Study Number: KIN-1901-2001

Study Title: A Multi-Center, Adaptive, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Gimsilumab in Subjects With Lung Injury or Acute Respiratory Distress Syndrome (ARDS) Secondary to Coronavirus Disease 2019 (COVID-19)

Clinical Study Protocol

Version 5.0 (Amendment 4): 17-Aug-2020

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CLINICAL STUDY PROTOCOL

Study Title:	A Multi-Center, Adaptive, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Gimsilumab in Subjects With Lung Injury or Acute Respiratory Distress Syndrome (ARDS) Secondary to Coronavirus Disease 2019 (COVID-19)
Protocol Number:	KIN-1901-2001
Compound Name and/or Number:	Gimsilumab (KIN-1901, formerly MORAb-022)
Sponsor:	Kinevant Sciences GmbH ("KSG"), a Swiss Limited Liability Company, is the sponsor of this study. Kinevant Sciences, Inc. ("KSI"), a Delaware corporation and an affiliate of KSG, has been engaged by KSG to manage the day-to-day operations of the study. All references to "Sponsor" contained herein shall refer to KSI, acting pursuant to a services agreement with KSG.
Development Phase:	2
Indication:	For the treatment of lung injury or ARDS secondary to COVID-19
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Study Director:	[redacted]

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SPONSOR SIGNATURE PAGE

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This protocol has been approved by a representative of Kinevant Sciences GmbH. The following signature documents this approval.

8/17/2020

Date

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Sponsor Medical Contact/SAE Contact Information:

Role	Name
Primary Medical Monitor (Europe)	[redacted]
Primary Medical Monitor (US)	[redacted]
Secondary Medical Monitor	[redacted]
Contact for Serious Adverse Events (SAEs)	On discovery, all SAEs should be immediately reported (latest within 24 hours of knowledge of the event) to [redacted]

Study Sponsor

Kinevant Sciences GmbH ("KSG"), a Swiss Limited Liability Company, is the sponsor of this study. Kinevant Sciences, Inc. ("KSI"), a Delaware corporation and an affiliate of KSG, has been engaged by KSG to manage the day-to-day operations of the study. All references to "Sponsor" contained herein shall refer to KSI, acting pursuant to a services agreement with KSG.

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INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	Signature
Date	Site

Study Site

Name of Primary Investigator Site

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1. PROTOCOL SUMMARY FOR STUDY KIN-1901-2001

Synopsis

Study Rationale	In December 2019, the city of Wuhan, China experienced an outbreak of coronavirus disease 2019 (COVID-19), caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of March 2020, COVID-19 has become a global pandemic, and there are currently no approved agents available to treat coronaviruses [World Health Organization (WHO) COVID-19 Situation Report, 2020]. SARS-CoV-2 infection often induces an overactive immune response that causes significant lung damage, leading to acute respiratory distress syndrome (ARDS) and ultimately death. Granulocyte macrophage-colony stimulating factor (GM-CSF), a hematopoietic growth factor and immunomodulatory cytokine, is believed to be a key driver of cytokine storm and lung hyper-inflammation [Molfino, 2016; Sterner, 2019; Zhou, 2020]. Targeting GM-CSF using an anti-GM-CSF antibody, gimsilumab (KIN-1901), represents a promising strategy to treat patients who have developed lung injury or ARDS secondary to COVID-19.
Study Design	Randomized, double-blind, placebo-controlled
Study Objectives	**Primary Objective:** • The primary objective is to evaluate the impact of intravenous (IV) treatment with gimsilumab on mortality in subjects with lung injury or ARDS secondary to COVID-19. **Key Secondary Objectives:** • To assess the effect of gimsilumab on ventilation requirements • To assess the effect of gimsilumab on overall duration of hospitalization **Additional Secondary Objectives:** • To assess the effect of gimsilumab on the need for Intensive Care Unit (ICU) level of care • To assess the effect of gimsilumab as measured by the National Early Warning Score (NEWS) • To assess the effect of gimsilumab as assessed by the Sequential Organ Failure Assessment (SOFA) score • To assess the effect of gimsilumab as measured by the 7-point ordinal scale • To assess the effect of gimsilumab on peripheral capillary oxygen saturation / fraction of inspired oxygen (SpO_2/FiO_2) • To assess the effect of gimsilumab on oxygenation requirements • To assess changes in on-treatment viral load • To assess the effect of gimsilumab on biomarkers of inflammation • To determine the pharmacokinetic (PK) properties of gimsilumab • To assess the immunogenicity of gimsilumab • To determine the safety and tolerability of gimsilumab

	Exploratory Objectives: • To explore the effect of gimsilumab on serum cytokine concentrations and surfactant protein D (SP-D) • To explore the effect of gimsilumab on other measurements of lung injury that may be performed during standard care (e.g., Lung Injury Score [LIS], chest radiography, PaO_2/FiO_2 [P/F ratio], need for extracorporeal membrane oxygenation [ECMO]) • To explore the effect of gimsilumab on cardiac function (if measured) • To assess the effect of gimsilumab on renal function
Study Population	270 subjects (135 subjects per arm) who have a confirmed diagnosis of COVID-19 with clinical evidence of acute lung injury or ARDS
Number of Planned Subjects	270 total subjects are planned for this study. Arm 1 (Active drug): 135 subjects Arm 2 (Placebo): 135 subjects
Study Treatments	Gimsilumab 400 mg IV on Day 1 and 200 mg IV on Day 8, or matching placebo (saline solution) IV on Day 1 and on Day 8. The Day 8 dose will be omitted if the subject is discharged from the hospital or is no longer in need of supplemental oxygen or ventilatory support for >48 hours.
Treatment and Study Duration	This study will consist of a 2-week Treatment Period (last dose Day 8, if administered) and a 22-week Follow-up Period, for a total study duration of 24 weeks for each subject.
Study Centers and Countries	This study will be conducted at approximately 20 centers in the United States and potentially 6 centers in Mexico; other countries may be added, if needed.

Study Endpoint(s)	**Primary Endpoint:** • Incidence of mortality by Day 43 **Key Secondary Endpoints:** • Proportion of subjects who survived and were not requiring mechanical ventilation on Day 29 • Mechanical ventilation-free days by Day 29 • Time to hospital discharge by Day 43 **Additional Secondary Endpoints:** • Incidence of mortality by Days 15, 22, 29, 85, and 169 (End-of-Study [EoS]) • Proportion of subjects who survived and were not requiring mechanical ventilation on Days 15, 22, and 43. • Mechanical ventilation-free days for all subjects by Days 15, 22, and 43 • ICU-free days for all subjects by Days 15, 22, 29, and 43. • Incidence of mechanical ventilation use for all subjects by Days 15, 22, 29, and 43. • Incidence of ICU use for all subjects by Days 15, 22, 29, and 43 • Time to death by Day 43 and Day 169 (EoS) • NEWS assessed daily while hospitalized • SOFA score, and each of the components, assessed daily while in the ICU • The percentage of subjects reporting each severity rating on the 7-point ordinal scale, assessed daily while hospitalized and, if discharged from hospital, on Days 15, 22, 29, 36, 43, 85, and 169 (assessed by phone) • Status on the 7-point ordinal scale, assessed daily while hospitalized and, if discharged from hospital, on Days 15, 22, 29, 36, 43, 85, and 169 (assessed by phone) • Time to clinical improvement by 2 points on the 7-point ordinal scale • Change from Baseline in SpO_2/FiO_2, assessed daily while hospitalized • Incidence and duration of oxygen use during the study • Change from Baseline in viral load as measured by quantitative polymerase chain reaction (PCR) test on Days 2, 9, and day-of-discharge (DoD) • Change from Baseline in D-dimer, cardiac troponin I, lactate dehydrogenase (LDH), ferritin, and C-reactive protein (CRP) • Serum gimsilumab concentrations • Analysis of anti-gimsilumab antibodies (ADAs) **Safety Endpoints:** • Safety and tolerability, including assessment of clinical safety laboratory measurements, physical examinations, vital signs,

	concomitant medications; cumulative incidence of adverse events (AEs), serious adverse events (SAEs), and severe AEs **Exploratory Endpoints:** • Change from Baseline in the cytokine panel and serum SP-D • Change from Baseline in LIS (if performed) • Change from Baseline in chest radiographic assessment (if performed) • Change from Baseline in P/F ratio, if performed • Incidence and duration of ECMO use • Change from Baseline in left ventricular ejection fraction (LVEF) (when measured) • Change from Baseline in estimated glomerular filtration rate (eGFR) [Modification of Diet in Renal Disease (MDRD) equation], assessed when central clinical safety laboratory measurements are collected during hospitalization

Inclusion Criteria	**An individual will be eligible for participation in this study only if all of the following inclusion criteria are met:** 1. Male or non-pregnant female age ≥18 years 2. Subject (or legally authorized representative [LAR]) is able and willing to provide written or verbal informed consent, which includes compliance with study requirements and restrictions listed in the consent form. NOTE: If a subject or LAR must be consented verbally, the site must have a site policy for verbal consent and the consent must be clearly documented in the subject's chart. 3. Has documented laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other approved clinical testing prior to randomization 4. CRP ≥50 mg/L or serum ferritin ≥1,000 ng/mL. Results from CRP and ferritin tests performed within 8 days of randomization are acceptable for enrollment. 5. Radiographic evidence of bilateral infiltrates. Acceptable imaging tests (chest X-ray, CT scans) done within 3 days of Day 1 can be used for inclusion. 6. Subject has clinical evidence of lung injury [defined as (1) requiring supplemental oxygen ≥4L O_2 to attempt to maintain ≥92% SpO_2, or (2) P/F ratio ≤300 mmHg (can be imputed)], or meets clinical classification criteria for ARDS [ARDS Berlin Definition, 2012], secondary to COVID-19. 7. Female subjects must agree to use an approved highly effective birth control (BC) method (<1% failure rate per year) throughout the study (until completion of the Day 85 Follow-up Visit), unless documented to have a reproductive status of non-childbearing potential or is postmenopausal: • Non-childbearing potential defined as pre-menopausal female with medical history of bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries), or hysterectomy; hysteroscopic sterilization, • Postmenopausal defined as 12 months of spontaneous amenorrhea or with follicle stimulating hormone (FSH) confirmation. • Woman of childbearing potential (WCBP) who is already using an established method of highly effective contraception or agrees to use one of the allowed BC methods, for at least 28 days prior to the start of dosing (as determined by the Investigator Brochure or Investigator or designee) to sufficiently minimize the risk of pregnancy throughout study participation (until completion of the Day 85 Follow-up Visit). 8. Males who are sexually active must agree to use one of the allowed BC methods. Male subjects must also agree to sufficiently minimize the risk of pregnancy throughout study participation (until completion of the Day 85 Follow-up Visit).

Exclusion Criteria	1. Subject requires norepinephrine at a dose of >0.5 mcg/kg/min, or equivalent 2. Subject has been intubated for >72 hours. Note: in the event of extubation and re-intubation, the calculation for the number of hours the subject has been intubated begins at the first intubation. 3. Evidence of life-threatening dysrhythmia (e.g., ventricular tachycardia [VT], ventricular fibrillation [VF]), or cardiac arrest on presentation 4. Evidence of new or preexisting decompensated heart failure. 5. At the time of screening, subject is anticipated to require ECMO 6. Absolute neutrophil count <1,000 per mm^3 7. Platelet count <50,000 per mm^3 8. History of known anti-GM-CSF autoantibodies (autoAb) or pulmonary alveolar proteinosis. Note: A negative anti-GM-CSF autoAb test result is not required at screening. 9. Severe chronic respiratory disease (e.g., known chronic obstructive pulmonary disease [COPD], pulmonary arterial hypertension [PAH], idiopathic pulmonary fibrosis [IPF], interstitial lung disease [ILD]) requiring supplemental oxygen therapy or mechanical ventilation pre-hospitalization (e.g., prior to COVID-19 diagnosis) 10. Known or suspected active and untreated tuberculosis (TB), human immunodeficiency virus (HIV), hepatitis B or C infection • Results of TB, hepatitis B and C, and HIV tests are not required prior to enrollment if there is no suspicion of active infection, as per KIN-1901 Guidance on Active Infections Testing. 11. Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) >5 × upper limit of normal (ULN). 12. eGFR <30 mL/min/1.73m^2 (MDRD equation) or requiring hemofiltration or dialysis 13. Use of any immunomodulatory biologic (e.g., anti-IL-1, anti-IL-6R, anti-TNF, inhibitors of complement signaling), cell therapies (e.g., mesenchymal stem cells), or small molecule Janus kinase [JAK] inhibitors within the past 7 days or within five half-lives (whichever is longer), or planned use of any of these agents from Screening until Day 43 of the study, unless approved by the Medical Monitor. The following will be allowed/disallowed: • Immunomodulatory biologics for COVID-19 treatment are excluded and should not be used until Day 43 unless discussed with the Medical Monitor. Other non-biologic immunomodulators (non-JAK inhibitors), e.g., medicines for previous transplantation, or disease modifying anti-rheumatic drugs (DMARDS), and have had a stable dose for ≥8 weeks are permitted. • Subjects who have been treated with convalescent plasma (CP) prior to enrollment are eligible if the subject continues to meet all inclusion criteria at screening. Ongoing therapy with CP is allowable if clinically indicated in the view of the treating physician or the Investigator. • The use of investigational anti-viral treatment (e.g., remdesivir) is allowed if the subject continues to meet all inclusion criteria at screening.

	14. Ongoing chronic (≥4 weeks) use of corticosteroids >10 mg/day of prednisone or equivalent at the time of randomization. A corticosteroid dose that has been tapered to 10 mg or less within 14 days of randomization is also prohibited. 15. Pregnancy and/or breast feeding 16. Unable to receive invasive or non-invasive ventilatory support 17. Moribund condition in the opinion of the clinical team
Database Locks	The study database will be locked when all subjects complete the Day 43 Visit, discontinue from the study early, or meet the primary mortality endpoint. The second lock will occur when the last subject completes the Day 169 EoS visit. In addition, there will be 2 database extracts (soft locks) for interim analyses, the first of which will be conducted when 60 subjects have been treated and have completed through Day 15; the DMC will review the data for safety and futility and provide their recommendations. The second interim analysis will be conducted when 100 subjects have completed at least the Day 29 Visit for non-mortality endpoints and have the data for the endpoint of mortality (by Day 43).

Statistical Analyses	**Sample Size and Power** There will be 270 subjects with confirmed COVID-19 and clinical evidence of lung injury or ARDS (135 subjects per arm) with 1:1 randomization. The comparisons between the treatment arms will have approximately 80% power and alpha level 0.05 (two-sided) to demonstrate the significant reductions (15% versus 30%) of the primary endpoint between gimsilumab versus placebo. The study will enroll at least 40%, but no more than 60%, of total subjects in each of the two categories of clinical status : ([lung injury/mild ARDS] or [moderate/severe ARDS]) at Baseline, which will be used as the stratified factor in the randomization. **Randomization** The central stratified randomization will be used to assign subjects into one of the study treatment arms with an equal randomization ratio (1:1) with the stratification factors of subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) and country. Key Analysis Sets • The Intent-to-Treat (ITT) Population will include all randomized subjects who receive any amount of study drug. The ITT subjects will be analyzed according to randomized treatment, irrespective of whether or not they have prematurely discontinued. Subjects who withdraw from treatment and/or the study early will be followed for Day 43 all-cause mortality. All efficacy analyses will be performed using the ITT Population. • The Safety Population (SP) will include all randomized subjects who receive any amount of study drug. The SP will be analyzed according to the treatment received. This set will be used for the safety analyses. • The Per-Protocol (PP) Population will include all subjects in the ITT Population who complete the Day 43 Visit with no major protocol violations. The PP Population will be used for supportive analyses of the efficacy measurements.

Statistical Methods in General

All statistical analyses will be conducted using SAS, Version 13.1 or later. Baseline characteristics will be summarized by treatment arm. For continuous measures the mean and standard deviation (SD) will be summarized. Categorical variables will be described by the proportion in each category.

Efficacy Analyses

The primary analysis of the efficacy endpoint (Mortality by Day 43) will be performed by using logistic regression [Ge, 2011] with treatment, country, and subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) as covariates. The subjects who meet the criteria of endpoint will be summarized by the numbers and percentages of the incidence, with odds ratio and its 95% confidence interval (CI) presented for gimsilumab versus placebo, and p-value.

The secondary analysis of the primary endpoint will be conducted by the Cox Proportional hazard model on the time to death. The median of the time to event from Kaplan-Meier curves will be presented for each treatment, and the hazard ratio of gimsilumab versus placebo will be presented with 95% CI, and p-value.

Adjustment of Multiple Comparisons and Interim Analysis

The interim analysis will be conducted when 60 subjects have been treated and have completed through Day 15; the DMC will review the data for safety and futility and provide their recommendations.

The second interim analysis will be conducted when 100 subjects have completed at least the Day 29 Visit for non-mortality endpoints and have the data for the endpoint of mortality by Day 43. The objectives of the second interim analysis will be to stop the study by superiority, futility, or perform the sample size re-estimation. For controlling overall two-sided alpha of 0.05 overall for the final analysis on the primary endpoint of Mortality Day 43, 0.001 of the alpha will be used for the superiority comparison during the second interim analysis, and 0.049 will be used for the final analysis. The weighted average of two summary measures by Cui L, Hung HM, Wang [Cui, 1999] will be used, one based on the data collected in the interim analysis, and the other based on the data collected after the interim.

Analyses in General

All the continuous variables, including the changes from Baseline, will be summarized by the treatment with the means, SD, medians and the ranges. The Mixed Model with Repeated Measurements (MMRM) /Analysis of Covariance (ANCOVA) model with the treatment, country, subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]), and visit as the model term, and Baseline value as the covariate will be used to test for the significance of the treatment difference. The least square means, standard errors, 95% CIs and p-values will be presented.

	All the categorical variables will be summarized by the treatment with the numbers and percentages of the subjects, and the treatment difference will be tested by using CMH test stratified by 1) country and 2) subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]). The time to event endpoints will be analyzed by using the Cox Proportional Hazard model with the treatment, country, and subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) as the model term. The hazard ratio of gimsilumab versus placebo will be presented with 95% CI and p-value from the model. The Kaplan-Meier curves of the time to events will be presented for treatments on each endpoint. **Handling of Missing Data** Sensitivity analyses will be performed for the primary and key secondary endpoints by using multiple imputations for the missing data: • Tipping-point multiple imputation analysis Missing data will be imputed for Mortality by Day 43 with all possible combinations of Death or Survival in the two arms. The combination which alters the conclusion will be defined as the tipping point for evaluation on the robustness of the results. • Imputation differentiating the reasons of missing data from the early drop out The reasons of the lost to follow-up, SAEs/AEs, and the use of rescue medications will be identified, and the percentage of these subjects will be summarized by treatment. The data for informative censoring, such as the unfavorable or worst outcome, can be used to impute the missing data. More details will be pre-specified in the statistical analysis plan (SAP). **Safety Analyses** Safety will be assessed based on the SP for AEs, laboratory parameters, physical examination, vital signs, and clinical chemistries throughout the duration of the study. The safety analyses will include descriptive summaries by treatment arm of AEs. The number and percentage of participants reporting AEs and SAEs will be presented. Adverse events will be categorized by system organ class (SOC) and preferred term (PT) and summarized by the number of participants (and percentage) with at least 1 event, and the number of events. Adverse events will also be summarized by seriousness, grade, and study drug relationship for all participants. The continuous variables, including the changes from Baseline, will be summarized by descriptive statistics: mean, SD, and the range. The categorical variables, such as normal/abnormal will be summarized by the numbers and percentages at each visit, and the shift table from Baseline to each visit will be presented. **Timing of Analyses with All Subjects** The first unblinded analyses will be conducted when the last subject completes the Day 43 Visit, discontinues from the study early, or meets

	the primary mortality endpoint (by Day 43). The second unblinded analyses will be conducted when the last subject completes the Day 169 Follow-up Visit (EoS). The DMC will be responsible for closely reviewing the safety data from the unblinded interim analysis and for providing their recommendations. The detailed objectives and procedures of the interim analyses will be described in the DMC Charter. **Pharmacokinetic, Biomarker, and Immunogenicity** Data will be summarized by treatment arm. **Statistical Analysis Plan (SAP)** A detailed (revised) SAP will be signed and submitted to the agencies prior to the interim analysis of 100 subjects.

2. INTRODUCTION

2.1. Study Rationale

2.1.1. COVID-19 Background, Clinical Course, and Immunopathogenesis

In December 2019, the city of Wuhan, China experienced an outbreak of coronavirus disease 2019 (COVID-19), caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of March 2020, COVID-19 has become a global pandemic [World Health Organization (WHO) COVID-19 Situation Report, 2020], and there are currently no approved agents available to treat coronaviruses.

Although most infections are mild, approximately 20% of COVID-19 patients experience severe viral pneumonia that can progress to acute respiratory distress syndrome (ARDS) and death [Wu, 2019]. Clinical features of serious cases of COVID-19 resemble infections from severe acute respiratory syndrome coronavirus (SARS-CoV), which caused an epidemic in 2002-2003 [Huang, 2020]. Immunopathological research into SARS-CoV defined three phases of disease: (1) fever, cough, and other systemic symptoms accompanied by an increase in viral load, (2) severe pneumonia that persists, despite a decline in viral load, due to a hyperactive immune response consisting of cytokine storm and significant macrophage/neutrophil lung infiltration, (3) pulmonary destruction and death [Lam, 2004; Channappanavar, 2017]. Emerging evidence suggests that cytokine storm and aberrant lung inflammation are similarly key features contributing to clinical worsening in COVID-19 [Huang, 2020; COVID-19 Investigation Team, 2020; Kristas, 2020; Mehta, 2020]. Specifically, high concentrations of proinflammatory cytokines were found in COVID-19 patients, particularly those who were severely ill [Huang, 2020]. The observed cytokine signature was indicative of a T-helper-1 (Th1) cell inflammatory response [Huang, 2020], and activation of Th1 cells was found to increase as patients progressed to more severe disease [Zhou, 2020]. Analyses of bronchoalveolar lavage fluid revealed that severe COVID-19 patients also experienced overwhelming lung infiltration by highly inflammatory monocyte-derived macrophages [Liao, 2020].

