Clinical Study Protocol: KPL-301-C203

Global Version 6.0 (Amendment 5) (08 Nov 2021)

Study Title:	A Phase 2/3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mavrilimumab (KPL-301) treatment in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation
Study Number:	KPL-301-C203
US IND #	149,300
Study Phase:	2/3
Product Name:	mavrilimumab (KPL-301)
Indication:	Severe coronavirus disease 2019 (COVID-19) pneumonia and hyper-inflammation
Sponsor:	Kiniksa Pharmaceuticals, Ltd. [redacted]
Sponsor Contact/Medical Monitor:	[redacted]

Version:	Date:
Original Global Protocol - Version 1	14 May 2020
South Africa Version 1 (Amendment 1)	27 July 2020
Global Version 2 (Amendment 1)	13 August 2020
Global Version 3 (Amendment 2)	15 December 2020
Brazil Version 4 (Amendment 3)	27 April 2021
Global Version 5 (Amendment 4)	14 June 2021
Global Version 6 (Amendment 5)	08 November 2021

Clinical Study Protocol: KPL-301-C203

Global Version 6.0 (Amendment 5) (08 Nov 2021)

Study Title:	A Phase 2/3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mavrilimumab (KPL-301) treatment in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation
Study Number:	KPL-301-C203
US IND #	149,300
Study Phase:	2/3
Product Name:	mavrilimumab (KPL-301)
Indication:	Severe coronavirus disease 2019 (COVID-19) pneumonia and hyper-inflammation
Sponsor:	Kiniksa Pharmaceuticals, Ltd. [redacted]
Sponsor Contact/Medical Monitor:	[redacted]

Version:	Date:
Original Global Protocol - Version 1	14 May 2020
South Africa Version 1 (Amendment 1)	27 July 2020
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Brazil Version 4 (Amendment 3)	27 April 2021
Global Version 5 (Amendment 4)	14 June 2021
Global Version 6 (Amendment 5)	08 November 2021

PROTOCOL APPROVAL

Protocol Title: A Phase 2/3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mavrilimumab (KPL-301) treatment in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation

Protocol Number: KPL-301-C203

This study will be conducted in compliance with the clinical study protocol, International Council on Harmonisation (ICH) Good Clinical Practice and applicable regulatory requirements.

Sponsor Signatory:

Sponsor's electronic signature appended to the end of this protocol.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for mavrilimumab (KPL-301). I have read the KPL-301-C203 Clinical Study Protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

EMERGENCY CONTACT INFORMATION

Table 1: Emergency Contact Information

Role in Study	Name	Email and Telephone Number
Clinical Study Leader/Responsible Physician	[redacted]	[redacted]
Drug Safety Physician	[redacted]	[redacted]

1. SYNOPSIS

Name of Sponsor/Company:
Kiniksa Pharmaceuticals, Ltd.

Name of Investigational Product:
KPL-301

Name of Active Ingredient:
Mavrilimumab

Title of Study:
A Phase 2/3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mavrilimumab (KPL-301) treatment in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation

Study center(s): Approximately 50 study centers are planned in the United States, EMEA, Latin America, and Africa

Studied period (years):	**Phase of development:**
Date first subject enrolled: July 2020 Estimated date last subject completed: TBD	Phase 2/Phase 3

Objectives:

Primary:

To evaluate the clinical efficacy of a single intravenous (IV) dose of mavrilimumab (10 mg/kg or 6 mg/kg) relative to placebo in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation to reduce progression to respiratory failure or death.

Secondary:

To assess the impact of treatment on clinical status, mortality, and safety of a single IV dose of mavrilimumab (10 mg/kg or 6 mg/kg) relative to placebo in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation.

Other:

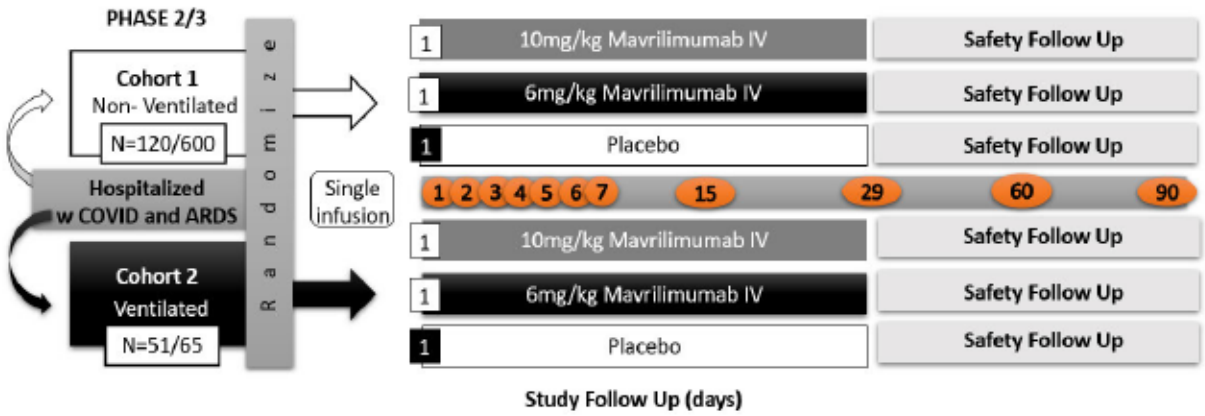
[redacted]

Methodology:

This is an interventional, randomized, double-blind, placebo-controlled study encompassing 2 development phases (Phase 2 and Phase 3). The Phase 2 portion of the study is intended to evaluate the efficacy and safety of 2 dose levels of mavrilimumab relative to placebo (standard of care) in subjects who have tested positive for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with x-ray/computed tomography (CT) evidence of bilateral pneumonia and active or recent signs of hyperinflammation (fever or clinical laboratory results indicative of hyper-inflammation). The Phase 3 portion is intended to confirm Phase 2 efficacy and safety findings. In both Phase 2 and Phase 3, subjects will be enrolled into 2 cohorts: Cohort 1 will include non-mechanically ventilated, hospitalized subjects who require supplemental oxygen to maintain oxygen saturation (SpO_2) $\geq$ 92%, ie, "non-ventilated" subjects; Cohort 2 will include hospitalized subjects for whom mechanical ventilation was recently initiated (within 48 hours prior to randomization), ie, "ventilated" subjects. Following Screening, enrolled subjects in each cohort will be randomized 1:1:1 to receive mavrilimumab 10 mg/kg or 6 mg/kg, or placebo as a single IV infusion (Day 1) in addition to standard of care as per institutional protocol and at the discretion of the investigator (provided that the

medication/therapy is not explicitly prohibited per protocol). There will be a seamless transition in enrollment of subjects in both cohorts between the Phase 2 and Phase 3 portions of the study. For each cohort, once the last subject in Phase 2 is enrolled, all subsequent subjects will be considered Phase 3 subjects. This will allow for continued enrollment during the analysis of the Phase 2 cohort-specific data. Once the last subject in Phase 2 completes Day 29, primary efficacy and safety analyses of the Phase 2 data will be conducted by the Sponsor. Following demonstration of efficacy and safety in Phase 2, the Phase 3 portion of the study will be continued/completed.

Study Schematic



Number of subjects (planned):

Phase 2: Approximately 171 subjects

- Cohort 1: Approximately 120 non-ventilated subjects
- Cohort 2: Approximately 51 ventilated subjects

Phase 3: Approximately 665 subjects

- Cohort 1: Approximately 600 non-ventilated subjects
- Cohort 2: Approximately 117 ventilated subjects (approximately 65 subjects at time of enrollment closure)

Based on review of the Phase 2 Cohort 2 results of the primary and secondary endpoints at day 29, Phase 3 Cohort 2 is closed to further enrollment, as there was no evidence that mavrilimumab provided clinical benefit over placebo in recently ventilated patients.

Diagnosis and main criteria for inclusion:

Adult subjects who have tested positive for SARS-CoV-2 with confirmed pneumonia and hyper-inflammation

Investigational product, dosage and mode of administration:

Mavrilimumab 10 mg/kg or 6 mg/kg (total dose not to exceed 1000 mg) administered as a single IV infusion over approximately 60 minutes

Duration of treatment:

Subjects will receive a single IV dose of mavrilimumab or placebo infused over approximately 60 minutes on Day 1.

Reference therapy, dosage and mode of administration:

Placebo administered as a single IV infusion over approximately 60 minutes

Criteria for evaluation:

The following efficacy endpoints will be used for both the Phase 2 and Phase 3 parts of the study. Endpoints will be evaluated for both Cohorts 1 and 2, unless otherwise specified.

Efficacy:

Primary Efficacy Endpoint:

Cohort 1 (non-ventilated subjects):

Proportion of subjects alive and free of mechanical ventilation at Day 29. Mechanical ventilation is defined as invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO).

Mechanical ventilation status will be evaluated based on the National Institute of Allergy and Infectious Diseases (NIAID) clinical outcome 8-point ordinal scale. Subjects whose clinical outcome has met an NIAID score of 2 will be considered as using mechanical ventilation.

Scale	Description
1	Death
2	Hospitalized, on invasive mechanical ventilation or ECMO
3	Hospitalized, on non-invasive ventilation or high flow oxygen devices
4	Hospitalized, requiring supplemental oxygen
5	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)
6	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7	Not hospitalized, limitation on activities and/or requiring home oxygen
8	Not hospitalized, no limitations on activities

Cohort 2 (ventilated subjects):

The primary efficacy endpoint is mortality rate at Day 29, defined as the proportion of subjects who have died by Day 29.

Secondary Endpoints:

Secondary efficacy endpoints will be examined based on the hierarchical order below:

Cohort 1 (non-ventilated subjects):

- Mortality rate at Day 29
- Ventilation-free survival (Time to ventilation or death) by Day 29

  Defined as time from randomization to ventilation or death; subjects still alive will be censored at Day 29
- Overall survival by Day 29

  Defined as time from randomization to death; subjects still alive will be censored at Day 29

Cohort 2 (ventilated subjects):

- Time to 1-point clinical improvement by Day 29

  Defined as time from randomization to a 1-point improvement on the NIAID 8-point ordinal scale, or discharge from the hospital, whichever comes first. Subjects who die before Day 29 will be censored at Day 35.

Other Efficacy Endpoints:

[redacted]

[redacted]

Safety Endpoints and Oversight:

Safety endpoints will include adverse events (AEs), laboratory parameters, vital signs, electrocardiogram (ECG), and other condition-specific events. Frequency and specific details will be described in the Clinical Monitoring Plan.

A Safety Review Committee (SRC) including 2 physicians from the Sponsor, 1 physician from the Sponsor's contract research organization (CRO), and 1 independent physician who is an expert in critical care medicine, pulmonary disorders, infectious diseases and/or COVID-19 treatment (SRC Chairperson) will meet periodically to review AEs/serious AEs (SAEs), reasons for study discontinuations, and key clinical and laboratory assessments. The initial SRC meeting will be triggered once 4 subjects have completed Day 8. SRC members will be blinded to treatment assignment.

A Data Monitoring Committee (DMC) will be established by the Sponsor to conduct periodic reviews of unblinded safety data from study Phases 2 and 3. The initial meeting will be triggered at 1 month after enrollment of the first patient. More details on the DMC are provided in the protocol and the DMC charter.

Statistical Methods:

The Phase 2 and Phase 3 parts of this study and the cohorts within each phase will be independently analyzed unless otherwise specified.

Analysis Sets:

Intent-to-Treat (ITT) Analysis Set:

All randomized subjects who meet eligibility criteria will be included in the ITT analysis set.

Modified ITT (mITT) Analysis Set:

All randomized subjects who meet eligibility criteria and received study drug will be included in the mITT analysis set.

Safety Analysis Set:

All randomized subjects who received study drug will be included in the safety analysis set.

Per-Protocol (PP) Analysis Set:

All mITT/ITT subjects without protocol deviations deemed to impact efficacy or ethical conduct will be included in the PP analysis set.

Randomization Strata:

There will be 3 stratification factors for randomization:

1. Use of authorized standard of care antiviral therapy for COVID-19 (eg, remdesivir): yes vs. no
2. Age: < 65 vs. ≥ 65 years
3. Acute respiratory distress syndrome (ARDS) status by partial pressure of oxygen to fractional inspired oxygen (PaO_2/FiO_2) ratio*: normal-mild (> 200) vs. moderate-severe (≤ 200). ARDS status will only be used for Cohort 1 (non-ventilated subjects).

   * If PaO_2 is unavailable, use SpO_2/FiO_2: normal–mild (> 235) vs. moderate–severe (≤ 235).

Statistical Analysis:

All statistical analyses will be performed using SAS® Version 9.4 or higher. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation, median, interquartile range, minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables.

Efficacy Analysis:

All efficacy analyses will be based on the mITT for the Phase 2 endpoints and based on the ITT analysis set for the Phase 3 endpoints. Analyses based on other analysis sets will be considered as sensitivity analyses. All efficacy comparisons will be primarily based on each of the mavrilimumab arms versus the placebo arm.

Primary Efficacy Endpoint:

For the Phase 2 part of the study, the Fisher's exact test will be performed for the primary efficacy endpoint for both cohorts. The Cochran-Mantel-Haenszel (CMH) test adjusting for randomization strata (authorized standard of care antiviral therapy for COVID-19 (eg, remdesivir), age, and ARDS status) will be used as supportive analysis of the primary efficacy endpoint for Cohort 1.

For both cohorts in the Phase 3 part of the study, the CMH test adjusted by randomization strata will be used to test the primary efficacy endpoint.

The number of subjects and percentages will be summarized by treatment. The 80% (for Phase 2) and 95% (for Phase 2 and 3) confidence intervals will also be provided as appropriate.

Secondary and Other Efficacy Endpoints:

Ventilation free survival, overall survival, [redacted], time to clinical improvement, and all other time to event endpoints will be analyzed using log-rank test stratified by randomization strata. The hazard ratio for mavrilimumab vs. placebo and the corresponding Wald 80% (for Phase 2) and 95% (for Phase 2 and 3) CI will be calculated based on a Cox proportional-hazards model with treatment as covariate, stratified by randomization strata.

All binary endpoints in both cohorts for Phase 2 will be analyzed by using primarily the Fisher's exact test. The CMH test adjusting for randomization strata (authorized standard of care antiviral therapy for COVID-19 [eg, remdesivir], age, and ARDS status) will be used as supportive analysis for Cohort 1.

For the Phase 3 part of the study, the CMH test adjusted by randomization strata will be used to test all binary secondary and other efficacy endpoint for both cohorts.

Safety Analysis

All safety summaries will be presented for the safety analysis set. No formal statistical analysis of safety endpoints will be performed.

Descriptive statistics will be used to summarize all safety endpoints by treatment group and/or study visit. Data summaries will display parameters such as incidence of AEs, clinical laboratory variables, vital signs, body weight and body mass index, ECG parameters, and physical examinations, where available.

Other Analyses

Pharmacokinetic parameters of mavrilimumab will be summarized. The presence of anti-drug antibodies will be explored. Parameters of mechanical ventilation, respiratory status, Sequential Organ Failure Assessment (SOFA)/quick SOFA, and health care resource utilization (eg, days and/or length in hospital/ICU/oxygen use) will be summarized.

Interim Analysis

There is no interim analysis planned for the Phase 2 or Phase 3 part of the study. Instead, the Sponsor will conduct a primary and/or final efficacy analysis (ie, review of unblinded study results) when the last subject in each Phase and Cohort completes the Day 29/Day 90 assessments.

Sample Size Estimation:

Phase 2:

Approximately 171 subjects will be randomized to the Phase 2 part of this study.

Sample size estimation for Cohort 1 (non-ventilated subjects) in Phase 2 is based on the primary efficacy endpoint of proportion of subjects alive and free of mechanical ventilation at Day 29, using the Fisher's exact test. Approximately 120 subjects will be randomized with a 1:1:1 allocation ratio. Assuming the proportions of subjects alive and free of mechanical ventilation at Day 29 is 95% and 75% for the active treatment arm and placebo arm, respectively, 40 subjects per arm will achieve a

minimum 80% power for a pairwise comparison versus control when the two-sided alpha value is 0.20, after accounting for 15% drop out.

Sample size for Cohort 2 (ventilated subjects) in Phase 2 is based on the primary efficacy endpoint mortality rate at Day 29, using the Fisher's exact test. Approximately 51 subjects will be randomized with a 1:1:1 allocation ratio. Assuming the mortality rates at Day 29 are 40% and 80% for the active treatment arm and placebo arm, respectively, 17 subjects per arm will achieve an 80% power for a pairwise comparison versus control when the two-sided alpha value is 0.20.

Phase 3

Approximately 665 subjects will be randomized to the Phase 3 part of this study.

Sample size for Cohort 1 (non-ventilated subjects) of the Phase 3 part is determined based on the primary efficacy endpoint of proportion of subjects alive and free of mechanical ventilation at Day 29 (mavrilimumab 6 mg/kg vs placebo) using the Chi square test. The assumptions used for the calculation are adjusted based on the results of Phase 2 portion. Approximately 600 subjects will be randomized with a 1:1:1 allocation ratio. Assuming the proportions for the active arm and placebo arm are 87.5% and 74.4% respectively, approximately 200 subjects per arm are sufficient to achieve at least 90% power for the treatment comparison at the two-sided significance level of 0.05.

Sample size for Cohort 2 (ventilated subjects) of the Phase 3 part is determined based on the mortality rate at Day 29 using a Fisher's exact test. Approximately 117 subjects will be randomized with a 1:1:1 allocation ratio. Assuming the mortality rates for the active arm and placebo arm are 40% and 80% respectively, approximately 39 subjects per arm are required to achieve a 90% power for a pairwise comparison versus control when the two-sided alpha value is 0.025. However, based on review of the Phase 2 Cohort 2 results of the primary and secondary endpoints at day 29, Phase 3 Cohort 2 is closed to further enrollment (approximately 65 subjects randomized at the time of enrollment closure), as there was no evidence that mavrilimumab provided clinical benefit over placebo in recently ventilated patients.

Multiplicity Adjustment

The cohorts within the Phase 2 and Phase 3 study parts will be analyzed separately unless otherwise specified.

The two-sided type I error rate is 0.2 for each Phase 2 cohort and 0.05 for each Phase 3 cohort. No multiplicity adjustment will be done for the Phase 2 part and Phase 3 Cohort 2 (no formal testing will be done as enrollment to cohort 2 stopped early).

Multiplicity adjustment for Phase 3 Cohort 1 will be done to guarantee strong control of the overall Type I error rate at a two-sided alpha value of 0.05. Conventional Hochberg method will be used to adjust for multiplicity in the analysis of the two dose levels and the sequence of efficacy endpoints. Details are provided in Section 13.4.

Eligibility Criteria:

Inclusion Criteria:

Subjects must meet all the following inclusion criteria to be eligible for enrollment.

1. Subject (or legally authorized representative) is able and willing to provide informed consent, which includes compliance with study requirements and restrictions listed in the consent form. Consent must be performed per institutional regulations.
2. Age of ≥ 18 years
3. Positive SARS-CoV-2 (2019-nCoV) test within 14 days prior to randomization
4. Hospitalized for SARS-CoV-2 (2019-nCoV)
5. Bilateral pneumonia on chest x-ray or CT
6. *[Original Criteria Deleted]*
7. At least one of the following within 7 days prior to randomization:
   - Ferritin > 500 ng/mL
   - CRP > 5 mg/dL
   - D-dimer > 1,000 ng/mL
   - LDH > 250 U/L
   - Fever - a measured temperature of at least 100.4 °F [38 °C]
8. For Cohort 1: Receiving any form of non-invasive ventilation OR oxygenation to maintain SpO2 ≥ 92% and non-mechanically ventilated (examples include nasal cannula, face mask, venturi mask, high-flow nasal cannula, and non-invasive ventilation or non-invasive positive pressure ventilation)
9. For Cohort 2: Recently ventilated with mechanical ventilation beginning within 48 hours prior to randomization
10. Female subjects must be:
    - postmenopausal, defined as at least 12 months post cessation of menses (without an alternative medical cause), or
    - permanently sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or tubal ligation or having a male partner with vasectomy as affirmed by the subject, or
    - nonpregnant, nonlactating, and if sexually active having agreed to use a highly effective method of contraception (ie, hormonal contraceptives associated with inhibition of ovulation or intrauterine device [IUD], or intrauterine hormone-releasing system [IUS], or sexual abstinence) from Screening Visit until Day 90.
11. Male subjects must have documented vasectomy or if sexually active must agree to use a highly effective method of contraception with their partners of childbearing potential (ie, hormonal contraceptives associated with the inhibition of ovulation or IUD, or IUS, or sexual abstinence) from Screening until Day 90. Male subjects must agree to refrain from donating sperm during this time period.

Exclusion Criteria:

General Exclusion Criteria:

1. Onset of COVID-19 symptoms > 14 days prior to randomization
2. Hospitalized > 7 days prior to randomization
3. [For Cohort 1 only] Need for invasive mechanical ventilation
4. Need for ECMO
5. Serious prior or concomitant illness that in the opinion of the Investigator precludes the subject from enrolling in the trial, including (but not limited to):
   - History of pulmonary alveolar proteinosis
   - Severe and uncontrolled pulmonary disease other than COVID-19 pneumonia (eg, asthma, chronic obstructive pulmonary disease, or others)
   - Pre-existing (prior to development of COVID-19) severe left ventricular systolic dysfunction (ie, left ventricular ejection fraction < 35%)
   - Hemodynamic instability with pressor requirements of norepinephrine at a dose of > 0.5 mcg/kg/min or equivalent (total if multiple pressors used) for more than 12 hours continuously, myocardial infarction, stroke, and cardiogenic septic shock within 30 days prior to randomization
   - Known active tuberculosis (TB) determined by history and local standard of care, or history of incompletely treated TB or at high risk for latent TB (exposure or prior incarceration)
     - If tuberculosis testing is required per local regulations, one positive (or two indeterminate) interferon gamma release assay test results or one positive PCR test is exclusionary
   - Concomitant uncontrolled systemic bacterial or fungal infection
   - Concomitant respiratory viral infection other than COVID-19 and influenza that, in the opinion of the Investigator, represents a higher mortality risk (eg, SARS, Middle East respiratory syndrome [MERS])
6. Recent treatment with cell-depleting biological therapies (eg, anti-CD20) within 12 months, non-cell-depleting biological therapies (such as anti-tumor necrosis factor [TNF], anakinra, anti-IL-6 receptor [eg, tocilizumab], or abatacept) within 8 weeks (or 5 half-lives, whichever is longer), treatment with alkylating agents within 12 weeks, treatment with cyclosporine A, azathioprine, cyclophosphamide, mycophenolate mofetil (MMF), or other immunosuppressant (except for corticosteroids) within 4 weeks prior to randomization. Medications that become standard of care for COVID-19 and/or receive emergency use authorization may be allowed after discussion with the medical monitor.
7. *[Original Criteria Deleted]*

8. If subject is receiving or has received hydroxychloroquine within 3 months prior to screening visit, a corrected QT interval by Fridericia's method (QTcF) on Screening ECG of ≥ 500ms is exclusionary. If subject has a pacemaker, this criterion does not apply.
9. *[Original Criteria Deleted]*
10. Enrolled in another investigational study of a medical intervention within 30 days prior to randomization. Participation in open label trials involving investigational treatments for COVID-19 may be allowed upon approval by the Sponsor.
11. Known hypersensitivity to mavrilimumab or any of its excipients
12. In the opinion of the Investigator, unable to comply with the requirements to participate in the study
13. *[Original Criteria Deleted]*
14. *[Original Criteria Deleted]*
15. At Screening blood tests, any of the following:
    - Aspartate transaminase > 10 × upper limit of normal (ULN)
    - Alanine transaminase > 10 × ULN
    - Hemoglobin < 7.5 g/dL
    - Neutrophils < 1,500/mm^3
    - Absolute platelet count < 50,000/mm^3
    - Creatinine clearance < 30 mL/min (by Cockcroft-Gault formula)
16. Life expectancy less than 48 hours, in the opinion of the Investigator
17. Known human immunodeficiency virus infection (regardless of immunological status), known hepatitis B virus surface antigen positivity and/or anti-hepatitis C virus positivity

Table 2: Schedule of Activities

		Study Day													
	Screening	Study Period											Follow-up Period		Date of Discharge or UNS Visit[3]
Activity	Up to 3 days prior to study drug[1]	1	2	3	4	5	6	7	8	15[2] ±2	22[2] ±2	29[2] +4	60 +14	90 +14	
Informed consent	X														
Medical history	X														
Demographics	X														
Known co-morbidities (incl. COVID-19 risk factors)	X														
Medication history (30 days prior to Screening)	X														
Eligibility	X														
SARS-CoV-2 Test (COVID-19)	X[4]	O	O	O	O	O	O	O	O	O	O	O			O
Physical exam (including body weight & height)	X														X
qSOFA (Cohort 1 only)[5]	X[5]														
SOFA (Cohort 2 only)[5]	X[5]								X						
Electrocardiogram	X														X
Chest X-ray or CT scan[6]	X														
Chest X-ray															X[7]
Respiratory Viral Panel[8]	X														
Tuberculosis screening[9]	X														
Pregnancy test for WOCBP (urine or serum)	X													O	X
Randomization and Study Drug Administration		X[10]													
Vital signs	X	Collect daily[11] until date of discharge											O	O	O

		Study Day													
	Screening	Study Period											Follow-up Period		Date of Discharge or UNS Visit[3]
Activity	Up to 3 days prior to study drug[1]	1	2	3	4	5	6	7	8	15[2] ±2	22[2] ±2	29[2] +4	60 +14	90 +14	
Body Temperature (Celsius)	X	Collect daily[11] until date of discharge											O	O	O
Echocardiogram (ECHO)[12]	O														
Clinical assessment (NIAID 8-point scale)[13]	X	Collect daily[11] until date of discharge											X	X	X[14]
Mechanical ventilation parameters[15]	X	Collect daily[11] until date of discharge													X
Respiratory function parameters[16]	X	Collect daily[11] until date of discharge													X
[redacted]	[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]		[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]			[redacted]				[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Hematology, Coagulation, Chemistry, Liver Profile[17]	X[18]			X						X		X	O	O	X
Lipid panel[17]	X[18]														X
Urinalysis[17]	X[18]											O	O	O	X
Pharmacokinetic sample[21]		X[22]		X				X		X		X			X
Anti-mavrilimumab antibody	X														X
Adverse events[13, 23]	X	Continuous collection during hospitalization											X	X	X
Concomitant medications[13, 24]		Continuous collection during hospitalization											X	X	X
Health care resource utilization[13]	X	Continuous collection during hospitalization											X	X	X
Assessment of survival[13]										X	X	X	X	X	X

X = required assessment for all subjects; may be collected remotely if subject has been discharged and is unable to be evaluated at the clinical site
O = optional assessment for subjects, including those discharged from hospital and are unable to be evaluated at the clinical site, or as per standard of care
CRP = C-reactive protein; INR = international normalized ratio; LDH = lactate dehydrogenase; [redacted]; SOFA/qSOFA = (quick) Sequential Organ Failure Assessment; TNF = tumor necrosis factor; WOCBP = women of childbearing potential; UNS = unscheduled visit

Schedule of Activities Footnotes

1	Screening activities can occur up to 3 days prior to study drug administration, except for COVID-19 testing (see footnote #4), screening labs (see footnote #17) and chest x-ray or CT scan (see footnote #6). Subject eligibility should be confirmed at Day 1 prior to study drug administration.
2	For hospitalized subjects, this visit will include activities listed. For subjects discharged before Day 15, the Day 15, 22 and 29 visits may be conducted by phone and will not include any laboratory tests, vital signs, or body temperature. For subjects who remain hospitalized after Day 29, the same assessments should be completed on a weekly basis.
3	At the time of discharge, complete **ONLY** the Date of Discharge / UNS visit assessments on the discharge date (ie, study day assessments are not required). If a subject is discharged and the Investigator judges that it is not safe for the subject to return to the site, or the subject is not willing to return to the site, the required visits (Days 15, 22, 29, 60 and 90) that occur thereafter may be done by phone call follow-up and lab tests will not be performed.
4	Subjects must have a positive SARS-CoV-2 (2019-nCoV) test within 14 days prior to randomization. It does not have to be the first positive test but a positive test is required within 14 days prior to randomization. The test may be performed locally (at the clinical site or from another institution) or by central laboratory if local testing is not available. If SARS-CoV-2 testing is completed post-screening, please enter data into the eCRF.
5	If there is a 1-point worsening in NIAID scale in a subject, it is recommended to re-assess qSOFA (Cohort 1) or SOFA (Cohort 2) at the time of worsening or as per standard of care during hospitalization.
6	Screening x-ray or CT can be done within 7 days from randomization. If performed at additional timepoints by the Investigator/site staff as part of standard of care through Day 29, results will be collected and entered into the eCRF.
7	The discharge X-ray can be done within 72 hours of discharge.
8	Panel includes influenza – A/H3N2, A/H1N1pdm09, A/H7N9, A/H5N1, A, not typed, B, or other (specify); coronavirus – novel CoV, MERS CoV, other CoV (specify); RSV; adenovirus; bacteria; other infectious respiratory diagnosis (specify); clinical pneumonia.
9	Tuberculosis screening is mandatory for South Africa sites and is at the discretion of the Investigator elsewhere. If required, one positive (or 2 indeterminate) interferon gamma release assay test results or one positive PCR test is exclusionary.
10	The NIAID score should be recorded at the time of randomization for all eligible subjects. For subjects in Cohort 1 only, also record 1) either PaO2 (mmHg), if available, or SpO2 (%), and 2) FiO2 (%) for subjects on assistive ventilation or L/min of oxygen supplementation for subjects not on assistive ventilation (e.g., simple mask/cannula). Initiation of study drug administration should occur within 24 hours of randomization.
11	If the subject remains hospitalized after Day 8 these assessments should be collected daily until the day of discharge (ie, Days 9-14, 16-21, 23-28 or after Day 29). On Day 1, assessments should be collected at the time closest to and prior to the initiation of study drug administration. Daily collection guidelines after Day 1: collect assessment in the morning at approximately the same time each day and closest to the collection of the NIAID score assessment, except for respiratory parameters (see footnote #16)
12	If available, ECHO performed from 90 days prior to randomization through Day 90 will be collected (report only).
13	If discharged, these assessments must be performed via phone call at Days 15, 22, and 29.
14	The NIAID at discharge to home should reflect status immediately post-discharge (ie, either 7 or 8).
15	Collect ventilation supportive measures (eg, pronation, nitric oxide use, tracheostomy) received by subjects on mechanical ventilation; details in the Site Manual.
16	Respiratory function parameters will be recorded daily until the date of Discharge. Daily values based on the highest daily FiO2, including PaO_2, FiO_2, SpO_2 and oxygen requirement, Other arterial blood gas parameters if available should be recorded. In addition, other supportive measures including pronation, neuromuscular blockade, tracheostomy, ECMO, vasopressor or inotropic therapy, inhaled nitric oxide or other should be recorded.

