed consent being granted must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after informed consent is given which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's eCRF.

Height, weight

Height in centimeters (cm) will be measured at the Screening visit as specified in the table of assessments (Table 1). Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at the Screening visit as specified in the table of assessments (Table 1).

Electrocardiogram (ECG)

An ECG will be taken at Screening visit locally except for those who have had a valid ECG done within 2 weeks prior to first dosing

Clinically significant abnormalities should be recorded on the relevant section of the medical history/Current medical conditions/AE CRF /eCRF page as appropriate. If necessary, a cardiologist may be consulted.

Pregnancy and assessments of fertility

All women of child-bearing potential will have a serum pregnancy test at Screening (Table 1). Pregnancy tests will be conducted at the local lab and documented in the source documents.

Chest x-ray or CT scan

Standard chest x-ray (PA view) or CT scan will be performed for eligibility except for those who have had a valid x-ray or CT scan done within 4 days prior to first dosing. The results must be known prior to randomization to determine the subject's eligibility for the study. Additional chest x-rays (or CT scan) will be performed, as needed.

Chest x-ray or CT scan results will be recorded in the CRF.

8.6 Additional assessments

Additional studies may include, but are not limited to, the determination of the levels of: IL-6, IL-1β, IL-1RA, TNF, IL-10, IL-18, sIL-2R, SARS-Cov-2 viral load, antibodies to SARS-CoV-2.

9. Study discontinuation and completion

9.1 Discontinuation and completion

Study treatment discontinuation and study discontinuation

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

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the participant
- Following emergency unblinding
- Emergence of adverse events that in the judgment of the investigator, taking into account the participant's overall status, prevent the participant from continuing participation in the study
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study
- Severe hypersensitivity reaction occurs, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, hypotension. Immediate interruption of the infusion to administer study treatment is required in such cases.

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

Participants 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. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/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 participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

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

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent (WoC) occurs only when a participant:

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal

data. Study treatment must be discontinued, and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.
Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up. All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

Lost to follow-up

For participants 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 participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the time point of his/her scheduled last study visit has passed.

Early study termination

The study can be terminated if any of the following happens:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from the external data monitoring committee (DSMB) after review of safety and efficacy data

In taking the decision to terminate, the Promoter will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. 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 participant's interests. The Promoter will be responsible for informing IRBs/IECs of the early termination of the trial.

Study completion and post-study treatment

Study completion is defined as when the last participant 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. Continuing care should be provided by the investigator and/or referring physician based on participant availability for follow-up.

10. Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

According to Regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 for definition of adverse events, adverse reactions and reporting including causality. For the purpose of this protocol adverse events are classified into the following categories:

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 clinical investigation participant 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 participant and identifying adverse events. The Promoter 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 participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible):

1. 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 participant

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 serious adverse event (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:

- o Dose not changed
- o Dose Reduced/increased
- o Drug interrupted/withdrawn

6. Its outcome (i.e. recovery status or whether it was fatal)

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

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 to the end of study visit.

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's 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 participant with the underlying disease.

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 participant 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
- 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 participant'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 participant 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

participant 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 (please refer to the ICH-E2D Guidelines).

All new 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.

SAE reporting

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

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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, an associate from the Chief Medical Office and Patient Safety (CMO & PS) Departments from Kiniksa Pharmaceuticals may urgently require further information from the investigator for health authority reporting. Kiniksa Pharmaceuticals may need to issue an IN to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Reported. The Investigator or the Promoter will voluntary report such events (serious, related) to Kiniksa within 24 hours of awareness.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and requires close monitoring and rapid communication by the investigator to the promoter. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product.

Hepatic Function Abnormality

Adverse events of hepatic function abnormality of special interest are defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event. Investigational product will not be administered to any subject reporting ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN

Acute and Delayed Hypersensitivity Reactions

Biologic therapies are known to be associated with an increased risk of immediate and delayed hypersensitivity reactions as well as anaphylaxis. Anaphylaxis and severe hypersensitivity reactions are required to be reported within 24 hours of knowledge of the event, and ADA samples should be collected as possible.