2.1.2. Rationale for Targeting GM-CSF in COVID-19

Granulocyte macrophage-colony-stimulating factor (GM-CSF), an important hematopoietic growth factor and immunomodulatory cytokine, is believed to be a key mediator of cytokine storm [Ishii 2016; Sterner, 2019; Turgues, 2018] and to contribute to SARS-CoV-induced ARDS [Channappanavar, 2016; Channappanavar, 2017]. GM-CSF was has been identified as a cytokine that is upregulated in the serum of COVID-19 patients [Huang, 2020]. Soon after, Zhou and colleagues reported that SARS-CoV-2 infection induced activation of immune cells that secreted large amounts of GM-CSF [Zhou, 2020]. The percentages of GM-CSF-expressing $CD4^+$ T cells (Th1), $CD8^+$ T cells, NK cells, and B cells were significantly higher in the blood of severe Intensive Care Unit (ICU)-admitted patients compared with healthy controls. This pan-lymphocyte observation was not seen when assessing IL-6 and TNF-α. Further, a $GM\text{-}CSF^+IFN\gamma^+CD4^+$ T cell signature, which is associated with autoimmune encephalomyelitis [Stienne, 2020] and arthritis [Piper, 2014], was found in peripheral blood of ICU patients. These T cell responses were accompanied by significant upregulation of $CD14^+CD16^+$ inflammatory

monocytes, and a high percentage of monocytes secreted GM-CSF and IL-6, consistent with cytokine release syndrome (CRS) [Barrett, 2016]. The reported immunological changes appeared to be more pronounced in ICU-admitted patients versus non-ICU patients. Taken together, these results suggest that dysregulated GM-CSF expression from Th1 cells licenses pathogenic myeloid cell infiltration into the lung [Zhou, 2020]. These findings are consistent with the mechanisms of action of GM-CSF observed in other inflammatory lung conditions [Puljic, 2007; Willart, 2012; Shiomi, 2014; Molfino, 2016; Sheih, 2017; Kwon, 2018; Nobs, 2019] and in an animal model of SARS-CoV infection [Channappanavar, 2016]. Indeed, administration of recombinant GM-CSF (Leukine®) in a clinical setting can induce respiratory symptoms and even acute lung injury due to excessive myeloid cell mobilization [Kudlak, 2013].

This evidence suggests that GM-CSF stands as a key contributor to and regulator of the cytokine storm that characterizes progression to respiratory failure in COVID-19. Therefore, targeting GM-CSF represents a promising strategy for curbing immunopathological lung damage while buying time for viral clearance. This immunomodulatory strategy is supported by current guidelines from the China National Health Commission stating that glucocorticoids, intravenous immunoglobulin, and the anti-IL-6R antibody tocilizumab, which is U.S. Food and Drug Administration (FDA)-approved for CAR-T-related CRS, may be used to treat severely ill COVID-19 patients [Novel Coronavirus Pneumonia Diagnosis and Treatment Plan, 2020]. GM-CSF is thought to act upstream and stimulate the expression of IL-6 and other pro-inflammatory cytokines during CRS, making a GM-CSF-targeting strategy potentially more advantageous for dampening overactive immune responses than other cytokine-targeting approaches [Ishii, 2016; Barrett, 2016]. Based on significant preclinical evidence in animal models [Sterner, 2019; Tugues, 2018] a Phase 1/2 clinical trial is ongoing to assess the benefit of an anti-GM-CSF antibody (lenzilumab) in CAR-T-related CRS, and a Phase 2/3 trial of lenzilumab is planned for the treatment of CRS in graft versus host disease [Humanigen, Inc., 2020]. Interestingly, a randomized, placebo-controlled phase 2 trial demonstrated statistically significant efficacy of lenzilumab on pulmonary function in eosinophilic asthmatics, consistent with the overall hypothesis that GM-CSF is a critical mediator of lung hyper-inflammation [Molfino, 2016].

Ultimately, GM-CSF's master regulatory effect on cytokine storm and lung inflammation warrants the clinical investigation of an anti-GM-CSF antibody, gimsilumab (KIN-1901), in patients with lung injury or ARDS secondary to COVID-19. Gimsilumab administered intravenously or subcutaneously was shown to be well-tolerated in phase 1 clinical trials in healthy volunteers and rheumatoid arthritis patients (Studies MORAb-022-001 and KIN-1901-1001). Over 1,000 patients have been administered anti-GM-CSF(R) antibodies in clinical trials, with acceptable safety profiles seen to date [Hamilton, 2020].

2.2. Dose Rationale

Gimsilumab will be administered intravenously (IV) on 2 occasions, 400 mg on Day 1 and 200 mg on Day 8.

A Phase 1 first-in-man study (MORAB-022-001) was conducted to assess safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single-dose IV gimsilumab in healthy subjects and subjects with rheumatoid arthritis (RA) [Gimsilumab Investigator Brochure, current edition]. Doses ranged from 0.0085 to 10 mg/kg in that study, with the highest doses (0.36 mg/kg

to 10 mg/kg) administered to subjects with RA. Study MORAB-022-001 showed the PK were dose-proportional over the entire dose range, with no differences noted between healthy subjects and subjects with RA. Although AEs (headache, nasopharyngitis, flu-like symptoms) were encountered more frequently in the gimsilumab group, they were graded mild to moderate and were not dose-related.

Subcutaneous administration of gimsilumab was evaluated in ongoing study KIN-1901-1001. Single- and repeat-dose (once weekly for 4 doses) gimsilumab was administered to healthy volunteers to evaluate safety and pharmacokinetics. Based on a blinded safety data review on 26 Feb 2020, gimsilumab was well-tolerated with no serious adverse events (SAEs), the majority AEs (67%) were injection site reactions (erythema, tenderness, bruising) [Gimsilumab Investigator Brochure, current edition].

GM-CSF stimulates increased levels of CD11b on neutrophils, thus inhibition of GM-CSF signaling can be measured through suppression of CD11b stimulation index [Sakagami, 2010; Nadicksbernd, 2013]. PD measurements with *ex vivo* stimulation of CD11b from study MORAb-022-001 suggested IV doses as low as 0.7 mg/kg caused suppression of CD11b expression, demonstrating pharmacologic activity. Observed serum concentrations from the gimsilumab first-in-human study suggested serum concentrations of ~20 µg/mL were associated with an ACR20 response in subjects with RA and the IC90 determined from the CD11b stimulation assay was 25 µg/mL [Gimsilumab Investigator Brochure, current edition]. As there is no nonclinical data at this time that can further inform the expected efficacious dose range for gimsilumab in the treatment of ARDS, a target trough serum concentration of 20 µg/mL was selected for this study. The intent is to maintain a trough concentration above ~20 µg/mL in the majority of subjects for the entire 2-week dosing period to maximize the potential to bind excessive levels of GM-CSF during ARDS.

A population PK model of IV gimsilumab was developed from the IV first-in-human study. Based on this model, simulations were conducted to a select an appropriate dose regimen. While the prior study using IV gimsilumab utilized mg/kg dosing, a 'flat dose' regimen (not body weight adjusted) was selected for this study to simplify administration in this setting. Simulations accounted for a range in subject body weight to select an appropriate flat dose. Using this model, a dose of 400 mg on Day 1 results in a median trough serum concentration of 29 µg/mL on Day 8. Based on the expected variability in exposure and range in subject body weight, the serum trough concentration at the lower bound of the 80% prediction interval (i.e., the 10^{th} percentile) is expected to be ~20 µg/mL (Figure 2-1), i.e., 90% of subjects are expected to achieve serum concentrations above the target. A second dose of gimsilumab 200 mg on Day 8 maintains the trough concentration at these levels for an additional week. Based on the duration of ICU time in both survivors and non-survivors from a Chinese cohort of ~7 days [Zhou, 2020], two doses, i.e., a 14-day treatment period, was considered appropriate for this study. If subjects are discharged from the hospital or are no longer in need of supplemental oxygen or ventilatory support for >48 hours, the planned Day 8 dose will be omitted.

The predicted exposure after gimsilumab 400 mg IV on Day 1 (the highest exposure expected during the study) is approximately half that observed at 10 mg/kg IV in subjects with RA (Table 2-1). The expected C_{max} at the 90^{th} percentile is also expected to be less than the geometric mean C_{max} observed previously at 10 mg/kg IV. In addition, the predicted exposure margins after 400 mg IV compared to the monkey 26-week IV toxicology study is presented in Table 2-1. The no-observed-effect level (NOEL) in the monkey was 200 mg/kg IV once weekly; the NOEL was

the highest dose tested. The exposures observed in monkeys were at least 40× greater than those expected in the current study. Thus, given the observed safety profile and the pharmacologic activity at the expected exposures in the current study, gimsilumab 400 mg Day 1 and 200 mg Day 8 was selected for the present study.

Gimsilumab vials are to be diluted in 0.9% saline, the resultant concentration [redacted] is similar or less than those demonstrated to be safe in monkey IV toxicology studies. Gimsilumab is to be infused over a [redacted] resulting in a rate no higher than [redacted] This rate is similar to the highest rate previously administered to subjects with RA, that was well tolerated.

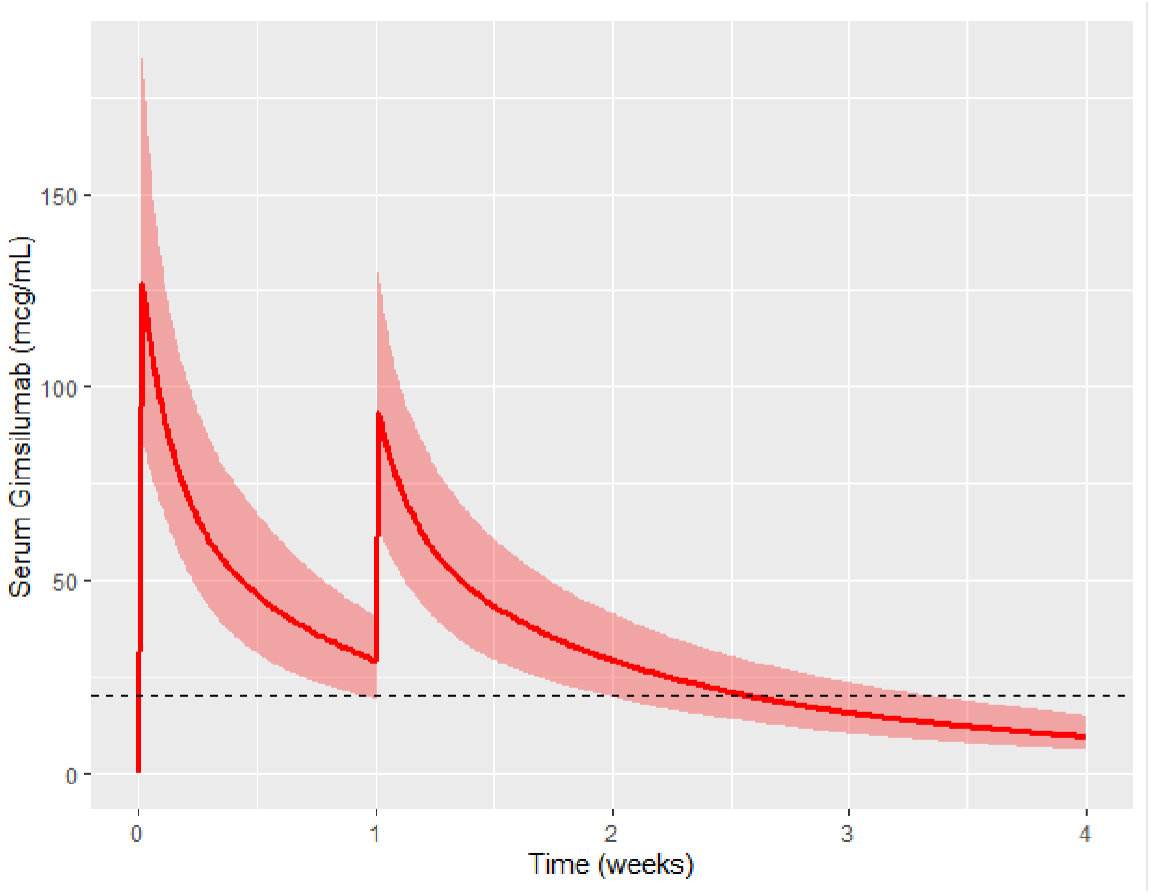
Table 2-1: Predicted Gimsilumab Exposure and Exposure Margins after Gimsilumab 400 mg IV Compared to Highest IV Dose Studied in Study MORAb-022-001 in Humans and the NOEL IV Dose Studied in Cynomolgus Monkeys

Gimsilumab Dose	Median Predicted Gimsilumab Exposure		Predicted Exposure Margin (X-fold) Compared to RA Patients Gimsilumab 10 mg/kg IV[a]		Predicted Exposure Margin (X-fold) Compared to Cynomolgus Monkey 200 mg/kg/week, IV[b]	
	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC
400 mg IV	128 µg/mL	17,860 µg/mL	2.1	2.0	92	41

a. Median predicted exposure after planned dose divided by observed geometric mean at 10 mg/kg IV in RA patients (C_{max} = 267 µg/mL; $AUC_{0-\infty}$ = 35,100 µg.h/mL)

b. Median predicted exposure after planned dose divided by observed mean at 200 mg/kg IV in male and female monkeys at Day 176 (gender averaged C_{max} = 11,800 µg/mL; $AUC_{0-\infty}$ = 731,000 µg.h/mL)

Figure 2-1: Simulated Serum Gimsilumab PK Profile After Gimsilumab 400 mg IV Day 1 and 200 mg IV Day 8[a]



a. Median (line) and 10th and 90th percentiles (shaded area); 20 µg/mL target concentration (dashed)

2.3. Benefit/Risk Assessment

Summaries of findings from both non-clinical and clinical studies conducted to date can be found in the Gimsilumab Investigator Brochure, current edition.

Gimsilumab is a new molecular entity. There are limited data on the therapeutic effect of gimsilumab in humans, signals of clinical benefit and pharmacodynamic effects were observed in subjects with RA treated with single doses of IV gimsilumab ≥0.7 mg/kg and provide a gimsilumab dose range that has the potential to show clinical benefit in subjects with lung injury and ARDS secondary to COVID-19. In healthy subjects, the most frequently reported AE was headache. Other reported AEs included nasopharyngitis and flu-like symptoms in subjects receiving gimsilumab. For subjects with RA, no AE was reported by more than 1 subject. One subject with RA who received gimsilumab 3 mg/kg experienced a SAE of follicular neoplasia of thyroid/thyroid neoplasm which was considered by the investigator to be mild in severity and not related to test article.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
• The primary objective is to evaluate the impact of intravenous (IV) treatment with gimsilumab on mortality in subjects with lung injury or ARDS secondary to COVID-19.	• Incidence of mortality by Day 43
Secondary	
Key secondary objectives include the following: • To assess the effect of gimsilumab on ventilation requirements • To assess the effect of gimsilumab on overall duration of hospitalization Additional secondary objectives include the following: • To assess the effect of gimsilumab on the need for Intensive Care Unit (ICU) level of care • To assess the effect of gimsilumab as measured by the National Early Warning Score (NEWS) • To assess the effect of gimsilumab as assessed by the Sequential Organ Failure Assessment (SOFA) score • To assess the effect of gimsilumab as measured by the 7-point ordinal scale • To assess the effect of gimsilumab on peripheral capillary oxygen saturation / fraction of inspired oxygen (SpO_2/FiO_2) • To assess the effect of gimsilumab on oxygenation requirements • To assess changes in on-treatment viral load • To assess the effect of gimsilumab on biomarkers of inflammation • To determine the pharmacokinetic (PK) properties of gimsilumab • To assess the immunogenicity of gimsilumab • To determine the safety and tolerability of gimsilumab	Key secondary endpoints include the following: • Proportion of subjects who survived and were not requiring mechanical ventilation on Day 29 • Mechanical ventilation-free days by Day 29 • Time to hospital discharge by Day 43 Additional secondary endpoints include the following: • Incidence of mortality by Days 15, 22, 29, 85, and 169 (End-of-Study [EoS]) • Proportion of subjects who survived and were not requiring mechanical ventilation on Days 15, 22, and 43 • Mechanical ventilation-free days for all subjects by Days 15, 22, and 43 • ICU-free days for all subjects by Days 15, 22, 29, and 43 • Incidence of mechanical ventilation use for all subjects by Days 15, 22, 29, and 43 • Incidence of ICU use for all subjects by Days 15, 22, 29, and 43 • Time to death by Day 43 and Day 169 (EoS) • NEWS assessed daily while hospitalized • SOFA score, and each of the components, assessed daily while in the ICU • The percentage of subjects reporting each severity rating on the 7-point ordinal scale, assessed daily while hospitalized and, if discharged from hospital, on Days 15, 22, 29, 36, 43, 85, and 169 (assessed by phone) • Status on the 7-point ordinal scale, assessed daily while hospitalized and, if discharged from hospital, on Days 15, 22, 29, 36, 43, 85, and 169 (assessed by phone) • Time to clinical improvement by 2 points on the 7-point ordinal scale • Change from Baseline in SpO_2/FiO_2, assessed daily while hospitalized • Incidence and duration of oxygen use during the study

OBJECTIVES	ENDPOINTS
	• Change from Baseline in viral load as measured by quantitative polymerase chain reaction (PCR) test on Days 2, 9, and day-of-discharge (DoD) • Change from Baseline in D-dimer, cardiac troponin I, lactate dehydrogenase (LDH), ferritin, and C-reactive protein (CRP) • Serum gimsilumab concentrations • Analysis of anti-gimsilumab antibodies (ADAs) Safety endpoints: • Safety and tolerability, including assessment of clinical safety laboratory measurements, physical examinations, vital signs, concomitant medications; cumulative incidence of adverse events (AEs), serious adverse events (SAEs), and severe AEs
Exploratory	
Exploratory objectives include the following: • To explore the effect of gimsilumab on serum cytokine concentrations and surfactant protein D (SP-D) • To explore the effect of gimsilumab on other measurements of lung injury that may be performed during standard care (e.g., Lung Injury Score [LIS], chest radiography, PaO_2/FiO_2 [P/F ratio], need for extracorporeal membrane oxygenation [ECMO]) • To explore the effect of gimsilumab on cardiac function (if measured) • To assess the effect of gimsilumab on renal function	Exploratory endpoints include the following: • Change from Baseline in the cytokine panel and serum SP-D • Change from Baseline in LIS (if performed) • Change from Baseline in chest radiographic assessment (if performed) • Change from Baseline in P/F ratio, if performed • Incidence and duration of ECMO use • Change from Baseline in left ventricular ejection fraction (LVEF) (when measured) • Change from Baseline in eGFR [Modification of Diet in Renal Disease (MDRD) equation], assessed when central clinical safety laboratory measurements are collected during hospitalization

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a randomized, adaptive, double-blind, placebo-controlled study in male and/or female subjects who are at risk of developing, or have developed, ARDS consequent to moderate to severe COVID-19.

This study will include subjects with moderate-to-severe disease. There will be 2 treatment arms, one receiving blinded gimsilumab, and one receiving blinded placebo.

Efficacy, safety, tolerability, PK, and PD of gimsilumab will be assessed in hospitalized adult subjects diagnosed with COVID-19.

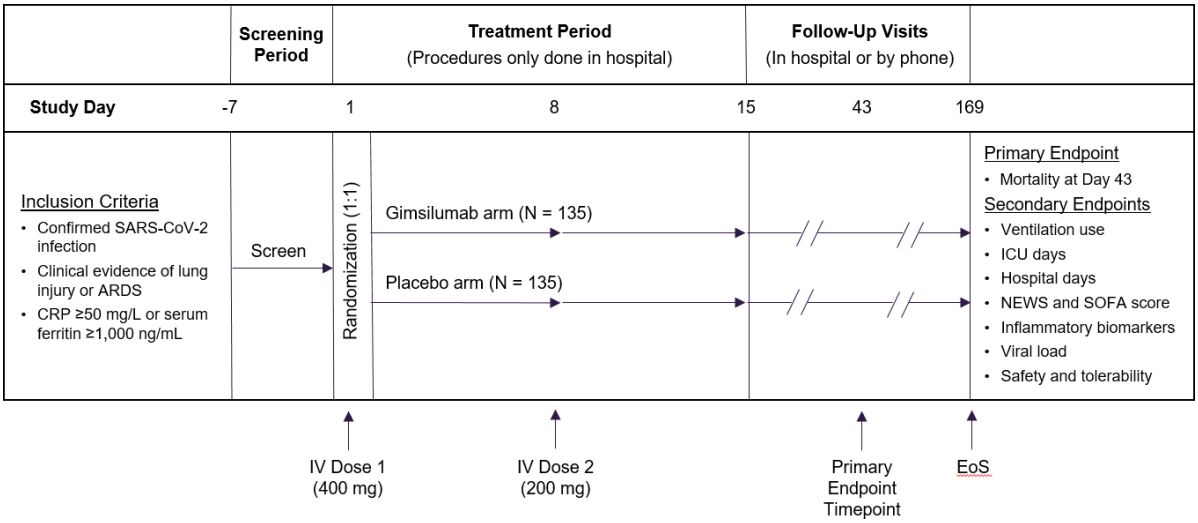
Randomization will be stratified by country and subject's clinical status at Baseline:

- Lung injury/mild ARDS
- Moderate/severe ARDS

Clinical classification criteria are defined in Section 9.1.