17	All samples after screening may be collected ±1 day from designated collection date, ±2 days after Day 7. Additional samples collected as standard of care through Discharge will be collected.
[redacted]	[redacted]
19	If sample at Screening was obtained > 48 hours prior to start of study drug infusion, another sample should be obtained prior to dosing on Day 1.
[redacted]	[redacted]
21	Serum collected for pharmacokinetics studies to be conducted by the Sponsor. No pharmacokinetic samples are required after Day 29.
22	On Day 1, pharmacokinetic sample to be collected before infusion and when infusion is complete.
23	Collect a blood sample for cytokine assessment if a serious infusion reaction occurs, or a subject experiences new symptoms or worsening of symptoms of cytokine release syndrome (eg, malaise, nauseas and vomiting, diarrhea)
24	Prohibited medications include any cell-depleting biological therapies (eg, anti-CD20) within 12 months prior to Screening; or previous treatment with non-cell-depleting biological therapies (such as anti-TNF, anakinra, anti-IL-6 receptor [eg, tocilizumab], or abatacept) within 8 weeks (or 5 half-lives, whichever is longer) prior to Screening; treatment with alkylating agents within 12 weeks prior to Screening; treatment with cyclosporine A, azathioprine, cyclophosphamide, MMF, or other immunosuppressant (except for corticosteroids) within 4 weeks of Screening. Medications that become standard of care for COVID-19 and/or receive emergency use authorization may be allowed after discussion with the medical monitor. Concomitant medications to track include antipyretics, anti-infectives related to COVID-19, and corticosteroids. Other concomitant medications recorded at Baseline Day 1 and maximum dose.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 3: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
2019-nCoV	2019 novel coronavirus
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BAL / BALF	Bronchoalveolar lavage / bronchoalveolar lavage fluid
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
COVID-19	Corona Virus Disease 2019
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CT	Computerized tomography
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
FiO_2	Fraction of inspired oxygen
GM-CSF	Granulocyte-macrophage colony-stimulating factor
ICH	International Council on Harmonisation
ICU	Intensive care unit
IEC	Independent Ethics Committee
IFN-g	Interferon-gamma
IgG	Immunoglobulin G
IL	Interleukin
IMV	Invasive mechanical ventilation
IND	Investigational New Drug Application

Abbreviation or Specialist Term	Explanation
IRB	Institutional Review Board
ISARIC	International Severe Acute Respiratory and Emerging Infection Consortium
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IWRS	Interactive web-based response system
LDH	Lactate dehydrogenase
MERS	Middle East respiratory syndrome
mITT	Modified intent-to-treat
MMF	Mycophenolate mofetil
MODS	Multiple organ dysfunction syndromes
NIAID	National Institute of Allergy and Infectious Diseases
NIV	Non-invasive ventilation
PaO_2	Partial pressure of oxygen
PCR	Polymerase chain reaction
PK	Pharmacokinetics
RA	Rheumatoid arthritis
RO	Receptor occupancy
SAD	Single-ascending-dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SOFA / qSOFA	Sequential Organ Failure Assessment / quick SOFA
SpO_2	Oxygen saturation
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TNF	Tumor necrosis factor
ULN	Upper limit of normal
UNS	Unscheduled site visit
US	United States

4. INTRODUCTION

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

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

In clinical and epidemiological data from the Chinese Center for Disease Control and Prevention regarding 72,314 case records providing an important illustration of the epidemiologic curve of the Chinese outbreak, the overall case-fatality rate (on confirmed cases) was 2.3% (Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020). Of note, the fatal cases were primarily elderly subjects, in particular those aged ≥ 80 years and 70 to 79 years (case fatality rates of 14.8% and 8.0%, respectively). Approximately half (49.0%) of the critical subjects who were often affected by preexisting comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, and oncological diseases died.

In one of the first reports on the disease, Huang et al. illustrated that subjects (n = 41) suffered from fever, cough, dyspnea, and myalgia or fatigue (Huang . Chest computerized tomography (CT) scans showed pneumonia with abnormal findings in all cases. The clinical spectrum of COVID-19 varies from asymptomatic or pauci-symptomatic forms to clinical conditions characterized by respiratory failure that necessitates mechanical ventilation and support in an intensive care unit (ICU), to multi-organ and systemic manifestations in terms of sepsis, septic shock, and multiple organ dysfunction syndromes (MODS). About a third of subjects required ICU care and 15% of cases were fatal. Similarly, in a more recent report of 201 hospitalized subjects, 41.8% developed ARDS and 52.4% of these subjects died (Wu Z, 2020).

Two recent studies provide valuable insight into the natural history of hospitalized subjects with COVID-19. The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) COVID-19 Report is updated regularly. As of 27 April 2020, the cohort constituted 19,463 individuals with a median age of 71 years (range of 0-104 years) from centers predominantly in the United Kingdom (ISARIC, 2020). Among subjects for whom outcome data were available (n = 11,873) there were a total of 4,278 deaths (19.5%). The mean number of days from hospital admission to outcome (death or discharge) was 8.7 days (standard deviation [SD] = 8.1 days). A total of 3,752 subjects were admitted into an ICU or high dependency unit (HDU), and of these, 989 died (26.4%). Among ICU/HDU subjects for whom outcome and treatment details were available (n = 1,804), 54.1% received invasive mechanical ventilation (IMV). The risk of death increased with increasing age. The median length of stay was 6 days. By day 15 following admission, the proportion of subjects who died, who were in the ICU, and who were discharged leveled out, suggesting that this time point is potentially important for determining the possible therapeutic impact of a drug.

The second recent study examined the use of protease inhibitors lopinavir-ritonavir in adults hospitalized with severe COVID-19 in a randomized, controlled, open-label trial (Cao B, 2020). Subjects were randomly assigned in a 1:1 ratio to receive either lopinavir–ritonavir (400 mg and 100 mg, respectively; n = 99) twice a day for 14 days, in addition to standard care, or standard care alone (n = 100). Treatment with lopinavir–ritonavir was not associated with a difference from standard care in the time to clinical improvement, which was measured using a 7-point ordinal scale. Mortality at 28 days was similar in the lopinavir–ritonavir group and the standard-care group (19.2% vs. 25.0%). The authors noted that the overall mortality in the study (22.1%) was higher than in previously published studies, indicating that this subject population had severe disease upon admission.

The two aforementioned studies provide valuable insight into the clinical progression of COVID-19 and have influenced the design of study KPL-301-C203. Although the lopinavir-ritonavir study did not show a therapeutic benefit for the treatment compared to standard-care, the study carefully evaluated clinical improvement using a 7-point scale at Days 7 and 14, and mortality at Day 28. The mortality rate reported by ISARIC was similar to the lopinavir-ritonavir study (19.5% vs. 22.1%); however, many outcomes are unavailable in the ISARIC study, and hence more deaths are likely. The median age of the lopinavir-ritonavir study was younger (58 vs. 71 years), and the percentage of males was similar (60.0 vs. 56.6 years) to demographics observed in the ISARIC population.

In Italy, the case-fatality rate has been reported at 7.2% (Livingston L, 2020). Furthermore, in an initial United States (US) experience of 21 critically ill subjects, 14 had died at the time of publication, and only 2 survived and transferred out of the ICU, highlighting the need for effective treatments before subjects become critically ill (Arentz M, 2020).

Among the severe clinical manifestations, there are severe pneumonia and ARDS. Although the clinical course of the disease seems to predict a favorable trend in the majority of subjects, in some cases, after about a week, there is a sudden worsening of their clinical conditions with rapidly worsening respiratory failure and MODS. Criteria for definition of specific subpopulations include:

- Severe Pneumonia. Fever associated with severe dyspnea, respiratory distress, tachypnea, and hypoxia. However, the fever symptom must be interpreted carefully as even in severe forms of the disease, the temperature may be only slightly elevated, fever may also be absent or confounded by concomitant anti-pyretic use. In this definition, the diagnosis is clinical, and radiologic imaging is used for excluding complications.
- ARDS. This is a syndrome of respiratory failure, suggestive of either:
  - a serious new-onset respiratory failure secondary to different etiology (pneumonia – viral or bacterial, acute pancreatitis, trauma, surgery, etc.) or
  - worsening respiratory failure from a previously identified etiology.
- The diagnosis requires radiographic and clinical criteria (Ranieri VM, 2012). Severity of ARDS is based on partial pressure of oxygen (PaO_2)/FiO_2: a ratio $PaO_2/FiO_2 \leq 300$ is suggestive of ARDS. Mild ARDS: $200 < PaO_2/FiO_2 \leq 300$. In non-ventilated

subjects or in those managed through non-invasive ventilation (NIV) by using positive end-expiratory pressure or a continuous positive airway pressure ≥ 5 cmH_2O.

  - Moderate ARDS: $100 < PaO_2/FiO_2 \leq 200$
  - Severe ARDS: $PaO_2/FiO_2 \leq 100$.

- Alternatively, if PaO_2 is unavailable, a determination of ARDS severity may be based on oxygen saturation (SpO_2)/FiO_2, whereby a ratio $SpO_2/FiO_2 \leq 235$ is suggestive of moderate-severe ARDS (Rice TW, 2007).

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 COVID-19, including vaccines, monoclonal antibodies, oligonucleotide-based therapies, peptides, interferon and small-molecules. Although the potential repurposing of existing antiviral agents to treat COVID-19 is being evaluated in clinical trials, new interventions based on drugs that are directly active on the virus itself are likely to require months to years to develop (ClinicalTrials.gov, 2020).

Accumulating evidence suggests that a subgroup of subjects with severe COVID-19 might have a cytokine storm syndrome (Mehta P, 2020). The identification and treatment of hyper-inflammation using existing therapies with understood safety profiles is a relevant option to address the immediate need to reduce the rising mortality.

In the setting of pathological findings of pulmonary edema and hyaline membrane formation, timely and appropriate use of drugs aimed at reducing inflammation together with ventilator support should be considered for severe subjects to prevent and treat ARDS. A cytokine profile resembling secondary hemophagocytic lymphohistiocytosis is associated with COVID-19 disease severity, characterized by increased IL-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor (TNF)-α. Predictors of fatality from recent studies included elevated ferritin, C-reactive protein (CRP), D-dimer, and IL-6, suggesting that mortality might be due to virally-driven hyper-inflammation.

In hyper-inflammation, immunomodulation is likely to be beneficial. In fact, in a subgroup analysis of a randomized controlled trial, subjects with sepsis and organ dysfunction or hyper-inflammation had improved survival with IL-1 receptor antagonism, and this therapy has not been associated with adverse events (AEs), even at high doses (Fisher CJ, 1994). A multicenter, randomized controlled trial of tocilizumab (IL-6 receptor blockade, licensed for cytokine release syndrome), has been approved in China in subjects with COVID-19 pneumonia and elevated IL-6; studies of sarilumab in COVID-19 are also underway (Xu X, 2020).

In this study, we aim to enroll subjects with severe COVID-19 pneumonia and hyper-inflammation to evaluate the clinical efficacy and safety of a single intravenous (IV) dose of mavrilimumab relative to placebo to reduce the incidence of progression to respiratory failure or death.

Study KPL-301-C203 will assess mavrilimumab 10 mg/kg and 6 mg/kg single IV infusion vs. placebo using a variety of parameters at baseline and at Days 1-8, 15, 22, 29, 60 and 90 following dosing. These include clinical improvement by the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale (ClinicalTrials.gov, 2020), mechanical ventilation assessment, respiratory parameters, survival, concomitant medications, AEs, and

laboratory measures [redacted]). Other laboratory tests (ie, hematology, coagulation, chemistry, liver profile, pharmacokinetics, anti-KPL antibody, [redacted] will be drawn less frequently throughout the study. The study will enroll subjects with less-severe disease (ie, non-ventilated) and more-severe disease (ie, requiring mechanical ventilation). Kiniksa believes that this approach will allow for the detection of a potential therapeutic benefit in the full range of severity of COVID-19 subjects with severe pneumonia and hyper-inflammation. The frequency of assessment following admission will allow for analysis of subjects who are discharged within the first week and for those who require more prolonged care. The extension of post treatment follow-up until 90 days post dose accounts for duration of Mavrilimumab exposure and an additional 30-day safety window. Mavrilimumab 6 mg/kg single dose IV infusion showed evidence of therapeutic benefit in an Expanded Access Treatment Protocol from Italy; however, this was not a randomized, placebo-controlled trial (De Luca G, 2020). In addition, lenzilumab, an anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) ligand monoclonal antibody developed by Humanigen showed promising results in an uncontrolled compassionate treatment protocol at the Mayo clinic (Humanigen, 2020). Of note, in both the mavrilimumab and lenzilumab treatment protocols, a high dose aimed at achieving lung distribution rather than only peripheric blockage of GM-CSF was used. The study design of KPL-301-C203 builds on the encouraging results of these trials and utilizes the data and experience from ISARIC and the lopinavir-ritonavir studies to estimate placebo/standard of care outcome rates.

Rationale for mavrilimumab

GM-CSF is considered to be a pro-inflammatory cytokine associated with tissue inflammation that promotes both innate and adaptive immune responses. GM-CSF drives the activation and differentiation of macrophages along with the activation of neutrophils, dendritic cells and eosinophils (Hamilton JA, 2008). 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 JA, 2002; Shiomi A, 2015). In addition, GM-CSF can also promote antigen-presentation by dendritic cells (Miller G, 2002). GM-CSF-activated macrophages and other myeloid cells produce reactive oxygen species and proinflammatory cytokines, including TNFα, IL-1β, IL-6, IL-23 and IL-12 (Hamilton JA, 2020). Neutrophil survival and function, including the induction of NETosis (ie, neutrophil cell death), are also modulated by GM-CSF (Saba S, 2002; Castellani S, 2019; Root RK, 1999).

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, monocytes/macrophages, dendritic cells, T cells, neutrophils, eosinophils and cancer cells, with most production occurring locally at the site of inflammation (Hamilton JA, 2002, Root RK, 1999). Alveolar macrophages and lung epithelial cells have also been shown to secrete GM-CSF in mice (Trapnell BC, 2002; Cakarova L, 2009, Yamamoto K, 2015). This secretion of GM-CSF exacerbates the inflammatory reaction via cytokine pathways that have been termed the colony stimulating factor network. GM-CSF can be induced by inflammatory cytokines and in turn increases production of other proinflammatory cytokines, thus functioning as a feed-forward inflammatory amplifier (Xu X, 2020).

A recent study reported elevated levels of GM-CSF in the lungs of subjects 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 and other proinflammatory cytokines (Zhou Y, 2020). 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-damaging role, causing lung functional disability and rapid mortality. Increased GM-CSF presence in bronchioalveolar lavage fluid (BALF) in COVID-19 patients may additionally promote enhanced neutrophil survival and NETosis, contributing to the hyperinflammation observed in severe patients (Matute-Bello G, 2000; Koupenova M, 2020). Moreover, BALF from patients with severe COVID-19 contain significant levels of circulating inflammatory monocyte-derived macrophages and GM-CSF may drive this infiltration (Liao M, 2020; Lang FM, 2020). Elevated serum levels of GM-CSF, IL1β, TNFα along with additional cytokines and chemokines have recently been described in COVID-19 patients as well. The elevated levels of GM-CSF in the lungs and circulation of COVID-19 patients along with its pleiotropic pro-inflammatory effects suggest that targeting GM-CSF to treat severe COVID-19 may reduce hyperinflammatory responses. Indeed, GM-CSF serves as a master regulator of cytokine expression and myeloid-mediated hyperinflammation and thus may modulate severe COVID-19 associated hyperinflammation more significantly than single downstream cytokine targeting approaches (Lang FM, 2020).

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, GM-CSF-R signaling can be specifically targeted with antibodies directed at GM-CSF-Rα (Zhou Y, 2020).

Mavrilimumab is an anti-GM-CSF-Rα monoclonal antibody (human isoform immunoglobulin G [IgG] 4) previously developed by MedImmune and now in development by Kiniksa Pharmaceuticals that has been shown to inhibit the GM-CSF signaling axis in humans and improve clinical outcomes measures in a Phase 2 program in rheumatoid arthritis (RA) (Crotti C, 2017).

Recent data indicate that the benefit of single cytokine blockade, eg, tocilizumab and sarilumab, conferred marginal to no clinical benefit (Roche Group, 2020; Regeneron, 2020). An upstream blockade of production and proliferation of inflammatory cells, eg, anti-GM-CSF blockade, still remains a relevant mechanism. At least two anti-GM-CSF agents in development, mavrilimumab and lenzilumab, have shown preliminary clinical benefit.

Rationale for Dose and Route of Administration

The dose rationale, and by extension the IV route of administration for COVID-19 subjects, is based on a combination of data from prior safety and efficacy evaluation of single and multiple doses in RA patients, the assessment of mavrilimumab lung distribution and pharmacodynamic effects in mice, and results from the Phase 2 portion (Cohort 1) of study KPL-301-C203.

In a Phase 1 single-ascending-dose (SAD) study, the pharmacokinetics (PK) of mavrilimumab were tested at IV doses of 0.01-10 mg/kg in subjects with mild-to-moderate RA. Mavrilimumab was well tolerated at all dose levels (Burmester GR, 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 EC_{90} (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 IV, the pharmacologic profiles indicated sustained peripheral inhibition of the GM-CSF-Rα signaling axis for at least three weeks. In the COVID-19 expanded access protocol conducted in Italy, a single-dose IV infusion of 6 mg/kg mavrilimumab was well-tolerated in 13 non-ventilated COVID-19 subjects. There did not appear to be any adverse safety signal on laboratory measures (eg, liver function tests) or AEs of special interest.

In preclinical studies, the potential systemic effects of mavrilimumab have been investigated in a 4-week and an 11-week repeat-dose cynomolgus monkey study. There were no effects attributable to IV administration of 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 mavrilimumab following 10 mg/kg/week, and the no observed AE level 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. Further details on safety studies in animals and humans are provided in the Investigator's Brochure.

The efficacy and safety results from the KPL-301-C203, Phase 2 Cohort 1 subjects, support use of both doses of mavrilimumab in the ongoing Phase 3 study. While generally there are no apparent differences between the two mavrilimumab arms for efficacy and safety, given the small number of primary events of ventilation and/or death analyzed to date, there are some differences between the two doses in mortality (10 mg/kg is numerically efficacious) or ventilation-free survival (6 mg/kg is numerically more efficacious). Overall, both the 10 mg/kg and the 6 mg/kg appear well-tolerated with no new identified safety risks in the COVID-19 study population. In fact, serious infections (e.g., septic shock, sepsis) were substantially lower in both mavrilimumab dose arms compared to placebo, and thrombosis events were only reported in the placebo arm. There were no serious adverse events related to mavrilimumab, no dose-related adverse events and no infusion reactions.

Important potential risks for mavrilimumab will continue to be monitored. These include severe hypersensitivity reactions, immune complex disease, serious infections (viral, bacterial, and opportunistic infections), malignancy, vaccine interactions, pulmonary alveolar proteinosis, reproductive toxicity and granulocytic effects, including neutropenia. Of note, there is no biological rationale for several of these potential risks in the setting of a single dose administration. More importantly, none of these potential risks have been identified in the RA development program through Phase 2b with approximately 900 subject-years of exposure. See Investigator's Brochure for additional details.

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

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

The primary objective of this study is to evaluate the clinical efficacy of a single IV dose of mavrilimumab relative to placebo in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation to reduce progression to respiratory failure or death.

5.2. Secondary Objectives

The secondary objectives of this study are to assess the impact of treatment on clinical status, mortality, and safety of a single IV dose of mavrilimumab (10 mg/kg or 6 mg/kg) relative to placebo in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation.

5.3. Other Objective

[redacted]

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a prospective, Phase 2/3, interventional, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of mavrilimumab (KPL-301) treatment in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation.

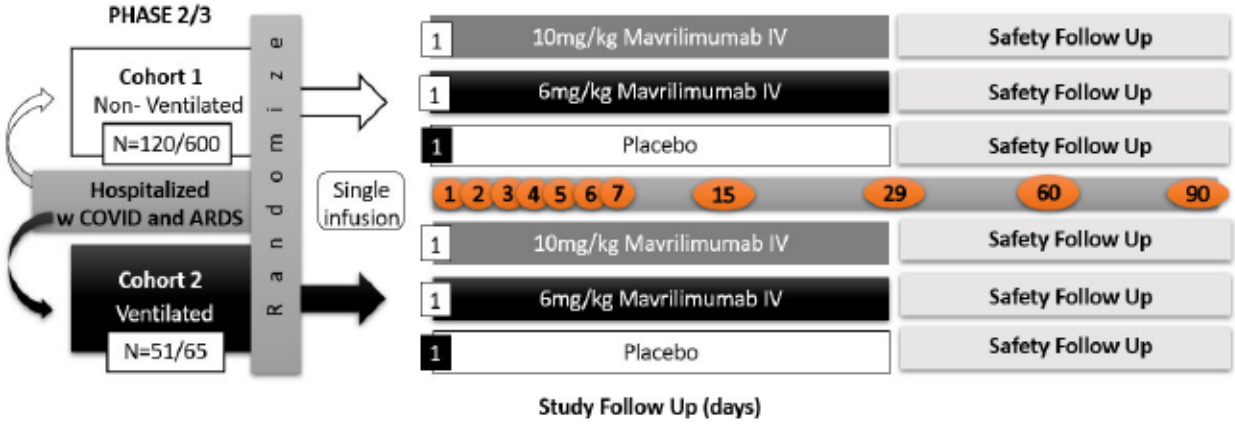
Approximately 836 subjects, divided into 2 cohorts, will be enrolled and randomized in a 1:1:1 allocation ratio to receive a single IV infusion of mavrilimumab (10 mg/kg or 6 mg/kg) or placebo in addition to standard of care as per institutional protocol and at the discretion of the investigator (provided that the medication/therapy is not explicitly prohibited per protocol). Cohort 1 will include non-mechanically ventilated hospitalized subjects who require supplemental oxygen to maintain $SpO_2 \geq 92\%$, ie, "non-ventilated" subjects. Cohort 2 will include hospitalized subjects for whom mechanical ventilation was recently initiated (within 48 hours prior to randomization), ie, "ventilated" subjects). The initial Phase 2 part of the study will enroll approximately 171 subjects, and the Phase 3 part will enroll approximately 665 subjects. There will be a seamless transition in enrollment of subjects in both cohorts between the Phase 2 and Phase 3 portions of the study. For each cohort, once the last subject in Phase 2 is enrolled, all subsequent subjects will be considered Phase 3 subjects. This will allow for continued enrollment during the analysis of the Phase 2 cohort-specific data. Once the last subject in Phase 2 completes Day 29, primary efficacy and safety analyses of the Phase 2 data will be conducted by the Sponsor. Following demonstration of efficacy and safety in Phase 2, the Phase 3 portion of the study will be continued/completed. Based on review of the Phase 2 Cohort 2 results of the primary and secondary endpoints at day 29, Phase 3 Cohort 2 is closed to further enrollment, as there was no evidence that mavrilimumab provided clinical benefit over placebo in recently ventilated patients.

The primary endpoint in both cohorts will be assessed for both the Phase 2 and Phase 3 parts of the study using the NIAID scale for clinical improvement. Subject clinical status will be assessed daily using this 8-point ordinal scale:

1. *Death;*
2. *Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);*
3. *Hospitalized, on non-invasive ventilation or high flow oxygen devices;*
4. *Hospitalized, requiring supplemental oxygen;*
5. *Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise);*
6. *Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care;*
7. *Not hospitalized, limitation on activities and/or requiring home oxygen;*
8. *Not hospitalized, no limitations on activities.*

Screening activities will be performed up to 3 days prior to randomization (Day 1). The study follow-up period will conclude on study Day 29, and subjects will be followed for AEs/serious AEs (SAEs), concomitant medications, mortality, and clinical improvement (NIAID scale) through study Day 90 (Figure 1). The Schedule of Activities is presented in Table 2.

Figure 1: Study Design for KPL-301-C203



A Safety Review Committee (SRC) including 2 physicians from the Sponsor, 1 physician from the Sponsor's contract research organization (CRO), and 1 independent physician who is an expert in critical care medicine, pulmonary disorders, infectious diseases and/or COVID-19 treatment (SRC Chairperson) will meet periodically to review AEs/SAEs, reasons for study discontinuations, and key clinical and laboratory assessments. SRC activities will be guided by an SRC Charter. The initial SRC meeting will be triggered once the initial 4 subjects have completed Day 8. SRC members will be blinded to subject treatment assignment.

A Data Monitoring Committee (DMC) has been established by the Sponsor to conduct periodic reviews and may meet more frequently as needed to review unblinded safety data from the Phase 2 and 3 portions of the study. The initial meeting will be triggered at 1 month after the first subject is enrolled. The DMC charter will detail the composition, roles and responsibilities and analysis plan for the DMC's activities.

The study may be terminated if unexpected, significant, or unacceptable safety risks to enrolled subjects arise, or if recommended by applicable board(s) after review of safety data.

6.2. Number of Subjects (planned)

A total of approximately 836 subjects will be enrolled in this study. Approximately 171 subjects will be randomized to the Phase 2 part, and approximately 665 subjects will be randomized to the Phase 3 part.

In Phase 2:

Cohort 1: Approximately 120 non-ventilated subjects, and

Cohort 2: Approximately 51 ventilated subjects

In Phase 3:

Cohort 1: Approximately 600 non-ventilated subjects, and

Cohort 2: Approximately 117 ventilated subjects (approximately 65 subjects at time of enrollment closure)

6.3. Treatment Assignment

Across the two study parts (Phase 2 and Phase 3), approximately 836 subjects will be randomized in a 1:1:1 allocation ratio to receive a mavrilimumab (10 mg/kg or 6 mg/kg) or placebo. No subject will receive more than one dose.

Details regarding randomization to treatment are provided in Section 8.4.1.

6.4. Dose Adjustment Criteria

Mavrilimumab will be administered as a single IV infusion over 60 minutes. No dose adjustments are planned.

6.4.1. Safety Criteria for Adjustment or Stopping Doses

At any time during the infusion of study drug, should a moderate reaction occur, the infusion will be stopped for a period of at least 30 minutes and restarted at the Investigator's discretion only after the events have resolved. The infusion rate should be re-started at a rate tolerated by the subject. Infusions must be completed within 4 hours of study drug preparation (see Pharmacy Manual for more details). Should a severe reaction occur, the infusion will be stopped permanently. Severity of infusion reactions are to be determined by the Investigator. No dose adjustments are planned. Additional details regarding study drug dosing are provided in Section 9.5.

6.5. Criteria for Study Termination

The study may be terminated or temporarily suspended in whole or in part by the Sponsor at any time. Reasons for such action include:

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

The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The Investigator or Sponsor, depending on the local regulation, will be responsible for informing the Institutional Review Board (IRB) of the early termination of the trial.

7. SELECTION CRITERIA AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Subjects must meet all the following inclusion criteria to be eligible for enrollment in the study.

1. Subject (or legally authorized representative) is able and willing to provide informed consent, which includes compliance with study requirements and restrictions listed in the consent form. Consent must be performed per institutional regulations.
2. Age of ≥ 18 years
3. Positive SARS-CoV-2 (2019-nCoV) test within 14 days prior to randomization
4. Hospitalized for SARS-CoV-2 (2019-nCoV)
5. Bilateral pneumonia on chest x-ray or CT
6. *[Original Criteria Deleted]*
7. At least one of the following, within 7 days prior to randomization:
   - Ferritin > 500 ng/mL
   - CRP > 5 mg/dL
   - D-dimer > 1,000 ng/mL
   - LDH > 250 U/L
   - Fever - a measured temperature of at least 100.4°F [38°C]
8. For Cohort 1: Receiving any form of non-invasive ventilation OR oxygenation to maintain SpO2 ≥ 92% and non-mechanically ventilated (examples include nasal cannula, face mask, venturi mask, high-flow nasal cannula, and NIV or non-invasive positive pressure ventilation)
9. For Cohort 2: Recently ventilated with mechanical ventilation beginning within 48 hours prior to randomization
10. Female subjects must be:
    - postmenopausal, defined as at least 12 months post cessation of menses (without an alternative medical cause), or
    - permanently sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or tubal ligation or having a male partner with vasectomy as affirmed by the subject, or
    - nonpregnant, nonlactating, and if sexually active having agreed to use a highly effective method of contraception (ie, hormonal contraceptives associated with inhibition of ovulation or intrauterine device [IUD], or intrauterine hormone-releasing system [IUS], or sexual abstinence) from Screening Visit until Day 90.
11. Male subjects must have documented vasectomy or if sexually active must agree to use a highly effective method of contraception with their partners of childbearing potential (ie, hormonal contraceptives associated with the inhibition of ovulation or IUD, or IUS, or

sexual abstinence) from Screening until Day 90. Male subjects must agree to refrain from donating sperm during this time period.

7.2. Subject Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be eligible for study enrollment.

General Exclusion Criteria

1. Onset of COVID-19 symptoms > 14 days prior to randomization
2. Hospitalized > 7 days prior to randomization
3. [For Cohort 1 only] Need for invasive mechanical ventilation
4. Need for ECMO
5. Serious prior or concomitant illness that in the opinion of the Investigator precludes the subject from enrolling in the trial, including (but not limited to):
   - History of pulmonary alveolar proteinosis
   - Severe and uncontrolled pulmonary disease other than COVID-19 pneumonia (eg, asthma, chronic obstructive pulmonary disease, or others)
   - Pre-existing (prior to development of COVID-19) severe left ventricular systolic dysfunction (ie, left ventricular ejection fraction < 35%)
   - Hemodynamic instability with pressor requirements of norepinephrine at a dose of > 0.5 mcg/kg/min or equivalent (total if multiple pressors used) for more than 12 hours continuously, myocardial infarction, stroke, and cardiogenic septic shock within 30 days prior to randomization
   - Known active tuberculosis (TB) determined by history and local standard of care, or history of incompletely treated TB or at high risk for latent TB (exposure or prior incarceration)
     - If tuberculosis testing is required per local regulations, one positive (or two indeterminate) interferon gamma release assay test results or one positive polymerase chain reaction test is exclusionary
   - Concomitant uncontrolled systemic bacterial or fungal infection
   - Concomitant respiratory viral infection other than COVID-19 and influenza that, in the opinion of the Investigator, represents a higher mortality risk (eg, SARS, Middle East respiratory syndrome [MERS])
6. Recent treatment with cell-depleting biological therapies (eg, anti-CD20) within 12 months, non-cell-depleting biological therapies (such as anti-tumor necrosis factor [TNF], anakinra, anti-IL-6 receptor [eg, tocilizumab], or abatacept) within 8 weeks (or 5 half-lives, whichever is longer), treatment with alkylating agents within 12 weeks, treatment with cyclosporine A, azathioprine, cyclophosphamide, mycophenolate mofetil (MMF), or other immunosuppressant (except for corticosteroids) within 4 weeks prior to

randomization. Medications that become standard of care for COVID-19 and/or receive emergency use authorization may be allowed after discussion with the medical monitor.

7. *[Original Criteria Deleted]*
8. If subject is receiving or has received hydroxychloroquine within 3 months prior to randomization, a corrected QT interval by Fridericia's method (QTcF) on Screening electrocardiogram (ECG) of ≥ 500ms is exclusionary. If subject has a pacemaker, this criterion does not apply.
9. *[Original Criteria Deleted]*
10. Enrolled in another investigational study of a medical intervention within 30 days prior to randomization. Participation in open label trials involving investigational treatments for COVID-19 may be allowed upon approval by the Sponsor.
11. Known hypersensitivity to mavrilimumab or any of its excipients
12. In the opinion of the Investigator, unable to comply with the requirements to participate in the study
13. *[Original Criteria Deleted]*
14. *[Original Criteria Deleted]*
15. At Screening blood tests, any of the following:
    - Aspartate transaminase (AST) > 10 × upper limit of normal (ULN)
    - Alanine transaminase (ALT) > 10 × ULN
    - Hemoglobin < 7.5 g/dL
    - Neutrophils < 1,500/mm^3
    - Absolute platelet count < 50,000/mm^3
    - Creatinine clearance < 30 mL/min (by Cockcroft-Gault formula) (Cockcroft DW, 1976)
16. Life expectancy less than 48 hours, in the opinion of the Investigator
17. Known human immunodeficiency virus infection (regardless of immunological status), known hepatitis B virus surface antigen positivity and/or anti-hepatitis C virus positivity

7.3. Withdrawal of Subjects

7.3.1. Treatment Stopping Criteria

Should a moderate reaction occur during infusion of the study drug, the infusion will be stopped and restarted at the Investigator's discretion after the events have resolved. Should a severe reaction occur, the infusion will be permanently discontinued, but subjects will continue their participation in the study. Such severe reactions include, but are not limited to, urticaria, hypersensitivity, hypotension, bradycardia, hypoxia, generalized rash, or a change in mental status. If four (4) causally related severe reactions with 24-hour of dosing occur, study enrollment will be paused until the DMC can review the cases and determine if there is an

adverse drug-related safety signal. Details regarding study drug dosing are provided in Section 9.5.