Clinically Significant Pulmonary Abnormality

Any subject who develops new clinically significant pulmonary symptoms or signs should be referred to a qualified specialist for further specific assessment. Symptoms and signs triggering such referral include but are not limited to an increase in shortness of breath or difficulty breathing, exacerbation of current respiratory symptoms, or a significant

deterioration in dyspnea score. Subjects who are referred for evaluation by a specialist will undergo a diagnostic evaluation to determine the nature and origin of the pulmonary symptom(s)/sign(s) and to determine if PAP may be present. At the discretion of the investigator or specialist additional tests may be required such as a repeat chest x-ray, and/or a chest high resolution computed tomography scan, full PFTs including DLCO measurement, bronchoscopy with bronchoalveolar lavage, and cytological and/or ultrastructural evaluation of the cells recovered by lavage to identify findings consistent with a diagnosis of PAP. Any subject who has been referred for a specialist pulmonary evaluation may be instructed to stop the investigational product until the symptom(s) or sign(s) causing the referral have resolved.

Neutropenia

Adverse events of neutropenia of special interest are defined as an ANC < 1.0 × 109 cells/L. Investigational product will not be administered to any subject who has an ANC < 1.0 × 109 cells/L. Administration of investigational product may continue in the event that the ANC > 1.5 × 109 cells/L and following agreement with the medical monitor.

Serious Infection

Grade 3 severity infections that require treatment with IV therapy (antibiotics, antiviral, or antifungal) and opportunistic infections will be considered serious even if they do not require in-patient hospitalization. Every effort should be made to identify the causative pathogen through prompt and appropriate investigation by the investigator or reporting physician.

Pregnancy reporting

Women should use effective contraceptives during treatment with mavrilimumab and for up to 3 months after dosing.

If a female trial participant becomes pregnant, the study should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to the Promoter 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.

Pregnancy should be recorded and reported by the investigator to CMO & PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Additional Safety Monitoring

Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation.

- These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include

- Based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.2 Data Safety Monitoring Board

This study will include an external data safety monitoring board (DSMB) which in collaboration with the Writing Committee will perform safety data reviews after each increment of 10 evaluable patients has reached day 14 in order to provide a high level of safety surveillance for patients enrolled in the study. The DSMB will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend whether to continue, modify, or terminate a trial.

10.3 Safety Evaluation

The end of enrollment will be based on interim results, with continuation of enrollment or discontinuation of the study according to the response of patients to treatment. The follow-up according to the protocol is 3 months for each patient enrolled. The end of the study, including statistical analysis and drafting of the final report, is expected at 1 month from the last follow-up of the last patient enrolled. The study will be performed in approximately 3 months starting from the first patient enrolled (depending on the speed of enrollment).

11. Statistical considerations and data analysis

11.1 Determination of sample size

The sample size estimation for this study is based on the primary efficacy endpoint, time to the absence of need for oxygen supplementation. When use a two-side alpha value of 0.05 and assume the proportions of patients who do not need oxygen supplementation by day 14 are 83% and 40% for mavrilimumab and placebo arms respectively, total 28 events are required to achieve a 90% power using a log-rank test.

Approximately total 50 patients will be randomized with a 1:1 ratio to obtain the total target number of events. Analysis for treatment effect will be based on the evaluable population which includes all subjects who are randomized and receive KPL-301/placebo treatment.

11.2 Statistical analysis

All efficacy analysis will be done based on the evaluable population.

The primary efficacy endpoint, time to the absence of need for oxygen supplementation will be assessed after all patients have reached day 14, with failure to reach absence of need for oxygen supplementation or death before day 14 considered as right-censored at day 14. Log-rank test stratified by randomization stratum respiratory insufficiency status (mild vs moderate) will be done to compare the efficacy between the two treatment arms. Hazard ratio and its 95% CI will be estimated using the Cox proportional hazards model. Kaplan–Meier curves will also be provided for each treatment arm.

Subgroup analysis for the primary efficacy endpoint will be done to evaluate the robustness of the data base on the following baseline characteristics using the same methodology as specified above:

- Age (<50 vs. 50-69 vs. ≥ 70)
- Respiratory insufficiency status (mild vs. moderate)

For other time to event endpoints, the same methodology used for the primary efficacy endpoints will be repeated. For binary endpoints, Cochran–Mantel–Haenszel test adjusted by the respiratory insufficiency status will be conducted. For continuous endpoints, ANCOVA will be done with treatment as the independent variable and baseline, baseline by treatment interaction, and baseline respiratory insufficiency status as the covariate.