A schematic of the study design is presented in Figure 4-1. Subjects will be assessed daily while hospitalized. Follow-up assessments are planned through Week 24, for a total study duration post-randomization of approximately 169 days (24 weeks). Follow-up visits at Days 15, 22, 29, 36, 43, 85, and 169 will be performed by phone if the subject has been discharged from the hospital. All subjects will undergo a series of efficacy, safety, and laboratory assessments as detailed in the Schedule of Assessments, Table 7-2.

Figure 4-1: Study Schematic



ARDS = acute respiratory distress syndrome; CRP = C-reactive protein; EoS = End of Study; IV = intravenous; ICU = Intensive Care Unit; NEWS = National Early Warning Score; SOFA = Sequential Organ Failure Assessment

4.2. Scientific Rationale for Study Design

COVID-19 is a newly emerging disease with a clinical spectrum that ranges from asymptomatic to severe and potentially lethal. The variability between clinical courses of different individuals may make uncontrolled data highly unreliable. Further, the immunopathogenesis of COVID-19 is currently not well understood, and thus the risk-benefit of immunomodulatory agents in COVID-19 has not been established. It is difficult to predict whether altering the immune response during an acute infection will have a harmful effect via prevention of viral clearance or a beneficial effect via dampening of overactive inflammation. For these reasons, this study will be prospective, randomized, double-blinded, and placebo-controlled to minimize bias. Preliminary evidence suggests that major deterioration, including progression to lung injury or ARDS, occurs within the first 1 to 2 weeks of hospitalization, warranting the 2-week treatment period chosen for this study [Huang, 2020; Zhou, 2020].

The target patient population, patients with lung injury or ARDS secondary to COVID-19, was selected based on the putative mechanism of action of the anti-GM-CSF approach in this disease. Severely ill COVID-19 patients have significant inflammatory macrophage infiltration into the damaged lung as well as cytokine storm syndrome [Liao, 2020; Mehta, 2020]. In inflammatory pulmonary conditions, GM-CSF acts to mobilize bone marrow progenitor cells to the lung and differentiate them into inflammatory myeloid cells [Kudlak, 2013; Molfino, 2016]. During cytokine storm, GM-CSF is thought to induce and perpetuate a "positive feedback" loop with other pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, thereby contributing to immunopathological consequences [Tugues, 2018; Sterner, 2019; Hamilton, 2020]. Taken together, targeting GM-CSF presents an opportunity to both block the damaging macrophage lung infiltration and quell the hyper-inflammation characteristic of this particular stage of COVID-19.

4.3. Treatment Arms and Duration

Each subject will participate for approximately 24 weeks, with a 2-week Treatment Period (last dose on Day 8) and a 22-week Follow-up Period. A summary of the treatment arms is presented in Table 4-1.

Table 4-1: Treatment Arms for KIN-1901-2001

Arm	Randomized Treatment and Population	N
Arm 1	Gimsilumab (400 mg) as a single IV infusion on Day 1 followed by a single 200 mg IV infusion on Day 8	135
Arm 2	Placebo (0.9% saline solution) IV infusion on Day 1 and Day 8[a]	135

a. The Day 8 dose will be omitted if the subject is discharged from the hospital or is no longer in need of supplemental oxygen or ventilatory support for >48 hours.

5. SUBJECT POPULATION

5.1. Type and Number of Subjects

A sufficient number of subjects will be enrolled to achieve approximately 270 evaluable subjects total, with 135 subjects per treatment arm.

In order to manage the total study enrollment, the Sponsor may suspend screening and/or enrolment at any site or study-wide at any time.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety; therefore, adherence to the criteria as specified in the protocol is essential.

5.2. Inclusion Criteria

An individual will be eligible for inclusion in this study only if all the following criteria are met.

1. Male or non-pregnant female age ≥18 years
2. Subject (or legally authorized representative [LAR]) is able and willing to provide written or verbal informed consent, which includes compliance with study requirements and restrictions listed in the consent form. NOTE: If a subject or LAR must be consented verbally, the site must have a site policy for verbal consent and the consent must be clearly documented in the subject's chart.
3. Has documented laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other approved clinical testing prior to randomization
4. C-reactive protein ≥50 mg/L or serum ferritin ≥1000 ng/mL. Results from CRP and ferritin tests performed within 8 days of randomization are acceptable for enrollment.
5. Radiographic evidence of bilateral infiltrates. Acceptable imaging tests (chest X-ray, CT scans) done within 3 days of Day 1 can be used for inclusion.
6. Subject has clinical evidence of lung injury [defined as (1) requiring supplemental oxygen ≥4L O_2 to attempt to maintain ≥92% SpO_2, or (2) PaO_2/FiO_2 ≤300 mmHg (can be imputed)] or meets clinical classification criteria for ARDS [ARDS Berlin Definition, 2012], secondary to COVID-19
7. Female subjects must agree to use an approved highly effective birth control (BC) method (<1% failure rate per year) throughout the study (until completion of the Day 85 Follow-up Visit), unless documented to have a reproductive status of non-childbearing potential or is postmenopausal:
    - Non-childbearing potential defined as pre-menopausal female with medical history of bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries), or hysterectomy; hysteroscopic sterilization,
    - Postmenopausal defined as 12 months of spontaneous amenorrhea or with follicle stimulating hormone (FSH) confirmation.
    - Woman of childbearing potential (WCBP) who is already using an established method of highly effective contraception or agrees to use one of the allowed BC

methods listed in Section 5.6.1, for at least 28 days prior to the start of dosing (as determined by the Investigator Brochure or Investigator or designee) to sufficiently minimize the risk of pregnancy throughout study participation (until completion of the Day 85 Follow-up Visit).

8. Males who are sexually active must agree to use one of the allowed BC methods listed in Section 5.6.1. Male subjects must also agree to sufficiently minimize the risk of pregnancy throughout study participation (until completion of the Day 85 Follow-up Visit).

5.3. Exclusion Criteria

An individual will NOT be eligible for inclusion in this study if any of the following criteria apply.

1. Subject requires norepinephrine at a dose of >0.5 mcg/kg/min, or equivalent
2. Subject has been intubated for >72 hours. Note: in the event of extubation and re-intubation, the calculation for the number of hours the subject has been intubated begins at the first intubation.
3. Evidence of life-threatening dysrhythmia (e.g., ventricular tachycardia [VT], ventricular fibrillation [VF]) or cardiac arrest on presentation
4. Evidence of new or preexisting decompensated heart failure
5. At the time of screening, subject is anticipated to require ECMO
6. Absolute neutrophil count <1,000 per mm^3
7. Platelet count <50,000 per mm^3
8. History of known anti-GM-CSF autoAb or pulmonary alveolar proteinosis. Note: A negative anti-GM-CSF autoAb test result is not required at screening.
9. Severe chronic respiratory disease (e.g., known chronic obstructive pulmonary disease [COPD], pulmonary arterial hypertension [PAH], idiopathic pulmonary fibrosis [IPF], interstitial lung disease [ILD]) requiring supplemental oxygen therapy or mechanical ventilation pre-hospitalization (e.g., prior to COVID-19 diagnosis)
10. Known or suspected active and untreated tuberculosis (TB), human immunodeficiency virus (HIV), hepatitis B or C infection.
    - Results of TB, hepatitis B and C, and HIV tests are not required prior to enrollment if there is no suspicion of active infection, as per KIN-1901 Guidance on Active Infections Testing.
11. Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) >5 × upper limit of normal (ULN)
12. eGFR <30 mL/min/1.73m^2 (MDRD equation) or requiring hemofiltration or dialysis
13. Use of any immunomodulatory biologic (e.g., anti-IL-1, anti-IL-6R, anti-TNF, inhibitors of complement signaling), cell therapies (e.g., mesenchymal stem cells), or small molecule JAK inhibitors within the past 7 days or within five half-lives (whichever is longer), or planned use of any of these agents from Screening until Day 43 of the study, unless approved by the Medical Monitor. The following will be allowed/disallowed:

- Immunomodulatory biologics for COVID-19 treatment are excluded and should not be used until Day 43 unless discussed with the Medical Monitor. Other non-biologic immunomodulators (non-JAK inhibitors), e.g., medicines for previous transplantation, or disease modifying anti-rheumatic drugs (DMARDS), and have had a stable dose for ≥8 weeks are permitted.
- Subjects who have been treated with convalescent plasma (CP) prior to enrollment are eligible if the subject continues to meet all inclusion criteria at screening. Ongoing therapy with CP is allowable if clinically indicated in the view of the treating physician or the Investigator.
- The use of investigational anti-viral treatment (e.g., remdesivir) is allowed if the subject continues to meet all inclusion criteria at screening.

14. Ongoing chronic (≥4 weeks) use of corticosteroids >10 mg/day of prednisone or equivalent at the time of randomization. A corticosteroid dose that has been tapered to 10 mg or less within 14 days of randomization is also prohibited.
15. Pregnancy and/or breast feeding
16. Unable to receive invasive or non-invasive ventilatory support
17. Moribund condition in the opinion of the clinical team

5.4. Other Eligibility Criteria Considerations

Individuals who marginally fail to meet eligibility requirements may be rescreened (once), on a case-by-case basis, as determined by the Medical Monitor.

To assess any potential impact on subject eligibility with regard to safety, the Investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the investigational product being used in this study:

- Gimsilumab Investigator Brochure, current edition

5.5. Screening/Baseline

Screen failures are defined as subjects who consent to participate in the clinical study but are never subsequently randomized. A minimal set of screen failure information is required including demography, screen failure details, eligibility criteria, and any SAEs. Screen failure data will not be recorded within the Case Report Form (CRF).

5.6. Lifestyle and/or Dietary Restrictions

5.6.1. Contraception

The potential effects of gimsilumab on embryofetal or postnatal development have not been assessed in animals or humans. ICH M2 (R2) defines “highly effective methods of birth control” as those, alone or in combination, that result in a low failure rate (<1 pregnancy per 100 women in a year).

All female and male study subjects must use a highly effective birth control method (<1% failure rate per year) until completion of the Day 85 Follow-up Visit, unless they have a reproductive status of, sterile, non-childbearing, or postmenopausal (confirmed by FSH). Additionally, female partners of eligible male study subjects must use, in parallel, an allowed method of contraception

Non-childbearing potential is defined as pre-menopausal female with documented bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries) or hysterectomy; hysteroscopic sterilization.

Postmenopausal female is defined as 12 consecutive months of spontaneous amenorrhea and with FSH confirmation.

Woman of Childbearing potential (WCBP) are required to use a highly effective BC method (<1% failure rate per year): [Hatcher, 2007]

- Subdermal implant that meets high effectiveness criteria (<1% rate of failure per year), stated in the product label
- Intrauterine device (IUD) or intrauterine system (IUS) that meets high effectiveness criteria (<1% rate of failure per year), stated in the product label
- Oral or injected contraceptives having established use (for at least 30 days); of either combined (estrogen- and progestogen) or progestogen alone
- Male partner with vasectomy and documentation of azoospermia
- "Double barrier" method, male partner(s) mutual agreement of male condom use in combination with:
    - female diaphragm/cervical cap plus spermicide (cream, gel, film, or suppository)
    - contraceptive vaginal ring
    - percutaneous contraceptive patches

Sexually active male subjects must agree to use highly effective birth control (BC) methods. As applicable, in parallel to his study participation, his female partner(s) must also use an effective method of contraception (listed above). Males allowed to enroll in this study are responsible for minimizing the risk of pregnancy (until completion of the Day 85 Follow-up Visit).

- Vasectomy and documentation of azoospermia
- Male condom plus female partner use of one of the highly effective contraceptive methods listed immediately above, based on the female partner's childbearing potential

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the Investigator Brochure. The Investigator is responsible for ensuring that all study subjects fully understand the importance of this requirement and how to properly use these methods of contraception.

5.7. Withdrawal Criteria

5.7.1. Reasons for Withdrawal

An Investigator may discontinue/withdraw a study subject's participation in the study if any of the following criteria apply:

- Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- Pregnancy of female subject
- Major protocol violation
- Behavioral and/or administrative reason
- Subject request to discontinue/withdraw consent for any reason. It is important to document whether the withdrawal of consent is primarily due to an AE, lack of efficacy, or other reason.
- Discontinuation of the study at the request of the Sponsor, regulatory agency, or an Institutional Review Board / Independent Ethics Committee
- Liver toxicity where criteria as specified in Section 5.8.1 are met and no compelling alternate cause is identified

If a subject meets a withdrawal criterion during treatment, an Early Termination Visit will be required. Subjects withdrawn for any reason will not be replaced.

5.7.2. Subject Withdrawal Procedures

If a subject is prematurely discontinued from investigational product(s), the Investigator must make every effort to perform an Early Termination (ET) Visit per the Schedule of Assessments (Table 7-2), and document the primary reason for withdrawal.

In cases where the subject cannot be reached for phone follow-up visits, the site should attempt to contact the subject as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study based on previous non-compliance. In cases where the subject cannot be reached, the site should make every effort to regain contact with the subject (3 documented telephone calls and if necessary a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up".

Subjects who withdraw from treatment and/or the study early, for any reason, will be followed for Day 43 all-cause mortality, whenever possible.

5.8. Toxicity Management Criteria

5.8.1. Liver Chemistry Management Criteria

Liver chemistry criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical Drug-induced Liver Injury guidance).

Timely results of local labs should be used to make the decision to proceed to the second dose.

Guidance on LFT abnormalities based upon results of LOCAL lab testing:

1) If a subject has ALT in the normal range prior to study drug administration and develops significant elevation >5× ULN after study drug administration, in the absence of a clear alternative reason for the change (e.g., hypotension, vasopressor support), this should be considered related to study drug and reported as a SAE; procedures described in **Appendix 2: Liver Safety Required Actions and Follow up Assessments** should be followed, and the Medical Monitor should be informed.
2) For subjects with elevated transaminase levels prior to study drug administration who **do not meet exclusion criterion #11 (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >5× upper limit of normal [ULN])**, if after administration of study drug the LFTs continue to worsen and no alternate explanation for elevation is provided, the following will apply:
    a. If **ALT >8× ULN**, then this should be reported as a SAE; procedures described in **Appendix 2: Liver Safety Required Actions and Follow up Assessments** will be followed, and the Medical Monitor should be informed. If the Investigator is considering withholding the second dose of study drug, then a discussion with the Medical Monitor is mandatory. Note that subjects with ALT or AST abnormalities secondary to multi-organ impairment due to COVID-19 may still benefit from the second dose of gimsilumab.
    b. If LFTs are elevated but are **not** >8× ULN, then daily LFTs (including AST, ALT, alkaline phosphatase, and total bilirubin with fractionation) should be followed.
        i. If during follow up **ALT or AST increases to >8× ULN**, then this should be reported as a SAE and then discussed with the Medical Monitor concerning the need to withhold the second dose.
        ii. If a subject has **AST or ALT 3 to 8× ULN** in conjugation with **total bilirubin >2× ULN or INR >1.5**, then this should be reported as a SAE; procedures described in **Appendix 2: Liver Safety Required Actions and Follow up Assessments** should be followed. Subjects meeting these criteria should not receive a second dose of study drug.
        iii. If during follow up the above stopping criteria are not met and the Investigator believes that the subject is suitable to receive a second dose of study drug and all eligibility criteria are met for the second dose, then the second dose (Day 8) of study drug may be administered.
3) Any worsening of LFTs that is greater than would be expected due to COVID-19 alone that do not rise to the level of an SAE should be reported as an AE.

4) A discussion with the Medical Monitor is **mandatory** prior to withholding the second dose of study drug.

5.8.2. Individual Stopping Criteria

Infusion of study treatment in an individual subject may be interrupted (and the Day 8 dose held, if appropriate) if the subject experiences a treatment-related Grade ≥3 AE or at the discretion of the investigator. Under these circumstances, the Medical Monitor must be notified.

5.8.3. Study Stopping Criteria

It is understood the safety profile of gimsilumab in the critical care setting of patients with impending or established ARDS is not yet understood. Reassuringly the anti-GM-CSF class of molecules has been studied in many subjects in multiple Phase 2 trials and to date no specific safety signal of concern has been noted to date. In principal, concerns for targeting GM-CSF include respiratory tract infection and pulmonary alveolar proteinosis. Hence while the rationale for targeting GM-CSF in the setting of severe viral pneumonia with or without ARDS is strong, there is concern over AEs and patient safety.

To ensure subject safety, the sponsor plans a number of measures. An independent Data Monitoring Committee (DMC) will be appointed to review unblinded safety and efficacy data on an ongoing basis. The Chair of the DMC will issue a Charter outlining the specific plan for safety review including both early stopping rules for adverse safety events and also early stopping rules for futility, and early stopping rules for efficacy.

5.8.4. Other Management Criteria

For an individual study participant, Medical Monitor notification criteria include, but are not limited to:

- Relevant severe signs or symptoms, or significant changes in any of the safety assessments, that put the safety of the individual at risk (e.g. laboratory tests or vital signs, etc.) as judged by the Investigator.

5.9. Subject and Study Completion

A completed subject is 1 who has completed the Treatment Period and the Follow-up Period (through the Day 169 End-of-Study [EoS] Follow-up Visit).

6. STUDY TREATMENT

6.1. Study Treatment

The term ‘study treatment’ is used throughout the protocol to describe any dose of gimsilumab or placebo; study treatments are presented in Table 6-1.

Table 6-1: Treatment Descriptions for KIN-1901-2001

Study Treatment		
Product name:	Gimsilumab	Placebo
Formulation description:	[redacted]	0.9% sodium chloride
Dosage form:	Vial	NA
Unit dose strength(s)/Dosage level(s):	[redacted]	
Route of Administration/Duration	Intravenous infusion on Day 1 and Day 8	Intravenous infusion on Day 1 and Day 8
Dosing instructions:	Infuse the entire contents of the IV bag via the intravenous route over a 1-hour period. Flush the line with 0.9% saline to ensure the entire contents is administered.	Infuse the entire contents of the IV bag via the intravenous route over a 1-hour period ±20 minutes. Flush the line with 0.9% saline to ensure the entire contents is administered.
Procurement	Gimsilumab: manufactured for Kinevant Sciences GmbH Saline: Procured by clinical site	Saline: Procured by clinical site

6.2. Administration of Study Treatments

Study treatment will be infused intravenously over a period of [redacted]. The start and stop time of the infusion will be recorded, including if the infusion had to be stopped or rate reduced. Further details are available in the Study Pharmacy Manual.

Administration of study treatment will be performed by qualified personnel as specified in the Schedule of Assessments (Table 7-2).

6.3. Randomization / Study Treatment Assignment

Randomization will occur centrally using an interactive voice or web response system using central stratified randomization. Subjects determined to be eligible for enrollment based upon screening evaluations will be randomized to receive study treatments according to one of the treatments listed in Table 6-2.

The study will enroll at least 40%, but no more than 60%, of total subjects in each of the two categories of clinical status: ([lung injury/mild ARDS] or [moderate/severe ARDS]) at Baseline, which will be used as the stratified factor in the randomization.

Table 6-2: Randomization Schema for KIN-1901-2001

Arm	Group	Ratio	Treatment Description
1	Active Study Drug	1	Gimsilumab 400 mg single IV infusion on Day 1 Gimsilumab 200 mg single IV infusion on Day 8
2	Placebo	1	Normal saline single IV infusion on Day 1 Normal saline single IV infusion on Day 8

6.4. Blinding

The study is double-blind. The study pharmacist (and/or qualified pharmacy staff member), and the bioanalytical laboratory analysts will be unblinded to study treatment.

Study treatment will be administered to each subject by blinded qualified personnel at the study site. Once diluted in 100 mL 0.9% saline, active gimsilumab and placebo infusion bags are indistinguishable.

The following will apply regarding the unblinding of study treatment:

- The Investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the Investigator.

- Investigators have direct access to the subject's individual study treatment.
- The Investigator should make every effort to first contact the Medical Monitor or appropriate study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If the Sponsor personnel are not contacted before the unblinding, the Investigator must notify the Sponsor as soon as possible after unblinding.
- The date and reason for the unblinding must be fully documented in the CRF.
- The Sponsor or their designee may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, will be sent to Investigators in accordance with local regulations.

A subject will be withdrawn if the subject's treatment code is unblinded by the Investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

6.5. Packaging and Labeling

Investigational study treatment clinical supplies will be provided in [redacted]

IV doses of gimsilumab or placebo will be prepared by the site pharmacy, dispensed, and administered to subjects by clinic staff at the study site in a container having a label that includes at a minimum the study number, subject number, and study treatment name ("gimsilumab or placebo").

All labels for gimsilumab vials to be distributed will meet all applicable requirements of Annex 13 of Good Manufacturing Practices: Manufacture of Investigational Medicinal Products (July 2010) and/or other local regulations as applicable.

6.6. Preparation/Handling/Storage/Accountability

Gimsilumab study treatment will be diluted in 100 mL 0.9% saline prior to infusion using aseptic technique by qualified personnel per the clinical site standard operating procedures.

Placebo study treatment will utilize 100 mL 0.9% saline solution with the addition of 4 mL (Day 1) or 2 mL (Day 8) sterile 0.9% saline solution using aseptic technique by qualified personnel per the clinical site standard operating procedures.

Refer to the Study Pharmacy Manual for additional details.

Gimsilumab vials are to be stored at [redacted] and require temperature monitoring. Temperature excursions are to be reported to the Sponsor.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to authorized site staff.
- The Investigator or delegated personnel is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the Study Pharmacy Manual.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or the Sponsor Study Contact.
- A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from the Sponsor.