7.3.2. Replacement policy

No subject replacement will be done, regardless of the reason for study discontinuation.

7.3.3. Withdrawal of informed consent

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

- Does not want to participate in the study anymore,

AND

- Does not allow further collection of personal data.

It is encouraged that the subject provides withdrawal of consent in writing.

In this situation, the Investigator should make a reasonable effort (eg, telephone call, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information. The subject's vital status can be verified upon contact with subject's primary care physician or other sources according to local rules and regulations.

No further assessments must be conducted, and the data that would have been collected at subsequent visits will be considered missing.

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table (Table 2).

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

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

7.3.4. Lost to follow-up

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

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

8.1.1. Investigational Product

Mavrilimumab (KPL-301, formerly known as CAM-3001) is a recombinant human monoclonal IgG4 antibody, which modulates activity of granulocyte-macrophage colony-stimulating factor (GM-CSF) by binding to the alpha subunit of its receptor (GM-CSFRα).

8.1.2. Description

Mavrilimumab is a sterile, clear to opalescent, colorless to slightly brown-yellow liquid, free from visible particles and is formulated [redacted] It is supplied by Kiniksa Pharmaceuticals as a liquid in accessorized pre-filled syringes or in vials for parenteral administration. Please see the Pharmacy Manual for additional details.

Matching placebo containing only product diluent/excipients will be provided as a liquid in accessorized pre-filled syringes or in vials for parenteral administration.

8.1.3. Dose and Administration

Subjects will receive a single IV infusion of either 10 mg/kg or 6 mg/kg mavrilimumab or placebo over approximately 60 minutes. The maximum dose may not exceed 1000 mg, which was approximately the maximum dose administered in the Phase 1 study with IV infusion. Dosing will be based on body weight obtained at Screening. Additional details regarding mavrilimumab dosing are provided in Section 9.5.

At any time during the infusion of study drug, should a moderate reaction occur, the infusion will be stopped and restarted at the Investigator's discretion only after the events have resolved. The infusion rate should be re-started at a rate tolerated by the subject. Infusions must be completed within 4 hours of study drug preparation (see Pharmacy Manual for more details).

Use of pre-medication to avoid or treat potential infusion-related reactions is at the discretion of the Investigator. In the event of an infusion reaction, the following interventions can be considered if needed using a separate IV line from that used for the mavrilimumab infusion: NaCl 0.9% IV infusion at 500 mL/hr, diphenhydramine 50 mg IV, hydrocortisone sodium succinate 100 mg IV, epinephrine 1 mg/mL 0.3 mg intramuscular.

8.2. Concomitant Medications

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

Use of concomitant medications including antipyretics, anti-infectives and anti-fungals, and corticosteroids will be recorded. All investigational and off-label therapies for COVID-19 will be recorded for each subject (eg, chloroquine, hydroxychloroquine, corticosteroids, antivirals [remdesivir, lopinavir/ritonavir]) along with the time, dose, and duration of their administration.

Medication history within 30 days of Screening will be collected.

8.2.1. Prohibited Medications

The following medications are also prohibited if use occurred within the timing specified:

- Treatment with cell-depleting biological therapies (eg, anti-CD20) within 12 months prior to Screening,
- Non-cell-depleting biological therapies (such as anti-TNF, anakinra, anti-IL-6 receptor [eg, tocilizumab], or abatacept) within 8 weeks (or 5 half-lives, whichever is longer) prior to Screening,
- Treatment with alkylating agents within 12 weeks prior to Screening,
- Treatment with cyclosporine A, azathioprine, cyclophosphamide, or MMF, or other immunosuppressant therapy (except for corticosteroids) within 4 weeks of Screening.

Medications that become standard of care for COVID-19 and/or receive emergency use authorization may be allowed after discussion with the medical monitor. Use of additional investigational agents using immunosuppressive therapy, as salvage/compassionate use therapy of an alternative agent, may be considered at the discretion of the Investigator in consultation with the Sponsor.

8.3. Treatment Compliance

A single IV infusion of mavrilimumab or placebo will be administered over approximately 60 minutes in a clinical setting. No additional procedures for monitoring compliance are necessary.

8.4. Randomization and Blinding

8.4.1. Randomization

After meeting all inclusion/exclusion criteria and obtaining informed consent, subjects will be randomized in a 1:1:1 allocation ratio to receive either a 10 mg/kg or 6 mg/kg single IV dose of mavrilimumab, or placebo.

There will be 3 stratification factors for randomization:

1. Use of authorized standard of care antiviral therapy for COVID-19 (eg, remdesivir): yes vs. no
2. Age: < 65 vs. ≥ 65 years
3. Acute respiratory distress syndrome (ARDS) status by PaO_2/FiO_2*: normal–mild (> 200 vs. moderate-severe (≤ 200). ARDS status will only be used for Cohort 1 (non-ventilated subjects).

* If PaO2 is unavailable, use SpO_2/FiO_2: normal–mild (> 235) vs. moderate-severe (≤ 235)

An Interactive Web Response System (IWRS) will be used during the study for assignment of a Subject Identification Number at enrollment, randomization to a treatment, and assignment of blinded study drug. A subject is considered randomized into the study when the Investigator confirms the eligibility criteria in the IWRS and the pharmacist has been provided with the investigational product number.

8.4.2. Treatment Blinding

Subjects, Investigator or designee, and the Sponsor or designee will be blinded to treatment. At the site level, only the clinical site pharmacist will have access to the treatment assignments. The DMC will review the unblinded safety data periodically. If the Investigator decides that unblinding the subject is essential for their clinical management, then the subject may be emergently unblinded, either before or after a discussion between the Sponsor's safety physician or designee and the Principal Investigator. The chair of the DMC will be alerted within 48 hours of any unblinding.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

A single IV infusion of mavrilimumab 10 mg/kg or mavrilimumab 6 mg/kg or matching placebo will be administered to study subjects. Total mavrilimumab dose is not to exceed 1000 mg.

9.2. Study Drug Packaging and Labeling

Each study site will be supplied with study drug in packaging as described in the Pharmacy Manual.

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

9.3. Study Drug Storage

All study treatment must be stored as specified on the label and in the Pharmacy Manual.

9.4. Study Drug Preparation

Individual subject infusions are to be prepared at the investigational site under the authority of the Investigator and in accordance with local regulations. Doses should be prepared for administration via a syringe pump. More detailed instruction will be provided to clinical sites in the Pharmacy Manual (to be developed prior to first Study Initiation Visit).

9.5. Administration

Blinded study drug will be administered as a single IV infusion over approximately 60 minutes by qualified health care personnel. All infusions will 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 will be required. The infusion should last approximately 60 minutes. Premedication to avoid or treat potential infusion-related reaction is at the discretion of the Investigator. The initial 15 minutes of infusion will be administered at an infusion rate to allow for delivery of approximately 1/6 of the total volume of the infusion. If no moderate or severe infusion reactions are observed, the rate will be doubled for the next 15 minutes. After the first 30 minutes the rate will be increased to deliver another 50% of the total volume if the infusion continues to be well tolerated. At any time during the infusion, if a moderate reaction occurs, the infusion will be stopped for a period of at least 30 minutes and restarted at the discretion of the Investigator only after the events have resolved. The infusion should be re-started a rate tolerated by the subject. The infusion should be stopped permanently if a severe reaction is observed. More detail is provided in Site Manual.

9.6. Study Drug Accountability

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

9.7. Study Drug Handling and Disposal

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

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all unused study drug, packaging, and drug labels to Kiniksa or their designee.

10. ASSESSMENT OF EFFICACY

The following efficacy endpoints will be used for both the Phase 2 and Phase 3 parts of the study. Endpoints will be evaluated for both Cohorts 1 and 2, unless otherwise specified.

10.1. Primary Efficacy Endpoint

10.1.1. Cohort 1 (Non-ventilated Subjects)

The primary efficacy endpoint is the proportion of subjects alive and free of mechanical ventilation at Day 29. Mechanical ventilation is defined as invasive mechanical ventilation or ECMO.

Mechanical ventilation status will be evaluated based on the NIAID clinical outcome 8-point ordinal scale. The scale is used to assess clinical status for each day, with the worst score from the previous day recorded. Subjects whose clinical outcome has met an NIAID score of 2 will be considered as using mechanical ventilation.

The NIAID scale is as follows:

- *Death;*
- *Hospitalized, on invasive mechanical ventilation or ECMO;*
- *Hospitalized, on non-invasive ventilation or high flow oxygen devices;*
- *Hospitalized, requiring supplemental oxygen;*
- *Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise);*
- *Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care;*
- *Not hospitalized, limitation on activities and/or requiring home oxygen;*
- *Not hospitalized, no limitations on activities.*

10.1.2. Cohort 2 (Ventilated Subjects)

The primary efficacy endpoint is mortality rate at Day 29, defined as the proportion of subjects who have died by Day 29.

10.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints will be examined based on the hierarchical order below.

Cohort 1 (Non-ventilated Subjects)

1. Mortality rate at Day 29
2. Ventilation free survival (Time to ventilation or death) by Day 29

   Defined as time from randomization to ventilation or death; subjects still alive will be censored at Day 29.

3. Overall survival by Day 29

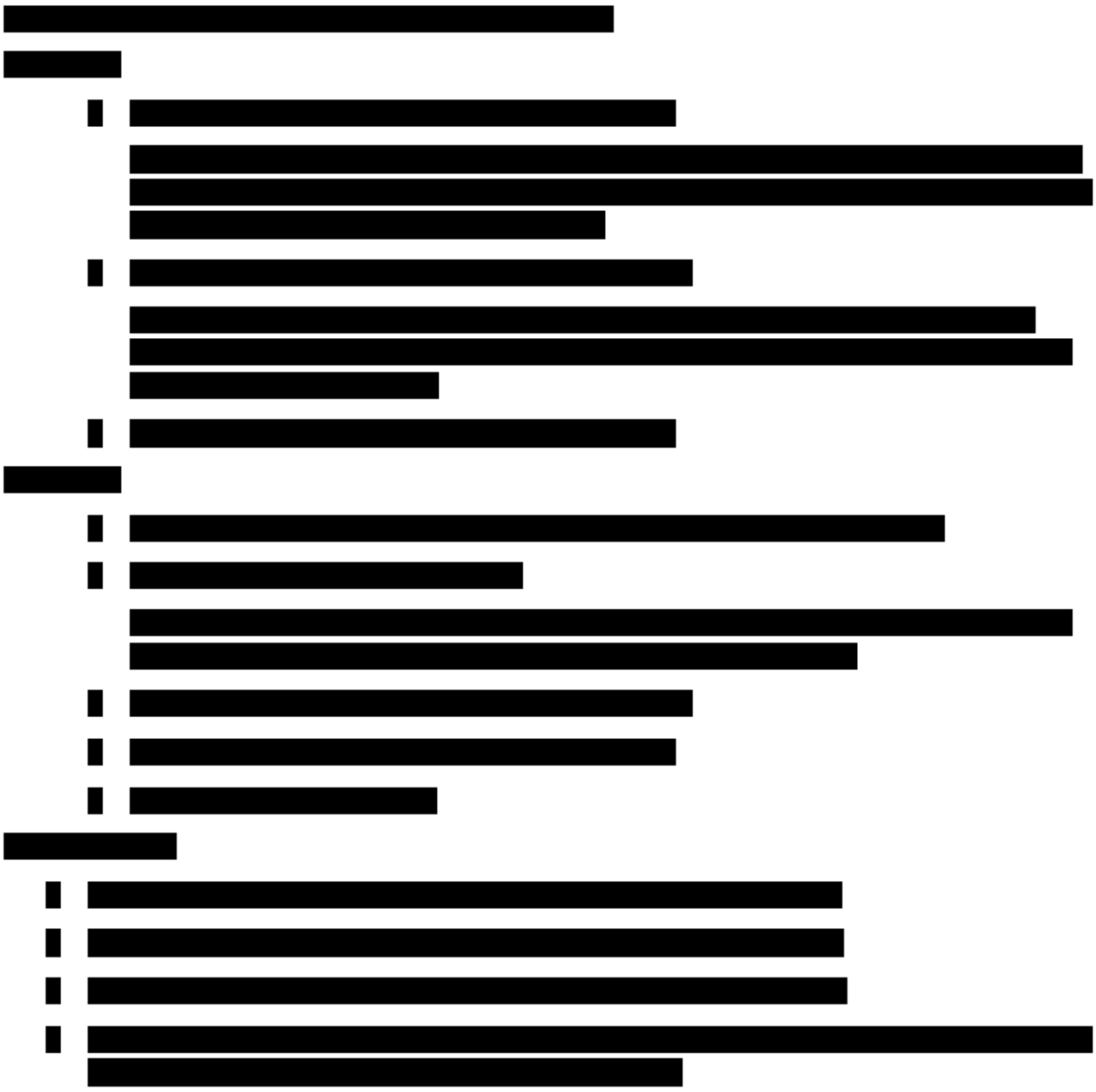
   Defined as time from randomization to death; subjects still alive will be censored at Day 29.

Cohort 2 (Ventilated Subjects)

1. Time to 1-point clinical improvement by Day 29

   Defined as time from randomization to a 1-point improvement on the NIAID 8-point ordinal scale, or discharge from the hospital, whichever occurs first. Subjects who die before Day 29 will be censored at Day 35.

10.3. Other Efficacy Endpoints



10.4. Efficacy Parameters

10.4.1. Mechanical Ventilation Parameters

Mechanical ventilation measures for each subject will be recorded daily until the date of Discharge. Ventilation and oxygenation mode and associated measures will be collected. This will include need for high flow oxygen, NIV, IMV, or ECMO and will be recorded daily until the date of Discharge. Effort will be made to collect ventilation supportive measures (eg, pronation, use of nitric oxide, or tracheostomy) received by subjects on mechanical ventilation; further details are provided in the Site Manual.

10.4.2. Respiratory Parameters

Respiratory function parameters will be recorded at the time of randomization for Cohort 1 subjects (abbreviated parameters per the Schedule of Activities) and daily for all subjects until the date of Discharge. At Day 1 the respiratory parameters should be collected at the time closest

to and prior to the initiation of study drug administration. For daily values after Day 1, collect at the time of highest daily FiO_2. The collected values will include the peripheral oxygen saturation (SpO2), PaO_2 in mmHg (if available) and the amount of oxygen the patient is requiring at the time. If the patient is on mechanical ventilation, noninvasive ventilation (CPAP or BiPAP) or high flow nasal cannula, the oxygen requirement will be the fractional inhalation of oxygen (FiO_2) and will be collected as a percentage. If the patient is on simple nasal cannula, simple face mask or trach collar, the oxygen requirement to be collected is the liter flow expressed as liters per minute (LPM). Other arterial blood gas parameters including pH, pCO2, HCO3, base excess should be recorded if available. In addition, other supportive measures including pronation, neuromuscular blockade, tracheostomy, ECMO, vasopressor or inotropic therapy, inhaled nitric oxide or others should be recorded.

11. ASSESSMENT OF PHARMACOKINETICS

Subjects will provide serum samples for pharmacokinetic studies to be conducted by Kiniksa.

11.1. Pharmacokinetic Sampling and Parameter Assessment

Samples will be collected at Screening, Day 1 (prior to the study drug infusion and once it is complete), and at Days 3, 7, 15 ± 2, 29 + 4, and at the Discharge/UNS visit.

The planned PK parameters for assessment include, but are not limited to, the following:

Parameter	Description
C_{max}	The maximum plasma concentration
T_{max}	Time of maximum plasma concentration
AUC_{last}	Area under the curve from time 0 to time of last measurable plasma concentration, calculated using linear trapezoidal integration
$AUC_{0-\infty}$	Area under the curve from time 0 extrapolated to infinity $AUC_{0-\infty} = AUC_{last} + C_{last}/\lambda_z$ where C_{last} is the last quantifiable concentration
CL	Clearance, $CL = Dose/ AUC_{0-\infty}$
V_z	Volume of distribution, $V_z = Dose/(\lambda_z \times AUC_{0-\infty})$
$t_{1/2}$	Terminal phase half life, $t_{1/2} = \ln(2)/\lambda_z$
λ_z	Terminal phase rate constant. Estimated by linear regression of the terminal log-linear phase of the log-transformed concentration vs. time data

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety will be assessed through routine medical monitoring of AEs/SAEs and laboratory parameters as described in the Schedule of Activities (Table 2). Specific assessments are discussed in detail below.

12.1.1. Demographic/Medical History

Medical history and medication history (up to 30 days prior to Screening), demographics, and known co-morbidities will be collected from all subjects at Screening. The number of days between onset of COVID-19 symptoms and initiation of treatment will be recorded in all subjects.

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

12.1.2. Vital Signs

Vital signs will be recorded at Screening, Day 1, and throughout the study period as specified in the Schedule of Activities (Table 2).

12.1.3. Physical Examination

A physical examination of each subject will be conducted at Screening and at the Discharge/UNS visit. Height and weight will be collected at Screening only.

12.1.4. Electrocardiogram, and Chest X-ray or CT Scan

An ECG will be obtained at Screening and at the Discharge/UNS visit. A chest x-ray or chest CT scan will be obtained at Screening. The chest x-ray will be repeated at the Discharge visit. Additional chest x-rays or CT scans may be performed from Screening through Day 29 at the discretion of the Investigator and these results must be recorded.

12.1.5. Laboratory Assessments

All safety laboratory parameters in the study will be conducted at Screening (as per Table 2) with additional post-dose timepoints noted in Table 4.

Subjects who are discharged should complete the Discharge/UNS visit (the study day assessments are not required). If a subject is discharged and the Investigator judges that is it not safe for the subject to return to the site, or the subject is not willing to return to the site, the visits that occur thereafter may be done by telemedicine and lab tests and other procedures will not be performed. Additional laboratory assessment may be performed from Screening through Day 29 at the discretion of the Investigator and these results must be recorded.

Table 4: Schedule of Laboratory Assessments

Activity / Parameter	Collection Detail	Collection Timepoints
CENTRAL LABORATORY		
Respiratory Panel	A/H3N2, A/H1N1pdm09, A/H7N9, A/H5N1, A, not typed, B, or other (specify); coronavirus – novel CoV, MERS CoV, other CoV (specify); RSV; adenovirus; bacteria; other infectious respiratory diagnosis (specify); clinical pneumonia	Screening
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Anti-mavrilimumab antibody		Screening and the Discharge/UNS visit
Pharmacokinetic sample		Day 1 (before infusion and when infusion is complete), Days 3±1, 7±1, 15±2, 29+4 and at the Discharge/UNS visit
LOCAL LABORATORY		
Pregnancy test (women of child-bearing potential)	Urine or serum βhCG	Screening and at the Discharge/UNS visit; Day 90+14 is optional
[redacted]		[redacted]
Hematology	Complete blood count + differential	Screening (up to 7 days prior to randomization), Days 3±1, 15±2, 29+4 and at the Discharge/UNS visit; Days 60+14 and 90+14 are optional
Coagulation	PT, PTT, and INR	
Chemistry	electrolytes, blood urea nitrogen, glucose and CR	
Liver Profile	AST, ALT, Alb, AlkP, Tbili, Dbili	

Activity / Parameter	Collection Detail	Collection Timepoints
Lipid Panel	Cholesterol, total; high-density lipoprotein (HDL) cholesterol; low-density lipoprotein (LDL) cholesterol (calculation); triglycerides; very low-density lipoprotein (VLDL) cholesterol (calculation)	Screening (up to 7 days prior to randomization) and at the Discharge/UNS visit
Urinalysis		Screening (up to 7 days prior to randomization) and Discharge/UNS visit; Day 29+4, Days 60+14 and 90+14 are optional
Tuberculosis		Optional at Screening - at Investigator's discretion **South Africa only:** TB testing required for all subjects at Screening
SARS-CoV-2	COVID-19	Screening* Days 1, 2, 3, 4, 5, 6, 7, 8, 15 ±2, 22 ±2, 29 +4 and Discharge/UNS are optional

Screening = up to 3 days prior to randomization
*For SARS-CoV-2 testing (COVID-19), a positive test within 14 days of randomization is required. Sites that are unable to perform SARS-CoV-2 locally (at the clinical site or from another institution) may use Central Laboratory testing.

The full Schedule of Activities is presented in Table 2.

12.1.5.1. Pregnancy Screen

All pre-menopausal women who are not surgically sterile will have a urine or serum pregnancy test performed at Screening. Pregnancy testing is not required for post-menopausal women. For female subjects of childbearing potential who are discharged and return to the site later, a pregnancy test must be repeated at the last visit the subject completes on the study.

12.1.6. Sequential Organ Failure Assessment (SOFA) and Quick SOFA

Sequential Organ Failure Assessment (SOFA) and Quick SOFA (qSOFA) are clinical assessments to identify subjects with worsening health status in ICU and non-ICU environments, respectively. Cohort 1 (non-ventilated) subjects will be assessed using qSOFA at Screening. Cohort 2 (ventilated) subjects will be assessed using SOFA at Screening and at Day 8.

If a subject experiences a 1-point worsening in NIAID, it is recommended to re-assess qSOFA (Cohort 1) or SOFA (Cohort 2) at the time of worsening or as per standard of care during hospitalization.

Additional SOFA/qSOFA assessments may be performed from Screening through Day 29 at the discretion of the Investigator and these results must also be recorded.

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event (AE)

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

Abnormal laboratory values or test results constitute AEs 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 non-typical in subjects with the underlying disease.

12.2.1.2. Adverse Drug Reaction

An adverse drug reaction is defined as, "A response to a medicinal product which is noxious and unintended [DIR 2001/83/EC Art 1(11)]. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility" (see Annex IV, ICH-E2A Guideline).

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure.

12.2.1.3. Adverse Events of Special Interest

An AE of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and requires close monitoring and communication by the Investigator to the Sponsor within 24 hours of knowledge of the event, regardless of seriousness criteria. 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 / Drug-induced Liver Injury

Drug-induced liver injury (DILI) is considered an AESI and should be reported within 24 hours of knowledge of the event. In subjects with normal liver function at baseline, DILI is defined as an increase in ALT or AST to greater than 3 × ULN with concurrent increase in bilirubin to greater than 2 × ULN, without another explanation. In subjects with abnormal ALT and/or AST and/or bilirubin at baseline, it is operationally defined as a doubling of ALT or AST and bilirubin, without another explanation. 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.

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 is defined below in Table 5 using Sampson's criteria (Sampson HA, 2006). Anaphylaxis and severe hypersensitivity reactions are required to be reported within 24 hours of knowledge of the event.

Table 5: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any <u>one</u> of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) *AND AT LEAST ONE OF THE FOLLOWING:* a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a <u>likely</u> allergen for that patient* (minutes to several hours): a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *<u>known</u> allergen for that patient* (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP* b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg 1 + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Neutropenia

AEs of neutropenia of special interest to the Sponsor (defined as an ANC $< 1.0 \times 10^9$ cells/L) will be considered an AESI and should be reported within 24 hours of knowledge of the event.

Serious Infection

Infections meeting SAE criteria (eg, required hospitalization) or infections with a severity grade of "severe" that require treatment with IV therapy (antibiotics, antiviral, or antifungal) and opportunistic infections will be considered AESI and should be reported within 24 hours of knowledge of the event.

Every effort should be made to identify the causative pathogen through prompt and appropriate investigation by the Investigator or reporting physician.

Worsening of Cytokine Release Syndrome

There is limited experience with mavrilimumab or other anti-GM-CSF agents in patients with COVID-19. In the expanded access protocol conducted by Italian investigators with mavrilimumab (De Luca G, 2020), all except for one of the subjects treated with mavrilimumab experienced a decrease in CRP and IL-6. Given the limited experience, in this study [worsening of] cytokine release syndrome (CRS) will be assessed as an AESI and should be reported within 24 hours of knowledge of the event. If a suspected CRS occurs, eg, symptoms such as malaise, nausea and vomiting, diarrhea, unscheduled blood sample kits should be collected, which will include serial cytokines and inflammatory biomarkers. These samples should be immediately shipped to the central laboratory and the study site should collect local available cytokines and inflammatory biomarkers in parallel.

12.2.1.4. Serious Adverse Event (SAE)

An SAE is defined as any AE (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:

- results in death
- is life-threatening
  - Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines)
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (coronary heart disease, cerebrovascular disease or peripheral vascular disease)

  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, eg, defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

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

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

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

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

12.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Not Related, Unlikely Related, Possibly Related or Definitely Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "Not related." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the SAE and the investigational product is determined to be "Possibly" or "Definitely" related, the event will be considered related to the investigational product for the purposes of expedited regulatory reporting. If the relationship between the SAE and investigational product is deemed to be "unlikely related," the case is considered expedited in Japan but not expedited in the USA or European Union.

12.4. Recording Adverse Events

The Investigator has the responsibility for managing the safety of individual subject and identifying AEs.

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

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

AEs must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 12.2.1.4):

1. The severity grade:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities.
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (ie, progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject.
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 12.2.1.4 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding with study treatment.

   All AEs must be treated appropriately. This study includes a single IV dose administration. No dose adjustment is anticipated. Actions may include:
   - Not applicable
   - Dose temporarily interrupted but later completed
   - Dose interrupted and not completed
6. Its outcome
   - not recovered/not resolved
   - recovered/resolved
   - recovering/resolving
   - recovered/resolved with sequelae
7. fatal; or unknown.

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

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

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

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (eg, 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.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

12.5. Reporting Serious Adverse Events

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until the last study visit must be reported to the Sponsor or designee, within 24 hours of learning of its occurrence. Additionally, Investigator reporting of SAEs to IRB/EC and other Regulatory Health Authorities may be required per local rules and regulations. For the purpose of determining the expectedness of Serious Suspected Adverse Reactions in ongoing studies conducted by Kiniksa, the following Serious Suspected Adverse Reaction is considered an expected reaction: Pneumonia.

More specifically, the Investigator will report all SAEs to the Kiniksa Pharmaceuticals safety CRO vendor no later than 24 hours after the Investigator's initial receipt of this information.

The event must also be recorded on the clinical database. Preliminary reports of SAEs must be followed by detailed descriptions as soon as possible including clear and redacted photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested as applicable and if available.

If the SAE is not previously documented in the Investigator's Brochure and is thought to be related to the study treatment, then the event is considered a suspected unexpected serious adverse reaction (SUSAR), and Kiniksa or designee may need to issue an Investigator Notification to inform all Investigators involved in any study with the same study treatment that this SAE has been reported. The standard timelines for SUSAR reporting as per ICH E2A will be followed.

The Sponsor or designee will report all SUSARs to the applicable Regulatory Authorities no later than 15 calendar days after the Sponsor's initial receipt of this information. Fatal or life-threatening unexpected experiences for which there is a possibility that the experience may have been caused by the drug will be reported by the Sponsor or designee to the Regulatory Authorities by telephone or facsimile transmission no later than 7 calendar days after receipt of this information.

Any SAEs experienced after completion of the study should only be reported to the Sponsor/Investigator.

Exceptions to SAE Reporting

Events that are captured as protocol-mandated clinical outcome measures (ie, part of the 8-point NIAID scale) should not be reported as SAEs. This would include initiation of invasive mechanical ventilation and/or ECMO, non-invasive ventilation or high-flow oxygen, and supplemental oxygen. In addition, procedures associated with these clinical outcome measures (eg, intubation or tracheostomy) should not be reported as SAEs. Events that in the judgment of the investigator are clearly a part of the natural history of severe COVID-19 pneumonia with hyper-inflammation should not be reported as SAEs (eg, fever, elevated CRP). All deaths, serious infections and severe granulocytopenia and neutropenia should be reported as SAEs. Per the Investigator Brochure, pneumonia is the only event that is included in the Reference Safety Information (RSI) and would be considered expected or listed. Any other serious related adverse drug reactions would be considered unexpected and would require expedited reporting.

12.5.1. Pregnancy Reporting

Formal reproduction toxicology testing of KPL-301 has not yet been performed.

Female subjects of childbearing potential must therefore agree to use a highly effective and protocol-approved contraceptive method (Section 7.1) for the duration of the study (until Day 90), which is 90 days after dosing and covers 5 ½ half-lives of mavrilimumab (approximately 15 days). Regular pregnancy tests will be performed for female subjects of childbearing potential, as defined in the Schedule of Activities (Table 2).

Male subjects who have a female partner of childbearing potential must agree to use a highly effective and protocol approved contraceptive method (Section 7.1) for the duration of the study and until 16 weeks after last study drug administration under this protocol.

If a subject becomes pregnant while participating in the study, study drug dosing must be discontinued immediately.

A female subject must immediately inform the Investigator if she becomes pregnant during the study. A male subject must inform the Investigator if his female partner becomes pregnant during the study. Pregnancies occurring up to 16 weeks after last study drug administration must be reported to the Investigator. The Investigator must report all pregnancies to the Sponsor or designee immediately and no later than 24 hours of their first knowledge of the pregnancy. The Investigator should counsel the subject that it is unknown what effects study drug might have on a fetus. Monitoring of the subject should continue until conclusion of the pregnancy. The newborn should be monitored for a minimum of 6 months after birth, or longer as per local requirement.

Instances of fetal death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, must be reported to the Sponsor as an SAE.

12.5.2. Reporting of Study Treatment Errors

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the eCRF irrespective of whether associated with an AE/SAE and reported to Safety within 24 hours of awareness only if associated with an SAE.

13. STATISTICAL METHODS AND PLANNED ANALYSES

The Phase 2 and Phase 3 parts of this study and the cohorts within each phase will be independently analyzed unless otherwise specified.

13.1. Analysis Sets

13.1.1. Intent-to-Treat Analysis Set

All randomized subjects who meet eligibility criteria will be included in the intent-to-treat (ITT) analysis set. Efficacy analyses for the Phase 3 part of the study will be based on the ITT analysis set. All ITT analyses will be based on the randomized treatment.

13.1.2. Modified Intent-to-Treat Analysis Set

All randomized subjects who meet eligibility criteria and receive study drug (ie, initiation of study drug infusion) will be included in the modified intent-to-treat (mITT) analysis set. Efficacy analyses for the Phase 2 part of the study will be based on the mITT analysis set. All mITT analyses will be based on the randomized treatment.

13.1.3. Safety Analysis Set

All randomized subjects receive study drug will be included in the Safety analysis set. Safety analyses will be based on the actual treatment received.

13.1.4. Per-Protocol Analysis Set

All mITT/ITT subjects without protocol deviations deemed to impact efficacy or ethical conduct will be included in the per-protocol (PP) analysis set.

13.2. Statistical Analysis

This section outlines the overall methodologies. Details of the statistical analyses, methods, and data conventions will be described in the Statistical Analysis Plan (SAP).

13.2.1. General Methods

All statistical analyses will be performed using SAS® Version 9.4 or higher. All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, SD, median, interquartile range, minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables. The final SAP will be confirmed in a separate document prior to study unblinding. An abbreviated summary of the SAP populations and methods is provided below.

13.2.2. Stratified Analysis

There will be 3 stratification factors for randomization:

1. Use of authorized standard of care antiviral therapy for COVID-19 (eg, remdesivir): yes vs. no
2. Age: < 65 vs. ≥ 65 years

3. Acute respiratory distress syndrome (ARDS) status by partial pressure of oxygen to fractional inspired oxygen (PaO_2/FiO_2) ratio*: normal-mild (> 200) vs. moderate-severe (≤ 200). ARDS status will only be used for Cohort 1 (non-ventilated subjects)

   * If PaO_2 is unavailable, use SpO_2/FiO_2: normal–mild (> 235) vs. moderate-severe (≤ 235)

When an analysis is to be stratified by these variables and a stratum has ≤ 5 events of interest in a log-rank test or the same response in all subjects in a Cochran-Mantel-Haenszel (CMH) test, the strata for the last stratification factor will be pooled. If the same situation occurs, strata for the second factor will be pooled. If the same situation still exists, the analysis will be done without stratification.

13.2.3. Handling of Dropouts and Missing Data

No dropouts will be replaced. Every effort will be made to avoid missing data. Missing data will not be imputed unless otherwise specified. For time-to-event analyses, subjects without the event will be censored. Details on handling missing data will be specified in the SAP.