Other than respiratory insufficiency status, no other randomization strata will be used in the stratified analysis due to the small sample size of this study. For any stratified analyses, if one stratum has ≤5 events of interest in a log-rank test or the same response in all patients in a CMH test, the analysis will be done without stratification.

Incidence rate of treatment emergent adverse events will be summarized. Descriptive statistics will be done for other safety assessments.

12. Ethical and legal aspects

The study will be conducted according to the principles of Good Clinical Practice (GCP) as reported in current Italian and European legislation. The responsible investigator will ensure that this study is conducted in agreement with the declaration of Helsinki and the Italians laws and regulations, whichever provides the greatest protection of the patient. The protocol has been written and the study will be conducted according to the ICH Harmonized Tripartite Guideline for GCP, issued by the European Union. The relevant Ethical Committee approval must be obtained before starting the trial. A copy of the patient informed consent form must be submitted to the appropriate authority or committee, together with the protocol for written approval. Written approval of the protocol and informed consent by the responsible and appropriate authority or committee must be obtained prior to recruitment of patients to the study. The investigator must inform the appropriate authority or committee of subsequent protocol amendments, which must be approved by this one.

13. Publication of study results

Principal Investigator and/or The Writing Committee of the study will publish the final results of the trial as abstracts to national and international conferences and full manuscript.

14. References

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15. Appendices

15.1 Appendix 1: WHO 7-point Ordinal Scale determination

The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worse score for the previous day will be recorded. i.e. on Day 3, Day 2 score is obtained and recorded as Day 2.

The scale is as follows:

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities
3. Hospitalized, not requiring supplemental oxygen
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, on non-invasive ventilation or high flow oxygen device
6. Hospitalized, on invasive mechanical ventilation or ECMO
7. Death

Reference: WHO Master protocol 2020. A Multi-center, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19

15.2 Appendix 2: National Early Warning Score 2 (NEWS2)

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

SpO2 = oxygen saturation

The oxygen saturation should be scored according to either the SpO_2 Scale 1 or 2 presented in the table above. The SpO_2 Scale 2 is for patients with a target oxygen saturation requirement of 88%–92% (e.g., in patients with hypercapnic respiratory failure related to advanced lung diseases, such as chronic obstructive pulmonary disease [COPD]). This should only be used in patients confirmed to have hypercapnic respiratory failure by blood gas analysis on either a prior or their current hospital admission.

The decision to use the SpO_2 Scale 2 should be made by the treating physician and should be recorded in the eCRF. In all other circumstances, the SpO_2 Scale 1 should be used.

For physiological parameter "Air or Oxygen?": Any patients requiring the use of oxygen or other forms of ventilation to maintain oxygen saturations and support respiration should be assigned a score of 2.

The consciousness level should be recorded according to the best clinical condition of the patient during the assessment. Patients who are assessed as "Alert" (A) should be assigned a score of 0. Patients assessed as "New Confusion" (C), "Responsive to Voice" (V), "Responsive to Pain" (P), or "Unconscious" should be assigned a score of 3.

Scores should be assigned for respiratory rate, systolic blood pressure, pulse, and temperature according to the table above.

NEWS2 values will be calculated electronically throughout the study based upon entry of vital sign parameters by the investigator in the appropriate eCRF.

Reference

Royal College of Physicians. National early warning score (NEWS) 2. Standardizing the assessment of acute-illness severity in the NHS. London: RCP, 2017.

15.3 Appendix 3: Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APFS	Accessorized Pre- Filled Syringes
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
COVID-19	Coronavirus disease 2019
CRF	Case Report/Record Form (paper or electronic)
CTCAE	Common Terminology Criteria of Adverse Events v.5.0
CXR	Chest x-ray
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
hr	Hour
hsCRP	High sensitivity C-reactive protein
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
IL	Interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology
mg	milligram(s)
mL	milliliter(s)
NEWS2	National Early Warning Score 2
PK	Pharmacokinetic(s)
s.c.	subcutaneous
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TTCI	Time to clinical improvement
ULN	upper limit of normal
WHO	World Health Organization
WoC	Withdrawal of Consent