6.7. Compliance with Study Treatment Administration

Subjects are dosed in the hospital. They will receive study treatment directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the hospital will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.8. Treatment of Study Treatment Overdose

For this study, any single administration of gimsilumab >400 mg will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose. There have been no previous reports of overdose (accidental or deliberate) with gimsilumab.

In the event of an overdose the Investigator or treating physician should:

- contact the Medical Monitor immediately;
- closely monitor the subject for AEs/SAEs and laboratory abnormalities;
- obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis);
- document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.9. Concomitant Medications and Non-Drug Therapies

Best possible medication history for the 30 days prior to enrollment will be collected, and include, at a minimum, the drug name (generic or tradename) and start date and stop date (or ongoing).

It would be expected that gimsilumab would reduce the effectiveness of GM-CSFs, such as Luekine® (sargramostim), Leucomax® (molgramostim) and Regramostim. No other drug interactions are known or expected.

6.9.1. Permitted Medications and Non-Drug Therapies

Treatment with convalescent plasma or investigational anti-viral therapies (e.g., remdesivir) will be allowed.

Use of any concomitant medication (including investigational agents) should be recorded in the study source records, including the doses administered, dates and times of administration and the reason for administration.

6.9.2. Prohibited Medications and Non-Drug Therapies

Use of tocilizumab or any other immunomodulatory biologic (e.g., anti-IL-1, anti-IL-6R, anti-TNF), cell therapies (e.g., mesenchymal stem cells), or small molecules (e.g., JAK inhibitors) is prohibited from Screening until Day 43 of the study unless approved by the Medical Monitor.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Assessments (Table 7-2), are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Schedule of Assessments, (Table 7-2).

Note: All subjects who are discharged from the hospital will undergo all Day-of-Discharge (DoD) Visit assessments. All subjects who discontinue from the study prematurely will undergo all Early Termination (ET) Visit assessments, whenever possible.

Once a subject is discharged from the hospital every effort MUST be made to ensure visit timepoints listed on the Schedule of Assessments (Table 7-2) are completed via phone or telemed. All visits are required to be completed for every subject unless the subject dies or withdraws consent. If a subject is deemed lost to follow-up every effort should be made to check vital status records at each visit time point to obtain survival status. Proper follow-up and documentation should be completed per GCP/ICH guidelines before deeming a subject lost to follow-up.

The following points must be noted, if assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

1. vital signs
2. blood draws

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

If the subject completes all in hospital assessments, approximately 250 mL of blood will be collected over the duration of the study (Table 7-1).

Table 7-1: Estimated Sample Requirements Per Subject

	Approximate sample volume per collection (mL)	Number of collection time points	Approximate total volume collected (mL)
Clinical laboratory tests	16.5	9	148.5
Viral screen / Quantiferon®	11	1	11
Anti-GM-CSF autoAb	4	1	4
PK blood sampling	4	3	12
Anti-gimsilumab antibodies	4	4	16

Cytokine panel	8.5	5	42.5
SP-D	3.5	4	14
FSH (if necessary)	3.5	1	3.5
Total:			**251.5**

7.1. Schedule of Assessments (Treatment and Follow-up Periods)

Table 7-2: Schedule of Assessments

Schedule of Assessments: Screening and Treatment Period				
	Screen	**Baseline[a]**	**On-Treatment Assessments (only done if in hospital)**	**DoD[o] / ET**
Study Day (± Window)	**-7 to 1**	**1**	**Days 2 – 14, inclusive (All ± 1 day)**	**-1**
Week	**0**	**0**	**1 to 2**	**—**
Informed consent and randomization	X			
Inclusion/Exclusion criteria	X	X[b]		
Demographic information, medical history, prior medications[c]	X			
Local QuantiFERON® test[d]	X			
Local Viral Screen (HBsAG, HCV RNA/Ag, HIV)[d]	X			
Height and Weight[e]	X			
Local Urine pregnancy test β-hCG and follicle-stimulating hormone (FSH, women only)[f]	X			
Central sample for anti-GM-CSF autoAb[d] (result not required for determination of eligibility)	X			
Chest X-ray or chest CT scan (within 3 days of Day 1)	X			
Local qualitative sample (e.g., nasopharyngeal swab) for PCR SARS-CoV-2 (if not already documented)	X			
Central quantitative sample (e.g., nasopharyngeal swab) for PCR SARS-CoV-2[g]		X	Days 2 and 9	X
Physical examination[h] and vital signs (blood pressure, heart rate, respiration rate, and body temperature)[i]	X	X	Daily, only while hospitalized	X
Central clinical laboratory measurements (hematology, blood chemistry [including CRP, ferritin, LDH, procalcitonin, troponin I], coagulation [including D-dimer], and urinalysis)[j]	X	X	Days 4 and 8	X
Administration of IV study drug[k]		X	Day 8	
Central PK samples for quantification of gimsilumab serum concentration		Predose	Predose on Day 8	X
Central samples for cytokine panel		X	Days 4 and 8	X

Schedule of Assessments: Screening and Treatment Period				
	Screen	**Baseline[a]**	**On-Treatment Assessments (only done if in hospital)**	**DoD[o] / ET**
Study Day (± Window)	**-7 to 1**	**1**	**Days 2 – 14, inclusive (All ± 1 day)**	**-1**
Week	**0**	**0**	**1 to 2**	**—**
Central samples for SP-D measurement		X	Day 8	X
Central sample for immunogenicity (antibodies to gimsilumab)		X		X
7-point Ordinal Scale		X	Daily, only while hospitalized	X
National Early Warning Score (NEWS)		X	Daily, only while hospitalized	X
SOFA score		X	Daily, only while in ICU	X
SpO_2/FiO_2, and if performed, PaO_2/FiO_2 (can be imputed)	X	X	Daily, only while hospitalized	X
Oxygenation requirements	X	X	Daily, only while hospitalized	X
Ventilation requirements[l]	X	X	Daily, only while hospitalized	X
ECMO requirements		X	Daily, only while hospitalized	X
Concomitant medications/concurrent procedures[m]		X	Daily, only while hospitalized	X
Adverse event monitoring[n]		X	Daily, only while hospitalized	X

β-hCG = beta human chorionic gonadotropin; anti-GM-CSF autoAb = anti-granulocyte macrophage colony- stimulating factor auto-antibody; DoD = Day of Discharge from hospital; ECMO = extracorporeal membrane oxygenation; EoS = End-of-Study; ET = early termination; FiO_2 = fraction of inspired oxygen; FSH = follicle stimulation hormone; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibodies; HIV = human immunodeficiency virus; ICU = Intensive Care Unit; IGRA = interferon gamma release assay; IV = intravenous; PCR = polymerase chain reaction; PK = pharmacokinetics; PPD = purified protein derivative; PPE = personal protective equipment; SOFA = sequential organ failure assessment; SP-D = serum surfactant protein D; SpO_2 = peripheral capillary oxygen saturation; TB = tuberculosis

a. Baseline assessments should be performed prior to study drug administration. Assessments performed within 48 hours of Baseline do not need to be repeated at Baseline.
b. Verification that no changes affecting eligibility have occurred since Screening will be performed at the Baseline/Day 1 Visit.
c. Collect medication history from the 30 days leading up to, and including, the time of the Screening Visit, including date of onset of COVID-19 symptoms, prescription medications, over-the-counter medications, and herbal supplements/vitamins.
d. Sample will be collected, but enrollment can continue without receiving results first. HCV testing can be RNA or Ag, only to confirm suspected infection. If a subject is diagnosed with latent TB (positive QuantiFERON Gold or PPD), hepatitis B or C, or HIV during the study, the Investigator must discuss this with the medical monitor and a decision will then be made concerning the second dose of gimsilumab, if applicable. In the event the QuantiFERON Gold assay is not available, and the site performs a different IGRA such as T Spot, then the alternative IGRA will be acceptable for patient screening and enrollment. Enrollment should not be delayed to obtain the QuantiFERON Gold assay in lieu of the IGRA available at the site. If no IGRA test is available, PPD can be used. If TB testing and viral serology is missed during screening it must be completed and results received prior to the second dose of study drug. If not completed or unable to obtain results further discussion with the medical monitor is required.

Schedule of Assessments: Screening and Treatment Period				
	Screen	**Baseline**[a]	**On-Treatment Assessments (only done if in hospital)**	**DoD**[o] **/ ET**
Study Day (± Window)	**-7 to 1**	**1**	**Days 2 – 14, inclusive (All ± 1 day)**	**-1**
Week	**0**	**0**	**1 to 2**	**—**

e. Height will be assessed only once (at Screening). Estimated height and weight are acceptable if unable to be measured due to patient clinical condition.
f. The Screening sample can be assessed using local laboratory services for Screening/Eligibility purposes. The local laboratory values must also be documented in the eCRF.
Note: FSH will be performed to confirm postmenopausal status only in women who have not had 12 months of spontaneous amenorrhea.
g. When at all possible, if only 1 nostril is swabbed for viral assessments, the same nostril should be used for all subsequent samples.
h. An abbreviated, targeted physical examination will be performed based on the subject's clinical status and what the clinic staff feel is appropriate. Note: If a physical examination is performed as standard of care by appropriate personnel the same day that consent is signed or the same day of any scheduled study visit, results from that examination may be used if PPE is not available or if study site staff consider additional examinations are unwarranted due to already having been performed as standard of care..
i. Vital signs will be assessed at all timepoints specified above. On study drug administration days, vital signs will be assessed pre-dose (within 15 minutes) and ± 30 minutes post end of infusion. Note: If vital signs measurements are performed as standard of care by appropriate personnel the same day that consent is signed or the same day of any scheduled study visit, results from that assessment may be used if PPE is not available or if study site staff consider additional measurements are unwarranted due to already having been performed as standard of care..
j. ALT, AST, CRP, and Ferritin can be assessed using local laboratory services for Screening The local laboratory values must be documented in the eCRF.
k. Subjects will receive a single IV infusion of blinded study treatment on Day 1 and Day 8. The Day 8 dose will be omitted if the subject is discharged or is no longer in need of supplemental oxygen or ventilatory support for >48 hours.
l. If subject is receiving mechanical ventilation, the following parameters will be recorded: type of ventilation (CPAP, BiPAP, or intubation), FiO_2, SpO_2, ventilation rate, pulse, tidal volume, positive end-expiratory pressure (PEEP), and airway pressure.
m. Collect information on concomitant medications and concurrent procedures from the time of informed consent through the EoS Visit (or ET Visit if subject discontinues early), including prescription medications, over-the-counter medications, and herbal supplements/vitamins.
n. Adverse event monitoring will include assessment of treatment-emergent AEs (TEAEs), serious adverse events (SAEs), and severe AEs (Grade 3 or 4 events).
o. DoD assessments can be performed one day prior to discharge if the subject has been labelled as "ready for discharge."

Note: SCREENING LABORATORY ASSESSMENTS: For all screening laboratory assessments, if more than one result is available during the screening period, the most recent value will be used as the screening value and for determination of eligibility.

Note: All subjects who are discharged from the hospital will undergo all Day-of-Discharge (DoD) Visit assessments; daily in-hospital assessments will only need to be performed once on DoD. All subjects who discontinue from the study prematurely will undergo all Early Termination (ET) Visit assessments, whenever possible. All subjects who discontinue treatment and/or the study early will be followed for Day 43 all-cause mortality.

Schedule of Assessments: Follow-up Period (Visits will be in-hospital or by phone, if subject has been discharged)								
Study Day (± Window)	**15 (± 2)**	**22 (± 2)**	**29 (± 2)**	**36 (± 2)**	**43[a] (± 2)**	**85 (± 2)**	**EoS 169 (± 2)**	**DoD / ET**
Week	**2**	**3**	**4**	**5**	**6**	**12**	**24**	**—**
Procedures/Assessments								
SOFA Score	Daily, only if in ICU, through Day 43							X
National Early Warning Score (NEWS)	Daily, only while hospitalized, through Day 43							X
Central samples for cytokine panel	Hosp		Hosp					
Central samples for SP-D measurement	Hosp		Hosp					
Central sample for immunogenicity (antibodies to gimsilumab)	Hosp		Hosp		Hosp			
Central clinical laboratory measurements (hematology, blood chemistry [including CRP, ferritin, LDH, procalcitonin, troponin I], coagulation [including D-dimer], and urinalysis)[b]	Hosp	Hosp	Hosp	Hosp	Hosp			X
SpO_2/FiO_2, and if performed, PaO_2/FiO_2 (can be imputed)	Daily, only while hospitalized, through Day 43							X
Oxygenation requirements	Daily, only while hospitalized, through Day 43[c]							X
Ventilation requirements	Daily, only while hospitalized, through Day 43							X
ECMO requirements	Daily, only while hospitalized, through Day 43							X
Concomitant medications/concurrent procedures	Daily, only while hospitalized[d]					X	X	X
Physical examination and vital signs (blood pressure, heart rate, respiration rate, and body temperature)	Hosp	Hosp	Hosp	Hosp	Hosp			X
7-point Ordinal Scale	Daily, only while hospitalized, through Day 43[d]					X	X	X
Adverse event monitoring[e]	Daily, only while hospitalized[d]					X	X	X

ECMO = extracorporeal membrane oxygenation; EoS = End-of-Study; FiO_2 = fraction of inspired oxygen; Hosp = Assessment to be performed only if subject has not been discharged; ICU = Intensive Care Unit; SOFA = sequential organ failure assessment; SP-D = serum surfactant protein D; SpO_2 = peripheral capillary oxygen saturation

a. Day 43 will be used for the primary all-cause mortality endpoint.
b. For all on-study laboratory assessments, if central laboratory assessments cannot be collected for any reason, best efforts will be made to record local laboratory data.
c. IF DISCHARGED, will be measured via phone follow-up on Day 15, 22, 29, 36, and 43.
d. IF DISCHARGED, will be measured via phone follow-up on Day 15, 22, 29, 36, 43, 85, and 169.

Schedule of Assessments: Follow-up Period (Visits will be in-hospital or by phone, if subject has been discharged)								
Study Day (± Window)	**15 (± 2)**	**22 (± 2)**	**29 (± 2)**	**36 (± 2)**	**43[a] (± 2)**	**85 (± 2)**	**EoS 169 (± 2)**	**DoD / ET**
Week	**2**	**3**	**4**	**5**	**6**	**12**	**24**	**—**
Procedures/Assessments								

e. Adverse event monitoring will include assessment of treatment-emergent AEs (TEAEs), serious adverse events (SAEs), and severe AEs (Grade 3 or 4 events)

Note: Assessments at time points indicated with "Hosp" will only be conducted if the subject has not yet been discharged from the hospital. Assessments indicated with an 'X' will be performed in-hospital if the subject has not been discharged or via phone if subject has been discharged from the hospital.

Note: All subjects who are discharged from the hospital will undergo all Day-of-Discharge (DoD) Visit assessments; daily in-hospital assessments will only need to be performed once on DoD.
All subjects who discontinue from the study prematurely will undergo all Early Termination (ET) Visit assessments, whenever possible.
All subjects who discontinue treatment and/or the study early will be followed for Day 43 all-cause mortality.

7.2. Informed Consent

Documented consent (including regulatory compliant electronic methods) must be obtained from each potential subject prior to participating in all study procedures. Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about the study and the study population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.3. Inclusion/Exclusion Criteria Eligibility Review

All inclusion and exclusion criteria will be reviewed by the Investigator or qualified designee at the Screening Visit to ensure that the subject qualifies for the study.

All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

Subjects found ineligible during review of inclusion/exclusion will not proceed through the remaining screening process.

7.4. Study Assessments and Procedures

7.4.1. Efficacy Assessments

7.4.1.1. Measures of clinical support

At each assessment day, the following measure of clinical support should be assessed:

- Hospitalization
- Oxygen requirement (via nasal cannula, mask, or high-flow nasal cannula)
- Non-invasive mechanical ventilation (i.e., CPAP or BiPAP)

- Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube)
- ECMO requirement

7.4.1.2. 7-Point Ordinal Scale

The ordinal scale is an assessment of the clinical status at the first assessment of a given study day [WHO COVID-19 Master Protocol, 2020]. Each day, the worse score for the previous day will be recorded (i.e., on Study Day 3, the worse Day 2 score is obtained and recorded as the score for Day 2).

The scale is as follows:

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

7.4.1.3. Sequential Organ Failure Assessment (SOFA)

The SOFA score will be assessed daily for subjects while in the ICU.

7.4.1.4. National Early Warning Score (NEWS)

The NEW Score has demonstrated an ability to discriminate patients at risk of poor outcomes [WHO Master Protocol, 2020]. This score is based on 7 clinical parameters (Figure 7-1). The NEW Score is used as an efficacy measure.

These parameters can be obtained from the hospital chart using the last measurement prior to the time of assessment. This is recorded for the day obtained (i.e., on Study Day 3, the Day 3 score is obtained and recorded as Day 3). Each parameter and the final score will be recorded.

This should be evaluated at the first assessment of a given study day.

Figure 7-1: National Early Warning Score

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level of Consciousness				A			V, P, or U

Level of consciousness = alert (A), and arousable only to voice (V) or pain (P), and unresponsive (U)

7.4.2. Safety and Other Assessments

7.4.2.1. Physical Examinations

Abbreviated, targeted physical examinations (i.e., assessments of the skin, respiratory, cardiovascular system, and abdomen [liver and spleen]), will be performed at time points specified in the Schedule of Assessments (Table 7-2) and will be based on the subject's clinical status and what the clinic staff feel is appropriate.

Height and weight will be measured and recorded at Screening only, if possible.

Note: If a physical examination is performed as standard of care by appropriate personnel the same day that consent is signed or the same day of any scheduled study visit, results from that examination may be used if personal protective equipment (PPE) is not available or if study site staff consider additional examinations are unwarranted due to already having been performed as standard of care.

7.4.2.2. Vital Signs

Vital signs including blood pressure, heart rate, respiration rate, and temperature (oral, tympanic, or axillary) will be obtained at time points specified in the Schedule of Assessments (Table 7-2).

The same method for assessing temperature should be used at all visits for each individual subject, if possible.

Note: If vital signs measurements are performed as standard of care by appropriate personnel the same day that consent is signed or the same day of any scheduled study visit, results from that examination may be used if PPE is not available or if study site staff consider additional measurements are unwarranted due to already having been performed as standard of care.

7.4.2.3. Cardiovascular Assessments

7.4.2.3.1. Echocardiograms

Echocardiograms may be performed as standard of care, at the discretion of the Investigator. If an echocardiogram is performed, LVEF will be recorded, if assessed.

7.4.2.4. Follicle Stimulating Hormone (FSH), Viral Serology, and Tuberculosis Assessments

Follicle stimulating hormone (FSH) will be performed at screening, for women only, to confirm postmenopausal status in women who have not had 12 months of spontaneous amenorrhea.

A blood sample will be collected at Screening as specified in the Schedule of Assessments (Table 7-2), for viral serology and TB testing, but enrollment can continue without receiving the results first. HCV testing can be RNA or Ag, only to confirm suspected infection. If a subject is diagnosed with latent TB (positive QuantiFERON Gold or purified protein derivative [PPD]), hepatitis B or C, or HIV during the study, the Investigator must discuss this with the medical monitor and a decision will then be made concerning the second dose of gimsilumab, if applicable. In the event the QuantiFERON Gold assay is not available, and the site performs a different IGRA such as T Spot, then the alternative IGRA will be acceptable for patient screening and enrollment. Enrollment should not be delayed to obtain the QuantiFERON Gold assay in lieu of the IGRA available at the site. If no IGRA test is available, PPD can be used. If TB testing and viral serology is missed during screening it must be completed and results received prior to the second dose of study drug. If not completed or unable to obtain results further discussions with the medical monitor will be required.

7.4.2.5. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments must be conducted in accordance with the Laboratory Manual, and the Schedule of Assessments (Table 7-2). Laboratory requisition forms must be completed, and samples must be clearly labelled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Laboratory Manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

For all on-study laboratory assessments, if central laboratory assessments cannot be collected for any reason, best efforts will be made to record local laboratory data.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically

significant by the Investigator (e.g., SAE or AE or dose modification) the results must be recorded.

Hematology, clinical chemistry, coagulation, urinalysis and additional parameters to be tested are listed in (Table 7-3).

Table 7-3: List of Clinical Laboratory Analyses

Hematology			**Coagulation**
Platelet Count	MCV	Eosinophils	Prothrombin Time (PT)
RBC Count	MCH	Basophils	D-dimer
WBC Count (absolute)	MCHC		Activated partial thromboplastin time (aPTT)
Reticulocyte Count	Neutrophils		Fibrinogen
Hemoglobin	Lymphocytes		**Cardiac Enzymes**
Hematocrit	Monocytes		Troponin I

Clinical Chemistry			
BUN	Total CO_2	AST (SGOT)	Creatine Kinase
Creatinine	Calcium	ALT (SGPT)	NT-proBNP
Glucose	Ferritin	Albumin	FSH (blood) (only at screening for postmenopausal confirmation)
Sodium	C-reactive Protein (CRP)	Alkaline phosphatase	
Potassium	Lactate dehydrogenase (LDH)	Total bilirubin	
Chloride	Procalcitonin	Total Protein	

Urinalysis		
Glucose	pH	Clarity
Protein	Blood	Color
Ketones	Nitrite	Urobilinogen
Specific gravity	Leukocytes	Bilirubin

7.4.2.6. SARS-CoV-2 Viral Assessments

A local qualitative sample (e.g., nasopharyngeal swab) for PCR SARS-CoV-2 will be collected at Screening for determination of eligibility (if not already documented); all other on-study samples will be central quantitative samples.

When at all possible, if only 1 nostril is swabbed for viral assessments, the same nostril should be used for all subsequent samples.