13.2.4. Efficacy Analyses

All efficacy analyses will be based on the mITT for the Phase 2 endpoints and based on the ITT analysis set for the Phase 3 endpoints. Analyses based on other analysis sets will be considered as sensitivity analyses. All efficacy comparisons will be primarily based on each of the mavrilimumab arms versus the placebo arm.

13.2.4.1. Primary Efficacy Endpoint

For the Phase 2 part of the study, the Fisher's exact test will be done for the primary efficacy endpoint for both cohorts. The CMH test adjusting for randomization strata (authorized standard of care antiviral therapy for COVID-19 [eg, remdesivir], age, and ARDS status) will be used as supportive analysis of the primary efficacy endpoint for Cohort 1.

For both cohorts in the Phase 3 part of the study, the CMH test adjusted by randomization strata (authorized standard of care antiviral therapy for COVID-19 (eg, remdesivir), age, and ARDS status) will be used to test the primary efficacy endpoint.

Number of subjects and percentages will be summarized by treatment. The 80% (for Phase 2) and 95% (for Phase 2 and 3) confidence intervals (CIs) will also be provided as appropriate.

Missing data at Day 15 will be considered as non-responder unless otherwise specified. Details for handling missing data will be specified in the SAP.

13.2.4.2. Secondary and Other Efficacy Endpoints

Ventilation-free survival, overall survival, [redacted] time to clinical improvement, and all other time to event endpoints will be analyzed using log-rank test stratified by randomization strata. These time to event endpoints will be summarized with the 25th, 50th (median), and 75th percentiles using the Kaplan-Meier method. The 80% (for Phase 2) and 95% (for Phase 2 and 3) CIs for the percentiles will be calculated using a log-log transformation. The percentage of subjects with events and its 80% (for Phase 2) and 95% (for Phase 2 and 3) CI will

be calculated at Day 4, 8, 15, 22 and Day 29 since randomization as appropriate, using Greenwood's formula with a log-log transformation.

The hazard ratio for mavrilimumab vs. placebo and the corresponding Wald 80% (for Phase 2) and 95% (for Phase 2 and 3) CI will be calculated based on a Cox proportional-hazards model with treatment as covariate, stratified by randomization strata.

All binary endpoints in both cohorts for Phase 2 will be primarily analyzed using the Fisher's exact test. The CMH test adjusting for randomization strata (authorized standard of care antiviral therapy for COVID-19 [eg, remdesivir], age, and ARDS status) will be used as supportive analysis for Cohort 1 (non-ventilated subjects).

For the Phase 3 part of the study, the CMH test adjusted by randomization strata will be used to test all binary secondary and other efficacy endpoint for both cohorts.

13.2.5. Safety Analysis

All safety summaries will be presented for the safety analysis set. No formal statistical analysis of safety endpoints will be performed.

Descriptive statistics will be used to summarize all safety endpoints by treatment group and/or study visit. Data summaries will display parameters such as incidence of AEs, clinical laboratory variables, vital signs, body weight and body mass index, ECG parameters, and physical examinations, where available.

13.2.6. Other Analyses

Pharmacokinetic parameters of mavrilimumab will be summarized. The presence of anti-drug antibodies will be explored. Parameters of mechanical ventilation, respiratory status, SOFA/qSOFA, and health care resource utilization (eg, days and/or length in hospital/ICU) will be summarized.

13.2.7. Interim Analysis

There is no interim analysis planned for the Phase 2 or Phase 3 part of the study. Instead, the Sponsor will conduct a primary and/or final efficacy analysis (ie, review of unblinded study results) when the last subject in each Phase and Cohort completes the Day 29/Day 90 assessments.

13.3. Sample Size Estimation

13.3.1. Phase 2

Approximately 171 subjects will be randomized to the Phase 2 part of this study.

Sample size estimation for Cohort 1 (non-ventilated subjects) in Phase 2 is based on the primary efficacy endpoint proportion of subjects alive and free of mechanical ventilation at Day 29, using a Fisher's exact test.

Approximately 120 subjects will be randomized with a 1:1:1 allocation ratio. Assuming the proportion of subjects alive and free of mechanical ventilation at Day 29 is 95% and 75% for the active treatment arm and placebo arm, respectively, 40 subjects per arm will achieve a minimum

80% power for a pairwise comparison versus control when the two-sided alpha value is 0.20, after accounting for 15% drop out.

Sample size for Cohort 2 (ventilated subjects) in Phase 2 is based on the primary efficacy endpoint of mortality rate at Day 29, using the Fisher's exact test. Approximately 51 subjects will be randomized with a 1:1:1 allocation ratio. Assuming the mortality rates at Day 29 are 40% and 80% for the active treatment arm and placebo arm, respectively, 17 subjects per arm will achieve an 80% power for a pairwise comparison versus control when the two-sided alpha value is 0.20.

13.3.2. Phase 3

Approximately 665 subjects will be randomized to the Phase 3 part of this study.

Sample size for Cohort 1 (non-ventilated subjects) of the Phase 3 part is determined based on the primary efficacy endpoint proportion of subjects alive and free of mechanical ventilation at Day 29 (mavrilimumab 6 mg/kg vs placebo), using the Chi square test. The assumptions used for the calculation are adjusted based on the results of Phase 2 portion. Approximately 600 subjects will be randomized with a 1:1:1 allocation ratio. Assuming the proportions for the active arm and placebo arm are 87.5% and 74.4% respectively, approximately 200 subjects per arm are sufficient to achieve at least 90% power for the treatment comparison at the two-sided significance level of 0.05.

Sample size for Cohort 2 (ventilated subjects) of the Phase 3 part is determined based on the mortality rate at Day 29 using a Fisher's exact test. Approximately 117 subjects will be randomized with a 1:1:1 allocation ratio. Assuming the mortality rates for the active arm and placebo arm are 40% and 80% respectively, approximately 39 subjects per arm are required to achieve a 90% power for a pairwise comparison versus control when the two-sided alpha value is 0.025. However, based on review of the Phase 2 Cohort 2 results of the primary and secondary endpoints at day 29, Phase 3 Cohort 2 is closed to further enrollment (approximately 65 subjects randomized at the time of enrollment closure), as there was no evidence that mavrilimumab provided clinical benefit over placebo in recently ventilated patients.

13.4. Multiplicity Adjustment

The cohorts within the Phase 2 and Phase 3 study parts will be analyzed separately unless otherwise specified.

The two-sided type I error rate is 0.2 for each Phase 2 cohort and 0.05 for each Phase 3 cohort. No multiplicity adjustment will be done for the Phase 2 part and Phase 3 Cohort 2 (no formal testing will be done as enrollment for this cohort stopped early).

Multiplicity adjustment for Phase 3 Cohort 1 will be done to guarantee strong control of the overall Type I error rate at a two-sided alpha value of 0.05. For each endpoint, the test statistics for the two comparisons asymptotically follow a bivariate normal distribution and are positively correlated due to sharing a common control arm (placebo). Thus, the conventional Hochberg method will be used to adjust for multiplicity in the analysis of the two dose levels and the sequence of efficacy endpoints. Below are the details.

Considering the hypothesis testing of both the 10 mg/kg and the 6 mg/kg individually versus placebo for each endpoint to be a family, the testing on the primary endpoint and the three ordered secondary endpoints correspond to Family 1, Family 2, Family 3, and Family 4, respectively.

Testing will be done sequentially (Family 1, then 2, 3, and 4) based on the following decision rules (p-values are all two-sided):

- If both p-values in a family are ≤ 0.05, statistically significant treatment effects for the endpoint can be claimed for both dose levels, and testing may proceed to the next family to test those hypotheses at two-sided significance level of 0.05.
- If the larger p-value is > 0.05 and the smaller p-value is ≤ 0.025, a statistically significant treatment effect can be claimed only for the one dose level corresponding to the smaller p-value. Sequential testing stops here, and no further inferential testing can be done. The remaining data analyses will be provided for completeness (with p values as nominal) to inform the discussion of benefit-risk.
- If both p-values in the family are > 0.05, a statistically significant treatment effect cannot be claimed for either dose level. Sequential testing stops here, and no further inferential testing can be done. The remaining data analyses will be provided for completeness (with p values as nominal) to inform the discussion of benefit-risk.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enroll a subject into the study, a representative of Kiniksa or designee will contact the investigational study site to:

- Determine the adequacy of the investigational study site and facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Kiniksa or its representatives. This will be documented in a Clinical Study Agreement between Kiniksa and the Investigator.

During the study, a monitor from Kiniksa or designee will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification
- Record and report any protocol deviations not previously sent to Kiniksa
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Kiniksa and those SAEs that met criteria for reporting have been forwarded to the IRB/EC.

14.2. Audits and Inspections

Authorized representatives of Kiniksa, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Kiniksa audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact Kiniksa immediately if contacted by a regulatory agency about an inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Kiniksa may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

Before initiating a trial, the Investigator/Institution must obtain approval/favorable opinion from the IRB or Independent Ethics Committee (IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures and any other written information to be provided to subjects.

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

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

The IRB/EC will be informed by the Investigator of any changes to the approved protocol. Any amendments to the protocol will require IRB/IEC approval. Any administrative amendments to the protocol will be provided to IRBs/IECs according to IRB/IEC procedures.

The IRB/IEC will be informed by the Investigator of serious and unexpected SAEs in accordance with the IRB/IEC reporting requirements. The Investigator will provide the IRB/IEC with progress reports per IRB/IEC procedures.

16.2. Ethical Conduct of the Study

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

16.3. Informed Consent

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

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable, 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 (eg, all procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

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

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

17. DATA HANDLING AND RECORD KEEPING

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

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

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

17.1. Inspection of Records

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

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

17.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Kiniksa or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18. PUBLICATION POLICY

Publication of the study results shall be done in accordance with, and are subject to, the publication provision in the clinical trial agreement governing this study.

19. LIST OF REFERENCES

Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA 2020;323(16):1612-1614.

Burmester GR, Feist E, Sleeman MA, et al. Mavrilimumab, a human monoclonal antibody targeting GM-CSF receptor-α, in subjects with rheumatoid arthritis: a randomized, double-blind, placebo-controlled, phase I, first-in-human study. Ann Rheum Dis. 2011;70:1542-1549.

Cakarova L, Marsh LM, Wilhelm J, et al. Macrophage tumor necrosis factor-α induces epithelial expression of granulocyte–macrophage colony-stimulating factor: impact on alveolar epithelial repair. Am J Resp Crit Care Med. 2009;180(6):521-532.

Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med 2020; 382(19):1787-1799.

Castellani S, D'Oria S, Diana A, et al. G-cSf and GM-cSf Modify neutrophil functions at concentrations found in cystic fibrosis. Sci Rep. 2019;9(1):1-1.

ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT04280705, Adaptive COVID-19 Treatment Trial (ACTT); 2020 Feb 21 [cited 2020 May 1]. https://clinicaltrials.gov/ct2/show/NCT04280705?term=NCT04280705&draw=2&rank=1

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

Crotti C, Raimondo MG, Becciolini A, et al. Spotlight on mavrilimumab for the treatment of rheumatoid arthritis: evidence to date. Drug Des Devel Ther.2017:11:211-223.

De Luca G, Cavalli G, Campochiaro C, et al. GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. Lancet Rheumatol. 2020;2(8):e465-e473.

Fisher CJ, Dhainaut J-FA, Opal SM, et al. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome - results from a randomized, double-blind, placebo-controlled trial. JAMA 1994;271(23):1836-1843.

Hamilton JA. GM-CSF in inflammation and autoimmunity. Trends Immunol. 2002; 23(8):403-408.

Hamilton JA. Colony-stimulating factors in inflammation and autoimmunity. Nat Rev Immunol. 2008;8(7):533-544.

Hamilton JA. GM-CSF in inflammation. J Exp Med. 2020;217(1):e20190945.

Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506.

Humanigen, Inc. Humanigen reports additional analysis of lenzilumab in severe and critical COVID-19 Patients. 16 June 2020. https://www.humanigen.com/press/Humanigen-Reports-Additional-Analysis-of-Lenzilumab-in-Severe-and-Critical-COVID-19-Patients

International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC). COVID-19 Report: 27 April 2020.

https://media.tghn.org/medialibrary/2020/05/ISARIC_Data_Platform_COVID-19_Report_27APR20.pdf (1 May 2020)

Koupenova M. Potential role of platelets in COVID-19: Implications for thrombosis. Res Pract Thromb Haemost. 2020;4(5):737-740.

Lang FM, Lee KM, Teijaro JR, et al. GM-CSF-based treatments in COVID-19: reconciling opposing therapeutic approaches. Nat Rev Immunol. 2020;20(8):507-514.

Liao M, Liu Y, Yuan J, et al. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Nat. Med. 2020;26(6):842-844.

Livingston L, Bucher K. JAMA Infographic – Coronavirus disease 2019 (COVID-19) in Italy. JAMA 2020;323(14):1335.

Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034.

Miller G, Pillarisetty VG, Shah AB, et al. Endogenous granulocyte-macrophage colony stimulating factor overexpression in vivo results in the longterm recruitment of a distinct dendritic cell population with enhanced immunostimulatory function. J Immunol 2002;169(6):2875-2885.

Matute-Bello G, Liles WC, Radella F II, et al. Modulation of neutrophil apoptosis by granulocyte colony-stimulating factor and granulocyte/macrophage colony-stimulating factor during the course of acute respiratory distress syndrome. Crit Care Med. 2000;28(1):1–7.

Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus disease (COVID-19) — China, 2020. China CDC Weekly 2020;2:1-10.

Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: The Berlin Definition. JAMA 2012;307(23):2526-33.

Regeneron. Regeneron and Sanofi provide Update on Kevzara® (sarilumab) Phase 3 US Trial in COVID-19 Patients. 2 July 2020. https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-provide-update-kevzarar-sarilumab-phase-3

Rice TW, Wheeler AP, Bernard GR, et al. Comparison of the SpO2/FiO2 ratio and the PaO2/FiO2 ratio in patients with acute lung injury or ARDS. Chest 2007;132(2):410-417.

Roche Group. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia.29 July 2020. https://www.roche.com/investors/updates/inv-update-2020-07-29.htm

Root RK, Dale DC. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor: comparisons and potential for use in the treatment of infections in nonneutropenic patients. J Infect Dis. 1999;179:S342-S352.

Saba S, Soong G, Greenberg S, et al. Bacterial stimulation of epithelial G-CSF and GM-CSF expression promotes PMN survival in CF airways. Am J Respir Cell Mol Biol 2002;27:561-567.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and

Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med. 2006;47(4):373-380.

Shiomi A, Usiu T. Pivotal roles of GM-CSF in autoimmunity and inflammation. Mediators of Inflammation, 2015;2015:568543.

Tatsiy O, McDonald PP. Physiological stimuli induce PAD4-dependent, ROS-independent NETosis, with early and late events controlled by discrete signaling pathways. Front Immunol. 2018;9:2036.

Trapnell BC, Whitsett JA. GM-CSF regulates pulmonary surfactant homeostasis and alveolar macrophage-mediated innate host defense. Annu Rev Physiol. 2002;64:775-802.

Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-2019) outbreak in China: Summary of a report of 72,314 cases from the Chinese center for disease control and prevention. JAMA 2020;323(13):1239-1242.

Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA. 2020;117(20):10970-10975Yamamoto K, Ahyi AN, Pepper-Cunningham ZA, et al. Roles of lung epithelium in neutrophil recruitment during pneumococcal pneumonia. Am J Resp Cell Molec Biol. 2014;50(2):253-262.

Yamamoto K, Ahyi A, Pepper-Cunningham Z, et al. Roles of Lung Epithelium in Neutrophil Recruitment during Pneumococcal Pneumonia. Am J Respir Cell Mol Biol. 2014; 50(2): 253–262.

Zhou Y, Fu B, Zheng X, et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. Natl Sci Rev. 2020;7(6):998-1002.

20. SUMMARY OF CHANGES

20.1. Changes from Global Protocol Version 5 (Amendment 4) to Global Protocol Version 6 (Amendment 5)

The following are changes to the KPL-301-C203 protocol (Global version 5: 14Jun2021), which summarizes major changes to the protocol. Additional minor changes were also made with respect to use of abbreviations, correction of typos, renumbering of sections (when necessary), and revising/formatting references. The table of contents was updated.

Protocol Section (Page Number[1])	Modification	Rationale
Emergency Contact Information (p4)	Updated Drug Safety Physician from [redacted]	Administrative update
Synopsis (p7-8) and Section 10.2 (p48)	***Secondary Endpoints:*** Secondary efficacy endpoints will be examined based on the hierarchical order ~~specified in the multiplicity adjustment section~~ below: <u>Cohort 2 (Ventilated Subjects)</u> • Time to 1-point clinical improvement by Day 29 Defined as time from randomization to a 1-point improvement on the NIAID 8-point ordinal scale, or discharge from the hospital, whichever occurs first. Subjects who die before Day 29 will be censored at Day ~~30~~ 35.	Unnecessary text. Censoring of time to event endpoints revised to incorporate day 29 visit window (+4 days) and 1 day for difference between randomization and dosing
Synopsis (p8) and Section 10.3 (p48)	[redacted]	[redacted]

[1] Page number for the tracked change version.

Protocol Section (Page Number[1])	Modification	Rationale
	[redacted]	
Synopsis (p10) and Section 13.2.4 (p64)	All efficacy analyses will be based on the mITT for the Phase 2 endpoints and based on the ITT analysis set for the Phase 3 endpoints. Analyses based on other analysis sets will be considered as sensitivity analyses. All efficacy comparisons will be primarily based on each of the mavrilimumab arms versus the placebo arm. ~~Comparison between the pooled mavrilimumab arm versus placebo arm will be supportive. Phase 3, Cohort 1 primary and secondary endpoints will be examined in a hierarchical order as specified in Section 13.4~~.	There will be no pooled mavrilimumab arm analysis. Third sentence is in the synopsis and was added here for consistency.
Synopsis (p12) and Section 13.4 (p66)	The two-sided type I error rate is 0.2 for each Phase 2 cohort and 0.05 for each Phase 3 cohort. No multiplicity adjustment will be done for the Phase 2 part and~~or~~ Phase 3 Cohort 2 (no formal testing will be done as enrollment to cohort 2 stopped early). ~~Type I error rate for each Phase 2 cohort is at a two-sided alpha value of 0.2.~~ Multiplicity adjustment for Phase 3 Cohort 1 will be done to guarantee strong control of the overall Type I error rate at a two-sided alpha value of 0.05 ~~within each cohort~~. ~~Since~~ For each endpoint, the ~~two~~ test statistics for the two comparisons ~~doses~~ asymptotically follow a bivariate normal distribution and are positively correlated due ~~because they share~~ to sharing a common control arm (placebo) ~~in this trial~~. Conventional Hochberg method	Change to the statistical analysis for multiplicity adjustment due to the bivariate normal distribution of endpoints. Note: Sentence in grey appears only in Section 14.4.

<table>
<tr><th>Protocol Section (Page Number[1])</th><th>Modification</th><th>Rationale</th></tr>
<tr><td></td><td>will be used to adjust for multiplicity in the analysis of the two dose levels and the sequence of efficacy endpoints. Details are provided in Section 13.4.

~~Sequential gate keeping procedure will be used to control the type I error rate. Statistical testing will be done based on the hierarchical order specified below.~~

<table><tr><th>~~Order~~</th><th>~~Endpoint~~</th><th>~~Comparison~~</th></tr><tr><td>~~1~~</td><td>~~Proportion of subjects alive and free of mechanical ventilation at Day 29~~</td><td>~~mavrilimumab 6 mg vs. placebo~~</td></tr><tr><td>~~2~~</td><td>~~Mortality rate at Day 29~~</td><td>~~mavrilimumab 6 mg vs. placebo~~</td></tr><tr><td>~~3~~</td><td>~~Ventalation free survival by Day 29~~</td><td>~~mavrilimumab 6 mg vs. placebo~~</td></tr><tr><td>~~4~~</td><td>~~Mortality rate at Day 29~~</td><td>~~mavrilimumab 10 mg vs. placebo~~</td></tr><tr><td>~~5~~</td><td>~~Proportion of subjects alive and free of mechanical ventilation at Day 29~~</td><td>~~mavrilimumab 10 mg vs. placebo~~</td></tr><tr><td>~~6~~</td><td>~~Ventalation free survival by Day 29~~</td><td>~~mavrilimumab 10 mg vs. placebo~~</td></tr><tr><td>~~7~~</td><td>~~Overall survival by Day 29~~</td><td>~~mavrilimumab 6 mg vs. placebo~~</td></tr><tr><td>~~8~~</td><td>~~Overall survival by Day 29~~</td><td>~~mavrilimumab 10 mg vs. placebo~~</td></tr></table></td><td>The table was deleted because analysis is no longer done by hierarchical level by dose.</td></tr>
<tr><td>Section 10 (p47)</td><td>The following efficacy endpoints will be used for both the Phase 2 and Phase 3 parts of the study. Endpoints will be evaluated for both Cohorts 1 and 2, unless otherwise specified. ~~Phase 3, Cohort 1 primary and secondary endpoints will be examined in a hierarchical order as specified in Section 13.4.~~</td><td>Sentence was deleted because analysis is no longer done by hierarchical level by dose.</td></tr>
<tr><td>Section 11.1 (p51)</td><td>Samples will be collected at Screening, Day 1 (prior to the study drug infusion and once it is complete), and at Days ~~4~~ 3, 7, 15 ± 2, 29 + ~~2~~ 4, and at the Discharge/UNS visit.</td><td>Correction to Section 11.1 to align with Schedule of Activities.</td></tr>
</table>

<table>
<tr><th>Protocol Section (Page Number[1])</th><th>Modification</th><th>Rationale</th></tr>
<tr><td>Section 12.1.5
Table 4 (p53-54)</td><td>As shown in Table 4 below:

Changed Day 29 window from ± 2 days to +4 days
Changed Day 60 window from to ± 7 days +14 days
Changed Day 90 window ± 7 days to +14 days

Table 4: Schedule of Laboratory Assessments
<table>
<tr><th>Activity / Parameter</th><th>Collection Detail</th><th>Collection Timepoints</th></tr>
<tr><td colspan="3">CENTRAL LABORATORY</td></tr>
<tr><td>Respiratory Panel</td><td>A/H3N2, A/H1N1pdm09, A/H7N9, A/H5N1, A, not typed, B, or other (specify); coronavirus – novel CoV, MERS CoV, other CoV (specify); RSV; adenovirus; bacteria; other infectious respiratory diagnosis (specify); clinical pneumonia</td><td>Screening</td></tr>
<tr><td colspan="3">[redacted]</td></tr>
<tr><td>Anti-mavrilimumab antibody</td><td></td><td>Screening and the Discharge/UNS visit</td></tr>
<tr><td>Pharmacokinetic sample</td><td></td><td>Day 1 (before infusion and when infusion is complete), Days 3±1, 7±1, 15±2, 29+4~~±2~~ and at the Discharge/UNS visit</td></tr>
<tr><td colspan="3">LOCAL LABORATORY</td></tr>
<tr><td>Pregnancy test (women of child-bearing potential)</td><td>Urine or serum βhCG</td><td>Screening and at the Discharge/UNS visit;
Day 90+14±7 is optional</td></tr>
<tr><td colspan="3">[redacted]</td></tr>
<tr><td>Hematology</td><td>Complete blood count + differential</td><td rowspan="4">Screening (up to 7 days prior to randomization), Days 3±1, 15±2, 29+4~~±2~~ and at the Discharge/UNS visit;
Days 60±7+14 and 90+14±7 are optional</td></tr>
<tr><td>Coagulation</td><td>PT, PTT, and INR</td></tr>
<tr><td>Chemistry</td><td>electrolytes, blood urea nitrogen, glucose and CR</td></tr>
<tr><td>Liver Profile</td><td>AST, ALT, Alb, AlkP, Tbili, Dbili</td></tr>
</table></td><td>Correction to Section 12.1 to align with Schedule of Activities.</td></tr>
</table>

<table>
<tr><th>Protocol Section (Page Number[1])</th><th>Modification</th><th>Rationale</th></tr>
<tr><td></td><td>
<table>
<tr><th>Activity / Parameter</th><th>Collection Detail</th><th>Collection Timepoints</th></tr>
<tr><td>Lipid Panel</td><td>Cholesterol, total; high-density lipoprotein (HDL) cholesterol; low-density lipoprotein (LDL) cholesterol (calculation); triglycerides; very low-density lipoprotein (VLDL) cholesterol (calculation)</td><td>Screening (up to 7 days prior to randomization) and at the Discharge/UNS visit</td></tr>
<tr><td>Urinalysis</td><td></td><td>Screening (up to 7 days prior to randomization) and Discharge/UNS visit;
Day 29+4±2, Days 60+14±7 and 90+14±7 are optional</td></tr>
<tr><td>Tuberculosis</td><td></td><td>Optional at Screening - at Investigator's discretion
South Africa only: TB testing required for all subjects at Screening</td></tr>
<tr><td>SARS-CoV-2</td><td>COVID-19</td><td>Screening*
Days 1, 2, 3, 4, 5, 6, 7, 8, 15 ±2, 22 ±2, 29 +4±2 and Discharge/UNS are optional</td></tr>
</table>
</td><td></td></tr>
<tr><td>Section 13.4 (p67)</td><td>~~Details for multiplicity adjustment will be provided in the SAP.~~ Considering the hypothesis testing of both the 10 mg/kg and the 6 mg/kg individually versus placebo for each endpoint to be a family, the testing on the primary endpoint and the three ordered secondary endpoints correspond to Family 1, Family 2, Family 3, and Family 4, respectively.

Testing will be done sequentially (Family 1, then 2, 3, and 4) based on the following decision rules (p-values are all two-sided):
• If both p-values in a family are ≤ 0.05, statistically significant treatment effects for the endpoint can be claimed for both dose levels, and testing may proceed to the next family to test those hypotheses at two-sided significance level of 0.05.
• If the larger p-value is > 0.05 and the smaller p-value is ≤ 0.025, a statistically significant treatment effect can be claimed only for the one dose level corresponding to the smaller p-value. Sequential testing stops here, and no further inferential testing can be done. The remaining data analyses will be provided for completeness (with p values as nominal) to inform the discussion of benefit-risk.
• If both p-values in the family are > 0.05, a statistically significant treatment effect cannot be claimed for either dose level. Sequential testing stops here, and no further inferential testing can be done. The remaining data analyses will be provided for completeness (with p-values as nominal) to inform the discussion of benefit-risk.</td><td>Explanation of the new multiplicity of adjustment scheme which uses endpoint grouping by family and sequential testing by family.</td></tr>
</table>

20.2. Changes from Brazil Protocol Version 4 (Amendment 3) to Global Protocol Version 5 (Amendment 4)

The following are changes to the KPL-301-C203 protocol (Brazil version 4: 27Apr2021), which summarizes major changes to the protocol. Additional minor changes were also made with respect to use of abbreviations, correction of typos, renumbering of sections (when necessary), and revising/formatting references. The table of contents was updated.

Protocol Section (Page Number[2])	Modification	Rationale
Synopsis + Section 6.1 *Overall Study Design* (page 42)	Updated study schematic to reflect increase in sample size in Phase 3 Cohort 1 from 550 to 600 subjects and closure of enrollment in Phase 3 Cohort 2 (approximately 65 subjects enrolled at time of enrollment closure)	Updated based on FDA feedback
Synopsis + Section 6.2 *Number of Subjects (planned)* (page 43)	**Number of subjects (planned):** Phase 3: Approximately 665 ~~667~~ subjects • Cohort 1: Approximately 600 ~~550~~ non-ventilated subjects • Cohort 2: Approximately 117 ventilated subjects (approximately 65 subjects at time of enrollment closure) Based on review of the Phase 2 Cohort 2 results of the primary and secondary endpoints at day 29, Phase 3 Cohort 2 is closed to further enrollment, as there was no evidence that mavrilimumab provided clinical benefit over placebo in recently ventilated patients.	Increased Phase 3 Cohort 1 to 600 subjects based on Phase 2 Cohort 1 results of primary endpoint. Decision to close enrollment in Phase 3 Cohort 2 based on results of Phase 2 Cohort 2 results.
Synopsis + Section 13.2.4 *Efficacy Analysis* (page 71)	Efficacy Analysis: All efficacy analyses will be based on the mITT for the Phase 2 endpoints and based on the ITT analysis set for the Phase 3 endpoints. Analyses based on other analysis sets will be considered as sensitivity analyses. All efficacy comparisons will be primarily based on each of the mavrilimumab arms versus the placebo arm. Comparison between the pooled mavrilimumab arm versus placebo arm will be supportive. Phase 3, Cohort 1 primary and secondary endpoints will be examined in a hierarchical order as specified in Section 13.4. *Primary Efficacy Endpoint:* For the Phase 2 part of the study, the Fisher's exact test will be performed for the primary efficacy endpoint for	Updated the proposed primary analysis for primary efficacy endpoint based on Phase 2 results. Revised secondary and other efficacy endpoints based on Phase 2, Cohort 1 results

[2] Page number for the tracked change version.

Protocol Section (Page Number[2])	Modification	Rationale
	both cohorts. The Cochran-Mantel-Haenszel (CMH) test adjusting for randomization strata (authorized ~~approved~~ standard of care antiviral therapy for COVID-19 (eg, remdesivir), age, and ARDS status) will be used as supportive analysis of the primary efficacy endpoint for Cohort 1. For both cohorts in the Phase 3 part of the study, the CMH test adjusted by randomization strata will be used to test the primary efficacy endpoint ~~for pooled mavrilimumab arm versus placebo arm, as well as each mavrilimumab dose arm versus placebo. The testing for the pooled mavrilimumab arm will be the primary analysis~~.	
Synopsis + Section 13.2.2 *Stratified Analysis* (page 70)	***Randomization Strata:*** There will be 3 stratification factors for randomization: 1. Use of authorized ~~approved~~ standard of care antiviral therapy for COVID-19 (eg, remdesivir): yes vs. no	Changed 'approved' to 'authorized' for clarity.
Synopsis + Section 13.2.7 *Interim Analysis* (page 72)	***Interim Analysis*** There is no interim analysis planned for the Phase 2 or Phase 3 part of the study. Instead, the Sponsor will conduct a primary and/or final efficacy analysis (ie, review of unblinded study results) when the last subject in each Phase and Cohort completes the Day 29/Day 90 assessments.	Clarified the conduct of the primary and/or final efficacy analysis.
Section 13.3.2 *Sample Size Estimation Phase 3* (page 73)	***Sample Size Estimation:*** Phase 3 Approximately 665 ~~667~~ subjects will be randomized to the Phase 3 part of this study. Sample size for Cohort 1 (non-ventilated subjects) of the Phase 3 part is determined based on the primary efficacy endpoint of proportion of subjects alive and free of mechanical ventilation at Day 29 (mavrilimumab 6 mg/kg vs placebo) using the Chi square. The assumptions used for the calculation are adjusted based on the results of Phase 2 portion. Approximately 600 ~~550~~ subjects will be randomized with a 1:1:1 allocation ratio. Assuming the proportions for the active arm and placebo	The assumptions for the proportion of subjects alive and free of ventilation were updated based on Phase 2 Cohort 1 results. Power estimate was updated. Decision to close enrollment in Phase 3 Cohort 2 based on results of Phase 2 Cohort 2 results.