7.4.2.7. Respiratory Assessments

Safety assessment includes FiO_2 and SpO_2. If indicated, additional follow up tests may be performed at Investigator discretion after consultation with the Medical Monitor.

If subject is receiving mechanical ventilation, the following parameters will be recorded: type of ventilation (high-flow nasal cannula, non-rebreather mask, CPAP, BiPAP, or intubation), F_iO_2, SpO_2, ventilation rate, pulse, tidal volume, positive end-expiratory pressure (PEEP), and airway pressure.

Respiratory assessments, when available, will be used to determine the Lung Injury Score (LIS) as an exploratory endpoint. The LIS is a composite scoring system including P/F ratio, the level of PEEP, the extent of infiltrates on chest X-ray or computerized tomography (CT) scan and respiratory static compliance.

7.4.2.8. Pharmacokinetic Assessments

Blood samples for PK analysis of serum gimsilumab will be collected at the time points indicated in the Schedule of Assessments (Table 7-2). The actual date and time of each blood sample collection will be recorded. The time of gimsilumab/placebo dosing on Day 1 will be t=0 for relative timing of PK samples.

Processing, storage, and shipping procedures are provided in the Laboratory Manual.

Serum PK analysis will be performed under the oversight and control of the Sponsor, the details of which will be included in the Laboratory Manual. Concentrations of gimsilumab will be determined in serum samples using the currently approved bioanalytical methodology.

7.4.2.9. Biomarker Assessments

Blood samples for determination of serum cytokines and a safety biomarker SP-D will be collected at the time points indicated in the Schedule of Assessments (Table 7-2). The actual date and time of each blood sample collection will be recorded. The time of gimsilumab/placebo dosing on Day 1 will be t=0 for relative timing of PD samples.

The cytokine/chemokine panel may include: GM-CSF, G-CSF, IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, IL-15, IL-17A, IL-17A/F, IL-23p19, IFN-γ, TNF-α, IP10 (CXCL10), MCP1 (CCL2), MIP1A (CCL3), and CCL17.

A subset of these cytokines/chemokines will be tested initially, further testing may be performed based on results of other study endpoints and emerging scientific information.

Concentrations of biomarkers will be determined using qualified or validated assays.

7.4.2.10. Immunogenicity Assessments

A single blood sample for the assessment of anti-GM-CSF autoAb will be collected at Screening (this result is not required to determine eligibility).

Blood samples for serum ADA analysis will be collected at the time points indicated in the Schedule of Assessments (Table 7-2). The actual date and time of each blood sample collection will be recorded. The time of gimsilumab/placebo dosing on Day 1will be t=0 for relative timing of ADA samples.

Processing, storage, and shipping procedures are provided in the Laboratory Manual.

Serum analysis will be performed under the oversight and control of the Sponsor, the details of which will be included in the Laboratory Manual. ADAs will be determined in serum samples using the currently approved bioanalytical methodology.

7.4.2.11. Safety Monitoring

It is understood the safety profile of gimsilumab in the critical care setting of patients with impending or established ARDS is not yet understood. Reassuringly the anti-GM-CSF class of molecules has been studied in many subjects in multiple Phase 2 trials [Hamilton, 2020] and to date no specific safety signal of concern has been noted to date. In principal concerns for targeting GM-CSF include respiratory tract infection and pulmonary alveolar proteinosis. Hence while the rationale for targeting GM-CSF in the setting of severe viral pneumonia with or without ARDS is strong, there is concern over AEs and patient safety.

To ensure subject safety, the sponsor will appoint an independent DMC to review unblinded safety and efficacy data on an ongoing basis. The Chair of the DMC will issue a Charter outlining the specific plan for safety review including both early stopping rules for adverse safety events and also early stopping rules for futility, and early stopping rules for efficacy.

8. DATA MANAGEMENT

For this study, subject data will be entered into Sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the Sponsor or designee.

Management of clinical data will be performed in accordance with applicable Sponsor approved standards and data cleaning procedures to ensure the integrity of the data, e.g., re resolving errors data queries, and inconsistencies in the data, and datasets in CDISC SDTM/AdaM formats.

AEs and concomitant medication terms will be coded using the most current versions of the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced (WHO-DDE), respectively.

The Principal Investigator will retain original source documents and the Sponsor will receive CRF-required data as electronic datasets. Subject initials will not be collected or transmitted to the Sponsor.

The detailed Data Management Plan (DMP) will be generated and approved prior to the study database lock when all subjects complete the Day 43 Visit, discontinue from the study early, or meet the primary endpoint of mortality (by Day 43).

The study database will be locked when all subjects complete the Day 43 Visit, discontinue from the study early, or meet the primary mortality endpoint. The second lock will occur when the last subject completes the Day 169 EoS visit.

In addition, there will be 2 database extracts (soft locks) for interim analyses, the first of which will be conducted when 60 subjects have been treated and have completed through Day 15; the DMC will review the data for safety and futility and provide their recommendations. The second interim analysis will be conducted when 100 subjects have completed at least the Day 29 Visit for non-mortality endpoints and have the data for the endpoint of mortality (by Day 43).

9. STATISTICAL CONSIDERATIONS AND ANALYSES

9.1. Sample Size Determination

There will be 270 subjects (135 subjects per treatment arm) with 1:1 randomization.

The comparisons between the treatment arms will have approximately 80% power and two-sided alpha level 0.05 to demonstrate the significant reduction of the incidences (15% versus 30%) in the primary endpoint between gimsilumab versus placebo.

The study will enroll at least 40%, but no more than 60%, of total subjects in each of the 2 categories of clinical status : ([lung injury/mild ARDS] or [moderate/severe ARDS]) at Baseline, which will be used as the stratified factor in the randomization.

Lung injury is defined as (1) requiring supplemental oxygen >4L O_2 to maintain >92% SpO_2, or (2) PaO_2/FiO_2 ≤300 mmHg (can be imputed).

ARDS [ARDS Berlin Definition, 2012] is defined as:

- Bilateral opacities — not fully explained by effusions, lobar/lung collapse, or nodules;
- Respiratory failure not fully explained by cardiac failure or fluid overload;
- Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present.
- ARDS severity categories are defined as:
  - Mild: 200 mmHg, < PaO_2/FiO_2, ≤300 mmHg with PEEP or CPAP ≥5 cm H_2O.
  - Moderate: 100 mmHg, < PaO_2/FiO_2, ≤200 mmHg with PEEP ≥5 cm H_2O.
  - Severe: PaO_2/FiO_2 ≤100 mmHg with PEEP ≥5 cm H_2O.

9.2. Randomization

The central stratified randomization will be used to assign subjects into 1 of the 2 study treatment arms with an equal randomization ratio (1:1) with the stratification factors of subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) and country.

Hypotheses

This is a double-blind, placebo-controlled, randomized trial testing a superiority hypothesis of significant reduction of the gimsilumab versus placebo in the percentage of the primary endpoint.

9.3. Analysis Endpoints

9.3.1. Efficacy Endpoints

Primary endpoint:

- Incidence of mortality by Day 43

Key Secondary Endpoints:

- Proportion of subjects who survived and were not requiring mechanical ventilation on Day 29
- Mechanical ventilation-free days by Day 29
- Time to hospital discharge by Day 43

Additional Secondary Endpoints:

- Incidence of mortality by Days 15, 22, 29, 85, and 169 (End-of-Study [EoS]).
- Proportion of subjects who survived and were not requiring mechanical ventilation on Days 15, 22, and 43.
- Mechanical ventilation-free days for all subjects by Days 15, 22, and 43
- ICU-free days for all subjects by Days 15, 22, 29, and 43.
- Incidence of mechanical ventilation use for all subjects by Days 15, 22, 29, and 43.
- Incidence of ICU use for all subjects by Days 15, 22, 29, and 43
- Time to death by Day 43 and Day 169 (EoS)
- NEWS assessed daily while hospitalized
- SOFA score, and each of the components, assessed daily while in the ICU
- The percentage of subjects reporting each severity rating on the 7-point ordinal scale, assessed daily while hospitalized and, if discharged from hospital, on Days 15, 22, 29, 36, 43, 85, and 169 (assessed by phone)
- Status on the 7-point ordinal scale, assessed daily while hospitalized and, if discharged from hospital, on Days 15, 22, 29, 36, 43, 85, and 169 (assessed by phone)
- Time to clinical improvement by 2 points on the 7-point ordinary scale
- Change from Baseline in SpO2/FiO2, assessed daily while hospitalized
- Incidence and duration of oxygen use during the study
- Change from Baseline in viral load as measured by quantitative PCR test on Days 2, 9, and DoD
- Change from Baseline in D-dimer, cardiac troponin I, LDH, ferritin, and CRP
- Serum gimsilumab concentrations

- Analysis of anti-gimsilumab antibodies (ADAs)

Exploratory Endpoints:

- Change from Baseline in the cytokine panel and SP-D
- Change from Baseline in LIS (if performed)
- Change from Baseline in chest radiographic assessment (if performed)
- Change from Baseline in P/F ratio, if performed
- Incidence and duration of ECMO use
- Change from Baseline in LVEF (when measured)
- Change from Baseline in eGFR (MDRD equation), assessed when central clinical safety laboratory measurements are collected during hospitalization

9.3.2. Safety Endpoints

Safety and tolerability, including assessment of clinical safety laboratory measurements, physical examinations, vital signs, concomitant medications; cumulative incidence of AEs, SAEs, and severe AEs.

9.3.3. Pharmacokinetic Endpoints

Serum gimsilumab concentration at time points as specified in the Schedule of Assessments (Table 7-2).

9.3.4. Biomarker Endpoints

Change from Baseline in the cytokine panel and serum SP-D will be measured at time points as specified in the Schedule of Assessments (Table 7-2).

9.4. Analysis Populations

Key Analysis Sets

- The Intent-to-treat (ITT) Population will include all randomized subjects who receive any amount of study drug. The ITT subjects will be analyzed according to randomized treatment, irrespective of whether or not they have prematurely discontinued. Subjects who withdraw from treatment and/or the study will be followed for Day 43 all-cause mortality. All efficacy analyses will be performed using the ITT Population.
- The Safety Population (SP) will include all randomized subjects who receive any amount of study drug. The SP will be analyzed according to the treatment received. This set will be used for the safety analyses.
- The per-protocol (PP) Population will include all subjects in the ITT Population who complete the Day 43 Visit with no protocol major violations. The PP Population will be used for supportive analyses of the efficacy measurements.

9.5. Statistical Analyses/Methods

All statistical analyses will be conducted on SAS Version 13.1 or later.

In general, all the continuous variables, including the changes from Baseline, will be summarized by the treatment with the mean, standard deviation (SD), median and the range. The Mixed Model with Repeated Measurements (MMRM) /Analysis of Covariance (ANCOVA) model with the treatment, country, subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]), and visits as the model term will be used to test for the significance of the treatment difference. The least square means, standard errors, 95% CIs and p-values will be presented.

All the categorical variables will be summarized by the treatment with the numbers and percentages of the subjects, and the treatment difference, the odds ratio and 95% CI will be tested by using logistical model (Ge, 2011) with the Treatment, country, and subject's clinical status at baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) for binary outcome. The CMH test will be used for other categorical outcomes.

The time to event endpoints will be analyzed by using the Cox Proportional Hazard model with the treatment, country , and subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) as the model term. The hazard ratio of gimsilumab versus placebo will be presented with 95% CI and p-value from the model. The Kaplan-Meier curves of the time to events will be presented for treatments on each endpoint.

The sites, which enrolled small number of subjects, will be combined in the statistical models. A blinded data review will be conducted for pooling the sites.

An SAP will be prepared and sent to agencies prior to the interim analysis.

9.5.1. Primary Efficacy Analyses

The primary analysis of the primary endpoint will be performed by using the logistical regression with the Treatment, country, and subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]). The subjects who died by Day 43 (by Day 169) will be summarized by the numbers and percentages, difference of the percentages, the odds ratio and its 95% CI presented for gimsilumab versus placebo, and p-value.

The secondary analysis of the primary endpoint will be conducted by using the Cox Proportional Hazard model with treatment, country and subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS] on the time to death. The median of the time to event from Kaplan-Meier curves will be presented for each treatment, and the hazard ratio of the gimsilumab dose level versus placebo will be presented with 95% CI, and p-values.

9.5.2. Sensitivity Analysis of the Primary Endpoint

Sensitivity analyses will be performed using all randomized subjects and using a multiple imputation method, such as the tipping point method, to handle missing data, as described in Section 9.5.5.

The Per-Protocol (PP) Population will be used for the primary and secondary analysis of the primary endpoint as additional supportive analyses.

9.5.3. Analysis of the Key and Other Secondary Endpoints

Secondary endpoints will be analyzed as follows:

- Incidence data (e.g., incidence of new or increased oxygen use) will be summarized as a percent with 95% CIs. The logistic regression model with treatment, country, and subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) will be used for the odds ratio of gimsilumab versus placebo, 95% CIs and p-values.
- Change in ordinal scale at specific time points will be summarized by proportions (e.g., proportion who have a 1-, 2-, 3-, or 4-point improvement or 1-, 2-, 3-, 4-point worsening). The CMH test on combined subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) will be used for treatment difference. The odds ratio of gimsilumab versus placebo, 95% CIs and p-values will be provided.
- Duration of event free (e.g., mechanical ventilation free days) will be summarized according to median days with quartiles. The Wilcoxon rank test will be used for the treatment difference.
- The continuous variables, including the changes from baseline, will be summarized by the treatment with the mean, standard deviation (SD), median, and the range. PK summaries will include geometric mean and geometric coefficient of variation. The Mixed Model with Repeated Measurements (MMRP)/Analysis of Covariance (ANCOVA) with the treatment, country, subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]), and visit as the model term, and baseline value as the covariate will be used for the treatment difference. The least square means, standard errors, 95% CIs and p-values will be presented.
- The time-to-event endpoints will be summarized with Kaplan Meier curves and 95% confidence bounds by the treatment. The Cox Proportional Hazard model with treatment, country, and subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) as model terms will be used. The hazard ratio of gimsilumab versus placebo will be presented with 95% CI and p-values.

9.5.4. Adjustment of Multiple Comparisons and Interim Analyses

The interim analysis will be conducted when 60 subjects have been treated and have completed through Day 15; the DMC will review the data for safety and futility and provide their recommendations.

The second interim analysis will be conducted when 100 subjects have completed at least the Day 29 Visit for non-mortality endpoints and have the data for the endpoint of mortality (by Day 43).

The objectives of the second interim analysis will be to stop the study by superiority, futility, or perform the sample size re-estimation. For controlling overall two-sided alpha of 0.05 overall for the final analysis on the primary endpoint of Mortality Day 43, 0.001 of the alpha will be used

for the superiority comparison during the second interim analysis, and 0.049 will be used for the final analysis for Day 43. The weighted average of two summary measures by Cui L, Hung HM, Wang [Cui, 1999] will be used, one based on the data collected in the interim analysis, and the other based on the data collected after the interim.

9.5.5. Handling of Missing Data

Sensitivity analyses will be performed for the primary and key secondary endpoints using multiple imputations for the missing data:

- Tipping-point multiple imputation analysis

Missing data will be imputed for mortality by Day 43 with all possible combinations of death or survival in the two arms. The combination which alters the conclusion will be defined as the tipping point for evaluation on the robustness of the results.

- Imputation differentiating the reasons of missing data from the early drop out

The reasons of the lost to follow-up, SAEs/AEs, and the use of rescue medications will be identified, and the percentage of these subjects will be summarized by treatment. The data for informative censoring, such as the unfavorable or worst outcome, can be used to impute the missing data.

9.5.6. Safety Analyses

Safety will be assessed based on the SP for AEs, laboratory parameters, physical examination, vital signs, and clinical chemistries throughout the duration of the study. The safety analyses will include descriptive summaries by treatment arm of AEs. The number and percentage of participants reporting AEs and SAEs will be presented. Adverse events will be categorized by system organ class (SOC) and preferred term (PT) and summarized by the number of participants (and percentage) with at least 1 event, and the number of events. Adverse events will also be summarized by seriousness, grade, and study drug relationship for all participants. The continuous variables, including the changes from Baseline, will be summarized by descriptive statistics: mean, SD, and the range. The categorical variables, such as normal/abnormal will be summarized by the numbers and percentages at each visit, and the shift table from Baseline to each visit will be presented.

9.5.7. Sub-Group Analyses

Subgroup analyses for the primary outcomes will evaluate the treatment effect across the following subgroups: country, subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]), country, age, and sex. A forest plot will display confidence intervals across subgroups. Interaction tests will be conducted to determine whether the effect of treatment varies by subgroup.

9.5.8. Timing of Analyses

The first unblinded analysis will be conducted when the last subject completes the Day 43 Visit, discontinues the study early, or meets the primary endpoint of mortality (by Day 43). The final analysis will be conducted when the last subject completes the Day 169 (EoS) Visit. The first interim analysis will be conducted when 60 subjects have been treated and have completed through Day 15; the DMC will review the data for safety and futility and provide their recommendations.

The second interim analysis will be conducted when 100 subjects have completed at least the Day 29 Visit for non-mortality endpoints and have the data for the endpoint of mortality (by Day 43). The objectives of the second interim analysis will include the claim of superiority or futility to stop the study, or the reassessment of sample size, and/or modifications of the populations.

The DMC will be responsible for closely reviewing the safety data from the unblinded interim analysis and for providing their recommendations. The detailed objectives and procedures, including close monitoring of the safety data and the boundaries of futility will be described in the SAP and the DMC Charter.

9.5.9. Pharmacokinetic, Biomarker, and Immunogenicity Analyses

Serum gimsilumab concentrations will be summarized using descriptive statistics.

Biomarker analyses will be based on the Safety Population and biomarker (SP-D, cytokine/chemokine, anti-GM-CSF autoAb) concentrations will be summarized by treatment using descriptive statistics.

Immunogenicity analysis will be based on the Safety Population and anti-drug antibody data will be reported in the format provided by the bioanalytical laboratory.

Further details will be provided in the SAP.

10. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAES)

The Investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

The Investigator is not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product or study participation, the Investigator should promptly notify the Sponsor.

10.1. Special Consideration for Assessment of Adverse Events

It is recognized that the patient population in the ICU will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of their underlying disease and the impact of standard therapies. These will not necessarily constitute an AE unless

they require significant intervention, lead to discontinuation of blinded study drug, or are considered to be of concern in the investigator's clinical judgement.

Death should be recorded both as a SAE and as the outcome of ONE event, i.e. one event should be determined to be the primary cause of death. The 'clinical' AE that resulted in death is the AE and the death information supports the clinical AE. 'Death' is not entered as an AE unless the cause of death is unknown. In such case the AE term is 'Unspecified fatal event' until the cause of the death is known.

10.2. Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE **include but are not limited to**:

- Any clinically significant, new or worsening, abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or findings from other safety assessments (e.g., ECGs, radiological scans, vital signs measurements. Clinical significance is determined by the medical and scientific judgement of the Investigator.
- Worsening of a chronic or intermittent pre-existing condition including an increase in frequency, intensity and/or duration of a condition.
- Signs, symptoms, or the clinical sequelae of a suspected interaction (e.g., with medications or food).
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose without the presence of an AE are to be reported as a protocol violation).
- New infections occurring on-study, regardless of infection type (i.e., viral, bacterial, fungal, etc.) will be reported as AEs.

Events that **do not** meet the definition of an AE include:

- Anticipated day-to-day fluctuations of a pre-existing condition(s), (including the disease under study), that do not represent a clinically significant exacerbation or worsening.
- Abnormal or worsening laboratory, (including imaging) findings or other safety findings that are not clinically significant.
- Medical or surgical procedure (e.g., endoscopy, appendectomy). However, the condition that leads to the procedure is to be considered a reportable AE.

- If applicable, the disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

10.3. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization

  NOTE: "Hospitalization" includes admission to the hospital of any duration. Complications that occur during hospitalization are AE sand are SAEs if they prolong a hospitalization or meets any other serious criteria. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
- Results in disability/incapacity

  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is an important medical event that may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are invasive or malignant cancers, allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.4. Time Period and Frequency for Collecting AE and SAE Information

- AEs will be collected from the start of Study Treatment until the follow-up contact, at the timepoints specified in the Schedule of Assessments (Table 7-2).

- SAEs related to study procedures or investigational product will be collected from the time of subject informed consent until the follow-up contact is completed.
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to the Sponsor within 24 hours of awareness.

10.5. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

10.6. Assessing Severity of AEs and SAEs

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on participant/event outcome or action taken. The Investigator must determine the severity of each AE according to the following criteria.

Criteria for Determining the Grade/Severity of Adverse Event Terms

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant[a]	Not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
4/Life-threatening[a]	Life threatening consequences; urgent intervention indicated
5/Death	Death related adverse events

[a] Severe AEs include both Grade 3 and Grade 4 AEs.

10.7. Assessing Causalities of AEs and SAEs

Regulatory authorities require that both investigator and sponsor assess whether there is a reasonable possibility that the study treatment caused each AE. This assessment requires careful medical consideration of each event in relationship to the timing of drug administration, the presence of other factors which may have caused the event (underlying illness, concomitant medication, complications, exposure to other toxins or allergens, environmental factors, etc.), and the effects of stopping and/or restarting the study treatment.

The investigator will assess the causality of each reported AE as follows:

- Probably related: an AE occurring at a reasonable time following administration of a drug, where other causes are unlikely, there is evidence to suggest that the drug caused the event, and/or where the event recurs after reintroduction of the drug (without other explanation for the recurrence).
- Possibly related: an AE occurring at a reasonable time following administration of a drug and for which there is a reasonable possibility that the drug caused the event, e.g., there is some evidence to suggest a causal relationship.
- Not related: an AE with poor or no relationship to the timing of drug administration, or where another cause such as underlying disease, complications, or other medications reasonably explains the event, or where the event does not recur after continued administration or reintroduction of the drug for an adequate period.

10.8. Follow-up of (non-serious) AEs and Serious AEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs, will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Ongoing AEs may be closed after consultation between the Sponsor and Medical Monitor.

10.9. Regulatory Reporting Requirements for SAEs

On discovery, all SAEs should be immediately reported (latest within 24 hours of knowledge of the event) to [redacted]

See Section 6.4 for emergency unblinding service contact information.

Prompt notification by the Investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and any other regulatory agencies about the safety of a product under clinical investigation. The Sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and Investigator.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and are forwarded to Investigators as necessary.

11. PREGNANCY REPORTING

- All female subjects will be tested for pregnancy prior to dosing. Subjects testing positive for pregnancy will be ineligible for study participation.
- Any pregnancy reported between the time of informed consent and completion of the Day 85 Follow-up Visit or an Early Termination Visit must be reported to the Sponsor within 2 weeks of learning of the pregnancy.
- Female subjects who become pregnant will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be provided to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

12. RESPONSIBILITIES

12.1. Principal Investigator Responsibilities

12.1.1. Good Clinical Practice

The Principal Investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a United States IND, the Investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR 312), subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical trial, the Principal Investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that Principal Investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the Sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the Investigator and any sub-investigator. The Principal Investigator and sub-investigator agree to notify the Sponsor of any change reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol defined activities.

12.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the Investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

12.1.3. Informed Consent

The Principal Investigator or designee is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The Investigator must utilize an IRB or IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

12.1.4. Confidentiality

The Principal Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject number, date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. The Principal Investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The Principal Investigator agrees that all information received from the Sponsor, including but not limited to the Investigator Brochure, this protocol, CRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

12.1.5. Study Files and Retention of Records

The Principal Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) Investigator's study file, and (2) subject clinical source documents.

The Investigator's study file will contain the protocol/amendments, CRF and query forms, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include the following for each subject:

- subject identification (name, date of birth, gender);
- documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- participation in trial (including trial number);
- trial discussed and date of informed consent;
- dates of all visits;
- documentation that protocol specific procedures were performed;
- results of efficacy parameters, as required by the protocol;
- start and end date (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well);
- record of all AEs and other safety parameters (start and end date, and preferably including causality and intensity);
- concomitant medication (including start and end date, dose if relevant; dose changes should be motivated);
- date of trial completion and reason for early discontinuation, if applicable.

All clinical study documents must be retained by the Principal Investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The Principal Investigator may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the Sponsor. The Investigator must notify the Sponsor before destroying any clinical study records.

Should the Principal Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Principal Investigator and the Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

Unused biological samples remaining at the conclusion of this study may be retained in an appropriate storage facility by the Sponsor for a period up to 10 years for purposes of this study.

12.1.6. Electronic Case Report Forms (eCRF)

For each subject enrolled, an eCRF must be completed and signed by the Principal Investigator or sub-investigator (as appropriate) within a reasonable time period after data collection. This also applies to records for those subjects who fail to complete the study (even during a pre-randomization screening period if an eCRF was initiated). If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

12.1.7. Drug Accountability

The Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational medicinal product, placebos, and comparators. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the Sponsor and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the Sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will ship all unused investigational medicinal product supplies to the designated depot, according to these procedures. If the site cannot meet the Sponsor's requirements for disposal, arrangements will be made between the site and the Sponsor or its representative for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

12.1.8. Inspections

The Principal Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

12.1.9. Protocol Compliance

The Principal Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

12.2. Sponsor Responsibilities

12.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor. All protocol modifications must be submitted to the IRB or IEC in

accordance with local requirements. Approval must be obtained before changes can be implemented.

12.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

12.3. Joint Investigator/Sponsor Responsibilities

12.3.1. Access to Information for Monitoring

In accordance with ICH Good Clinical Practice guidelines, the study monitor must have direct access to the Principal Investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

12.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the Sponsor may conduct inspections or audits of the clinical study. If the Principal Investigator is notified of an inspection by a regulatory authority the Principal Investigator or designee agrees to notify the Medical Monitor immediately. The Principal Investigator agrees to provide to representatives of a regulatory agency or the Sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

12.3.3. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the Sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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14. APPENDICES

14.1. Appendix 1: Abbreviations and Trademarks

Antibody	Ab
ADA(s)	Anti-drug antibodies
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BC	Birth control
CI	Confidence interval
CKD	Chronic kidney disease
C_{max}	Maximum concentration
CMO	Cochran-Mantel-Haenszel
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CPAP	Continuous positive airway pressure
CPK	Serum creatine phosphokinase
CRF	Case Report Form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CT	Computerized tomography
DMC	Data Monitoring Committee
DMP	Data Management Plan
DoD	Day-of-Discharge (from hospital)
ECG(s)	Electrocardiogram(s)
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EoS	End-of-Study

ET	Early Termination
FDA	U.S. food and drug administration
FiO_2	fraction of inspired oxygen
FSH	Follicle stimulating hormone
G-CSF	Granulocytecolony stimulating factor
GFR	Glomerular filtration rate
GM-CSF	Granulocyte macrophage-colony stimulating factor
HBsAg	Hepatitis B
HCVAb	Hepatitis C
HIV	Human immunodeficiency virus
HR	Heart rate
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent ethics committee
IGRA	Interferon gamma release assay
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional review board
ITT	Intent-to-Treat
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous(ly)
KSG	Kinevant Sciences GmbH
KSI	Kinevant Sciences, Inc.
LDH	Lactate dehydrogenase
LIS	Lung Injury Score
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities

MMRM	Mixed model with repeated measures
MSDS	Material safety data sheet
NEWS	National Early Warning Score
NOEL	No-observed-effect level
PAH	Pulmonary arterial hypertension
PaO_2	Partial pressure of oxygen
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PEEP	Positive end-expiratory pressure
P/F	PaO_2/FiO_2 ratio
PK	Pharmacokinetic
PP	Per-Protocol
PT	Preferred term
RA	Rheumatoid arthritis
RBC	Red blood cell
RR	Respiration Rate
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SOC	System organ class
SOFA	Sequential Organ Failure Assessment
SP	Safety Population
SP-D	Surfactant protein D
SpO_2	peripheral capillary oxygen saturation
t1/2	Elimination half-life
TB	Tuberculosis
Th1	T-helper-1
TNF-α	Tumor Necrosis Factor- alpha
ULN	Upper limit or normal
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WBC	White blood cell count

WCBP	Woman of childbearing potential
WHO	World Health Organization
WHO-DDE	World health organization drug dictionary enhanced

14.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase I Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA Drug-induced Liver Injury: Premarketing Clinical Evaluation).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Liver Safety Process

The procedures listed below are to be followed if a subject has ALT, bilirubin and/or INR elevations that meet the definition of an SAE (defined in Section 10.3):

- Notify the Medical Monitor within 24 hours of learning of the abnormality to confirm follow-up.
- Complete the liver event case report forms.
- Upon completion of the safety follow-up withdraw the subject from the study unless further safety follow-up is required.
- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within Baseline values.
- Obtain viral hepatitis serology including:
  - Hepatitis A IgM antibody.
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).
  - Hepatitis C ribonucleic acid (RNA).
  - Cytomegalovirus IgM antibody.
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
  - Hepatitis E IgM antibody.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) on the AE CRF.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications CRF.

- Record alcohol use on the Liver Events CRF.
- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009].

The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

References

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14.3. Appendix 3: Summary of Changes for Protocol Amendments

The original Protocol (Version 1.0) was approved on 22-March-2020, and has been amended 4 times; Protocol Amendment 1 (Version 2.0) was approved on 05-April-2020, Protocol Amendment 2 (Version 3.0) was approved on 06-May-2020, Protocol Amendment 3 (Version 4.0) was approved on 12-June-2020, and Protocol Amendment 4 (Version 5.0) was approved on 17-August-2020.

Summaries of changes are presented in Table 14-1 for Amendment 1, Table 14-2 for Amendment 2, Table 14-3 for Amendment 3, and Table 14-4 for Amendment 4.

Table 14-1: Summary of Changes: Amendment 1

Section(s) Changed	**Description of Changes** Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
Justification of Changes	The protocol was amended, prior to implementation, based on feedback from the FDA. These changes are summarized below.
Global change: Version and date were updated throughout the entire protocol.	Version ~~1~~: ~~22-March-~~2020 Version 2: 05-April-2020
Contact information for serious adverse events was added to the administrative information at the beginning of the document.	~~Monitors listed above (may be contacted during daytime or after-hours).~~ On discovery, all SAEs should be immediately reported (latest within 24 hours of knowledge of the event) to [redacted]
Synopsis and Section 3	Study objectives were revised to identify key secondary objectives and clarify secondary and exploratory objectives. **Primary Objective:** • The primary objective is to evaluate the impact ~~on mortality~~ of ~~the~~ intravenous (IV) treatment ~~of~~with gimsilumab on mortality in subjects with lung injury or ARDS secondary to COVID-19. **Key Secondary Objectives:** • To assess the effect of gimsilumab on ventilation requirements • To assess the effect of gimsilumab on the need for Intensive Care Unit (ICU) level of care • To assess the effect of gimsilumab on overall duration of hospitalization **Additional Secondary ~~efficacy~~ Objectives:** o ~~Time to an improvement of 1 category from admission on the 7-point ordinal scale;~~ o ~~Subject clinical status on the 7-point ordinal scale;~~

Table 14-1: Summary of Changes: Amendment 1

Section(s) Changed	Description of Changes Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
	~~○ Mean change from Baseline in ranking on the 7-point ordinal scale;~~ ~~• Time to hospital discharge (DoD) or to a~~ To assess the effect of gimsilumab as measured by the National Early Warning Score (NEWS)~~of ≤4 and maintained for 24 hours, whichever occurs first;~~ ~~○ Change from Baseline in NEWS (only if hospitalized).~~ • To assess the effect of gimsilumab as assessed by the Sequential Organ Failure Assessment (SOFA) score • To assess the effect of gimsilumab as measured by the 7-point ordinal scale • To assess the effect of gimsilumab on peripheral capillary oxygen saturation / fraction of inspired oxygen (SpO_2/FiO_2) • To assess the effect of gimsilumab on oxygenation requirements • To assess changes in on-treatment viral load~~over time~~ • To assess the effect of gimsilumab on biomarkers of inflammation • To determine the pharmacokinetic (PK) properties of gimsilumab • To assess the immunogenicity of gimsilumab • To determine the safety and tolerability of ~~IV~~ gimsilumab ~~• To assess immunogenicity in subjects receiving IV gimsilumab.~~ ~~• To assess the effects of IV gimsilumab on renal function over time.~~ ~~• To assess the pharmacodynamic (PD) effects of IV gimsilumab on the following:~~ ~~○ Duration of need of supplemental oxygenation;~~ ~~○ Need for mechanical ventilatory support;~~ ~~Duration of hospitalization.~~ **Exploratory Objectives:** • To explore the ~~laboratory parameters~~effect of ~~sepsis during therapy including sequential organ failure assessment (SOFA) score ≥2 for any organ parameter, white blood cell count (WBC) >12,000 or <4,000 per mm^3, heart rate (HR) >100 beats/minute, respiration rate (RR) >20 breaths/minute.~~ ~~• Serum anti-GM-CSF autoantibodies, C-reactive protein,~~gimsilumab on serum cytokine concentrations~~,including GM-CSF,~~ and surfactant protein D (SP-D~~).~~ ~~• Percent~~To explore the effect of ~~subjects with SARS-CoV-2 detectable in oropharyngeal (OP) sample at Days 8, 15, and 29 (if hospitalized), and at DoD.~~ ~~• To assess the effects of IV gimsilumab on cardiac function over time.~~ ~~• Incidence of~~ gimsilumab on other measurements of lung injury that may be performed during standard care (e.g., Lung Injury Score [LIS], chest radiography, PaO_2/FiO_2 [P/F ratio], need for extracorporeal membrane oxygenation ([ECMO) ~~procedures (if applicable).~~])

Table 14-1: Summary of Changes: Amendment 1

Section(s) Changed	Description of Changes Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
	• To explore the ~~pharmacokinetics~~effect of gimsilumab on cardiac function (if measured) To assess the effect of ~~IV~~gimsilumab on renal function
Synopsis and Section 4.3	Study duration was revised to allow for a longer follow-up period. This study will consist of a 2-week Treatment Period (last dose Day 8, if administered) and a ~~4~~22-week Follow-up Period, for a total study duration of ~~6~~24 weeks for each subject.
Synopsis, Section 3, and Section 9.3.1	Endpoints were revised to correspond with the revised objectives. **Primary Endpoint:** • Incidence of mortality by Day 43 ~~(End-of-Study [EoS])~~ **Key Secondary Endpoints:** • Incidence and duration of mechanical ventilation use during the study • Number of days in the ICU • Number of days of inpatient hospitalization **Additional Secondary Endpoints:** • Incidence of mortality by Day 15, ~~Day~~ 29, ~~Day~~ 85, and ~~Day29~~ 169 (End-of-Study [EoS]) • NEWS assessed daily while hospitalized • SOFA score assessed daily while in the ICU • The percentage of subjects reporting each severity rating on the 7-point ordinal scale ~~(time frame: study duration). The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. The scale is as follows:~~, assessed daily while hospitalized and, if discharged from hospital, on Days 15, 22, 29, 36, 43, 85, and 169 (assessed by phone) ~~1. Not hospitalized, no limitations on activities;~~ ~~2. Not hospitalized, limitation on activities;~~ ~~3. Hospitalized, not requiring supplemental oxygen;~~ ~~4. Hospitalized, requiring supplemental oxygen;~~ ~~5. Hospitalized, on non-invasive ventilation or high-flow oxygen devices;~~ ~~6. Hospitalized, on invasive mechanical ventilation or ECMO;~~ ~~7. Death.~~ • Status on the 7-point ordinal scale, assessed daily while hospitalized and, if discharged from hospital, on ~~the day of discharge (DoD), and on~~ Days 15, 22, 29, 36, 43, 85, and ~~43 (~~169 (assessed by phone~~if~~

Table 14-1: Summary of Changes: Amendment 1

Section(s) Changed	Description of Changes Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
	~~discharged from the hospital).~~]~~NEWS assessed daily while hospitalized~~ • ~~Safety~~Change from Baseline in SpO_2/FiO_2, assessed daily while hospitalized • Incidence and ~~tolerability, including assessment~~duration of ~~changes~~oxygen use during the study • Change from Baseline in viral load ~~(~~as measured by quantitative polymerase chain reaction [~~(~~PCR]~~)~~ test~~), physical examinations, vital signs, electrocardiograms (ECGs), clinical safety laboratory measurements, local injection site tolerability; concomitant medications; cumulative incidence of adverse events (AE)s, serious adverse events (SAEs),~~on Days 2, 9, and ~~severe AEs.~~day-of-discharge (DoD) • Change from Baseline in D-dimer, cardiac troponin I, lactate dehydrogenase (LDH), ferritin, and C-reactive protein (CRP) • Serum gimsilumab concentrations • Analysis of anti-gimsilumab antibodies (ADAs) • ~~Assessment of change from Baseline to Day 15 (if hospitalized) and at DoD in the following parameters:~~ ~~○ Peripheral capillary oxygen saturation/fraction of inspired oxygen (SpO_2^-/FiO_2^-) ratio by day~~ ~~○ Glomerular filtration rate (GFR), calculated~~ • ~~Oxygenation-free days in the first 28 days (to Day 29).~~ • ~~Incidence and duration of new or increased oxygen use during the study.~~ • ~~Ventilator free days in the first 28 days (to Day 29).Incidence and duration of new mechanical ventilation use during the study.~~ **Safety Endpoints:** • Safety and tolerability, including assessment of clinical safety laboratory measurements, physical examinations, vital signs, ~~electrocardiograms (ECGs), local injection site tolerability,~~ concomitant medications; cumulative incidence of adverse events (AEs), serious adverse events (SAEs), and severe AEs **Exploratory Endpoints:** • ~~Changes~~Change from Baseline in the ~~following biomarkers:~~cytokine panel and serum SP-D~~, and C-reactive protein (CRP).~~ • ~~Serum anti-GM-CSF autoantibodies~~Change from Baseline in ~~Lung Injury Score (~~LIS) (if performed). • Change fro~~m~~ Baseline in chest radiographic assessment (if performed).

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	• Change from Baseline in P/F ratio, if performed • Incidence and duration of ECMO use • ~~Serum gimsilumab concentrations.~~ • ~~If bronchoalveolar lavage (BAL) is performed as standard of care: Change in BAL biomarkers of fibroproliferation (procollagen and cytokine panel) and cell count differential (BAL sample will be collected and stored for possible future analysis).~~Change from Baseline in left ventricular ejection fraction (LVEF) (when measured). • ~~Change from Baseline partial pressure of oxygen (PaO_2)/FiO_2 (P/F ratio), if performed~~ • ~~Number and percentage of subjects on ECMO.~~ • ~~Number of days on ECMO.~~ • ~~Number and percentage of subjects successfully removed from ECMO.~~Change from Baseline in estimated glomerular filtration rate (eGFR) [Modification of Diet in Renal Disease (MDRD) equation], assessed when central clinical safety laboratory measurements are collected during hospitalization
Synopsis and Section 5.2	Inclusion criteria were revised to reflect feedback from the FDA, including a longer Follow-up Period. **An individual will be eligible for participation in this study only if all of the following inclusion criteria are met:** 1. Male or non-pregnant female age 18 to 79 years, inclusive 2. Subject (or legally authorized representative) is able and willing to provide written informed consent, which includes compliance with study requirements and restrictions listed in the consent form. 3. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other approved clinical testing ~~<72 hours~~ prior to randomization 4. ~~Subject~~CRP ≥50 mg/L or serum ferritin ≥1,000 ng/mL 5. Radiographic evidence of bilateral infiltrates 6. Subject has clinical evidence of lung injury [defined as (1) requiring supplemental oxygen >4L O_2 to maintain >92% SpO_2, or (2) P/F ratio ≤300 mmHg (can be imputed)], or meets clinical classification criteria for ARDS [ARDS Berlin Definition, 2012~~] or has clinical evidence of lung injury,~~], secondary to COVID-19. ~~• Lung injury is defined as PaO_2/FiO_2 ≤300 mmHg, without invasive or non-invasive ventilation (or with positive end-expiratory pressure [PEEP] or continuous positive airway pressure [CPAP] <5 cm H_2O).~~ ~~• ARDS is defined as:~~

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	~~○ Bilateral opacities — not fully explained by effusions, lobar/lung collapse, or nodules;~~ ~~○ Respiratory failure not fully explained by cardiac failure or fluid overload;~~ ~~○ Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present.~~ ~~○ Mild: 200 mm Hg, < PaO_2/FiO_2, ≤300 mm Hg with PEEP or CPAP ≥5 cm H_2O.~~ ~~○ Moderate: 100 mm Hg, < PaO_2/FiO_2, ≤200 mm Hg with PEEP ≥5 cm H_2O.~~ 7. ~~Severe: PaO_2/FiO_2 ≤100 mm Hg with PEEP ≥5 cm H_2O.~~Female subjects must agree to use an approved highly effective birth control (BC) method (<1% failure rate per year) throughout the study (until completion of ~~their EoS~~the Day 85 Follow-up Visit), unless documented to have a reproductive status of non-childbearing potential or is postmenopausal: • Non-childbearing potential defined as pre-menopausal female with medical history of bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries), or hysterectomy; hysteroscopic sterilization, • Postmenopausal defined as 12 months of spontaneous amenorrhea; with follicle stimulating hormone (FSH) confirmation. • Woman of childbearing potential (WCBP) who is already using an established method of highly effective contraception or agrees to use one of the allowed BC methods, for at least 28 days prior to the start of dosing (as determined by the Investigator Brochure or Investigator or designee) to sufficiently minimize the risk of pregnancy throughout study participation (until completion of ~~their EoS~~the Day 85 Follow-up Visit). 8. Males who are sexually active must agree to use one of the allowed BC methods. Male subjects must also agree to sufficiently minimize the risk of pregnancy throughout study participation (until completion of ~~their EoS~~the Day 85 Follow-up Visit).
Synopsis and Section 5.3	Exclusion criteria were revised to reflect feedback from the FDA. 1. ~~Clinical evidence of pneumonia due to bacterial infection or viral (not SARS-CoV-2) infection.Clinical~~ Subject requires norepinephrine at a dose of >0.5 mcg/kg/min, or equivalent 2. Subject has been intubated for >72 hours 3. Evidence of ~~multi-organ~~life-threatening dysrhythmia (e.g., ventricular tachycardia [VT], ventricular fibrillation [VF]), or cardiac arrest on presentation