Protocol Section (Page Number[2])	Modification	Rationale
	arm are 87.5 ~~86~~% and 74.4 ~~74~~% respectively, approximately ~~183~~ 200 subjects per arm are sufficient to achieve at least 90% power for the treatment comparison ~~of pooled mavrilimumab arms versus placebo and~~ at ~~least 80% power for the comparison of each individual mavrilimumab dose arm versus placebo~~ the two-sided ~~alpha value is~~ significance level of 0.05. Sample size for Cohort 2 (ventilated subjects) of the Phase 3 part is determined based on the mortality rate at Day 29 using a Fisher's exact test. Approximately 117 subjects will be randomized with a 1:1:1 allocation ratio. Assuming the mortality rates for the active arm and placebo arm are 40% and 80% respectively, approximately 39 subjects per arm are required to achieve a 90% power for a pairwise comparison versus control when the two-sided alpha value is 0.025. However, based on review of the Phase 2 Cohort 2 results of the primary and secondary endpoints at day 29, Phase 3 Cohort 2 is closed to further enrollment (approximately 65 subjects randomized at the time of enrollment closure), as there was no evidence that mavrilimumab provided clinical benefit over placebo in recently ventilated patients.	
Synopsis + Section 13.4 *Multiplicity Adjustment* (page 73 - 74)	Multiplicity Adjustment The cohorts within the Phase 2 and Phase 3 study parts will be analyzed separately unless otherwise specified. No multiplicity adjustment will be done for the Phase 2 part. Type I error rate for each Phase 2 cohort is at a two-sided alpha value of 0.2. Multiplicity adjustment for Phase 3 Cohort 1 will be done to guarantee strong control of the overall Type I error at a two-sided alpha value of 0.05 ~~within each cohort for the comparisons of pooled mavrilimumab arms versus placebo in Phase 3 part.~~ Details are provided in Section 13.4. Sequential gate keeping procedure will be used to control the type I error rate. Statistical testing will be done based on the hierarchical order specified below. [new table]	Updated based on FDA feedback.

<table>
<tr><th>Protocol Section (Page Number[2])</th><th>Modification</th><th>Rationale</th></tr>
<tr><td></td><td>
<table>
<tr><th>Order</th><th>Endpoint</th><th>Comparison</th></tr>
<tr><td>1</td><td>Proportion of subjects alive and free of mechanical ventilation at Day 29</td><td>mavrilimumab 6 mg vs. placebo</td></tr>
<tr><td>2</td><td>Mortality rate at Day 29</td><td>mavrilimumab 6 mg vs. placebo</td></tr>
<tr><td>3</td><td>Ventilation free survival by Day 29</td><td>mavrilimumab 6 mg vs. placebo</td></tr>
<tr><td>4</td><td>Mortality rate at Day 29</td><td>mavrilimumab 10 mg vs. placebo</td></tr>
<tr><td>5</td><td>Proportion of subjects alive and free of mechanical ventilation at Day 29</td><td>mavrilimumab 10 mg vs. placebo</td></tr>
<tr><td>6</td><td>Ventilation free survival by Day 29</td><td>mavrilimumab 10 mg vs. placebo</td></tr>
<tr><td>7</td><td>Overall survival by Day 29</td><td>mavrilimumab 6 mg vs. placebo</td></tr>
<tr><td>8</td><td>Overall survival by Day 29</td><td>mavrilimumab 10 mg vs. placebo</td></tr>
</table>
</td><td></td></tr>
<tr><td>Synopsis + Section 7.2 Exclusion Criteria (page 47) and Section 8.2.1 Prohibited Medications (page 50)</td><td>Added sentence to end of exclusion criterion #6, schedule of activities footnote #24 and to Section 8.2.1:
“Medications that become standard of care for COVID-19 and/or receive emergency use authorization may be allowed after discussion with the medical monitor.”</td><td>To allow medical monitor discretion regarding concomitant medications relative to COVID-19.</td></tr>
</table>

20.3. Changes from Global Protocol Version 3 (Amendment 2) to Global Protocol Version 5 (Amendment 4)

The following are changes to the KPL-301-C203 protocol (global version 3: 15Dec 2020), which summarizes major changes to the protocol. Additional minor changes were also made with respect to use of abbreviations, correction of typos, renumbering of sections (when necessary), and revising/formatting references. The table of contents was updated.

Note: There is no Global Protocol Version 4.

Protocol Section (Page Number[3])	Modification	Rationale
Emergency Contact Information	Changed Drug Safety Physician from [redacted]	Updated
Synopsis + Section 6.1 *Overall Study Design* (page 44)	Updated study schematic to reflect increase in sample size in Phase 3 Cohort 1 from 300 to 600 subjects and closure of enrollment in Phase 3 Cohort 2 (approximately 65 subjects enrolled at time of enrollment closure)	Updated based on Phase 2 results
Section 4 (page 39-41)	**Rationale for Dose and Route of Administration** The dose rationale, and by extension the IV route of administration for COVID-19 subjects, is based on a combination of data from prior safety and efficacy evaluation of single and multiple doses in RA patients, ~~and~~ the assessment of mavrilimumab lung distribution and pharmacodynamic effects in mice, and results from the Phase 2 portion (Cohort 1) of study KPL-301-C203. ~~An extrapolation of these findings taken together with known pathophysiology of COVID-19, in particular lung disease and hyperinflammation, led to the proposed doses for this study.~~ […] **The efficacy and safety results from the KPL-301-C203, Phase 2 Cohort 1** subjects, support use of both doses of mavrilimumab in the ongoing Phase 3 study. While generally there are no apparent differences between the two mavrilimumab arms for efficacy and safety, given the small number of primary events of ventilation and/or death analyzed to date, there are some differences between the two doses in mortality (10 mg/kg is numerically efficacious) or ventilation-free survival (6 mg/kg is numerically more efficacious). Overall, both the 10 mg/kg and the 6 mg/kg appear well-tolerated with no	Modified the dose rationale in light of the Phase 2, Cohort 1 results.

[3] Page number for the tracked change version.

Protocol Section (Page Number[3])	Modification	Rationale
	new identified safety risks in the COVID-19 study population. In fact, serious infections (e.g., septic shock, sepsis) were substantially lower in both mavrilimumab dose arms compared to placebo, and thrombosis events were only reported in the placebo arm. There were no serious adverse events related to mavrilimumab, no dose-related adverse events and no infusion reactions. Important potential risks for mavrilimumab will continue to be monitored. These include severe hypersensitivity reactions, immune complex disease, serious infections (viral, bacterial, and opportunistic infections), malignancy, vaccine interactions, pulmonary alveolar proteinosis, reproductive toxicity and granulocytic effects, including neutropenia. Of note, there is no biological rationale for several of these potential risks in the setting of a single dose administration. More importantly, none of these potential risks have been identified in the RA development program through Phase 2b with approximately 900 subject-years of exposure. See Investigator's Brochure for additional details. ~~With regards to mitigation of the aberrant immune response in the setting of COVID-19, it is unclear whether blockade of GM-CSF in the lung is required in addition to abolition of signaling in the periphery. Studies with the mavrilimumab surrogate anti-mouse GM-CSF-Rα antagonistic antibody, CAM-3003, were performed to interrogate the pulmonary vs. peripheral pharmacodynamics of ascending single and repeat doses. Single doses of 3-30 mg/kg delivered intra peritoneally showed no pharmacodynamic effects in the lungs (as assessed by BALF 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 30 mg/kg. In contrast, daily administration of 3 mg/kg did not affect IL-6 induction of BAL cells. This indicates that repeated, very high doses (≥10 x 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 J, 2016). Campbell et al. also indicate that significant pharmacodynamic effects of the antibody on the lung~~	

Protocol Section (Page Number[3])	Modification	Rationale
	~~cells could be observed after 5 daily doses of 30 mg/kg CAM-3003 (53% ± 23% inhibition). However, the authors warned that PK studies using BAL measurements to quantify portioning in the lung lumen may 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 subjects it is likely that the inflammatory process afflicting the lungs of severe pneumonia subjects 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 that have already migrated in the lungs.~~ ~~Taken together, a dose of up to 10 mg/kg (the highest tested in humans) may be required to confer significant pharmacodynamic effects in the lung to inhibit cytokine storm and prevent further lung damage. Supported by the safety data provided by the Phase 1 study, it would be reasonable to administer a single dose of mavrilimumab at levels up to 10 mg/kg in an attempt to provide desired pharmacodynamics in COVID-19 subjects, where direct inhibition of GM-CSF in the lung may be a requirement. Preliminary encouraging results from mavrilimumab and lenzilumab, two of the drugs used in compassionate treatment protocols to achieve the GM-CSF blockade, support use of higher doses than ones required to achieve 100% RO in circulation, in order to achieve therapeutic drug levels in the lung. Hypothetically, a dose of 3 mg/kg may be sufficient and reasonable to be tested, but only if the higher proposed doses in the study, ie,10 mg/kg and 6 mg/kg, are 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 (decision to be driven by Phase 2 data). Given the lethality of pulmonary complications from COVID-19, the Sponsor, with input from COVID-19 treating physicians, is proposing that, in Phase 2, higher doses~~	

Protocol Section (Page Number[3])	Modification	Rationale
	~~(higher than 3 mg/kg, given that this dose is apparently sufficient to completely block the signaling axis only in the periphery) be tested first. The IV route of administration is supported by Phase 1 safety results from the SAD study in RA subjects (Burmester GR, 2011). As a precaution, the IV infusion of mavrilimumab in the COVID-19 Phase 2/3 study will be administered at slower rates than those applied in the SAD study.~~	
Synopsis + Section 6.2 *Number of Subjects (planned)* (page 45)	**Number of subjects (planned):** Phase 3: Approximately 665 ~~417~~ subjects • Cohort 1: Approximately 600 ~~330~~ non-ventilated subjects • Cohort 2: Approximately 117 ventilated subjects (approximately 65 subjects at time of enrollment closure) ~~The sample size for the Phase 3 part of the study may be modified after review of the Phase 2 data. Phase 2 subjects will not be included in the analysis of Phase 3 results.~~ Based on review of the Phase 2 Cohort 2 results of the primary and secondary endpoints at day 29, Phase 3 Cohort 2 is closed to further enrollment, as there was no evidence that mavrilimumab provided clinical benefit over placebo in recently ventilated patients.	Increased Phase 3 Cohort 1 to 600 subjects based on Phase 2 Cohort 1 results of primary endpoint. Decision to close enrollment in Phase 3 Cohort 2 based on results of Phase 2 Cohort 2 results.
Synopsis + Section 10.2 *Secondary Efficacy Endpoints* (page 56-57)	Secondary efficacy endpoints will be examined based on the hierarchical order ~~as~~ specified ~~below~~ in the multiplicity adjustment section (Section 13.4). <u>Cohort 1 (non-ventilated subjects):</u> 1. [redacted] [demoted to Other Efficacy Endpoint] [redacted] 2. [redacted] [demoted to Other Efficacy Endpoint] [redacted]	Revised and reordered secondary endpoints based on Phase 2, Cohort 1 results. Specified that statistical examination to be performed as per the multiplicity adjustment section.

Protocol Section (Page Number[3])	Modification	Rationale
	[redacted] 1. Mortality rate at Day 29 2. Ventilation free survival (Time to ventilation or death) by Day 29 [promoted from Other Efficacy Endpoints] Defined as time from randomization to ventilation or death; subjects still alive will be censored at Day 29 3. Overall survival by Day 29 [promoted from Other Efficacy Endpoints] Defined as time from randomization to death; subjects still alive will be censored at Day 29	
Synopsis + Section 10.3 *Other Efficacy Endpoints* (page 57)	***Other Efficacy Endpoints:*** <u>Cohort 1:</u> 3. [redacted] [demoted from Secondary Endpoints] 4. [redacted] [demoted from Secondary Endpoints]	Revised and reordered other endpoints based on Phase 2, Cohort 1 results
Synopsis + Section 10.3 *Other Efficacy Endpoints* (page 58)	[redacted]	Revised and reordered other endpoints based on Phase 2, Cohort 1 results

Protocol Section (Page Number[3])	Modification	Rationale
	[redacted]	
Synopsis + Section 10.3 *Other Endpoints* (page 58)	[redacted] [remainder of endpoints unchanged]	Revised and reordered other endpoints based on Phase 2, Cohort 1 results. [redacted]
Synopsis + Section 13.1 *Analysis Sets* (page 72)	***Analysis Sets:*** Intent-to-Treat (ITT) Analysis Set: All randomized subjects who meet eligibility criteria will be included in the ITT analysis set. Modified ITT (mITT) Analysis Set: All randomized subjects who meet eligibility criteria and received study drug will be included in the mITT analysis set.	Update to analysis set definitions
Synopsis + Section 13.2.2 *Stratified Analysis* (page 72)	***Randomization Strata:*** There will be 3 stratification factors for randomization: 1. Use of authorized ~~approved~~ standard of care ~~antiretroviral~~ antiviral therapy for COVID-19 (eg, remdesivir): yes vs. no	Changed 'antiretroviral' to 'antiviral' to be inclusive and clarified that antiviral therapy is specific to COVID-19. Also changed 'approved' to 'authorized' for

Protocol Section (Page Number[3])	Modification	Rationale
		clarity.
Synopsis + Section 13.2.4 *Efficacy Analysis* (page 73-74)	Efficacy Analysis: All efficacy analyses will be based on the mITT for the Phase 2 endpoints and based on the ITT analysis set for the Phase 3 endpoints. Analyses based on other analysis sets will be considered as sensitivity analyses. All efficacy comparisons will be primarily based on each of the mavrilimumab arms versus the placebo arm. Comparison between the pooled mavrilimumab arm versus placebo arm will be supportive. Phase 3, Cohort 1 primary and secondary endpoints will be examined in a hierarchical order as specified in Section 13.4. *Primary Efficacy Endpoint:* For the Phase 2 part of the study, the Fisher's exact test will be performed for the primary efficacy endpoint for both cohorts. The Cochran-Mantel-Haenszel (CMH) test adjusting for randomization strata (authorized ~~approved~~ standard of care ~~antiretroviral~~ antiviral therapy for COVID-19 (eg, remdesivir), age, and ARDS status) will be used as supportive analysis of the primary efficacy endpoint for Cohort 1. For both cohorts in the Phase 3 part of the study, the CMH test adjusted by randomization strata will be used to test the primary efficacy endpoint for ~~both cohorts~~. The number of subjects and percentages will be summarized by treatment. The 80% (for Phase 2) and 95% (for Phase 2 and 3) confidence intervals will also be provided as appropriate. *Secondary and Other Efficacy Endpoints:* ~~Time to ventilation or death,~~ Ventilation free survival, overall survival, [redacted], time to clinical improvement, and all other time to event endpoints will be analyzed using log-rank test stratified by randomization strata. The hazard ratio for mavrilimumab vs. placebo and the corresponding Wald 80% (for Phase 2) and 95% (for Phase 2 and 3) CI will be calculated based on a Cox proportional-hazards model with treatment as covariate, stratified by randomization strata.	Updated the proposed primary analysis for primary efficacy endpoint based on Phase 2 results. Revised secondary and other efficacy endpoints based on Phase 2, Cohort 1 results

Protocol Section (Page Number[3])	Modification	Rationale
Synopsis + Section 13.2.7 *Interim Analysis* (page 74-75)	***Interim Analysis*** There is no interim analysis planned for the Phase 2 or Phase 3 part of the study. Instead, the Sponsor will conduct a primary and/or final efficacy analysis (ie, review of unblinded study results) when the last subject in each Phase and Cohort completes the Day 29/Day 90 assessments. ~~For the Phase 3 part of the study, one interim analysis for each cohort will be performed when 50% of the subjects are randomized and have been followed up for 29 days. The DMC will review the unblinded interim analysis results and provide the Sponsor with a recommendation based on the pre-specified early stopping rule below for overwhelming efficacy. There is no futility analysis planned. However, the DMC may recommend stopping the trial due to safety concerns.~~ ~~The O'Brien-Fleming stopping boundary based on the Lan-DeMets alpha spending function will be applied at the interim and final analyses. If the information fraction at the interim analysis is 50%, the two-sided significance levels at the interim and final analyses will be given by α_1=0.0030 and α_2=0.0490. The significance levels will be calculated based on the actual information fraction at the interim analysis.~~	Eliminated the interim analysis for Phase 3 due to rapid enrollment
Section 13.3.2 *Sample Size Estimation Phase 3* (page 75-76)	***Sample Size Estimation:*** <u>Phase 3</u> Approximately 665 ~~417~~ subjects will be randomized to the Phase 3 part of this study. Sample size for Cohort 1 (non-ventilated subjects) of the Phase 3 part is determined based on the primary efficacy endpoint of proportion of subjects alive and free of mechanical ventilation at Day 29 (mavrilimumab 6 mg/kg vs placebo) using the Chi square ~~Fisher's exact~~ test. The assumptions used for the calculation are adjusted based on the results of Phase 2 portion. Approximately 600 ~~300~~ subjects will be randomized with a 1:1:1 allocation ratio. Assuming the proportions for the active arm and placebo arm are 87.5 ~~95~~% and 74.4 ~~75~~% respectively, approximately ~~100~~ 200 subjects per arm are sufficient to achieve at least 90% power ~~for a pairwise~~	The assumptions for the proportion of subjects alive and free of ventilation were updated based on Phase 2 Cohort 1 results. Power estimate was updated. Decision to close enrollment in Phase 3 Cohort 2 based on results of Phase 2 Cohort 2 results.

Protocol Section (Page Number[3])	Modification	Rationale
	~~comparison versus control when~~ the treatment comparison at the two-sided ~~alpha value is~~ significance level of 0.05 ~~0.025~~. Sample size for Cohort 2 (ventilated subjects) of the Phase 3 part is determined based on the mortality rate at Day 29 using a Fisher's exact test. Approximately 117 subjects will be randomized with a 1:1:1 allocation ratio. Assuming the mortality rates for the active arm and placebo arm are 40% and 80% respectively, approximately 39 subjects per arm are required to achieve a 90% power for a pairwise comparison versus control when the two-sided alpha value is 0.025. However, based on review of the Phase 2 Cohort 2 results of the primary and secondary endpoints at day 29, Phase 3 Cohort 2 is closed to further enrollment (approximately 65 subjects randomized at the time of enrollment closure), as there was no evidence that mavrilimumab provided clinical benefit over placebo in recently ventilated patients. ~~Sample size for the Phase 3 part of the study may be modified after review of the Phase 2 data.~~	
Synopsis + Section 13.4 *Multiplicity Adjustment* (page 76-77)	Multiplicity Adjustment The cohorts within the Phase 2 and Phase 3 study parts will be analyzed separately unless otherwise specified. No multiplicity adjustment will be done for the Phase 2 part. Type I error rate for each Phase 2 cohort is at a two-sided alpha value of 0.2. ~~There are three sources of multiplicity in the Phase 3 part of this trial:~~ ~~• Analysis of the primary/secondary endpoints~~ ~~• Analysis of the dose-placebo comparisons~~ ~~• Analysis of treatment effects at the interim and the final analyses~~ Multiplicity adjustment for Phase 3 Cohort 1 will be done to guarantee strong control of the overall Type I error rate ~~with respect to all three sources of multiplicity~~ at a two-sided alpha value of 0.05 ~~within each cohort~~. Details are provided in Section 13.4. ~~To address multiplicity induced by the first two sources of multiplicity in this trial, namely, multiplicity induced by the analysis of the primary/secondary endpoints and~~	Updated based on the proposed analysis for pooled mavrilimumab arm versus placebo.

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~~multiplicity induced by the analysis of the dose-placebo comparisons, a gatekeeping procedure in conjunction with truncated Hochberg method will be applied. This gatekeeping procedure is derived using the mixture methodology originally proposed in Dmitrienko and Tamhane and later enhanced in Kordzakhia et al. (Dmitrienko A, 2013; Kordzakhia G and Dmitrienko A, 2018).~~

~~To account for the third source of multiplicity (analysis of treatment effects at the interim analysis and final analysis), the aforementioned O'Brien-Fleming stopping boundary will be used to determine the overall type I error rate at each interim and final analysis, and the multiplicity adjustment for multi-stage clinical trials defined in Kordzakhia, Dmitrienko and Ishida will be applied (Kordzakhia G and Brechenmacher T, 2018; Jennison C, 2000).~~

Sequential gate keeping procedure will be used to control the type I error rate. Statistical testing will be done based on the hierarchical order specified below.

Order	Endpoint	Comparison
1	Proportion of subjects alive and free of mechanical ventilation at Day 29	mavrilimumab 6 mg vs. placebo
2	Mortality rate at Day 29	mavrilimumab 6 mg vs. placebo
3	Ventilation free survival by Day 29	mavrilimumab 6 mg vs. placebo
4	Mortality rate at Day 29	mavrilimumab 10 mg vs. placebo
5	Proportion of subjects alive and free of mechanical ventilation at Day 29	mavrilimumab 10 mg vs. placebo
6	Ventilation free survival by Day 29	mavrilimumab 10 mg vs. placebo
7	Overall survival by Day 29	mavrilimumab 6 mg vs. placebo
8	Overall survival by Day 29	mavrilimumab 10 mg vs. placebo

Protocol Section (Page Number[3])	Modification	Rationale
Synopsis + Section 7.2 *Exclusion Criteria* (page 49) and Section 8.2.1 *Prohibited Medications* (page 52)	Added sentence to end of exclusion criterion #6, schedule of activities footnote #24 and also to Section 8.2.1: "Medications that become standard of care for COVID-19 and/or receive emergency use authorization may be allowed after discussion with the medical monitor."	To allow medical monitor discretion regarding concomitant medications relative to COVID-19.
Table 2: Schedule of Activities (pages 17-21) + Section 10.4.2 *Respiratory Parameters* (page 59)	1. Changed the acceptable visit windows for the Day 29 visit from ± 2 to + 4 and for the Day 60 and Day 90-visits from ± 7 days to + 14 days 2. Added a footnote (#10) to Randomization and Study Drug Administration, "The NIAID score should be recorded at the time of randomization for all eligible subjects. For subjects in Cohort 1 only, also record 1) either PaO2 (mmHg) if available or SpO2 (%) and 2) FiO2 (%) for subjects on assistive ventilation or L/min of oxygen for subjects not on assistive ventilation (eg, simple mask/cannula). Initiation of study drug administration should occur within 24 hours of randomization" [renumbered all subsequent footnotes] 3. Modified footnote #11 (former footnote #10): "If the subject remains hospitalized after Day 8 these assessments should be collected daily until the day of discharge (ie, Days 9-14, 16-21, 23-28 or after Day 29). On Day 1, assessments should be collected at the time closest to and prior to the initiation of study drug administration. Daily collection guidelines after Day 1: collect assessment in the morning at approximately the same time each day and closest to the collection of the NIAID score assessment, except for respiratory parameters (see footnote #16) 4. Revised the Assessment of Survival to only require at study visits beginning at Day 15 5. Added "to home" to footnote 13. 6. Revised text to footnote #16: "Daily values based on the highest daily FiO2, including PaO_2, FiO_2, SpO_2 and oxygen requirement. ~~calculated P to F ratio (if actual values are not available and the ratio is available),~~ Other ~~ABG (~~arterial blood gas~~es)~~ parameters if available ~~and respiratory rate (if subject~~	1. Shifted acceptable visit windows to ensure follow-up 2. Added collection of key parameters at the time of randomization and clarified the timing of randomization relative to initiation of study drug administration 3. Clarify data collection requirements 4. Survival information is only required post-discharge 5. Clarified that a NIAID score of 7 or 8 is required for subjects who are discharged to home 6. Clarified collection of respiratory parameters (note: respiratory rate is collected as part of vital signs)

Protocol Section (Page Number[3])	Modification	Rationale
	~~is not mechanically ventilated)~~ should be recorded. In addition, ~~rescue therapy (eg, Flonan), and~~ other supportive measures ~~(eg,~~ including pronation, neuromuscular blockade, tracheostomy, ECMO, vasopressor or inotropic therapy, inhaled nitric oxide or other~~s)~~ should be recorded.	

20.4. Changes from Global Protocol Version 2 (Amendment 1) to Global Protocol Version 3 (Amendment 2)

The following are changes to the KPL-301-C203 protocol (version 2: 13Aug 2020), which summarizes major changes to the protocol. Additional minor changes were also made with respect to use of abbreviations, correction of typos, renumbering of sections (when necessary), and revising/formatting references.

Protocol Section (Page Number)	Modification	Rationale
Synopsis	**Study center(s):** Approximately 50 study centers are planned in the United States, EMEA, Latin America, and Africa ~~and Australia~~	Update to planned countries
Synopsis	**Studied period (years):** ~~Estimated~~ Ddate first subject enrolled: ~~TBD~~ July 2020 Estimated date last subject completed: TBD	Updated information on study period
Synopsis + Section 5.2 *Secondary Objectives* (page 35)	Changed secondary objectives to: "To assess the impact of treatment on clinical status ~~time to return to room air, changes in need for invasive ventilation or critical care over time~~, mortality, ~~respiratory parameters~~, and safety of a single IV dose of mavrilimumab (10 mg/kg or 6 mg/kg) relative to placebo in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation."	Simplification
Synopsis + Section 5.3 *Other Objective* (page 35)	"Exploratory objective" renamed "other objectives"	Align with change to endpoint section where and "exploratory endpoints" into "other endpoints" were merged and renamed "other endpoints"
Synopsis	Methodology - revised description of the patient population to: "…subjects who have tested positive for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with x-ray/computed tomography (CT) evidence of bilateral pneumonia and active or recent signs of hyperinflammation (fever ~~and/~~or clinical laboratory results indicative of hyper-inflammation).	Align with revisions to Inclusion Criterion #7 (Fever)
Synopsis	Methodology -revised statement on randomization to: "Following Screening, enrolled subjects in each cohort will be randomized 1:1:1 to receive mavrilimumab 10 mg/kg or 6 mg/kg, or placebo as a single IV infusion (Day 1) in addition to standard of care as per institutional protocol and at the discretion of the investigator	Clarified that study drug is in combination with standard of care

Protocol Section (Page Number)	Modification	Rationale
	(provided that the medication/therapy is not explicitly prohibited per protocol) ~~as a single IV infusion (Day 1).~~"	
Synopsis + Section 6.1 *Overall Study Design* (page 36)	Changed the timing of the Phase 2 primary efficacy and safety analyses: Once the last subject in Phase 2 completes Day ~~15~~ 29, primary efficacy and safety analyses of the Phase 2 data will be conducted by the Sponsor.	Aligns with the change in the primary efficacy analysis
Synopsis + Section 6.1 *Overall Study Design* (page 37)	Revise the description of the SRC independent physician: "A Safety Review Committee (SRC) including ~~safety physicians from the Sponsor, the Sponsor's contract research organization (CRO), and at least 1 medical expert in COVID-19 treatment~~ 2 physicians from the Sponsor, 1 physician from the Sponsor's contract research organization (CRO), and 1 independent physician who is an expert in critical care medicine, pulmonary disorders, infectious diseases and/or COVID-19 treatment (SRC Chairperson) will meet periodically to review AEs/serious AEs (SAEs), reasons for study discontinuations, and key clinical and laboratory assessments.	Clarify the qualifications of the independent physician
Synopsis + Section 10.1.1 *Cohort 1 (Non-ventilated Subjects)* (page 49)	Changed primary efficacy endpoint of Cohort 1 to: "Proportion of subjects alive and free of mechanical ventilation ~~without respiratory failure~~ at Day 29 ~~15~~., ~~where respiratory failure~~ Mechanical ventilation is defined as ~~the need for high-flow oxygen (HFO), non-invasive ventilation (NIV),~~ invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO)." Mechanical ventilation ~~Respiratory failure~~ status will be evaluated based on the National Institute of Allergy and Infectious Diseases (NIAID) clinical outcome 8-point ordinal scale. Subjects whose clinical outcome ~~meets~~ has met NIAID ~~categories~~ score of 2 ~~or 3~~ will be considered as using mechanical ventilation ~~having respiratory failure~~.	Primary endpoint focuses on mechanical ventilation and death in order to simplify assessment of benefit and avoid any confusion from the differences in practice(s) of non-invasive ventilation. The duration of observation is pushed to Day 29 to allow for sufficient time to assess the new primary endpoint
Synopsis + Section 10.1.2 *Cohort 2 (Ventilated Subjects)* (Page 49)	Changed the primary efficacy endpoint of Cohort 2 to: "The primary efficacy endpoint is mortality rate at Day 29 ~~15~~, defined as the proportion of subjects who have died by Day 29 ~~15~~."	The duration of observation is pushed to Day 29 to allow for sufficient time to assess the new primary endpoint and match Cohort 1
Synopsis + Section 10.2 *Secondary*	~~Key s~~Secondary efficacy endpoints will be examined based on the hierarchical order as specified below:	Revised and reordered secondary

Protocol Section (Page Number)	Modification	Rationale
Efficacy Endpoints (page 49-50)	Cohort 1 (non-ventilated subjects) 1. Time to 2-point clinical improvement by Day ~~15~~ 29 *[promoted to 1st secondary endpoint]* Defined as time from randomization to a 2-point improvement on the NIAID 8-point ordinal scale, or discharge from the hospital, whichever comes first. Subjects who die before Day ~~15~~ 29 will be censored at Day ~~15~~ 30. 2. Time to return to room air or discharge by ~~Day 15 and~~ Day 29 *[demoted to 2nd secondary endpoint]* Defined as time from ~~the date of~~ randomization to ~~the start of a period of 24 hours while~~ breathing room air (NIAID ~~scale~~score ≥ 5), or discharge from the hospital, whichever occurs first. Subjects who die before ~~Day 15 /~~ Day 29 will be censored at ~~Day 15 /~~ Day ~~29~~ 30. 3. Mortality rate at Day 29 Cohort 2 (ventilated subjects) 1. Time to 1-point clinical improvement by Day 29 ~~15~~ Defined as time from randomization to a 1-point improvement on the NIAID 8-point ordinal scale, or discharge from the hospital, whichever comes first. Subjects who die before Day ~~15~~ 29 will be censored at Day ~~15~~ 30 ~~2. Mortality rate at Day 29~~ ~~3. Time to return to room air by Day 29~~ ~~Defined as time from the date of randomization to the start of a period of 24 hours while breathing room air (NIAID scale ≥ 5), or discharge from the hospital, whichever occurs first. Subjects who die before Day 29 will be censored at Day 29~~	endpoints
Synopsis + Section 10.3 *Other Endpoints* (page 50 to 51)	[redacted]	Combined "other secondary endpoints" and "exploratory endpoints" into "other endpoints", reordered, and removed some endpoints; (for clarity the final version 3 text is shown)

Protocol Section (Page Number)	Modification	Rationale
	[redacted]	

Protocol Section (Page Number)	Modification	Rationale
	28. [redacted].	
Synopsis + Section 13.2.4.1 *Primary Efficacy Endpoint* (page 66)	Primary endpoint analysis modified: For the Phase 2 part of the study, the Fisher's exact test will be performed for the primary efficacy endpoint for both cohorts. The CMH test adjusting for randomization strata (standard of care antiretroviral therapy, age, and ARDS status) will be used as supportive analysis of the primary efficacy endpoint for Cohort 1. For the Phase 3 part of the study, the ~~Cochran-Mantel-Haenszel (~~CMH) test adjusted by ~~the~~ randomization strata (standard of care antiretroviral therapy, age, and ARDS status) will be used to test the primary efficacy endpoint for both c~~C~~ohort~~s 1 (non-ventilated subjects). Fisher's exact test will be performed for Cohort 2 (ventilated subjects).~~	Clarification and addition of supportive analysis in Phase 2. Simplification for Phase 3
Synopsis + 13.2.4.2 *Secondary and Other Efficacy Endpoints* (Page 66-67)	**13.2.4.2 Secondary and Other Efficacy Endpoints** Time to ventilation or death, ventilation-free ~~survival~~, [redacted] time to clinical improvement, and all other time to event endpoints will be analyzed using log-rank test stratified by ~~the~~ randomization strata. These time to event endpoints will be summarized with the 25th, 50th (median), and 75th percentiles using the Kaplan-Meier method. The 80% (for Phase 2) and 95% (for Phase 3) confidence interval (CI) for the percentiles will be calculated using a log-log transformation. The percentage of subjects with events and its 80% (for Phase 2) and 95% (for Phase 3) CI will be calculated at Day 4, 8, 15, 22 and Day 29~~15~~ since randomization as appropriate, using Greenwood's formula with a log-log transformation. The hazard ratio for mavrilimumab vs. placebo and the corresponding Wald 80% (for Phase 2) and 95% (for Phase 3) CI will be calculated based on a Cox proportional-hazards model with treatment as covariate, stratified by randomization strata. ~~Mortality rate and a~~All ~~other~~ binary endpoints in both cohorts for Phase 2 ~~and in Cohort 2 (ventilated subjects) only for Phase 3~~ will be primarily analyzed using the Fisher's exact test. The CMH test adjusting for randomization strata (standard of care antiretroviral therapy, age, and ARDS status) will be used as supportive analysis fFor Cohort 1 (non-ventilated subjects). ~~in Phase 3 they will be analyzed using a CMH test adjusted by the randomization strata.~~	Clarification of the tests used for secondary and other endpoints

Protocol Section (Page Number)	Modification	Rationale
	For the Phase 3 part of the study, the CMH test adjusted by randomization strata will be used to test all binary secondary and other efficacy endpoint for both cohorts.	
Synopsis + Section 13.2.6 *Other Analyses* (page 67)	***Other Analyses*** Pharmacokinetic parameters of mavrilimumab will be summarized. [redacted] -The presence of anti-drug antibodies ~~(ADAs)~~ will be explored. Parameters of mechanical ventilation, respiratory status, Sequential Organ Failure Assessment (SOFA)/quick SOFA, and health care resource utilization (eg, days and/or length in hospital/ICU/oxygen use) will be summarized.	Exploration of the association between serum inflammatory biomarkers and assessments of clinical responses will not be performed.
Synopsis + Section 13.2.7 *Interim Analysis* (page 67)	***Interim Analysis*** There is no interim analysis planned for the Phase 2 part of the study. Instead, the Sponsor will conduct a primary efficacy analysis (ie, review of unblinded study results) when the last subject in Phase 2 completes the Day 29~~15~~ assessments. For the Phase 3 study part, one interim analysis for each cohort will be done when 50% of the subjects are randomized and have been followed up for 29~~15~~ days. The DMC will review the unblinded interim analysis results and provide the Sponsor with a recommendation based on ~~the pre-specified early stopping rule below for overwhelming efficacy~~ the standard alpha spending approach.	Interim analysis changed to reflect changes to primary endpoint
Synopsis + throughout protocol	Number of subjects (planned): Phase 2: Approximately ~~156~~ 171 subjects • Cohort 1: Approximately ~~105~~ 120 non-ventilated subjects • Cohort 2: Approximately 51 ventilated subjects	Sample size for Phase 2 revised as per the change of primary endpoint
Synopsis + Section 13.3.1 *Sample Size Estimation* (page 68)	Phase 2 sample size: Sample size estimation for Cohort 1 (non-ventilated subjects) in Phase 2 is based on the primary efficacy endpoint of proportion of subjects alive and free of mechanical ventilation ~~without respiratory failure~~ at Day 29~~15~~, using a Fisher's exact test. Approximately 120 ~~105~~ subjects will be randomized with a 1:1:1 allocation ratio. Assuming the proportions of subjects alive and free of mechanical ventilation ~~without respiratory~~ failure at Day 29~~15~~ is~~are~~ 9~~5~~0% and 7~~6~~5% for the active treatment arm and placebo arm, respectively, 40 ~~35~~ subjects per arm will achieve a minimum 80% power for a pairwise comparison versus control when the	Revised sample size estimations

Protocol Section (Page Number)	Modification	Rationale
	two-sided alpha value is 0.20, after accounting for 15% drop out. Phase 3 sample size: Sample size for Cohort 1 (non-ventilated subjects) of the Phase 3 part is determined based on the primary efficacy endpoint of proportion of subjects alive and free of mechanical ventilation ~~without respiratory failure~~ at Day ~~15~~ 29 using a Fisher's exact test ~~CMH test~~. Approximately 300 subjects will be randomized with a 1:1:1 allocation ratio. Assuming the proportions for the active arm and placebo arm are ~~90~~ 95% and ~~70~~ 75% respectively, approximately 100 subjects per arm are ~~required~~ sufficient to achieve at least 90% power for a pairwise comparison versus control when the two-sided alpha value is 0.025.	
Synopsis + Section 7.1 *Subject Inclusion Criteria* (page 40)	Changed inclusion criterion #7: 7. At least one of the following, within 7 days prior to randomization: • Ferritin > 500 ng/mL • CRP > 5 mg/dL • D-dimer > 1,000 ng/mL • LDH > 250 U/L • Fever~~, including any of the following~~: – (a~~A~~ measured temperature of at least 100.4°F [38°C]) ~~– If no temperature measured (CDC criteria):~~ ~~▪ a self-reported history of feeling feverish when a thermometer is not available, or the ill person has taken medication that would lower the measured temperature (eg, antipyretics, corticosteroids)~~ ~~▪ an appearance of a flushed face, glassy eyes, or chills if it is not feasible to touch the person~~	Simplification
Synopsis + Section 7.2 *Subject Exclusion Criteria* (page 41)	Modified exclusion criterion #5, fourth bullet: • Hemodynamic instability with pressor requirements of norepinephrine at a dose of > 0.5 mcg/kg/min or equivalent (total if multiple pressors used) for more than 12 hours continuously, myocardial infarction, stroke, ~~hemodynamic instability,~~ and~~/or~~ cardiogenic septic shock within 30 days prior to randomization.	Allow subjects on low dose pressors used outside of shock situations to participate in the study

Protocol Section (Page Number)	Modification	Rationale
Synopsis + Section 7.2 *Subject Exclusion Criteria* (page 42)	Added exclusion criterion #17: Known human immunodeficiency virus infection (regardless of immunological status), known hepatitis B virus surface antigen positivity and/or anti-hepatitis C virus positivity	Exclusion of subjects with other viral infections
Table 2. *Schedule of Activities* (pages 16-19) + Table 4 *Schedule of Laboratory Assessments* (pages 55-56)	1. Added footnote 2 to Day 15, 22, and 29. 2. Clarified that the SARS-CoV-2 test is optional at Days 1-8, 15, 22, 29 and Date of Discharge/UNS visit. 3. Removed the physical exam at Day 15. 4. Removed Chest X-ray or CT scan at Day 29 and required chest x-ray (not a CT scan) at Date of Discharge/UNS visit. 5. For parameters collected daily, switch to single collection instead of collection of highest and lowest values. To this end, added footnote 10: If the subject remains hospitalized after Day 8 these assessments should be collected daily until the day of discharge (ie, Days 9-14, 16-21, 22-28 or after Day 29). Daily collection guidelines: collect assessment in the morning at approximately the same time each day and closest to the collection of the NIAID score assessment. 6. For NIAID at discharge, added footnote 13: The NIAID at discharge should reflect status immediately post-discharge (ie, either 7 or 8). [redacted] 8. [redacted], hematology/coagulation/chemistry/ liver profile, and PK sampling switched from Day 4 to Day 3, and [redacted] sampling switched from Day 8 to Day 7 to coincide with other blood sampling timing. 9. Removed lipid panel at Days 7, 15, and 29. 10. Removed PK sampling at Screening (unnecessary since pre-dose PK is performed at Day 1). 11. Changed footnote 1 to: ~~There is no Day 0.~~ Screening activities can occur ~~from~~ up to -3 ~~and -1~~ days prior to~~before enrollment~~ study drug administration, except for COVID-19 testing~~, which may occur within 14 days before enrollment~~(see footnote #4), screening labs (see footnote #17) and chest x-ray or CT scan (see footnote #6). Subject eligibility should be confirmed at Day 1 prior to study drug administration.	Simplify and reduce the number of procedures, clarify some footnotes, add footnotes for clarification.

Protocol Section (Page Number)	Modification	Rationale
	12. Changed footnote 2 to: For hospitalized subjects, this visit will include activities listed. For subjects discharged before Day 15~~29~~, the Day 15, 22, and 29~~this~~ visits will be conducted by phone and will not include any laboratory tests, vital signs, or body temperature. For subjects who remain hospitalized after Day 29, the same assessments should be completed on a weekly basis. 13. Changed footnote 3 to: ~~Subjects discharged before Day 29 (early termination) should~~ At the time of discharge, complete **ONLY** the Date of Discharge / UNS visit assessments on ~~their~~ the discharge date (ie, study day assessments are not required). If a subject is discharged and the Investigator judges that is it not safe for the subject to return to the site, or the subject is not willing to return to the site, the required visits (Days 15, 22, 29, 60 and 90) that occur thereafter may be done by phone call follow-up and lab tests will not be performed. 14. Added new footnote 7: The discharge X-ray can be done within 72 hours of discharge. 15. Changed footnote 15: Respiratory function parameters will be recorded daily until the date of Discharge/UNS. Daily~~Best and worst~~ values based on the highest daily FiO2, including ~~for~~ PaO_2, FiO_2, SpO_2, calculated P to F ratio (if actual values are not available and the ratio is available), other ABG (arterial blood gases) parameters if available and respiratory rate (if subject is not mechanically ventilated) should be recorded. In addition, rescue therapy used (eg, Flolan), and other supportive measures (eg, pronation, neuromuscular blockade, tracheostomy, ECMO, vasopressor or inotropic therapy, inhaled nitric oxide or other) should also be recorded. 16. Split former footnote 14 into 2 separate footnotes (16 and 17) for clarity. 17. Added to footnote 19: [redacted] 18. Added to footnote 20: No pharmacokinetic samples are required after Day 29.	

Protocol Section (Page Number)	Modification	Rationale
	19. Add new footnote 22: Collect a blood sample for cytokine assessment if a serious infusion reaction occurs, or a subject experiences new symptoms or worsening of symptoms of cytokine release syndrome (eg, malaise, nausea and vomiting, diarrhea). 20. Changed footnote 23: "Prohibited medications include any cell-depleting biological therapies (eg, anti-CD20) within 12 months prior to Screening; or previous treatment with non-cell-depleting biological therapies (such as anti-TNF, anakinra, anti-IL-6 receptor [eg, tocilizumab], or abatacept) within 8 weeks (or 5 half-lives, whichever is longer) prior to Screening; treatment with alkylating agents within 12 weeks prior to Screening; ~~receipt of live (attenuated) vaccine within the 4 weeks prior to Screening,~~ treatment with cyclosporine A, azathioprine, cyclophosphamide, ~~mycophenolate mofetil (~~MMF~~)~~, or other immunosuppressant (except for corticosteroids) within 4 weeks of Screening. Concomitant medications to track include antipyretics, anti-infectives related to COVID-19, and corticosteroids. Other concomitant medications recorded at Baseline Day 1 and maximum dose."	
Section 7.3.1 *Treatment Stopping Criteria* (Page 42)	Should a moderate reaction occur during infusion of the study drug, the infusion will be stopped and restarted at the Investigator's discretion after the events have resolved. Should a severe reaction occur, the infusion will be permanently discontinued, but subjects will continue their participation in the study. Such severe reactions include, but are not limited to, urticaria, hypersensitivity, hypotension, bradycardia, hypoxia, generalized rash, or a change in mental status. If four (4) causally related severe reactions with 24-hour of dosing occur, study enrollment will be paused until the DMC can review the cases and determine if there is an adverse drug-related safety signal. Details regarding study drug dosing are provided in Section 9.5.	Clarified and defined severe reaction criterion
Section 8.1.2 *Description* (page 44)	Mavrilimumab is a sterile, clear to opalescent, colorless to slightly brown-yellow liquid, free from visible particles and is formulated [redacted]	[redacted]

Protocol Section (Page Number)	Modification	Rationale
Section 8.1.3 *Dose and Administration* (page 44)	Subjects will receive a single IV infusion of either 10 mg/kg or 6 mg/kg mavrilimumab or placebo over approximately 60 minutes. ~~There is no body weight limit, t~~The maximum dose may not exceed 1000 mg, which was approximately the maximum dose administered in the Phase 1 study with IV infusion. Dosing will be based on body weight obtained at Screening. Additional details regarding mavrilimumab dosing are provided in Section 9.5.	Removed unnecessary information.
Section 8.4.2 *Treatment Blinding* (page 46)	If the Investigator decides that unblinding the subject is essential for their clinical management, then the subject may be emergently unblinded, either before or after a discussion between the Sponsor's safety physician or designee and the Principal Investigator.	Clarified the emergency unblinding procedure
Section 10.4.1 *Mechanical Ventilation Parameters* (page 51)	Mechanical ventilation measures for each subject will be recorded daily until the date of Discharge~~/UNS~~. Ventilation and ~~type~~, oxygenation mode and associated measures will be collected ~~including~~. This will include need for high flow oxygen ~~(HFO), non-invasive ventilation (~~NIV~~), invasive mechanical ventilation (~~IMV~~)~~, or ECMO and will be recorded daily until the date of Discharge~~/UNS~~.	Clarifications regarding collection of mechanical ventilation measures
Section 10.4.2 *Respiratory Parameters* (page 51)	Respiratory function parameters will be recorded daily until the date of Discharge~~/UNS~~. ~~Best and worst~~ Daily values for PaO2, FiO2, SpO2, or in non-ventilated patients the daily oxygen need (most prevalent daily regimen reported as liters/min) to calculate ~~reported~~ P to F ratio (if actual values are not available and the ratio is available), other ABG (arterial blood gases) parameters if available and respiratory rate (if subject is not mechanically ventilated) should be recorded.	Change to single daily collection based on clinical site feedback.
Section 12.1.3 *Physical Examination* (page 54)	A physical examination of each subject will be conducted at Screening~~, Day 15,~~ and at the Discharge/UNS visit. Height and weight will be collected at Screening only.	Align with revisions to the Schedule of Activities.
Section 12.1.4 *Electrocardiogram, and Chest X-ray or CT Scan* (page 54)	An ECG will be obtained at Screening and at the Discharge/UNS visit. A chest x-ray or chest CT scan will be obtained at Screening~~, and on Day 29, or at the~~ The chest x-ray will be repeated at the Discharge~~/UNS~~ visit ~~if the subject is discharged prior to Day 29~~.	Align with revisions to the Schedule of Activities.
Section 12.1.5 *Laboratory Assessments* (page 54)	All safety laboratory parameters in the study will be conducted at Screening (~~Day -3 to Day 1~~ as per Table 2) with additional post-dose timepoints noted in Table 4. Subjects who are discharged ~~or discontinue before Day 29~~ should complete the Discharge/UNS visit (the study day assessments are not required).	Table 2 provides detail on the permissible visit windows for safety laboratory testing at Screening. Clarify

Protocol Section (Page Number)	Modification	Rationale
		lab assessments at the time of discharge.
Section 12.2.1.2 *Adverse Drug Reaction* (page 57)	**12.2.1.2. Adverse Drug Reaction** An adverse drug reaction is defined as, "A response to a medicinal product which is noxious and unintended [DIR 2001/83/EC Art 1(11)]. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility" (see Annex IV, ICH-E2A Guideline). Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure.	Added definition of adverse drug reactions
Section 12.2.1.3 *Adverse Events of Special Interest* (page 58)	**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 is defined below using Sampson's criteria (Sampson HA, 2006). Anaphylaxis and severe hypersensitivity reactions are required to be reported within 24 hours of knowledge of the event. Added Table 5: Clinical Criteria for Diagnosing Anaphylaxis (page 58)	Added anaphylaxis definition
Section 12.2.1.3 *Adverse Events of Special Interest* (page 59)	**Worsening of Cytokine Release Syndrome** There is limited experience with mavrilimumab or other anti-GM-CSF agents in patients with COVID-19. In the expanded access protocol conducted by Italian investigators with mavrilimumab (De Luca G, 2020), all except for one of the subjects treated with mavrilimumab experienced a decrease in CRP and IL-6. Given the limited experience, in this study [worsening of] cytokine release syndrome (CRS) will be assessed as an AESI and should be reported within 24 hours of knowledge of the event. If a suspected CRS occurs, eg, symptoms such as malaise, nausea and vomiting, diarrhea, unscheduled blood sample kits should be collected, which will include serial cytokines and inflammatory biomarkers. These samples should be immediately shipped to the central laboratory and the study site should collect local available cytokines and inflammatory biomarkers in parallel.	Added CRS as an AESI per regulatory authority request
Section 12.3 *Relationship to Study Drug* (page 60)	**Relationship to Study Drug** An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (~~Unrelated~~ Not Related, Unlikely Related, Possibly Related or ~~Probably~~ Definitely Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility	Clarified definition of Adverse Event to align with eCRF data collection

Protocol Section (Page Number)	Modification	Rationale
	that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "Not ~~un~~related." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related." If the relationship between the SAE and the investigational product is determined to be ~~"possible" or "probable"~~ "Possibly" or "Definitely" related, the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.	
Section 12.4 *Recording of Adverse Events* (page 61)	5. Action taken regarding with study treatment. All AEs must be treated appropriately. This study includes a single IV dose administration. No dose adjustment is anticipated. Actions may include: ~~Treatment may include one or more of the following:~~ • ~~Dose not changed~~ Not applicable • Dose temporarily interrupted but later completed • Dose interrupted and not completed	Clarify study drug related actions given single IV dose administration
Section 12.5 *Reporting Serious Adverse Events* (pages 62)	To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until the last study visit must be reported to the Sponsor or designee, within 24 hours of learning of its occurrence. Additionally, Investigator reporting of SAEs to IRB/EC and other Regulatory Health Authorities may be required per local rules and regulations. For the purpose of determining the expectedness of Serious Suspected Adverse Reactions in ongoing studies conducted by Kiniksa, the following Serious Suspected Adverse Reaction is considered an expected reaction: Pneumonia. […] Added sentence: The standard timelines for SUSAR reporting as per ICH E2A will be followed.	Identification of pneumonia as an expected reaction. Added statement regarding SUSAR reporting as per ICH E2A

Signature Page for RIM-CLIN-000287 v5.0

Approval	[redacted]

Signature Page for RIM-CLIN-000287 v5.0

Statistical Analysis Plan

A Phase 2/3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mavrilimumab (KPL-301) treatment in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation

Phase 3 Part of the Study

Sponsor:	Kiniksa Pharmaceuticals, Ltd. Hamilton, Bermuda [redacted]
Study Drug:	Mavrilimumab (KPL-301)
Protocol Number:	KPL-301-C203
Version:	2.0
Date:	14 December 2021

History of Changes

Version Number	Version Date	Notes
1.0	November 9, 2021	Final, submitted to the FDA.
2.0	December 13, 2021	Amendment, to be submitted to the FDA. The following changes are madeper FDA feedback on SAP V1.0: 1) As per FDA guidance, the ITT definition was reverted back to the original definition to clarify unequivocally that all randomized subjects will be in the ITT analysis set. 2) For binary endpoints, specified the CMH test stratified by randomization strata as the main method for the 95% CI. Removed the 95% CI based on normal approximation. 3) Added sensitivity analysis using multiple imputation methods to handle missing data in binary endpoints. 4) Added details for tipping point analysis and reference. The definition of NIAID at randomization and Day 1 NIAID are further clarified via some editorial changes.

Table of Contents

List of Abbreviations

2019-nCoV	2019 novel coronavirus
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
ATC	Anatomic-therapeutic-chemical
BiPAP	Bi-level positive airway pressure
CMH	Cochran-Mantel-Haenszel
COVID-19	Corona Virus Disease 2019
CPAP	Continuous positive airway pressure
CRF	Case report form
CRP	C-reactive protein
CT	Computerized tomography
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EDC	Electronic Data Capture
eCRF	Electronic case report form
FiO2	Fraction of inspired oxygen
ICU	Intensive care unit
IL	Interleukin
IMV	Invasive mechanical ventilation
IRT	Interactive Response Technology
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
ITT	Modified intent-to-treat
NIAID	National Institute of Allergy and Infectious Diseases
PaO2	Partial pressure of oxygen
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PEEP	Positive end-expiratory pressure
PK	Pharmacokinetics
PT	Preferred term
qSOFA	Quick sequential organ failure assessment
SAP	Statistical analysis plan
SOC	System organ class
SOFA	Sequential Organ Failure Assessment Score
TEAE	Treatment-emergent adverse event

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analyses and data presentation to be performed for the Phase 3 part of the study KPL-301-C203 by Cohort. The efficacy endpoints are based on protocol amendment 6.0 dated November 8, 2021; while the data collection and visits might reflect previous versions of the protocol depending on the reconsent date. Selected outputs supporting efficacy of pooling Phase 2 and Phase 3 parts of the study by Cohort are covered under this SAP.

It contains definitions of analysis populations, derived variables, and statistical methods for the analyses of efficacy and safety. It is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

The SAP will be finalized and approved prior to the clinical database lock (DBL) for the primary analyses when the last subject in Cohort 1 completes Day 29. A follow-up analysis will be conducted at the end of a 90-day safety follow-up period for all subjects. Cohort 1 and 2 will be analyzed separately. The database locks might be combined for the two cohorts as appropriate.

Analyses of pharmacokinetics (PK), Pharmacodynamics (PD), other biomarkers, and health care resource utilization are outside the scope of this SAP and will be addressed separately.

1.1. Objectives

1.1.1. Primary Objective

The primary objective of this study is to evaluate the clinical efficacy of a single intravenous (IV) dose of mavrilimumab (10 mg/kg or 6 mg/kg) relative to placebo in adult subjects hospitalized with severe Corona Virus Disease 2019 (COVID-19) pneumonia and hyper-inflammation to reduce progression to respiratory failure or death.

1.1.2. Secondary Objectives

The secondary objectives of this study are to assess impact of treatment on clinical status, mortality, and safety of a single IV dose of mavrilimumab (10 mg/kg or 6 mg/kg) relative to placebo in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation.

1.1.3. Other Objective

[redacted].

1.2. Study Design

This is a prospective, Phase 2/3, interventional, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of mavrilimumab (KPL-301) treatment in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation.

Screening activities will be performed up to 3 days prior to randomization. The study main follow-up period for efficacy will conclude on study Day 29, and subjects will be further followed for AEs/SAEs, concomitant medications, mortality, and clinical improvement (National Institute of

Allergy and Infectious Diseases (NIAID) scale) through study Day 90. The schedule of activities is presented in Table 2 of the protocol.

The Phase 3 part of the study will enroll approximately 600 subjects in Cohort 1 (581 subjects at time of enrollment closure) and 117 subjects in Cohort 2 (63 subjects at time of enrollment closure). Each cohort will randomize subjects in a 1:1:1 allocation ratio to receive a single IV infusion of mavrilimumab (10 mg/kg or 6 mg/kg) or placebo. Cohort 1 will include non-intubated hospitalized subjects who require supplemental oxygen to maintain SpO2 ≥ 92%, i.e., "non-ventilated" subjects. Cohort 2 will include hospitalized subjects for whom mechanical ventilation was recently initiated (within 48 hours prior to randomization), i.e., "ventilated" subjects.

1.3. NIAID Scale

Subject clinical status will be assessed daily using the 8-point NIAID scale, which is the basis for assessment of primary and secondary endpoints for Cohort 1 and Cohort 2.

1. Death
2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)
6. Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care
7. Not hospitalized, limitation on activities and/or requiring home oxygen
8. Not hospitalized, no limitations on activities

1.4. Sample Size Justification

Sample sizes were calculated separately for each cohort based on their primary endpoint and other assumptions. Subjects will be randomized with a 1:1:1 allocation ratio within each cohort.

Sample size estimation for Cohort 1 (non-ventilated subjects) in Phase 3 is based on the primary efficacy endpoint proportion of subjects alive and free of mechanical ventilation at Day 29, using a Chi square test. The assumptions used for the calculation are adjusted based on the results of Phase 2 portion. Assuming the proportions of subjects alive and free of ventilation at Day 29 are 87.5% and 74.4% for the active treatment arm and placebo arm, respectively, approximately 200 subjects per arm will achieve a minimum 90% power for the treatment comparison at the two-sided alpha value of 0.05. A total of 600 subjects will be randomized. At the time of the enrollment closure, 581 subjects were randomized.

Sample size for Cohort 2 (ventilated subjects) in Phase 3 is based on the primary efficacy endpoint mortality rate at Day 29, using a Fisher's exact test. Approximately 117 subjects will be randomized with a 1:1:1 allocation ratio. Assuming the mortality rates at Day 29 are 40% and 95% for the active treatment arm and placebo arm, respectively, 39 subjects per arm will achieve 90% power for the treatment comparison when the two-sided alpha value is 0.05. Sixty-three subjects were randomized at the time of enrollment closure.

2. ENDPOINTS

The primary, secondary, and other efficacy endpoints are defined in this section and summarized by assessment day in Table 1~~Table 1~~ .

2.1. Primary Efficacy Endpoint

Cohort 1 (Non-ventilated Subjects)

The primary efficacy endpoint for cohort 1 is proportion of subjects alive and free of mechanical ventilation at Day 29. Mechanical ventilation is defined as invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO). Subjects whose clinical outcome meets NIAID (defined in Section 1.3) score 2 will be considered as using mechanical ventilation.

Cohort 2 (Ventilated Subjects)

The primary efficacy endpoint for cohort 2 is mortality rate at Day 29, defined as the proportion of subjects who die by Day 29.

2.2. Secondary Efficacy Endpoints

Cohort 1 (Non-ventilated Subjects)

1. Mortality rate at Day 29
2. Ventilation-free survival (Time to ventilation or death) by Day 29
3. Overall survival by Day 29

   Defined as time from randomization to death; subjects still alive will be censored at Day 29

Cohort 2 (Ventilated Subjects)

1. Time to 1-point clinical improvement by Day 29

   Defined as time from randomization to a 1-point improvement on the NIAID 8-point ordinal scale, or discharge from the hospital, whichever comes first. Subjects who die before Day 29 will be censored at Day 35.

2.3. Other Efficacy Endpoints

[redacted]

[redacted]

2.4. Safety Endpoints

The following are safety endpoints:

- Adverse events, adverse events of special interest, and serious adverse events
- Laboratory parameters
- Vital signs
- Electrocardiogram
- Chest x-ray or CT scan
- Physical examination

Table 1: Summary of Primary, Secondary and Selected Other Efficacy Endpoints

Endpoints	[redacted]	Day 29		[redacted]
	Cohort 1, 2	Cohort 1	Cohort 2	Cohort 1, 2
Proportion of subjects alive and free of mechanical ventilation		Primary	[redacted]	
Time to ventilation or death (NIAID≤2)		S2		
[redacted]			[redacted]	
Mortality rate	[redacted]	S1	Primary	[redacted]
Overall survival		S3	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
Time to 1-point clinical improvement	[redacted]	[redacted]	S1	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]				[redacted]
[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	
[redacted]		[redacted]	[redacted]	
[redacted]		[redacted]	[redacted]	
[redacted]				[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]		[redacted]	[redacted]	

S: secondary efficacy endpoint; S1: first secondary endpoint; S2, S3: second, and third secondary endpoints, respectively.
Y: other efficacy endpoints.
*: [redacted].
‡: [redacted]

3. ANALYSIS SETS

3.1. Intent-to-Treat (ITT) Analysis Set

All randomized subjects will be included in the ITT analysis set. All efficacy analyses of the study will be based on the ITT analysis set. All ITT analyses will be based on the randomized treatment.

3.2. Safety Analysis Set

All randomized subjects who receive study drug will be included in the safety analysis set. Safety analyses will be based on the actual treatment received.

3.3. Per-Protocol (PP) Analysis Set

All ITT subjects without protocol deviations deemed to impact efficacy or ethical conduct will be included in the PP analysis set and will be determined before the database lock. The primary and secondary efficacy endpoints will be further analyzed based on the PP set.

3.4. Day 90 Analysis Set

All ITT subjects who were randomized at least 90 days prior to the data cutoff date for the first database lock. Selected Day 90 efficacy endpoints, e.g., mortality will be analyzed based on Day 90 set and the randomized treatment.

4. GENERAL STATISTICAL CONSIDERATIONS

Analyses described in this SAP will be conducted separately for each of the two cohorts. Treatment comparison will be primarily between each of the KPL-301 treatment arms (10 mg/kg, 6 mg/kg) vs placebo. Comparisons between the pooled KPL-301 treatment arms vs placebo will also be provided.

Summary statistics for continuous variables will include n (non-missing observations), mean, standard deviation, minimum, median, and maximum. Summary statistics for categorical variables will be presented in terms of frequencies and percentages based on the analysis set unless otherwise specified. In by-visit summary tables, only scheduled visits/timepoints will be summarized.

Time to event data will be summarized using the Kaplan-Meier (KM) method, which will include the estimated median, 25th percentiles, 75th percentiles, and their 95% confidence interval (CI). The CIs will be calculated using a log-log transformation. The event-free probability and its 95% CI will be calculated at days 4, 8, 15, 22, 29, 60 and 90 as appropriate using Greenwood's formula with a log-log transformation.

The 95% confidence interval (CI) of the difference in the proportion (KPL-301 – placebo) will be primary based on Cochran Mantel-Haenszel (CMH) test stratified by the randomization strata for binary (proportion or rate) endpoints.

All relevant subject data will be listed by cohort, treatment, subject and visit/time point including both scheduled and unscheduled visits.

Analyses of selected Day 90 efficacy endpoints will be conducted in the Day 90 analysis set in the Day 29 database lock. All Day 90 efficacy endpoints will be analyzed based on the ITT analysis set at the Day 90 database lock.

4.1. Randomization, Stratification, and Blinding

An Interactive Web Response System (IWRS) will be used for assignment of the subject identification number at enrollment, randomization to a treatment arm (10 mg/kg KPL-301, 6 mg/kg KPL-301 or placebo), and assignment of blinded investigational product.

The randomization is stratified by the three following characteristics for subjects in Cohort 1 and by the first two following characteristics for subjects in Cohort 2:

1. Use of approved standard of care antiretroviral therapy: yes vs. no
2. Age: <65 vs. ≥ 65 years
3. Acute respiratory distress syndrome (ARDS) status: normal – mild (> 200 PaO2/FiO2) vs. moderate-severe (≤ 200 PaO2/FiO2). If PaO2 is unavailable, use SpO2/FiO2: normal–mild (>235) vs. moderate-severe (≤235)

There should be no overlap of subject populations between the two cohorts since Cohort 1 baseline NIAID should be 3 or 4 and Cohort 2 baseline NIAID should be 2. In case of subjects being erroneously randomized under the incorrect cohort, the subjects will be analyzed in the correct cohort defined by the baseline NIAID scale. Subjects with baseline NIAID ≥ 5 will be included in Cohort 1 for the ITT and safety populations but excluded from Cohort 1 in the per-protocol analyses.

If subjects were randomized based on incorrect baseline information for use of approved standard of care antiretroviral therapy and age, then the correct strata will be used for stratified analysis rather than the incorrect strata in the IRT.

For ARDS status, data collected in IRT will be used since actual ARDS status at randomization was not collected in EDC. For Cohort 1 subjects who were incorrectly randomized under Cohort 2, the actual ARDS status derived from baseline information in EDC will be used, since the randomization for Cohort 2 is not stratified by ARDS status in the IRT.

If fewer than 5 subjects are in a stratification group of all three (or two for cohort 2) factors, that group will be pooled with another stratification group. If the same situation occurs, strata for the second factor will be pooled. If the same situation still exists, the analysis will be done without stratification.

For stratified analyses, if there is no event for both arms of comparison, or all responses are the same within a stratification group, that group will be pooled with another stratification group per the order of the stratification factors listed previously. This principal will be analogously applied to subgroup analyses.

4.2. Data Analysis General Information and Definition

4.2.1. Study Drug

Study drug or study treatment refers to 10 mg/kg KPL-301 (mavrilimumab), 6 mg/kg KPL-301 (mavrilimumab) or placebo.

4.2.2. Day 1

Day 1 is defined as the day of the study treatment after randomization.

For subjects without dosing, Day 1 is defined as the randomization date in the analysis of efficacy while endpoints points are defined by study day, like Day 29, Day 90 endpoints.

4.2.3. Baseline Values

Baseline is defined as the last non-missing value obtained prior to the start of study treatment. The baseline NIAID is defined separately in Section 5.7.2.

The change from baseline values will be derived for each subject as the post-baseline evaluation minus the baseline evaluation.

4.2.4. Last Contact

Last contact or last date known alive is defined as the last non-imputed date of any subject record prior to or on the data cut-off date in the clinical database.