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	4. Evidence of new or preexisting decompensated heart failure. 5. At the time of screening, subject is anticipated to require ECMO 6. Absolute neutrophil count <2000 mm^3 7. Platelet count <50,000 mm^3 8. History of known anti-GM-CSF ~~antibodies~~autoantibodies (autoAb) or pulmonary alveolar proteinosis~~.~~ 9. Severe chronic respiratory disease (e.g., known chronic obstructive pulmonary disease [COPD], pulmonary arterial hypertension [PAH], idiopathic pulmonary fibrosis [IPF], interstitial lung disease [ILD]) requiring ~~long term~~baseline oxygen therapy or mechanical ventilation~~.~~ pre-hospitalization 10. ~~Positive QuantiFERON® test at Screening.~~ 10. ~~Positive serology for~~Suspected or confirmed untreated, active ~~hepatitis B (HBsAG), hepatitis C (HCVAb), or~~ tuberculosis (TB), human immunodeficiency virus (HIV~~) at Screening~~), hepatitis B or C infection 11. ~~Subject meets inclusion criteria but is not expected to be able to be managed by the institution personnel with invasive or non-invasive ventilatory support.~~Alanine aminotransferase (ALT) ~~/~~or Aspartate aminotransferase (AST) >5 × upper limit of normal (ULN) 12. ~~Stage 4 severe chronic kidney disease (CKD,~~ eGFR <30 mL/min/1.73m^2 (MDRD equation) or requiring hemofiltration or dialysis~~.~~ 13. ~~Use within the past 60 days, or planned use,~~Use of any investigational drug or any immunomodulatory biologic (e.g., anti-IL-1, anti-IL-6R, anti-TNF) within the past 60 days, or planned use of any of these agents during the study 14. Chronic (≥4 weeks) use of corticosteroids >10 mg/day of prednisone or equivalent 15. Pregnancy and/or breast feeding 16. ~~Anticipated transfer to another hospital which is not a study site within 72 hours.~~Unable to receive invasive or non-invasive ventilatory support 17. Moribund condition ~~as determined by~~in the opinion of the clinical team ~~investigator.~~ 18. ~~Allergy to any study medication.~~
Synopsis and Section 8, Section 9.5.4, and Section 9.5.8	Database lock information was update throughout the document to reflect longer study duration and database lock timeframes. The study database will be locked when all subjects complete the Day 43 ~~(EoS)~~ Visit, discontinue from the study early, or meet the primary mortality

Table 14-1: Summary of Changes: Amendment 1

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	endpoint. The second lock will occur when the last subject completes the Day 169 EoS visit. In addition, there will be ~~1~~2 database ~~extract~~extracts (soft ~~lock~~locks) for interim ~~analysis,~~ analyses, the first of which ~~is to~~will be ~~performed when ~40% of planned~~conducted when 60 subjects have been treated and have completed 7 days of follow-up; the DMC will review the data for safety and futility and provide their recommendations. The second interim analysis will be conducted when 50% of total subjects are discharged from the hospital, complete the Day 43 ~~(EoS)~~ Visit, discontinue the study early, or meet the ~~primary~~endpoint of mortality ~~endpoint.~~(by Day 43).
Synopsis and throughout	Statistical analysis information regarding analysis sets (Section 9.4), adjustments for multiple comparisons (Section 9.5.4), and timing of the analyses (Section 9.5.8) was updated to reflect the longer study duration and additional interim database lock. **Key Analysis Sets** • The Intent-to-Treat (ITT) Population will include all randomized subjects who receive any amount of study drug~~, have a Baseline assessment of efficacy endpoint, and at least 1 post treatment assessment of efficacy endpoint~~. The ITT subjects will be analyzed according to randomized treatment, irrespective of whether or not they have prematurely discontinued. Subjects who withdraw from treatment and/or the study early will be followed for Day 43 all-cause mortality. All efficacy analyses will be performed using the ITT Population. • The Safety Population (SP) will include all randomized subjects who receive any amount of study drug. The SP will be analyzed according to the treatment received. This set will be used for the safety analyses. • The Per-Protocol (PP) Population will include all subjects in the ITT Population who complete the Day 43 Visit with no major protocol violations. The PP Population will be used for supportive analyses of the efficacy measurements. **Adjustment of Multiple Comparisons**: There is no need to adjust the significance level 0.05 (two-sided) in the analysis since there is only ~~one~~ 1 primary endpoint and ~~one~~1 gimsilumab dose level versus placebo. ~~However,~~ The interim analysis will be conducted when ~~~40% of planned~~60 subjects ~~are discharged from the hospital, complete the Day 43 (EoS) Visit, discontinue the study early, or meet the primary mortality endpoint. There~~have been treated and have completed 7 days of follow-up; the DMC will ~~be~~review the ~~split of alpha 0.05 to be 0.001~~data for ~~the~~

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	~~interim analysis and 0.049 for the final analysis of the primary endpoint~~safety and futility and provide their recommendations. The second interim analysis will be conducted when 50% of total subjects are discharged from the hospital, complete the Day 43 Visit, discontinue the study early, or meet the endpoint of mortality (by Day 43). There will be the split of alpha 0.05 to be 0.001 for the 2nd interim analysis and 0.049 for the final analysis of the primary endpoint, as the 2nd interim analysis may claim for the superior efficacy for the stop of the study early. The 3 key secondary endpoints will be analyzed by hierarchical testing procedure following the order of the list of endpoints, and each endpoint will be analyzed at 0.05 alpha level. **Timing of Analyses** The ~~final~~ first unblinded analyses will be conducted when the last subject completes the Day 43 ~~(EoS)~~ Visit, discontinues from the study early, or meets the primary mortality endpoint (by Day 43). The second unblinded analyses will be conducted when the last subject completes the Day 169 Follow-up Visit (EoS). The first interim analysis ~~can be conducted when ~40%~~will be when 60 subjects have been treated and have completed 7 days of ~~planned~~follow-up; the DMC will review the data for safety and futility and provide their recommendations. The second interim analysis will be conducted when 50% of total subjects are discharged from the hospital, complete the Day 43~~(EoS)~~ Visit, discontinue the study early, or meet the ~~primary~~endpoint of mortality ~~endpoint. The Data Monitoring Committee (DMC)~~(by Day 43). The objectives of the second interim analysis will include the claim of superior efficacy or futility to stop the study, the reassessment of sample size, and/or modifications of the populations. The DMC will be responsible for ~~this~~ closely reviewing the safety data from the unblinded interim analysis and ~~for informing the sponsor about the results and the recommendation for the study.~~ providing their recommendations. The detailed objectives and procedures of the interim analyses will be described in the ~~study protocol,~~DMC Charter; these can be the claim of early stop of the study for superiority, futility, re-assessment of the final sample size, and/or the study population. ~~In addition, the DMC will review the safety data when 10%, 25%, 50%, and 75% of planned subjects complete the Day 43 (EoS) Visit.~~ A SAP and DMC Charter will be generated with detailed information, including the boundaries of the superiority and futility for the interim analysis.

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Section(s) Changed	Description of Changes Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
Section 4.1 Overall Study Design	The text and study schematic were revised to reflect the longer Follow-up Period. Subjects will be assessed daily while hospitalized. Follow-up ~~is~~assessments are planned through Week ~~6,~~24, for a total study duration post-randomization of approximately ~~43~~169 days~~.Subjects will be asked to participate in~~(24 weeks). Follow-up visits at Days 15, 22, 29, 36, 43, 85 and ~~43; these follow-up visits~~169 will be performed by phone if the subject has been discharged from the hospital.
Section 4.3 Treatment Arms and Duration	The text was revised to reflect longer overall study duration. Each subject will participate for approximately ~~6~~24 weeks, with a 2-week Treatment Period (last dose on Day 8) and a 4~~2~~2-week Follow-up Period.
Synopsis and Section 5.6.1 Contraception	The text was revised to update the contraception duration requirements. All female and male study subjects must use a highly effective birth control method (<1% failure rate per year) ~~throughout~~until completion of the ~~study~~Day 85 Follow-up Visit, unless they have a reproductive status of, sterile, non-childbearing, or postmenopausal (confirmed by FSH). Males allowed to enroll in this study are responsible for minimizing the risk of pregnancy (until completion of ~~study~~the Day 85 Follow-up Visit).
Section 5.7.1 Reasons for Withdrawal	Text was added to specify that withdrawn subjects will not be replaced. If a subject meets a withdrawal criterion during treatment, an Early Termination Visit will be required. Subjects withdrawn for any reason will not be replaced.
Section 5.7.2 Subject Withdrawal Procedures	Text regarding subject withdrawal procedures was revised. ~~Should a~~ In cases where the subject ~~fail to attend the clinic~~cannot be reached for ~~a required study visit~~phone follow-up visits, the site should attempt to contact the subject~~and re-schedule the missed visit~~ as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study based on previous non-compliance. In cases where the subject ~~does not return for the rescheduled visit or~~ cannot be reached~~to reschedule the missed visit~~, the site should make every effort to regain contact with the subject (3 documented telephone calls and if necessary a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up".

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	Subjects who withdraw from treatment and/or the study early, for any reason, will be followed for Day 43 all-cause mortality, whenever possible.
Section 5.9 Subject and Study Completion	Text regarding study completion was revised to reflect the longer Follow-up Period. A completed subject is ~~one~~1 who has completed the Treatment Period~~,~~ ~~including~~and the ~~scheduled Phone~~ Follow-up ~~Assessments (~~Period (through the Day ~~43;~~169 End-of-Study [EoS~~]).~~] Follow-up Visit).
Section 6.4 Blinding	Text regarding study blinding and treatment administration was revised for clarification and to add the emergency contact information. The study is double-blind. The study pharmacist (and/or qualified pharmacy staff member), ~~study treatment administration personnel,~~ and the bioanalytical laboratory analysts will be unblinded to study treatment. Study treatment will be administered to each subject by blinded qualified personnel at the study site. ~~The presentation of the study treatment (solution color) will be obscured from the study subject and other study personnel using a colored covering or sleeve for the IV bag containing study treatment and opaque IV line. Further details will be provided in the Study Reference Manual.~~Once diluted in 100 mL 0.9% saline, active gimsilumab and placebo infusion bags are indistinguishable. For this study you may contact: [redacted]
Section 7 Study Assessments and Procedures The text and Table 7-1 regarding blood sample amount were revised to account for the longer study duration.	The study assessments and procedures were revised to specify the follow-up for subjects who are discharged from the hospital and/or discontinue from the study early. Note: All subjects who are discharged from the hospital will undergo all Day-of-Discharge (DoD) Visit assessments. All subjects who discontinue from the study prematurely will undergo all Early Termination (ET) Visit assessments, whenever possible. ~~It is expected that no more than 150~~If the subject completes all in hospital assessments, approximately 250 mL of blood will be collected over the duration of the study~~, including any extra assessments that may be required~~ (Table 7-1).
Section 7.1 Schedule of Assessments	The Schedule of Assessments (Table 7-2) was revised to include additional assessments, remove assessments that will not be performed, and to accommodate the longer study duration.

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	Table 7-2 now has been split into 2 parts, one for the Treatment Period and one for the Follow-up Period. Laboratory assessments were clarified for local vs central labs; related conduct that is done at the same timepoints was combined (i.e., demographic information, medical history, and prior medication); viral sample swabs were corrected from oropharyngeal samples to nasopharyngeal samples; SOFA score was added; laboratory assessments were clarified; footnotes were revised for clarification.
Section 7.4.1.3 Sequential Organ Failure Assessment (SOFA)	Section was added to include Sequential Organ Failure Assessment (SOFA). The SOFA score will be assessed daily for patients while in the ICU.
Section 7.4.2.1 Physical Examinations	Text regarding physical examinations was revised to be more conducive to the in-patient hospital conditions. ~~An abbreviated~~Abbreviated, targeted physical ~~examination will include, at a minimum,~~examinations (i.e., assessments of the skin, respiratory, cardiovascular system, and abdomen ~~(~~[liver and spleen]), will be performed at time points specified in the Schedule of Assessments (Table 7-2) and will be based on the subject's clinical status and what the clinic staff feel is appropriate. Height and weight will ~~also~~ be measured and recorded at Screening only, if possible.
Section 7.4.2.2 Vital Signs	Text regarding vital signs was revised to remove position requirements. Vital signs including blood pressure, heart rate, respiration rate, and temperature (oral, tympanic, or axillary) will be obtained at time points specified in the Schedule of Assessments (Table 7-2~~after the subject has rested quietly in a supine position for 10 minutes.~~). The same method for assessing temperature should be used at all visits for each individual subject, if possible.
Section 7.4.2.3.1 Electrocardiograms	Section for 12-lead electrocardiograms was removed. ~~ECGs will be measured in supine position after at least 5 minutes rest.~~ ~~Standard, 12-lead electrocardiograms (ECGs) will be obtained during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.~~
Section 7.4.2.4 Clinical Safety Laboratory Assessments	Text was added to clarify sample collection information. Table 7-3 was revised to include additional laboratory samples.

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	For all on-study laboratory assessments, if central laboratory assessments cannot be collected for any reason, best efforts will be made to record local laboratory data. NT-proBNP, ferritin, C-reactive protein, lactate dehydrogenase, and procalcitonin were added to Table 7-3.
Section 7.4.2.5: SARS-CoV-2 Viral Assessments	SARS-CoV-2 Viral Assessments section was added to the protocol. A local qualitative sample (e.g., nasopharyngeal swab) for PCR SARS-CoV-2 will be collected at Screening for determination of eligibility (if not already documented); all other on-study samples will be central quantitative samples. When at all possible, if only 1 nostril is swabbed for viral assessments, the same nostril should be used for all subsequent samples.
Section 7.4.2.6 Respiratory Assessments	Additional examples of ventilation type were added. If subject is receiving mechanical ventilation, the following parameters will be recorded: type of ventilation (high-flow nasal cannula, non-rebreather mask, CPAP, BiPAP, or intubation), F_iO_2, SpO_2, ventilation rate, pulse, tidal volume, positive end-expiratory pressure (PEEP), and airway pressure.
Section 7.4.2.8 Biomarker Assessments	Text was revised to include “chemokine” and to remove text regarding bronchoalveolar lavage and CRP markers. The cytokine/chemokine panel may include: GM-CSF, G-CSF, IL-1β, IL-2, IL-6, IL-7 IL-10, IL-15, IL-17A, IL-17A/F, IL-23p19, IFN-γ, TNF-α, IP10 (CXCL10), MCP1 (CCL2), MIP1A (CCL3), and CCL17. A subset of these cytokines/chemokines will be tested initially, further testing may be performed based on results of other study endpoints and emerging scientific information. Concentrations of biomarkers will be determined using qualified or validated assays. ~~CRP markers are to be determined by the local laboratory (Section).~~ ~~If a bronchoalveolar lavage (BAL) is performed as standard of care, a sample will be collected for potential future analysis of select cytokines and procollagen. The actual date and time of the sample will be recorded.~~
Section 8 Data Management	The text was revised to reflect the longer study duration and additional interim analysis. The detailed Data Management Plan (DMP) will be generated and approved prior to the ~~start~~ study database lock when all subjects

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	complete the Day 43 Visit, discontinue from the study early, or meet with the primary endpoint of ~~enrolling subjects.~~mortality (by Day 43). The study database will be locked when all subjects complete the ~~Visit of Day 43 (~~Day 43 Visit, discontinue from the study early, or meet the primary mortality endpoint. The second lock will occur when the last subject completes the Day 169 EoS~~), reach the primary endpoint early, or discontinue from the study.~~ visit. In addition, there will be ~~1~~2 database ~~extract~~extracts (soft ~~lock~~locks) for interim analyses, the first of which will be conducted when 60 subjects have been treated and have completed 7 days of follow-up; the DMC will review the data for safety and futility and provide their recommendations. The second interim analysis~~, which is to~~will be ~~performed~~conducted when ~~~40~~50% of ~~planned~~total subjects are discharged from the hospital, complete the Day 43~~ (EoS)~~ Visit, discontinue the study early, or meet the ~~primary~~endpoint of mortality ~~endpoint.~~(by Day 43).
Section 9.1 Sample Size Determination	Sample size was updated to include the definitions of lung injury and ARDS. Lung injury is defined as (1) requiring supplemental oxygen >4L O_2 to maintain >92% SpO_2, or (2) PaO_2/FiO_2 ≤300 mmHg (can be imputed). ARDS [ARDS Berlin Definition, 2012] is defined as: • Bilateral opacities — not fully explained by effusions, lobar/lung collapse, or nodules; • Respiratory failure not fully explained by cardiac failure or fluid overload; • Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present. • ARDS severity categories are defined as: o Mild: 200 mmHg, < PaO_2/FiO_2, ≤300 mmHg with PEEP or CPAP ≥5 cm H_2O. o Moderate: 100 mmHg, < PaO_2/FiO_2, ≤200 mmHg with PEEP ≥5 cm H_2O. o Severe: PaO_2/FiO_2 ≤100 mmHg with PEEP ≥5 cm H_2O.
Section 9.3.2 Safety Endpoints	Text regarding safety endpoints was revised to remove viral load, ECGs, and local injection site tolerability. Safety and tolerability, including assessment of ~~changes from Baseline in viral load (PCR test),~~clinical safety laboratory measurements, physical examinations, vital signs,~~ECGs, clinical safety laboratory measurements, local injection site tolerability;~~ concomitant medications; cumulative incidence of AEs, SAEs, and severe AEs.

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Section 9.3.3Pharmacokinetic Endpoints	Text was revised to remove specific timepoints and refer to the Schedule of Assessments. Serum gimsilumab concentration at time points as specified in the Schedule of Assessments (Table 7-2). ~~pre-dose on Day 1 and Day 8.~~
Section 9.3.4 Biomarker Endpoints	"Pharmacodynamic" was replaced with "Biomarker" and serum CRP was removed. **~~Pharmacodynamic~~ Biomarker Endpoints** ~~Changes~~Change from Baseline in ~~serum CRP,~~the cytokine~~,~~ panel and serum SP-D ~~concentrations~~ will be measured at time points as specified in the Schedule of Assessments (Table 7-2).
Section 9.5.3 Analysis of the Secondary Endpoints	Section was revised to update the information regarding the continuous variables. The continuous variables, including the changes from baseline, will be summarized by the treatment with the ~~means~~mean, standard ~~deviations, medians~~deviation (SD), median, and the ~~ranges~~range. PK summaries will include geometric mean and geometric coefficient of variation.
Section 9.5.4 Adjustment of Multiple Comparisons	Section was revised to reflect the increased study duration, additional interim database lock, and methods for the key secondary endpoints. There is no need to adjust the significance level 0.05 (~~two~~2-sided) in the analysis since there is only ~~one~~ 1 primary endpoint and ~~one~~ 1 gimsilumab dose level versus placebo. ~~However,~~ The interim analysis will be conducted when ~~≈40%~~60 subjects have been treated and have completed 7 days of ~~planned~~follow-up; the DMC will review the data for safety and futility and provide their recommendations. The second interim analysis will be conducted when 50% of total subjects are discharged from the hospital, complete the Day 43 ~~(EoS)~~ Visit, discontinue the study early, or meet the ~~primary~~endpoint of mortality ~~endpoint.~~(by Day 43). There will be the split of alpha 0.05 to be 0.001 for the 2nd interim analysis and 0.049 for the final analysis of the primary endpoint, as the 2nd interim analysis may claim for the superior efficacy for the stop of the study early. The 3 key secondary endpoints will be analyzed by hierarchical testing procedure following the order of the list of endpoints, and each endpoint will be analyzed at 0.05 alpha level.
Section 9.5.8 Timing of Analyses	Text regarding timing of analyses was revised to reflect the longer study duration and the additional interim analysis. The ~~final analyses~~first unblinded analysis will be conducted when the last subject completes the ~~study at~~ Day 43 ~~(EoS)~~ Visit, ~~meet~~discontinues the

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	study early, or meets the primary endpoint ~~early, or early discontinued from the study.~~ of mortality (by Day 43). The final analysis will be conducted when the last subject completes the Day 169 (EoS) Visit. The first interim analysis ~~can be conducted when ~40% of planned~~will be conducted when 60 subjects have been treated and have completed 7 days of follow-up; the DMC will review the data for safety and futility and provide their recommendations. The second interim analysis will be conducted when 50% of total subjects are discharged from the hospital, complete the Day 43 (~~EoS~~) Visit, discontinue the study early, or meet the ~~primary mortality~~ endpoint~~.~~ of mortality (by Day 43). The objectives of the second interim analysis will include the claim of superior efficacy or futility to stop the study, the reassessment of sample size, and/or modifications of the populations. The DMC will be responsible for ~~this unblinded analysis and inform the sponsor about the results and the recommendation of conducting the study, which can be the early stop of the study for the superiority, futility, the re-assessment of the sample size, and/or~~ closely reviewing the ~~modification of the study population.~~safety data from the unblinded interim analysis and for providing their recommendations. The detailed objectives and procedures, including close monitoring of the safety data and the boundaries of the ~~interim analyses~~superiority or futility will be described in the SAP and the DMC Charter.~~In addition, the DMC will review the safety data when 10%, 25%, 50%, and 75% of planned subjects complete the Day 43 (EoS) Visit. A DMC Charter will be generated with detailed information~~
Section 9.5.9 Pharmacokinetic, Biomarker, and Immunogenicity Analyses	"Pharmacokinetic, Biomarker, and Immunogenicity Analyses" section was added. Serum gimsilumab concentrations will be summarized using descriptive statistics. Biomarker analyses will be based on the Safety Population and biomarker (SP-D, cytokine/chemokine, anti-GM-CSF autoAb) concentrations will be summarized by treatment using descriptive statistics. Immunogenicity analysis will be based on the Safety Population and anti-drug antibody data will be reported in the format provided by the bioanalytical laboratory. Further details will be provided in the SAP.
Section 10.1 Special Consideration for Assessment of Adverse Events	"Special Consideration for Assessment of Adverse Events" section was added.

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	It is recognized that the patient population in the ICU will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of their underlying disease and the impact of standard therapies. These will not necessarily constitute an AE unless they require significant intervention, lead to discontinuation of blinded study drug, or are considered to be of concern in the investigator's clinical judgement. Death should not be recorded as an event but should be recorded as the outcome of ONE event, i.e. one event should be determined to be the primary cause of death. The 'clinical' AE that resulted in death is the adverse event and the death information supports the clinical AE. 'Death' is not entered as an adverse event unless the cause of death is unknown. In such case the AE term is 'Unspecified fatal event' until the cause of the death is known.
Section 10.2 Definition of Adverse Events	Text regarding infections was added for clarification. New infections occurring on-study, regardless of infection type (i.e., viral, bacterial, fungal, etc.) will be reported as AEs.
Section 10.9 Regulatory Reporting Requirements for SAEs	Text was added regarding SAE reporting. On discovery, all SAEs should be immediately reported (latest within 24 hours of knowledge of the event) to [redacted] See Section 6.4 for emergency unblinding service contact information.
Section 11 Pregnancy Reporting	The text was revised to clarify the follow-up period for pregnancy reporting. Any pregnancy reported between the time of informed consent and completion of the ~~End of Study~~ Day 85 Follow-up Visit or an Early Termination Visit must be reported to the Sponsor within 2 weeks of learning of the pregnancy.
Section 12.1.7 Drug Accountability	Text regarding disposal of study drug was revised. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will ~~dispose of and/or destroy~~ ship all unused investigational medicinal product supplies~~, including empty containers~~ to the designated depot, according to these procedures.
Section 13 References	References were added.