4.2.5. Calculation Using Dates

Calculations using dates will adhere to the following conventions:

Study day for a date of interest (TARGET DATE) is calculated as

STUDY DAY = TARGET DATE – Date of Day 1 + 1 if TARGET DATE is on or after Day 1;

STUDY DAY = TARGET DATE – Date of Day 1 otherwise.

Day X in this document refer to the study day X, where X can be 4, 8, 15, 22, 29, 60, 90, etc.

4.2.6. Duration Derivation

Unless otherwise specified for a specific panel or variable, duration variables will be derived according to the following rules. Duration variables expressed in units greater than day will be rounded to 1 decimal place.

Duration (in days) = [end date – start date +1]

Duration (in weeks) = [end date – start date +1] / 7

Duration (in months) = [end date – start date +1] / 30.4375

4.3. Windowing of Visits

Data will be summarized by eCRF scheduled visits and allowed visit windows. When there are multiple assessments for a scheduled visit, the first non-missing value will be used. No additional windowing will be considered.

Due to changes of visit windows across protocol versions, the minimum window that can cover windows in all protocol versions will be used in the analysis of the efficacy endpoints: the window is (-2 days, + 2 days) for Day 15 endpoints, (-2 days, + 4 days) for Day 29 endpoints, (-7 days, +14 days) for Day 90 endpoints.

4.4. Methods for Handling Missing Data

For efficacy data, missing NIAID scale and survival status at target days will be handled per Section 5.7.2.

For safety data, refer to Section 8.1 for detailed date imputation guidelines.

4.5. Protocol Deviations

The study team will have a blinded review of protocol deviations to determine their classification (important, not important) periodically. Prior to the database lock, the study team will assess impact of all important protocol deviations on efficacy and whether they should be excluded from per-protocol analysis set.

The number of important protocol deviations, the number of subjects with at least one important protocol deviation, and the number of subjects with at least one important protocol deviation with/without a potential impact on efficacy will be summarized by treatment group. The protocol

deviation criterion types will also be summarized, with reference to an evaluability document that will be signed off prior to database lock.

All protocol deviations will be presented in by-subject listings, and subjects with protocol deviations that lead to exclusion from the per-protocol analysis set will be flagged.

4.6. Data Cut-off Date

Two DBLs are planned for Phase 3 Cohort 1:

- For the first DBL, unless otherwise specified, all analyses will be conducted based upon data through Day 29 for each subject instead of a fixed data cut-off date:
  - For Day 29 efficacy endpoints, a + 4-day window is allowed.
  - For Day 90 efficacy data, mortality rate will be produced.
  - Selected TEAE tables may be produced for a subgroup of subjects (for selected sites and randomization date) with complete TEAE data through Day 90.
  - Laboratory endpoints will only be analyzed for baseline values.
- For the second DBL, all analyses will be updated based on the complete study data. Data throughout Day 29 are expected to remain the same as the first DBL.

Only one DBL is planned for Phase 3 Cohort 2. All data through study completion/early discontinuation will be included.

5. STATISTICAL METHODOLOGY

5.1. Study Population

A summary of analysis sets by treatment will be presented along with percentages relative to the ITT Analysis Set.

- ITT Analysis Set
- Safety Analysis Set
- Per-protocol Analysis Set
- Day 90 Analysis Set

A listing will be provided to describe when informed consent was obtained and if the subject meets all inclusion/exclusion criteria. Reasons of subjects' exclusion from safety, or PP analysis sets will also be listed.

5.2. Subject Disposition

The number and percentage of subjects will be tabulated for the ITT analysis set by treatment:

- Subjects who are ongoing
- Subjects who completed the study
- Subjects who ended study early

Reasons for early study discontinuation will be summarized with the following categories:

- Adverse event
- Lost to follow-up
- Death
- Physician decision
- Site terminated by sponsor
- Study terminated by sponsor
- Technical problem
- Withdrawal by subject
- Other

A listing will be presented to describe whether the subject is on study, completed the study, date of completion or early withdrawal, and the reason for early study discontinuation.

5.3. Demographics and Baseline Disease Characteristics and History

5.3.1. Demographics

Demographic and other baseline characteristics will be summarized for each treatment group and overall based on the ITT analysis set. They will also be presented in by-subject listings. For categorical variables, missing category will be added when at least 1 subject does not have value.

Demographic descriptive statistics will be provided for the following:

- Age

- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)

Demographic frequency tabulations will be presented for:

- Age (< 65 years or ≥ 65 years)
- Sex (Male or Female)
- Childbearing potential of female (Yes or No)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Stated, Unknown)

5.3.2. Baseline Disease Characteristics

Baseline characteristics frequency tabulations will be summarized by the CRF categories, which are detailed below:

- Randomization strata from IWRS: use of approved standard antiretroviral therapy (Yes or No), age (< 65 years or ≥ 65 years), ARDS status (normal – mild or moderate-severe, for cohort 1 only)
- Actual randomization strata based on the baseline information
- Covid-19 symptom history findings (fever, fatigue, cough (productive), cough (non-productive), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, headache, diarrhea, nausea, vomiting, pneumonia, loss of taste, loss of smell, other)
- Tuberculosis (negative, positive, indeterminate)
- NIAID 8-point ordinal scale
- Receiving invasive ventilation
  - No
  - Yes (mode of ventilation at time of highest FiO2 requirement)
- Receiving non-invasive ventilation OR high flow nasal cannula?
  - No
  - Yes (mode of ventilation)
- Receiving supplemental oxygen
  - No
  - Yes (delivery method)
  - Other
- Required any other oxygen delivery methods since last assessment
  - No
  - Yes (modalities)
  - Unknown
- P/F ratio (PaO2/FiO2), conversion from S/F ratio (SpO2/FiO2) if PaO2 is unavailable **(Brown et al Chest, 2016; OpenCriticalCare.org, n.d.**)
- Currently requiring or since last assessment has required prone positioning

- Currently requiring or since last assessment has required neuromuscular blockade
- Currently requiring or since last assessment has required pulmonary vasodilators
- Currently have or since last assessment had tracheostomy
- Currently requiring or since last assessment has required ECMO
- Currently requiring or since last assessment has required vasopressor support
- Currently requiring or since last assessment has required renal replacement therapy
- SARS-CoV-2 (RT-PCR) (negative, positive, indeterminate)
- Anti-2019-nCoV (negative, positive, or not test/missing)

Continuous variables collected on respiratory and clinical assessment eCRF page will be summarized descriptively as appropriate.

5.3.3. SOFA and qSOFA

Sequential Organ Failure Assessment Score (SOFA) at baseline will be summarized for Cohort 2.

- Descriptive statistics will be provided for the following:
  - PaO2 (mmHg)
  - FiO2 (%)
  - P/F Ratio
  - SOFA Score
- Frequency tabulations will be presented for:
  - assessment performed (No (in ICU, Other) or Yes)
  - on mechanical ventilation (No or Yes)
  - platelets (x 10^3/uL) (≥ 150, 100-149, 50-99, 20-49, or <20)
  - Glasgow coma scale (15, 13-14, 10-12, 6-9, or <6)
  - bilirubin (mg/dl (umol/L)) (<1.2 (<20)), 1.2 - 1.9 (20 - 32), 2.0 - 5.9 (33 - 101), 6.0 - 11.9 (102 - 204), or ≥12.0(≥204))
  - mean arterial pressure OR administration of vasoactive agents required (Blood pressure stable without need for pressor support, MAP less than 70 mmHg, (Dopamine <=5 mcg/kg/min or Dobutamine), (Dopamine >5 mcg/kg/min, Epinephrine <=0.1 mcg/kg/min, or nor Epinephrine <=0.1 mcg/kg/min), or (Dopamine >15 mcg/kg/min, Epinephrine >0.1 mcg/kg/min, or nor Epinephrine >0.1 mcg/kg/min))
  - creatinine (mg/dL) (umol/L) (or urine output) (<1.2 (<110)), 1.2 - 1.9 (110 - 170), 2.0 - 3.4 (171 - 299), 3.5 - 4.9 (300 - 440), or 5.0 mL/day<=UOP<500 mL/day (>440))

Quick Sequential Organ Failure Assessment (qSOFA) at baseline will be tabulated for Cohort 1:

- qSOFA Score
- assessment performed (No (Invasive/noninvasive ventilation, Other) or Yes)
- respiration rate >=22 breaths/min (No or Yes)
- change in mental status (Glasgow score less than 15) (No or Yes)

- systolic blood pressure less than or equal to 100 mm/Hg (No or Yes)

By subject SOFA and qSOFA will be listed.

5.4. Medical History

Medical history data will be summarized by system organ class (SOC) and preferred term (PT) per Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 based on the safety analysis set. Subjects with multiple events coded to the same SOC or PT will only be counted once in the summary for that category.

All medical history data will be listed.

5.5. Prior and Concomitant Medications

Prior medications are defined as those taken before the date of the study drug. Concomitant medications are defined as any non-study medication taken during the study i.e., on or after the date of the study drug and within 90 days of the study drug treatment.

The number and percentage of subjects taking prior and concomitant medications will be tabulated separately by anatomical-therapeutic-chemical (ATC) level 2 and preferred drug name by treatment for the safety analysis set. A subject taking the same medication multiple times is counted only once under that preferred drug name. The summary will be sorted in the alphabetic order of ATC classes and preferred terms.

Prior and concomitant medications will be listed with flag.

Medications are coded using the World Health Organization (WHO) Drug dictionary B3 enhanced, version Mar 2020.

5.6. Study Treatments and Extent of Exposure

Study drug exposure will be summarized descriptively by treatment for the safety analysis set:

- Duration of infusion (minutes)
- Received the full injection volume (Yes or No)
- Infusion interrupted (Yes or No)
  - Reasons for infusion interruption (Adverse event, Technical Issue, Other)
- Infusion resumed (Yes or No)

The study drug administration details including the administration date and time will be presented in a by-subject listing.

5.7. Efficacy Analysis

All efficacy endpoints will be analyzed for the ITT analysis set. The primary and secondary endpoints will also be performed for the Per-protocol analysis set. Treatment comparisons will be for each KPL-301 arm vs placebo

5.7.1. Multiplicity Adjustment

Multiplicity adjustment for Phase 3 Cohort 1 will be done to guarantee strong control of the overall Type I error rate at a two-sided alpha value of 0.05. For each endpoint, the test statistics for the two comparisons asymptotically follow a bivariate normal distribution and are positively correlated due to sharing a common control arm (placebo). Thus, the conventional Hochberg method will be used to adjust for multiplicity in the analysis of the two dose levels and the sequence of efficacy endpoints. Below are the details.

Considering the hypothesis testing of both the 10 mg/kg and the 6 mg/kg individually versus placebo for each endpoint to be a family, the testing on the primary endpoint and the three ordered secondary endpoints correspond to Family 1, Family 2, Family 3, and Family 4, respectively.

Testing will be done sequentially (Family 1, then 2, 3, and 4) based on the following decision rules (p-values are all two-sided):

- If both p-values in a family are ≤ 0.05, statistically significant treatment effects for the endpoint can be claimed for both dose levels, and testing may proceed to the next family to test those hypotheses at two-sided significance level of 0.05.
- If the larger p-value is > 0.05 and the smaller p-value is ≤ 0.025, a statistically significant treatment effect can be claimed only for the one dose level corresponding to the smaller p-value. Sequential testing stops here, and no further inferential testing can be done. The remaining data analyses will be provided for completeness (with p values as nominal) to inform the discussion of benefit-risk.
- If both p-values in the family are > 0.05, a statistically significant treatment effect cannot be claimed for either dose level. Sequential testing stops here, and no further inferential testing can be done. The remaining data analyses will be provided for completeness (with p values as nominal) to inform the discussion of benefit-risk.

No multiplicity adjustment will be done for Phase 3 Cohort 2. No formal testing will be conducted as enrollment for this cohort stopped early.

5.7.2. NIAID Scale and Missing Data Imputation for Binary Endpoints

NIAID scores at randomization should be derived from the last NIAID assessment prior to randomization. When not able to be derived, the screening NIAID will be used unless missing, in which case the (first) score from Day 1 will be used.

Baseline NIAID scores should be derived from the last NIAID assessment prior to dosing.

When two or more NIAID scores are collected on the same study day, the lowest score will be used, except at the date of discharge, in which the highest NIAID score will be used. When the derived NIAID at randomization happens to be from Day 1, then the Day 1 NIAID should be the lowest score on or after the NIAID at randomization time.

For endpoints where the event of interest is favorable, like proportion of subjects alive and free of ventilation, and proportion of subjects with 1-point/2-point clinical improvement, the following imputation rule of NIAID scale will be adopted:

- When the NIAID assessment is missing at the target day (Day 15, 29, etc.), the NIAID score closest to and within the window of the target day will be used. In case of ties with equal number of days on either side of target day, the value before the target day will be used. The window is (-2 days, +2 days) for Day 15 endpoints, (-2 days, +4 days) for Day 29 endpoints, and (-7 days, +14 days) for Day 90 endpoints.
- When no NIAID assessment is available within the window of the target day, the primary treatment comparison will be based on a combination of responder imputation and non-responder imputation. The rules taking into consideration of missing data are mostly related to subjects being improved and discharged from the hospital.
  - Discharged subjects will be considered as having had the event (responders).
  - Subjects who are still in the hospital will be considered as not having had the event (non-responders).
  - Subjects who died will be considered as not having had the event for all subsequent target days after discontinuation (non-responders).

- Subjects who terminated study before the target day, if the NIAID met the endpoint criteria as of last assessment before the study termination, they will be considered as having had the event for all subsequent target days after discontinuation (responders).
- Subjects without any post randomization assessment will be considered non-responders.

In calculation of the mortality rate, a subject with the last known alive date on or after the target day is considered alive. If the last known alive date is before the target day but within their visit window, the subject is considered alive at the target day. Subjects terminated the study early will be considered alive since all subjects in the study are hospitalized and early termination other than due to death mostly happens to subjects improved or discharged.

Sensitivity analyses may be conducted to assess missing data assumptions for the primary endpoint and the mortality rate at Day 29. Two methods might be considered:

1) Multiple imputation approach with a covariate of discharge status at last assessment, adjusting for randomization strata.
2) Tipping point analyses. The goal is to explore the plausibility of missing data assumptions under which the conclusions change, i.e., under which there is no longer evidence of efficacy.

We plan to extend tipping points for binary data (**Yan et al., 2009)** to binary data with stratification. Let n_{1m} and n_{0m} be the number of missing values in the treatment and placebo arms respectively. When there is no stratification, the responders (Let r_{1m} and r_{0m} to denote the numbers) among the n_{1m} and n_{0m}subjects can range from 0 to n_{1m} and n_{0m}, respectively, by adding 1 responder at a time. A heat map plot can be drawn for assessment.

In our study when stratification exists, multiple imputation might be needed in extending Yan et al's approach. Repeat the following algorithm for each combination of r_{1m} and r_{0m}, where r_{1m} = 0, …, n_{1m} and r_{01m} = 0, …, n_{0m}, 1), and draw a heat map plot using data obtained.

1) Randomly select r_{1m} and r_{0m} subjects as responders and the rest as the non-responders.
2) Include the responders from step 1) in the observed responders without missing data, calculate the approximately normally distributed CMH test statistic instead of the usual Chi-square distributed CMH test statistic.
3) Repeat Step 1 and Step 2 a fixed number of times, e.g. 200. The statistics obtained are passed to PROC MIANALYZE to perform a combined CMH test to obtain a p-value.

5.7.3. Censoring Rules for Time to Event Endpoints

NIAID scores collected within visit windows (described in Section 4.3) of the target days will be used for time to event analysis by the corresponding target day. The last assessments referred to in this section include those occur after the target day but within the protocol-defined visit window. For example, if a subject has not had 2-point clinical improvement by Day 29 visit, which occurs on Day 30, the subject will be censored at Day 30 instead of Day 22 (the last assessment before Day 29).

For favorable time to event endpoints, death before the target date Day X (X=15, 29, or 90) will be censored at Day 19 for X = 15, and Day 35 for X = 29 unless otherwise specified. Details are below.

- Time to ventilation or death (Ventilation free survival) by Day 29
  Defined as time (in days) from randomization to the date of death or start date of using mechanical ventilation (NIAID ≤ 2) by Day 29 for Cohort 1. All subjects who have never had

NIAID ≤ 2 by Day 29 will be censored at the last assessment date of NIAID 8-point ordinal scale.

- [redacted]

- Overall survival by Day X (X=29, or [redacted])
  Defined as time (in days) from the randomization date to the date of death by Day X. All survival subjects will be censored at last date known alive on/before Day X.

- [redacted]

- Time to K-point clinical improvement by Day X (K=1, or [redacted], X=[redacted], or 29)
  Defined as time (in days) from randomization to the date of a K-point improvement on the NIAID 8-point ordinal scale, or discharge from the hospital, whichever occurs first, by Day X. Alive subjects who do not have K-point improvement nor discharge from the hospital will be censored at the date of the last NIAID 8-point ordinal scale assessment on/before Day X. Dead subjects will be censored at Day 19 for Day [redacted] endpoint and at Day 35 for Day 29 endpoint.

- [redacted]

- [redacted]

5.7.4. Analysis of Primary Efficacy Endpoint

The proportion of subjects alive and free of ventilation at Day 29 for Cohort 1, and the proportion of subjects who die (mortality rate) by Day 29 for Cohort 2 will be analyzed by the CMH test adjusted for the actual randomization strata (Cohort 1: standard of care antiretroviral therapy, age, and ARDS status; Cohort 2: standard of care antiretroviral therapy and age). The 95% confidence interval (CI) will be calculated using the Clopper-Pearson exact method. Number of subjects and percentages will be summarized by treatment.

The CMH method addresses the global null hypothesis of no difference between treatments. Hence, it corresponds to the risk difference being 0, the risk ratio being 1, and the odds ratio being 1. The CMH

p-value is the same across odds ratio/risk ratio/risk difference. In addition to CMH p-value, the stratified risk difference, stratified relative risk, and the stratified odds ratio and their 95% confidence interval (CI) will be provided in our analyses.

Analysis of the primary efficacy endpoint based on the per-protocol population will be conducted following the same methods.

5.7.5. Analysis of Secondary and Other Efficacy Endpoints

5.7.5.1. Time to event endpoints

For all time to event endpoints, the primary treatment comparison between the active treatment and the placebo (10 mg/kg mavrilimumab vs. placebo, and 6 mg/kg mavrilimumab vs. placebo) will be based on log-rank test stratified by the actual randomization strata.

The Kaplan-Meier (KM) method will be used to estimate the survival distribution function for all the time to event endpoints. The 25th, 50th (median), 75th percentiles and their two-sided 95% confidence interval (CI) will be estimated. In addition, the probability of favorable outcome (event rates, or event-free rates depending on the endpoints) at Day 4, 8, 15, 22, 29, 60, and 90 will be calculated as appropriate, along with their standard errors using Greenwood's formula (Klein, 2003) stratified by the actual randomization strata. Corresponding Kaplan-Meier plot will be produced. In case of favorable outcomes, the plot will be based on 1 - KM estimate.

The hazard ratio for (10 mg/kg mavrilimumab vs. placebo) or (6 mg/kg mavrilimumab vs. placebo) and the corresponding Wald 95% CI will be calculated based on a Cox proportional-hazards model with treatment as covariates, stratified by the actual randomization strata.

5.7.5.2. Binary (rate or proportion) endpoints

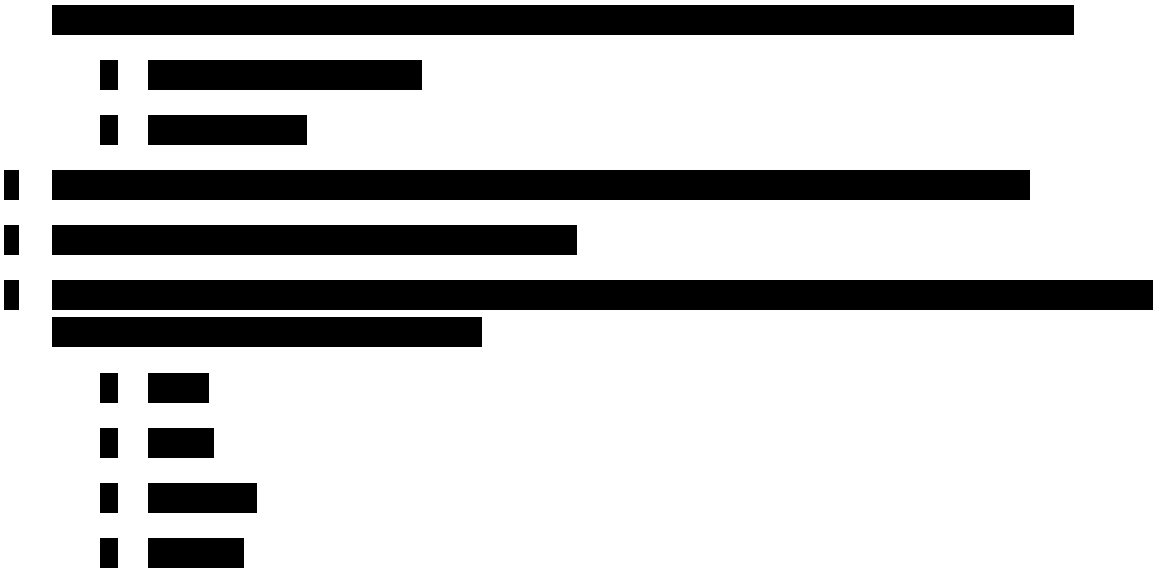
The primary treatment comparison for all binary endpoints will be based on the CMH test adjusted by actual randomization strata. Number of subjects and percentages will be summarized by treatment. The stratified risk difference, stratified relative risk, and the stratified odds ratio and their 95% CIs along with the CMH p-value will be provided in these analyses.

The event rates (or event-free) from the corresponding time to event analysis can serve as supportive analyses. For example, proportion of subjects with K-point clinical improvement can be estimated from time to K-point clinical improvement; mortality rate can be estimated from the overall survival. No formal testing will be conducted.

5.7.5.3. Endpoints to be summarized descriptively

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be used to summarize the following endpoints. No imputation will be done unless otherwise specified.

- [redacted]



5.7.6. Subgroup analysis

Subgroup analyses will be conducted for each of the randomization stratum for the primary efficacy endpoint and secondary endpoints.

5.8. Safety Analysis

The safety endpoints will be tabulated by treatment based on the Safety Analysis Set. All safety data including those collected during the safety follow-up will be listed by subject.

5.8.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have a causal relationship with this treatment. An AE will be defined as treatment-related if its relationship to the study drug is reported as Possibly Related or Definitely Related by Investigator.

An AE is considered treatment-emergent adverse event (TEAE) if the AE begins on/after and within 90 days of the study drug administration. If the date of AE onset is missing or coincides with the date of the study drug administration and AE time is not captured, AE will be considered treatment emergent.

All AEs will be coded using MedDRA version 23.0. A subject experiencing multiple AEs under the same preferred term (PT) or same system organ class (SOC) will be counted only once for that PT or SOC by maximum severity. If a subject experience the same AE more than once with more than one causal relationship to study drug, the strongest causal relationship to study drug will be given precedence. Any missing severity, causality, or outcome will not be imputed and classified as ‘Missing’. Detailed imputation rules for missing AE dates are in Section 8.1.1.

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 sponsor. An AESI may be serious or non-serious.

The number of subjects with at least one TEAE will be tabulated. The following tables summarize incidences of various aspects of TEAEs, treatment-emergent serious AEs (TESAEs), and treatment-emergent AESIs (TEAESIs):

- Overview of TEAEs (summary of all the subsequent items)
- TEAEs by SOC and PT
- TEAEs by PT
- TEAEs by maximum severity (mild, moderate, or severe)
- Drug related TEAEs (related or not related) by SOC and PT
- TESAEs by SOC and PT
- Drug related TESAEs by SOC and PT
- TESAEs by PT
- TEAESIs by SOC and PT
- TEAEs leading to dose interruption by SOC and PT
- TEAEs leading to death by SOC and PT

All information pertaining to adverse events will be listed by subject, detailing verbatim term given by the investigator, preferred term, system organ class, start date, stop date, severity, outcome, action taken and drug relatedness.

Separate listings will be created for Serious TEAEs, and TEAESI, and death.

Additionally, non-serious TEAEs by SOC and PT will be tabulated.

5.8.2. Clinical Laboratory Parameters

The following laboratory tests are performed at the Study Site/Clinic laboratories and recorded on the eCRF:

- Screening for tuberculosis
- Pregnancy
- SARS-CoV-2 test with RT-PCR
- Hematology: complete blood count + differential
- Chemistry: electrolytes, blood urea nitrogen, glucose, and CR
- Liver profile: AST, ALT, Alb, AlkP, Tbili, Dbili
- Lipid panel: Cholesterol, total; high-density lipoprotein (HDL) cholesterol; low-density lipoprotein (LDL) cholesterol (calculation); triglycerides; very low-density lipoprotein (VLDL) cholesterol (calculation)
- Urinalysis
- [redacted]

The following tests are performed by the central lab:

- Respiratory Viral Panel
- Anti-mavrilimumab Antibody

- [redacted]

Continuous laboratory data ([redacted], anti-mavrilimumab antibody, hematology, coagulation, chemistry, liver profile, and lipid panel) will be examined for trends using descriptive statistics of actual values and changes from baseline over time by treatment for the safety analysis set.

Shift tables will be produced for hematology and chemistry.

All laboratory results will be presented in by-subject listings.

5.8.3. Vital Signs

Vital signs include temperature, respiratory rate, systolic blood pressure/ diastolic blood pressure, and heart rate. Body weight and height will be reported in Body Measurements eCRF.

Actual values of vital signs (including weight) and changes from baseline will be summarized using descriptive statistics by visit.

All vital signs data will be listed.

5.8.4. Electrocardiogram (ECG)

All ECG data will be listed.

5.8.5. Physical Examination

All physical examination data will be listed.

5.8.6. Chest Imaging

Chest imaging data will be listed.

6. CHANGES TO PLANNED ANALYSES FROM THE PROTOCOL

- The following other efficacy endpoints are out of scope for this SAP, and will be reported separately
  - [redacted]
  - [redacted]
  - [redacted]
- All randomized subjects will be included in the ITT analysis set.
- Summary of Remdesivir and Corticosteroids Before Day 29 are added
- For favorable Day 29 endpoints, death will be censored at Day 35 instead of Day 30 as specified in the protocol
- The main analyses for the first database lock of Cohort 1 will not use a fixed data cut-off date. Subject level Day 29 dates will be used instead.
  - Efficacy endpoints based on Day 29 will consider data through Day 29 window.
  - Non-efficacy parameters that involve data after Day 29 by definition, e.g., TEAE, CM, will only include data through Day 29 in the first database lock.
  - Lab summary tables will only include baseline; and lab shift tables will not be provided since only baseline lab data will be cleaned in the first DBL.

7. REFERENCE

Brown SM, Grissom CK, Moss M, Rice TW, Schoenfeld D, Hou PC, Thompson BT, Brower RG; NIH/NHLBI PETAL Network Collaborators. Nonlinear Imputation of Pao2/Fio2 from Spo2/Fio2 Among Patients with Acute Respiratory Distress Syndrome. Chest. 2016 Aug;150(2):307-13. doi: 10.1016/j.chest.2016.01.003. Epub 2016 Jan 19.

Klein JP, Moeschberger ML. Survival analysis technique for censored and truncated data (second edition). Springer-Verlag; 2003.

OpenCriticalCare.org, n.d. https://opencriticalcare.org/imputed-pao2-calculator/.

Yan X, Lee S, Li N. Missing Data Handling Methods In Medical Device Clinical Trials. Journal of Biopharmaceutical Statistics, 19: 1085–1098, 2009.

8. APPENDICES

8.1. Handling of Missing Safety Data

No imputation will be made for completely missing date unless otherwise specified. General imputation rules mentioned below apply to partially missing or impossible dates:

- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date
- If the start date is not missing, and the imputed stop date is before the start date, then the imputed stop date will be equal to the start date
- Any imputed dates need to be logical. For example, last dose date should not be later than death date.

When imputation rules in subsequent sections contradicts the general rule, always follow the general rule.

8.1.1. Adverse Event Date Imputation

Follow the general rule specified in Section 8.1.

Incomplete Start Date:

Missing day, month, and year

No imputation will be made; the corresponding AE will be included.

Missing day and month

- If the year is the same as the year of the first dose date, then impute day and month as the day and month of the first dose
- If the year is prior to the year of the first dose date, then impute day and month as 31 Dec
- If the year is after the year of the first dose date, then impute day and month as 01 Jan.

Missing day only

- If the month and year are the same as those of the first dose date, then impute day as the day of the first dose date
- If either the year of partial date is before the year of the first dose date, or the years are the same, but the month of partial date is before the month of the first dose date then impute day as last day of the month
- If either the year of partial date is after the year of the first dose date, or the years are the same, but the month of partial date is after the month of the first dose date, then impute day as first day of the month.

Incomplete Stop Date:

Missing day, month, and year

- No imputation will be made.

Missing day and month

- If the year is the same as the year of the last dose date, then impute day and month as the day and month of the last dose date
- If the year is prior to the year of the last dose date, then impute day and month as 31 Dec
- If the year is after the year of last dose date, then impute day and month as 01 Jan.

Missing day only

- If the month and year are the same as those of the last dose date, then impute day as the day of the last dose date
- If either the year of partial date is not the same as the year of the last dose date, or the years are the same, but the month of partial date is not the same as the month of the last dose date, then impute day as last day of the month.

8.1.2. Concomitant Medication Date Imputation

Follow the general rules specified in Section 8.1 and Section 8.1.1.

Signature Page for RIM-CLIN-000916 v5.0

Approval	[redacted]
Approval	[redacted]
Approval	[redacted]
Approval	[redacted]

Signature Page for RIM-CLIN-000916 v5.0

Statistical Analysis Plan

A Phase 2/3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mavrilimumab (KPL-301) treatment in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation

Sponsor:	Kiniksa Pharmaceuticals, Ltd. [redacted]
Study Drug:	Mavrilimumab (KPL-301)
Protocol Number:	KPL-301-C203
Version:	1.0 for Phase 2
Date:	5 Feburary 2021

Table of Contents

List of Abbreviations

2019-nCoV	2019 novel coronavirus
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
ATC	Anatomic-therapeutic-chemical
BiPAP	Bi-level positive airway pressure
CMH	Cochran-Mantel-Haenszel
COVID-19	Corona Virus Disease 2019
CPAP	Continuous positive airway pressure
CRF	Case report form
CRP	C-reactive protein
CT	Computerized tomography
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
FiO2	Fraction of inspired oxygen
ICU	Intensive care unit
IL	Interleukin
IMV	Invasive mechanical ventilation
IWRS	Interactive web-based response system
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
mITT	Modified intent-to-treat
NIAID	National Institute of Allergy and Infectious Diseases
PaO2	Partial pressure of oxygen
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PEEP	Positive end-expiratory pressure
PK	Pharmacokinetics
PT	Preferred term
qSOFA	Quick sequential organ failure assessment
SAP	Statistical analysis plan
SOC	System organ class
SOFA	Sequential Organ Failure Assessment Score
TEAE	Treatment-emergent adverse event

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analyses and data presentation to be performed for the Phase 2 part of the study KPL-301-C203. The efficacy endpoints are based on protocol amendment 2.0 dated 25 December 2020; while the data collection and visits might reflect protocol amendment 1.0 dated 13 August 2020 depending on the reconsent date.

It contains definitions of analysis populations, derived variables, and statistical methods for the analyses of efficacy and safety. It is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

The SAP will be finalized and approved prior to the clinical database lock for the primary analyses when the last subject of the cohort that finishes enrollment first completes Day 29. The analyses of safety and efficacy will include all data collected in the database through the data cut-off date. A follow-up analysis will be conducted at the end of a 90-day safety follow-up period for all subjects. Cohort 1 and 2 will be analyzed separately. Depending on the enrollment of the two cohorts, the database lock might be separate for each of them at both the primary and follow-up.

Analyses of pharmacokinetics (PK), Pharmacodynamics (PD), other biomarkers, and health care resource utilization are outside the scope of this SAP and will be addressed separately.

1.1. Objectives

1.1.1. Primary Objective

The primary objective of this study is to evaluate the clinical efficacy of a single intravenous (IV) dose of mavrilimumab (10 mg/kg or 6 mg/kg) relative to placebo in adult subjects hospitalized with severe Corona Virus Disease 2019 (COVID-19) pneumonia and hyper-inflammation to reduce progression to respiratory failure or death.

1.1.2. Secondary Objectives

The secondary objectives of this study are to assess impact of treatment on clinical status, mortality, and safety of a single IV dose of mavrilimumab (10 mg/kg or 6 mg/kg) relative to placebo in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation.

1.1.3. Other Objective

[redacted]

1.2. Study Design

This is a prospective, Phase 2/3, interventional, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of mavrilimumab (KPL-301) treatment in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation.

Screening activities will be performed up to 3 days prior to randomization. The study main follow-up period for efficacy will conclude on study Day 29, and subjects will be further followed for AEs/SAEs, concomitant medications, mortality, and clinical improvement (National Institute of

Allergy and Infectious Diseases (NIAID) scale) through study Day 90. The schedule of activities is presented in Table 2 of the protocol.

The Phase 2 part of the study will enroll approximately 171 subjects (120 in Cohort 1 and 51 in Cohort 2). Each cohort will randomize subjects in a 1:1:1 allocation ratio to receive a single IV infusion of mavrilimumab (10 mg/kg or 6 mg/kg) or placebo. Cohort 1 will include non-intubated hospitalized subjects who require supplemental oxygen to maintain SpO2 ≥ 92%, i.e., "non-ventilated" subjects. Cohort 2 will include hospitalized subjects for whom mechanical ventilation was recently initiated (within 48 hours prior to randomization), i.e., "ventilated" subjects.

1.3. NIAID Scale

Subject clinical status will be assessed daily using the 8-point NIAID scale, which is the basis for assessment of primary and secondary endpoints for Cohort 1 and Cohort 2.

1. Death
2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)
6. Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care
7. Not hospitalized, limitation on activities and/or requiring home oxygen
8. Not hospitalized, no limitations on activities

1.4. Sample Size Justification

Sample sizes were calculated separately for each cohort and phase of the study based on their primary endpoint and other assumptions. Key elements for Phase 2 sample size are summarized below with type I error of 0.20 and power of 80%.

Cohort	KPL-301	Placebo	Sample Size	Primary Endpoint
1	95%	75%	120	D29 Proportion of subjects alive and free of ventilation
2	40%	80%	51	D29 Mortality rate

Approximately 171 subjects will be randomized to the Phase 2 part of this study.

Sample size estimation for Cohort 1 (non-ventilated subjects) in Phase 2 is based on the primary efficacy endpoint proportion of subjects alive and free of mechanical ventilation at Day 29, using a Fisher's exact test.

Approximately 120 subjects will be randomized with a 1:1:1 allocation ratio. Assuming the proportions of subjects alive and free of ventilation at Day 29 are 95% and 75% for the active treatment arm and placebo arm, respectively, 40 subjects per arm will achieve a minimum 80% power for a pairwise comparison versus control when the two-sided alpha value is 0.20.

Sample size for Cohort 2 (ventilated subjects) in Phase 2 is based on the primary efficacy endpoint mortality rate at Day 29, using a Fisher's exact test. Approximately 51 subjects will be randomized with a 1:1:1 allocation ratio. Assuming the mortality rates at Day 29 are 40% and 80% for the active treatment arm and placebo arm, respectively, 17 subjects per arm will achieve 80% power for a pairwise comparison versus control when the two-sided alpha value is 0.20.

2. ENDPOINTS

The primary, secondary, and other efficacy endpoints are defined in this section and summarized by assessment day in Table 1 .

2.1. Primary Efficacy Endpoint

Cohort 1 (Non-ventilated Subjects)

The primary efficacy endpoint for cohort 1 is proportion of subjects alive and free of mechanical ventilation at Day 29. Mechanical ventilation is defined as invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO). Subjects whose clinical outcome meets NIAID (defined in Section 1.3) score 2 will be considered as using mechanical ventilation.

Cohort 2 (Ventilated Subjects)

The primary efficacy endpoint for cohort 2 is mortality rate at Day 29, defined as the proportion of subjects who die by Day 29.

2.2. Secondary Efficacy Endpoints

Cohort 1 (Non-ventilated Subjects)

1. Time to 2-point clinical improvement by Day 29

   Defined as time from randomization to a 2-point improvement on the NIAID 8-point ordinal scale, or discharge from the hospital, whichever comes first. Subjects who die before Day 29 will be censored at Day 30.

2. Time to return to room air or discharge by Day 29

   Defined as time from randomization to breathing room air (NIAID scale ≥ 5), or discharge from the hospital, whichever occurs first. Subjects who die before Day 29 will be censored at Day 30.

3. Mortality rate at Day 29

Cohort 2 (Ventilated Subjects)

1. Time to 1-point clinical improvement by Day 29

   Defined as time from randomization to a 1-point improvement on the NIAID 8-point ordinal scale, or discharge from the hospital, whichever comes first. Subjects who die before Day 29 will be censored at Day 30.

2.3. Other Efficacy Endpoints

[redacted]

2.4. Safety Endpoints

The following are safety endpoints:

- Adverse events, adverse events of special interest, and serious adverse events
- Laboratory parameters
- Vital signs
- Electrocardiogram
- Chest x-ray or CT scan
- Physical examination

Table 1: Summary of Primary, Secondary and Selected Other Efficacy Endpoints

Endpoints	Day 15	Day 29		Day 90
	Cohort 1, 2	Cohort 1	Cohort 2	Cohort 1, 2
Proportion of subjects alive and free of mechanical ventilation		Primary	Y	
Time to ventilation or death (NIAID≤2)		Y		
Time to ventilation free (NIAID>2)			Y	
Mortality rate	Y	S3	Primary	Y
Overall survival		Y	Y	Y
[redacted]	[redacted]	S2	[redacted]	
Time to 1-point clinical improvement	Y	Y	S1	
Proportion of subjects with 1-point clinical improvement	Y	Y	Y	
[redacted]	[redacted]	S1	[redacted]	
[redacted]	[redacted]	Y	[redacted]	
Time to hospital discharge		Y	Y	Y
Days alive and out of hospital				Y
NIAID scale over time through Day 29		Y	Y	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	
[redacted]		[redacted]	[redacted]	
[redacted]		[redacted]	[redacted]	
[redacted]				[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]		[redacted]	[redacted]	

S: secondary efficacy endpoint; S1: first secondary endpoint; S2, S3: second, and third secondary endpoint respectively.
Y: other efficacy endpoints.

[redacted]

3. ANALYSIS SETS

3.1. Modified Intent-to-Treat (mITT) Analysis Set

All randomized subjects who receive study drug will be included in the mITT analysis set. All efficacy analyses of the study will be based on the mITT analysis set. All mITT analyses will be based on the randomized treatment.

3.2. Safety Analysis Set

All randomized subjects who receive study drug will be included in the safety analysis set. Safety analyses will be based on the actual treatment received.

3.3. Per-Protocol (PP) Analysis Set

All mITT subjects without protocol deviations deemed to impact efficacy will be included in the PP analysis set and will be determined before the database lock. The primary and secondary efficacy endpoints will be further analyzed based on the PP set.

4. GENERAL STATISTICAL CONSIDERATIONS

Analyses described in this SAP will be conducted separately for each of the two cohorts.

Summary statistics for continuous variables will include n (non-missing observations), mean, standard deviation, minimum, median, and maximum. Summary statistics for categorical variables will be presented in terms of frequencies and percentages based on the analysis set unless otherwise specified. In by-visit summary tables, only scheduled visits/timepoints will be summarized.

Time to event data will be summarized using the Kaplan-Meier (KM) method, which will include the estimated median, 25th percentiles, 75th percentiles, and their 80% confidence interval (CI). The CIs will be calculated using a log-log transformation. The event-free probability and its 80% CI will be calculated at days 4, 8, 15, 22, 29, 60 and 90 as appropriate using Greenwood's formula with a log-log transformation.

The 80% confidence interval (CI) of the difference in the proportion (KPL-301 – placebo) will be primary based on normal approximation when comparing treatment for binary (proportion or rate) endpoints.

All relevant subject data will be listed by cohort, treatment, subject and visit/time point including both scheduled and unscheduled visits.

4.1. Randomization, Stratification, and Blinding

An Interactive Web Response System (IWRS) will be used for assignment of the subject identification number at enrollment, randomization to a treatment arm (10 mg/kg KPL-301, 6 mg/kg KPL-301 or placebo), and assignment of blinded investigational product.

The randomization is stratified by three characteristics of the subjects in Cohort 1 and by the first two characteristics for Cohort 2.

1. Use of approved standard of care antiretroviral therapy: yes vs. no
2. Age: <65 vs. ≥ 65 years

3. Acute respiratory distress syndrome (ARDS) status: normal – mild (> 200 PaO2/FiO2) vs. moderate-severe (≤ 200 PaO2/FiO2). If PaO2 is unavailable, use SpO2/FiO2: normal–mild (>235 mmHg) vs. moderate-severe (≤235 mmHg)

There should be no overlap of subject populations between the two cohorts since Cohort 1 baseline NIAID should be 3 or 4 and Cohort 2 baseline NIAID should be 2. In case of subjects being erroneously randomized under the incorrect cohort, the subjects will be analyzed in the correct cohort defined by the baseline NIAID scale. Subjects with baseline NIAID ≥ 5 will be included in Cohort 1 for analyses based on mITT and safety populations but excluded from per protocol analyses.

If subjects were randomized based on incorrect baseline information (strata), then the correct strata will be used for stratified analysis rather than the incorrect strata recorded at randomization.

If fewer than 5 subjects are in a stratification group of all three (or two for cohort 2) factors, that group will be pooled with another stratification group. If the same situation occurs, strata for the second factor will be pooled. If the same situation still exists, the analysis will be done without stratification.

For stratified analyses, if there is no event for both arms of comparison, or all responses are the same within a stratification group, that group will be pooled with another stratification group per the order of the stratification factors listed previously. This principal will be analogously applied to subgroups, but only to those subgroups for which lack of events/responses require it.

4.2. Data Analysis General Information and Definition

4.2.1. Study Drug

Study drug or study treatment refers to 10 mg/kg KPL-301 (mavrilimumab), 6 mg/kg KPL-301 (mavrilimumab) or placebo.

4.2.2. Day 1

Day 1 is defined as the day of the study treatment after randomization.

4.2.3. Baseline Values

Baseline is defined as the last non-missing value obtained prior to the start of study treatment. The baseline NIAID is defined separately in Section 5.7.2.

The change from baseline values will be derived for each subject as the post-baseline evaluation minus the baseline evaluation.

4.2.4. Last Contact

Last contact or last date known alive is defined as the last non-imputed date of any subject record prior to or on the data cut-off date in the clinical database.

4.2.5. Calculation Using Dates

Calculations using dates will adhere to the following conventions:

Study day for a date of interest (TARGET DATE) is calculated as

STUDY DAY = TARGET DATE – Date of Day 1 + 1 if TARGET DATE is on or after Day 1;

STUDY DAY = TARGET DATE – Date of Day 1 otherwise.

Day X in this document refer to the study day X, where X can be 4, 8, 15, 22, 29, 60, 90, etc.

4.2.6. Duration Derivation

Unless otherwise specified for a specific panel or variable, duration variables will be derived according to the following rules. Duration variables expressed in units greater than day will be rounded to 1 decimal place.

Duration (in days) = [end date – start date +1]

Duration (in weeks) = [end date – start date +1] / 7

Duration (in months) = [end date – start date +1] / 30.4375

4.3. Windowing of Visits

Data will be summarized by eCRF visits without windowing.

4.4. Methods for Handling Missing Data

For efficacy data, a survival sweep will be conducted before the database lock to minimize the amount of missing survival status data. Missing NIAID scale and survival status at target days will handled per Section 5.7.2.

For safety data, refer to Section 8.1 for detailed date imputation guidelines.

4.5. Protocol Deviations

All protocol deviations will be entered into database by site staff. The study team will have a blinded review of protocol deviations to determine their classification (important, not important) periodically. Prior to the database lock, the study team will assess impact of all important protocol deviations on efficacy and whether they should be excluded from the per-protocol analysis set.

The number of important protocol deviations, the number of subjects with at least one important protocol deviation, and the number of subjects with at least one important protocol deviation with/without a potential impact on efficacy will be summarized by treatment group. The protocol deviation criteria types will also be summarized, with reference to an evaluability document that will be signed off prior to database lock.

All protocol deviations will be presented in by-subject listings, and subjects with protocol deviations that lead to exclusion from the per-protocol analysis set will be flagged.

5. STATISTICAL METHODOLOGY

5.1. Study Population

A summary of analysis sets by treatment will be presented along with percentages relative to the mITT Analysis Set.

- All Screened
- Randomized
- mITT Analysis Set
- Safety Analysis Set
- Per-protocol Analysis Set

A listing will be provided to describe when informed consent was obtained and if the subject meets all inclusion/exclusion criteria. Reasons of subjects' exclusion from safety, mITT or PP analysis sets will also be listed.

5.2. Subject Disposition

The number and percentage of subjects will be tabulated for the mITT analysis set by treatment:

- Subjects who are ongoing
- Subjects who completed the study
- Subjects who ended study early

Reasons for early study discontinuation will be summarized with the following categories:

- Adverse event
- Lost to follow-up
- Death
- Physician decision
- Site terminated by sponsor
- Study terminated by sponsor
- Technical problem
- Withdrawal by subject
- Other

A listing will be presented to describe whether the subject is on study, completed the study, date of completion or early withdrawal, and the reason for early study discontinuation.

5.3. Demographics and Baseline Disease Characteristics and History

5.3.1. Demographics

Demographic and other baseline characteristics will be summarized for each treatment group and overall based on the mITT analysis set. They will also be presented in by-subject listings. For categorical variables, missing category will be added when at least 1 subject does not have value.

Demographic descriptive statistics will be provided for the following:

- Age
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)

Demographic frequency tabulations will be presented for:

- Age (< 65 years or ≥ 65 years)
- Sex (Male or Female)
- Childbearing potential of female (Yes or No)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Stated, Unknown)

5.3.2. Baseline Disease Characteristics

Baseline characteristics frequency tabulations will be summarized by the CRF categories, which are detailed below:

- Randomization strata from IWRS: use of approved standard antiretroviral therapy (Yes or No), age (< 65 years or ≥ 65 years), ARDS status (normal – mild or moderate-severe, for cohort 1 only)
- Actual randomization strata based on the baseline information
- Covid-19 symptom history findings (fever, fatigue, cough (productive), cough (non-productive), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, headache, diarrhea, nausea, vomiting, pneumonia, loss of taste, loss of smell, other)
- Tuberculosis (negative, positive, indeterminate)
- NIAID 8-point ordinal scale
- Receiving invasive ventilation
  - No
  - Yes (mode of ventilation at time of highest FiO2 requirement)
- Receiving non-invasive ventilation OR high flow nasal cannula?
  - No
  - Yes (mode of ventilation)
- Receiving supplemental oxygen
  - No
  - Yes (delivery method)
  - Other
- Required any other oxygen delivery methods since last assessment
  - No
  - Yes (modalities)
  - Unknown

- Currently requiring or since last assessment has required prone positioning
- Currently requiring or since last assessment has required neuromuscular blockade
- Currently requiring or since last assessment has required pulmonary vasodilators
- Currently have or since last assessment had tracheostomy
- Currently requiring or since last assessment has required ECMO
- Currently requiring or since last assessment has required vasopressor support
- Currently requiring or since last assessment has required renal replacement therapy
- SARS-CoV-2 (RT-PCR) (negative, positive, indeterminate)
- Anti-2019-nCoV (negative, positive or not test/missing)

Continuous variables collected on respiratory and clinical assessment eCRF page will be summarized descriptively as appropriate.

5.3.3. SOFA and qSOFA

Sequential Organ Failure Assessment Score (SOFA) at baseline will be summarized for Cohort 2.

- Descriptive statistics will be provided for the following:
  - PaO2 (mmHg)
  - FiO2 (%)
  - P/F Ratio
  - SOFA Score
- Frequency tabulations will be presented for:
  - assessment performed (No (in ICU, Other) or Yes)
  - on mechanical ventilation (No or Yes)
  - platelets (x 10^3/uL) (≥ 150, 100-149, 50-99, 20-49, or <20)
  - Glasgow coma scale (15, 13-14, 10-12, 6-9, or <6)
  - bilirubin (mg/dl (umol/L)) (<1.2 (<20)), 1.2 - 1.9 (20 - 32), 2.0 - 5.9 (33 - 101), 6.0 - 11.9 (102 - 204), or ≥12.0(≥204))
  - mean arterial pressure OR administration of vasoactive agents required (Blood pressure stable without need for pressor support, MAP less than 70 mmHg, (Dopamine <=5 mcg/kg/min or Dobutamine), (Dopamine >5 mcg/kg/min, Epinephrine <=0.1 mcg/kg/min, or nor Epinephrine <=0.1 mcg/kg/min), or (Dopamine >15 mcg/kg/min, Epinephrine >0.1 mcg/kg/min, or nor Epinephrine >0.1 mcg/kg/min))
  - creatinine (mg/dL) (umol/L) (or urine output) (<1.2 (<110)), 1.2 - 1.9 (110 - 170), 2.0 - 3.4 (171 - 299), 3.5 - 4.9 (300 - 440), or 5.0 mL/day<=UOP<500 mL/day (>440))

Quick Sequential Organ Failure Assessment (qSOFA) at baseline will be tabulated for Cohort 1:

- qSOFA Score
- assessment performed (No (Invasive/noninvasive ventilation, Other) or Yes)
- respiration rate >=22 breaths/min (No or Yes)

- change in mental status (glascow score less than 15) (No or Yes)
- systolic blood pressure less than or equal to 100 mm/Hg (No or Yes)

By subject SOFA and qSOFA will be listed.

5.4. Medical History

Medical history data will be summarized by system organ class (SOC) and preferred term (PT) per Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 based on the safety analysis set. Subjects with multiple events coded to the same SOC or PT will only be counted once in the summary for that category.

All medical history data will be listed.

5.5. Prior and Concomitant Medications

Prior medications are defined as those taken before the date of the study drug. Concomitant medications are defined as any non-study medication taken during the study i.e. on or after the date of the study drug and within 90 days of the study drug treatment.

The number and percentage of subjects taking prior and concomitant medications will be tabulated separately by anatomical-therapeutic-chemical (ATC) level 2 and preferred drug name by treatment for the safety analysis set. A subject taking the same medication multiple times is counted only once under that preferred drug name. The summary will be sorted in the alphabetic order of ATC classes and preferred terms.

Prior and concomitant medications will be listed with flag.

Medications are coded using the World Health Organization (WHO) Drug dictionary B3 enhanced, version Mar 2020.

5.6. Study Treatments and Extent of Exposure

Study drug exposure will be summarized descriptively by treatment for the safety analysis set:

- Duration of infusion (minutes)
- Received the full injection volume (Yes or No)
- Infusion interrupted (Yes or No)
  - Reasons for infusion interruption (Adverse event, Technical Issue, Other)
- Infusion resumed (Yes or No)

The study drug administration details including the administration date and time will be presented in a by-subject listing.

5.7. Efficacy Analysis

All efficacy endpoints will be analyzed for the mITT analysis set. The primary and secondary endpoints will also be performed for the Per-protocol analysis set. Treatment comparisons will be for each KPL301 arm vs placebo.

5.7.1. Multiplicity Adjustment

No multiplicity adjustment will be applied for the Phase 2 part of the study.

5.7.2. NIAID Scale and Missing Data Imputation for Binary Endpoints

When two or more NIAID scores are collected on the same study day, the lowest score will be used, except at the date of discharge, in which the highest NIAID score will be used.

Baseline NIAID scores are derived from Day 1 or screening assessment:

- If screening and day 1 are the same day, and screening assessment is available, then the screening NIAID will be used as baseline.
- If screening and day 1 are not on the same day, or screening NIAID assessment is missing, the score from Day 1 will be used as baseline.

For endpoints where the event of interest is favorable, like proportion of subjects alive and free of ventilation, and proportion of subjects with 1-point/2-point clinical improvement, the following imputation rule of NIAID scale will be adopted:

- When the NIAID assessment is missing at the target day (Day 15, 29, etc.), the NIAID score closest to and within 2 days of the target day will be used. In case of ties with equal number of days on either side of target day, the value before the target day will be used.
- When no NIAID assessment is available within 3 days of the target day, the primary treatment comparison will be based on a combination of responder imputation and non-responder imputation:
  - Discharged subjects will be considered as having had the event (responders).
  - Subjects who are still in the hospital will be considered as not having had the event (non-responders).
  - Subjects who terminate the study early including death will be considered as not having had the event for all subsequent target days after discontinuation (non-responders).

In calculation of the mortality rate, a subject with the last known alive date on or after the target day is considered alive. If the last known alive date is before the target day but within 2 days of the visit window, the subject is considered alive at the target day. Since survival sweep will be conducted for each database lock, minimum missing mortality status is expected.

5.7.3. Censoring Rules for Time to Event Endpoints

Since scheduled visits allow windows (2-day for Day 15 and Day 29, and 7-day for Day 60 and 90), NIAID scores collected within visit windows of the the target days will be used for time to event analysis by the corresponding target day. The last assessments referred to in this section include those occur after the target day but within the protocol-defined visit window, in which cases the date of the target day instead of the actual day will be used for calculation of time. For example, if a subject has not had 2-point clinical improvement by Day 29 visit, which occurrs on Day 30, the subject will be censored at Day 29 instead of Day 30 or Day 22 (the assessment before Day 29).

- Time to ventilation or death by Day 29
  Defined as time (in days) from randomization to the date of death or start date of using mechanical ventilation (NIAID ≤ 2) by Day 29 for Cohort 1. All subjects who have never had

NIAID ≤ 2 by Day 29 will be censored at the last assessment date of NIAID 8-point ordinal scale.

- [redacted]

- Overall survival by Day X (X=29, or 90)
  Defined as time (in days) from the randomization date to the date of death by Day X. All survival subjects will be censored at last date known alive on/before Day X.

- [redacted]

- Time to K-point clinical improvement by Day X (K=1, or 2, X=15, or 29)
  Defined as time (in days) from randomization to the date of a K-point improvement on the NIAID 8-point ordinal scale, or discharge from the hospital, whichever occurs first, by Day X. Alive subjects who do not have K-point improvement nor discharge from the hospital will be censored at the date of the last NIAID 8-point ordinal scale assessment on/before Day X. Dead subjects will be censored at Day X +1.

- [redacted]

- [redacted]

5.7.4. Analysis of Primary Efficacy Endpoint

The proportion of subjects alive and free of ventilation at Day 29 for Cohort 1, and the proportion of subjects who die (mortality rate) by Day 29 for Cohort 2 will be analyzed by Fisher's exact test. The 80% confidence interval (CI) will be be calculated using the Clopper-Pearson exact method. Number of subjects and percentages will be summarized by treatment. The 80% CI of the difference in the proportion (KPL-301 – placebo) based on normal approximation will be provided.

Cochran-Mantel-Haenszel (CMH) test adjusting for the randomization strata (standard of care antiretroviral therapy, age, and ARDS status) will be used as supportive analysis of the primary efficacy endpoint for Cohort 1. The CMH method addresses the global null hypothesis of no difference between treatments in all of the strata. Hence, it corresponds to, in all strata, the risk difference being 0, the risk ratio being 1, and the odds ratio being 1. The CMH p-value is the same

across odds ratio/risk ratio/risk difference. In addition to CMH p-value, the stratified risk difference and the stratified odds ratio will be provided in our analyses.

Analysis of the primary efficacy endpoint based on the per protocol population will be conducted following the same methods.

5.7.5. Analysis of Secondary and Other Efficacy Endpoints

5.7.5.1. Time to event endpoints

For all time to event endpoints, the primary treatment comparison between the active treatment and the placebo (10 mg/kg mavrilimumab vs. placebo, and 6 mg/kg mavrilimumab vs. placebo) will be based on log-rank test stratified by the actual randomization strata.

The Kaplan-Meier (KM) method will be used to estimate the survival distribution function for all the time to event endpoints. The 25th, 50th (median), 75th percentiles and their two-sided 80% confidence interval (CI) will be estimated. In addition, the probability of favorable outcome (event rates, or event-free rates depending on the endpoins) at Day 4, 8, 15, 22 and 29 will be calcualted, along with their standard errors using Greenwood's formula (Klein, 2003) stratified by the actual randomization strata. Corresponding Kaplan-Meier plot will be produced. In case of favorable outcomes, the plot will be based on 1-KM.

The hazard ratio for (10 mg/kg mavrilimumab vs. placebo) or (6 mg/kg mavrilimumab vs. placebo) and the corresponding Wald 80% CI will be calculated based on a Cox proportional-hazards model with treatment as covariates, stratified by the actual randomization strata.

5.7.5.2. Binary (rate or proportion) endpoints

The primary treatment comparison for all binary endpoints will be based on the Fisher's exact test. Number of subjects and percentages will be summarized by treatment. The 80% confidence interval (CI) of the difference in the proportion (KPL-301 – placebo) based on normal approximation will be provided.

The event rates (or event-free) from the corresponding time to event analysis can serve as supportive analyses. For example, proportion of subjects with K-point clinical improvement can be estimated from time to K-point clinical improvement; mortality rate can be estimated from the overall survival. No formal testing will be conducted.

5.7.5.3. Endpoints to be summarized descriptively

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be used to summarize the following endpoints. No imputation will be done unless otherwise specified.

- [redacted]
- [redacted]

- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

5.7.6. Subgroup analysis

Subgroup analyses will be conducted for each of the randomization stratum for the primary efficacy endpoint. The same statistical methods and conventions used for the primary efficacy endpoint will apply.

5.8. Safety Analysis

The safety endpoints will be tabulated by treatment based on the Safety Analysis Set. All safety data including those collected during the safety follow-up will be listed by subject.

5.8.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have a causal relationship with this treatment. An AE will be defined as treatment-related if its relationship to the study drug is reported as Possibly Related or Definitely Related by Investigator.

An AE is considered treatment-emergent adverse event (TEAE) if the AE begins on/after and within 90 days of the study drug administration. If the date of AE onset is missing or coincides with the date of the study drug administration and AE time is not captured, AE will be considered treatment-emergent.

All AEs will be coded using MedDRA version 23.0. A subject experiencing multiple AEs under the same preferred term (PT) or same system organ class (SOC) will be counted only once for that PT or SOC by maximum severity. If a subject experience the same AE more than once with more than one causal relationship to study drug, the strongest causal relationship to study drug will be given precedence. Any missing severity, causality, or outcome will not be imputed and classified as 'Missing'. Detailed imputation rules for missing AE dates are in Section 8.1.1.

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 sponsor. An AESI may be serious or non-serious.

The number of subjects with at least one TEAE will be tabulated. The following tables summarize incidences of various aspects of TEAEs, treatment-emergent serious AEs (TESAEs), and treatment-emergent AESIs (TEAESIs):

- Overview of TEAEs (summary of all the subsequent items)
- TEAEs by SOC and PT
- TEAEs by PT
- TEAEs by maximum severity (mild, moderate, or severe)
- Drug related TEAEs (related or not related) by SOC and PT
- TESAEs by SOC and PT
- Drug related TESAEs by SOC and PT
- TESAEs by PT
- TEAESIs by SOC and PT
- TEAEs leading to dose interruption by SOC and PT
- TEAEs leading to death by SOC and PT

All information pertaining to adverse events will be listed by subject, detailing verbatim term given by the investigator, preferred term, system organ class, start date, stop date, severity, outcome, action taken and drug relatedness.

Separate listings will be created for Serious TEAEs, and TEAESI, and death.

Additionally, non-serious TEAEs by SOC and PT will be tabulated.

5.8.2. Clinical Laboratory Parameters

The following laboratory analyses are performed at the Study Site/Clinic laboratories and recorded on the eCRF:

- Screening for tuberculosis
- Pregnancy
- SARS-CoV-2 test with RT-PCR
- Hematology: complete blood count + differential
- Chemistry: electrolytes, blood urea nitrogen, glucose, and CR
- Liver profile: AST, ALT, Alb, AlkP, Tbili, Dbili
- Lipid panel: Cholesterol, total; high-density lipoprotein (HDL) cholesterol; low-density lipoprotein (LDL) cholesterol (calculation); triglycerides; very low-density lipoprotein (VLDL) cholesterol (calculation)
- Urinalysis
- [redacted]

The following tests are performed by the central lab:

- [redacted]
- [redacted]
- [redacted]

Continuous laboratory data ([redacted], hematology, coagulation, chemistry, liver profile, lipid panel, urinalysis) will be examined for trends using descriptive statistics of actual values and changes from baseline over time by treatment for the safety analysis set. Urinalysis will be summarized categorically.

Shift tables will be produced for hematology and chemistry.

All laboratory results will be presented in by-subject listings.

5.8.3. Vital Signs

Vital signs include temperature, respiratory rate, systolic blood pressure/ diastolic blood pressure, and heart rate. Body weight and height will be reported in Body Measurements eCRF.

Actual values of vital signs (including weight) and changes from baseline will be summarized using descriptive statistics by visit.

All vital signs data will be listed.

5.8.4. Electrocardiogram (ECG)

All ECG data will be listed.

5.8.5. Physical Examination

All physical examination data will be listed.

5.8.6. Chest Imaging

Chest imaging data will be listed.

6. CHANGES TO PLANNED ANALYSES FROM THE PROTOCOL

- The SAP is for Phase 2 only and a separate SAP will be developed for the Phase 3 part of the study
- The following other efficacy endpoints are out of scope for this SAP, and will be reported separately
  - [redacted]

- [redacted]

7. REFERENCE

Klein JP, Moeschberger ML. Survival analysis technique for censored and truncated data (second edition). Springer-Verlag; 2003.

8. APPENDICES

8.1. Handling of Missing Safety Data

No imputation will be made for completely missing date unless otherwise specified. General imputation rules mentioned below apply to partially missing or impossible dates:

- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date
- If the start date is not missing, and the imputed stop date is before the start date, then the imputed stop date will be equal to the start date
- Any imputed dates need to be logical. For example, last dose date should not be later than death date.

When imputation rules in subsequent sections contradicts the general rule, always follow the general rule.

8.1.1. Adverse Event Date Imputation

Follow the general rule specified in Section 8.1.

Incomplete Start Date:

Missing day, month, and year

No imputation will be made; the corresponding AE will be included.

Missing day and month

- If the year is the same as the year of the first dose date, then impute day and month as the day and month of the first dose
- If the year is prior to the year of the first dose date, then impute day and month as 31 Dec
- If the year is after the year of the first dose date, then impute day and month as 01 Jan.

Missing day only

- If the month and year are the same as those of the first dose date, then impute day as the day of the first dose date

- If either the year of partial date is before the year of the first dose date, or the years are the same, but the month of partial date is before the month of the first dose date then impute day as last day of the month
- If either the year of partial date is after the year of the first dose date, or the years are the same, but the month of partial date is after the month of the first dose date, then impute day as first day of the month.

Incomplete Stop Date:

Missing day, month, and year

- No imputation will be made.

Missing day and month

- If the year is the same as the year of the last dose date, then impute day and month as the day and month of the last dose date
- If the year is prior to the year of the last dose date, then impute day and month as 31 Dec
- If the year is after the year of last dose date, then impute day and month as 01 Jan.

Missing day only

- If the month and year are the same as those of the last dose date, then impute day as the day of the last dose date
- If either the year of partial date is not the same as the year of the last dose date, or the years are the same, but the month of partial date is not the same as the month of the last dose date, then impute day as last day of the month.

8.1.2. Concomitant Medication Date Imputation

Follow the general rules specified in Section 8.1 and Section 8.1.1.

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