Table 14-1: Summary of Changes: Amendment 1

Section(s) Changed	Description of Changes Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
	Nadicksbernd J. CD11b expression on granulocytes after induction by granulocyte-macrophase colony stimulating factor in EDT whole blood by flow cytometry. PPD Primary Validation Summary. 2013. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*. 2020; 395 (10229): 1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3.
Section 14.1: Abbreviations were added to the list of abbreviations, and unused abbreviations were removed from the list of abbreviations.	

Table 14-2: Summary of Changes: Amendment 2

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
Global change: Synopsis and throughout	Version and date were updated throughout the entire protocol. Version ~~2~~: ~~05-April~~ 2020 Version 3: 06-May-2020
Global change: Synopsis and throughout	Minor edits, including changing "patient(s)" to "subject(s)" where applicable and minor spacing and spelling corrections.
Medical Contact/Sponsor Information Page	Text referring to Medical Monitoring Plan was deleted because the Medical Monitoring Plan is not relevant to the protocol (only relevant to Sponsor and CRO). ~~See the Medical Monitoring Plan for more details.~~
Synopsis, Section 3 Objectives and Endpoints, and Section 9.3.1 Efficacy Endpoints	Key secondary endpoints were revised to clarify actual intent of the study, as follows: • Incidence ~~and duration~~ of subjects who survived and were not on mechanical ventilation ~~use~~ on Day 15, Day 22, Day 29, and Day 43 • Incidence of mechanical ventilation use, and ventilation-free days during the study • ~~Number~~Incidence of ICU use, and ICU-free days ~~in~~during the ~~ICU~~study • Number of days of inpatient hospitalization
Synopsis and Section 5.2 Inclusion Criteria	The following inclusion criteria were revised: 1. Male or non-pregnant female age ≥18 ~~to 79~~ years~~, inclusive~~ Justification: to be less restrictive, as sites were having to exclude patients who otherwise met all entry criteria. 3. Has documented laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other approved clinical testing prior to randomization Justification: to clarify the requirement for documentation of disease status 4. CRP ≥50 mg/L or serum ferritin ≥1,000 ng/mL. Results from CRP and ferritin tests performed within 8 days of randomization are acceptable for enrollment. Justification: to clarify the timing window for CRP and ferritin results used for entry criteria 5. Radiographic evidence of bilateral infiltrates. Acceptable imaging tests (chest X-ray, CT scans) done within 3 days of Day 1 can be used for inclusion.

Table 14-2: Summary of Changes: Amendment 2

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
	Justification: to clarify the timing window for imaging results used for entry criteria 6. Subject has clinical evidence of lung injury [defined as (1) requiring supplemental oxygen ~~>~~≥4L O_2 to attempt to maintain ~~>~~≥92% SpO_2, or (2) P/F ratio ≤300 mmHg (can be imputed)], or meets clinical classification criteria for ARDS [ARDS Berlin Definition, 2012], secondary to COVID-19. Justification: to clarify the intent of the requirements.
Synopsis and Section 5.3 Exclusion Criteria	The following exclusion criteria were revised: 6. Absolute neutrophil count <~~2000~~1000 per mm^3 Justification: limit was corrected to reflect the original intent of the protocol 7. Platelet count <50,000 per mm^3 Justification: clerical fix 8. History of known anti-GM-CSF autoantibodies (autoAb) or pulmonary alveolar proteinosis. Note: A negative anti-GM-CSF autoAb test result is not required at screening. Justification: to clarify that the site does not need to wait for the result before enrolling the subject into the study. 9. Severe chronic respiratory disease (e.g., known chronic obstructive pulmonary disease [COPD], pulmonary arterial hypertension [PAH], idiopathic pulmonary fibrosis [IPF], interstitial lung disease [ILD]) requiring ~~baseline~~supplemental oxygen therapy or mechanical ventilation pre-hospitalization (e.g., prior to COVID-19 diagnosis) Justification: "baseline" was removed to avoid confusion with Study baseline. 10. ~~Suspected~~Known or ~~confirmed~~ suspected active and untreated~~,active~~ tuberculosis (TB), human immunodeficiency virus (HIV), hepatitis B or C infection • Results of TB, hepatitis B and C, and HIV tests are not required prior to enrollment if there is no suspicion of active infection, as per KIN-1901 Guidance on Active Infections Testing. Justification: to clarify that the site does not need to wait for the result before enrolling the subject into the study as long as there is no suspicion or knowledge of active infection. 18. 13. Use of~~investigational drug or~~ any immunomodulatory biologic (e.g., anti-IL-1, anti-IL-6R, anti-TNF), cell therapies (e.g., mesenchymal stem cells), or small molecules (e.g., Janus kinase [JAK] inhibitors) within the past ~~60~~7 days or within five half-lives (whichever is longer), or planned use of any of these agents from

Table 14-2: Summary of Changes: Amendment 2

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
	Screening until Day 43 of the study, unless approved by the Medical Monitor~~during the study~~. The following will be allowed: • Subjects who have been treated with convalescent plasma (CP) prior to enrollment are eligible if the subject continues to meet all inclusion criteria at screening. • The use of investigational anti-viral treatment (e.g., remdesivir) is allowed if the subject continues to meet all inclusion criteria at screening. Justification: to further clarify what is allowed and disallowed based on emerging standards of care.
Synopsis and Section 9.5.1 Primary Efficacy Analyses	The following statistical analysis information was revised to clarify which statistical models are being used, and to remove hierarchical testing: **Efficacy Analyses:** The secondary analysis of the primary endpoint will be conducted by using log rank test and/or the Cox Proportional model on the time to event of the primary endpoint. The median of the time to event from Kaplan-Meier curves will be presented for each treatment, and the hazard ratio of gimsilumab versus placebo will be presented with 95% CI, and p-value. **Adjustment of Multiple Comparisons:** ~~The 3 key secondary endpoints will be analyzed by hierarchical testing procedure following the order of the list of endpoints, and each endpoint will be analyzed at 0.05 alpha level.~~
Section 5.8 Toxicity Management Criteria	Additional text was added for management of abnormalities in liver function tests (LFTs) to specify how the sites should address LFT abnormalities to maintain consistency across sites. **Guidance on LFT abnormalities based upon results of LOCAL lab testing:** 1) If a subject has ALT in the normal range prior to study drug administration and develops significant elevation >5× ULN after study drug administration, in the absence of a clear alternative reason for the change (e.g., hypotension, vasopressor support), this should be considered related to study drug and reported as a SAE; procedures described in **Appendix 2: Liver Safety Required Actions and Follow up Assessments** should be followed, and the Medical Monitor should be informed. 2) For subjects with elevated transaminase levels prior to study drug administration who **do not meet exclusion criterion #11 (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >5× upper limit of normal [ULN])**, if after administration of study drug the LFTs continue to worsen

Table 14-2: Summary of Changes: Amendment 2

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
	and no alternate explanation for elevation is provided, the following will apply: a. If **ALT >8× ULN**, then this should be reported as a SAE; procedures described in **Appendix 2: Liver Safety Required Actions and Follow up Assessments** will be followed, and the Medical Monitor should be informed. If the Investigator is considering withholding the second dose of study drug, then a discussion with the Medical Monitor is mandatory. Note that subjects with ALT or AST abnormalities secondary to multi-organ impairment due to COVID-19 may still benefit from the second dose of gimsilumab. b. If LFTs are elevated but are **not** >8× ULN, then daily LFTs (including AST, ALT, alkaline phosphatase, and total bilirubin with fractionation) should be followed. i. If during follow up **ALT or AST increases to >8× ULN**, then this should be reported as a SAE and then discussed with the Medical Monitor concerning the need to withhold the second dose. If a subject has **AST or ALT 3 to 8× ULN** in conjugation with **total bilirubin >2× ULN or INR >1.5**, then this should be reported as a SAE; procedures described in **Appendix 2**~~The Medical Monitor must be notified if a subject meets the following liver chemistry criteria:~~ ~~ALT ³5 × the ULN~~ ii. **: Liver Safety Required Actions and Follow up Assessments** should be followed. Subjects meeting these criteria should not receive a second dose of study drug. iii. If during follow up the above stopping criteria are not met and the Investigator believes that the subject is suitable to receive a second dose of study drug and all eligibility criteria are met for the second dose, then the second dose (Day 8) of study drug may be administered. 3) Any worsening of LFTs that is greater than would be expected due to COVID-19 alone that do not rise to the level of an SAE should be reported as an AE. 4) A discussion with the Medical Monitor is **mandatory** prior to withholding the second dose of study drug.

Table 14-2: Summary of Changes: Amendment 2

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
Section 6.1 Study Treatment	Unit dose strength/dosage level information was revised for placebo in Table 6-1 and in the text; information for placebo was not previously included, so it was added for completeness. ~~NA /~~ [redacted] of sterile 0.9% sodium chloride added to 100 mL 0.9% ~~saline~~sodium chloride.
Section 6.6 Preparation/ Handling/ Storage/ Accountability	Placebo mixing information was revised to reflect placebo preparation. Placebo study treatment will utilize 100 mL 0.9% saline solution with ~~no admixture~~the addition of [redacted] (Day 8) sterile 0.9% saline solution using aseptic technique by qualified personnel per the clinical site standard operating procedures.
Section 6.9 Concomitant Medications and Non-Drug Therapies	Spelling correction: It would be expected that gimsilumab would reduce the effectiveness of GM-CSFs, such as Luekine® (~~sargranostim~~sargramostim), Leucomax® (molgramostim) and Regramostim. No other drug interactions are known or expected.
Section 6.9.1 Permitted Medications and Non-Drug Therapies	Text regarding permitted medications was revised to include prior or concomitant use of convalescent plasma and/or anti-viral therapies to reflect emerging standards of care. Treatment with convalescent plasma or investigational anti-viral therapies (e.g., remdesivir) will be allowed. Use of any concomitant medication (including investigational agents) should be recorded in the study source records, including the doses administered, dates and times of administration and the reason for administration.
Section 6.9.2 Prohibited Medications and Non-Drug Therapies	Section was updated to further clarify what is allowed and disallowed based on emerging standards of care. Use of ~~any investigational drug (i.e., the subject is using the drug as part of a clinical trial),~~ tocilizumab or any other immunomodulatory biologic (e.g., anti-IL-1, anti-IL-6R, anti-TNF), cell therapies (e.g., mesenchymal stem cells), or small molecules (e.g., JAK inhibitors) is prohibited during the study, from Screening until Day 43 of the study unless approved by the Medical Monitor.
Section 7.1 Schedule of Assessments	The Schedule of Assessments was revised to clarify study days and weeks. Timepoints were clarified for the Follow-up Period. Clarifications were added regarding screening laboratory assessments to be consistent with revisions to entry criteria as follows:

Table 14-2: Summary of Changes: Amendment 2

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
	Central sample for anti-GM-CSF autoAb[d] (result not required for determination of eligibility) Footnote d: Sample will be collected, but enrollment can continue without receiving results first. HCV testing can be RNA or Ag, only to confirm suspected infection. If a subject is diagnosed with latent TB (positive QuantiFERON Gold or purified protein derivative [PPD]), hepatitis B or C, or HIV during the study, the Investigator must discuss this with the medical monitor and a decision will then be made concerning the second dose of gimsilumab, if applicable. Note: SCREENING LABORATORY ASSESSMENTS: For all screening laboratory assessments, if more than one result is available during the screening period, the most recent value will be used as the screening value and for determination of eligibility.
Section 7.4.2.8 Biomarker Assessments	IL-8 was added to the list of the cytokine/chemokine panel for completeness. The cytokine/chemokine panel may include: GM-CSF, G-CSF, IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, IL-15, IL-17A, IL-17A/F, IL-23p19, IFN-γ, TNF-α, IP10 (CXCL10), MCP1 (CCL2), MIP1A (CCL3), and CCL17.
Section 9.5.3 Analysis of the Secondary Endpoints	Text regarding time to event endpoints was moved, and other revisions were made as follows: • ~~The time-to-event endpoints will be summarized with Kaplan Meier curves and 95% confidence bounds by the treatment. the Cox Hazard Proportional model with treatment, country, and subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) as model terms will be used. The hazard ratio of gimsilumab versus placebo will be presented with 95% CI and p-values.~~ Justification: The time to event endpoints are now at the end of the secondary endpoints, so the statistical methods for the analysis is also moved to the end. • Change in ordinal scale at specific time points will be summarized by proportions (e.g., proportion who have a 1-, 2-, 3-, or 4-point improvement or 1-, 2-, 3-, 4-point worsening). The CMH test controlled by country and subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) will be used for treatment difference. The odds ratio of gimsilumab versus placebo, ~~90~~95% CIs and p-values will be provided. Justification: 90% was in error, corrected to 95% • Duration of event free (e.g., ~~duration of~~ mechanical ventilation free days) will be summarized according to median days with quartiles.

Table 14-2: Summary of Changes: Amendment 2

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
	The Wilcoxon rank test will be used for the treatment difference. Justification: to remove the bias introduced by death • Incidence data (e.g., incidence of new or increased oxygen use) will be summarized as a percent with 95% confidence intervals. The CMH test controlled by country and subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) will be used for treatment difference. The odds ratio of gimsilumab versus placebo, ~~90~~5% CIs and p-values will be provided. Justification: 90% was in error, corrected to 95% • The time-to-event endpoints will be summarized with Kaplan Meier curves and 95% confidence bounds by the treatment. The log rank test and/or the Cox Hazard Proportional model with treatment, country, and subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) as model terms will be used. The hazard ratio of gimsilumab versus placebo will be presented with 95% CI and p-values.
9.5.4 Adjustment of Multiple Comparisons	Text regarding hierarchical endpoint analyses was deleted as hierarchical testing was removed from the study. ~~The 3 key secondary endpoints will be analyzed by hierarchical testing procedure following the order of the list of endpoints, and each endpoint will be analyzed at 0.05 alpha level.~~
Section 10.1 Special Consideration for Assessment of Adverse Events	Language was revised to clarify that Death should be considered both an SAE and an outcome. Death should ~~not~~ be recorded both as ~~an event but should be recorded~~a SAE and as the outcome of ONE event, i.e. one event should be determined to be the primary cause of death.

Table 14-3: Summary of Changes: Amendment 3

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
Global change: Synopsis and throughout	Version and date were updated throughout the entire protocol. Version ~~3~~: ~~06 May~~ 2020 Version 4: 12 June 2020

Table 14-3: Summary of Changes: Amendment 3

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
Global change: Synopsis and throughout	Minor edits, including formatting, spelling, and grammar corrections.
Synopsis and Section 3 Objectives and Endpoints	One of the key secondary objectives was moved to additional secondary objectives due to changing criteria for ICU level of care during the evolution of the current pandemic: • To assess the effect of gimsilumab on the need for Intensive Care Unit (ICU) level of care
Synopsis, Section 3 Objectives and Endpoints, and Section 9.3.1 Efficacy Endpoints	Key secondary and additional secondary endpoints were revised to clarify actual intent of the study, as follows: Key secondary endpoints (only those changes are shown): • ~~Incidence~~ Proportion of subjects who survived and not ~~on~~ requiring mechanical ventilation on ~~Day 15, Day 22,~~ Day 2~~9, and Day 43~~ • Mechanical ventilation-free days by Day 29 • Time to hospital discharge by Day 43 • ~~Incidence of mechanical ventilation use, and ventilation-free days during the study~~ • ~~Incidence of ICU use, and ICU free days during the study~~ • ~~Number of days of inpatient hospitalization~~ Additional secondary endpoints (only those changed are shown): • Incidence of mortality by Day 15 Day 29, ~~and~~ Day 85, and Day 169 (End-of-Study [EoS]) • Proportion of subjects who survived and were not requiring mechanical ventilation on Day 15, 22, and 43 • Mechanical ventilation-free days for all subjects by Day 15, 22, and 43 • ICU-free days for all subjects by Day 15, 22, 29, and 43 • Incidence of mechanical ventilation use for all subjects by Day 15, 22, 29, and 43 • Incidence of ICU use for all subjects by Day 15, 22, 29, and 43 • Time to death by Day 43 and Day 169 (EoS) • SOFA score, and each of the components, assessed daily while in the ICU • Time to clinical improvement by 2 points on the 7-point ordinal scale
Synopsis and Section 9.5.1 Primary Efficacy Analyses	The following statistical analysis information was revised to clarify which statistical models are being used, and to remove hierarchical testing: **Efficacy Analyses:** The secondary analysis of the primary endpoint will be conducted by using log rank test and/or the Cox Proportional model on the time to event of the primary endpoint. The median of the time to event from Kaplan-

Table 14-3: Summary of Changes: Amendment 3

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
	Meier curves will be presented for each treatment, and the hazard ratio of gimsilumab versus placebo will be presented with 95% CI, and p-value. **Adjustment of Multiple Comparisons:** ~~The 3 key secondary endpoints will be analyzed by hierarchical testing procedure following the order of the list of endpoints, and each endpoint will be analyzed at 0.05 alpha level.~~
Synopsis, Section 8 (Data Management), and Section 9 (Statistical Considerations and Analyses section)	Revisions were made due to FDA feedback and Sponsor decision regarding timing of interim analyses, and to reflect that the study is currently being conducted in 1 country only. **Efficacy Analyses:** The primary analysis of the efficacy endpoint (Mortality by Day 43) will be performed by using logistic regression [Ge, 2011] with treatment, site, and ~~Cochran-Mantel-Haenszel (CMH) test, controlled by~~ subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]). Adjustment of Multiple Comparisons and Interim Analysis: The second interim analysis will be conducted when ~~50% of total~~ 100 subjects ~~are discharged from the hospital,~~ have completed the Day 29~~43~~ Visit~~, discontinue the study early,~~ or meet the endpoint of mortality (by Day 29~~43~~). The objectives of the second interim analysis will be to stop the study by futility, or perform the sample size re-estimation. ~~There will be the split of alpha 0.05 to be 0.001 for the 2nd interim analysis and 0.049 for the final analysis of the primary endpoint, as the 2nd interim analysis may claim for the superior efficacy for the stop of the study early.~~ For controlling overall two-sided alpha of 0.05 for the final analysis on the primary endpoint of Mortality Day 43, the weighted average of two summary measures by Cui L, Hung HM, Wang [Cui, 1999] will be used, one based on the data collected in the interim analysis, and the other based on the data collected after the interim. **Analyses in General:** All the categorical variables will be summarized by the treatment with the numbers and percentages of the subjects, and the treatment difference will be tested by using CMH test stratified by 1) ~~country~~site and 2) subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]). The time to event endpoints will be analyzed by using the Cox Proportional Hazard model with the treatment, subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]), and ~~country~~site as the model term. **Handling of Missing Data** ~~For the efficacy analyses, the multiple imputation method, including the tipping point method, will be used to handle the missing data as the~~

Table 14-3: Summary of Changes: Amendment 3

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
	~~sensitivity analyses. No imputation will be used for any missing data in safety analysis.~~ Separate analyses will be performed for the primary and key secondary endpoints by using multiple imputations for the missing data: • Tipping-point multiple imputation analysis Missing data will be imputed for Mortality by Day 43 with all possible combinations of Death or Survival in the two arms. The combination which alters the conclusion will be defined as the tipping point for evaluation on the robustness of the results. • Imputation differentiating the reasons of missing data from the early drop out The reasons of the lost to follow-up, SAEs/AEs, and the use of rescue medications will be identified, and the percentage of these subjects will be summarized by treatment. The data for informative censoring, such as the unfavorable or worst outcome, can be used to impute the missing data. More details will be pre-specified in the statistical analysis plan (SAP). **Timing of Analyses with All Subjects:** The first unblinded analyses will be conducted when the last subject completes the Day 43 Visit, discontinues from the study early, or meets the primary mortality endpoint (by Day 43). The second unblinded analyses will be conducted when the last subject completes the Day 169 Follow-up Visit (EoS). In addition, there will be 2 database extracts (soft locks) for interim analyses, the first of which will be conducted when 60 subjects have been treated and have completed through Day 15; the DMC will review the data for safety and futility and provide their recommendations. The second interim analysis will be conducted when ~~50% of total~~ 100 subjects ~~who~~ have completed the Day ~~43~~29 Visit, discontinue the study early, or have met the endpoint of mortality (by Day ~~43~~29). ~~The first interim analysis will be when 60 subjects have been treated and have completed 7 days of follow-up; the DMC will review the data for safety and futility and provide their recommendations.~~ ~~The second interim analysis will be conducted when 50% of total subjects are discharged from the hospital, complete the Day 43 Visit, discontinue the study early, or meet the endpoint of mortality (by Day 43). The objectives of the second interim analysis will include the claim of superior efficacy or futility to stop the study, the reassessment of sample size, and/or modifications of the populations.~~ The DMC will be responsible for closely reviewing the safety data from the unblinded interim analysis and for providing their recommendations. The detailed objectives and procedures of the interim analyses will be

Table 14-3: Summary of Changes: Amendment 3

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
	described in the DMC Charter. ~~; these can be the claim of early stop of the study for superiority, futility, re-assessment of the final sample size, and/or the study population. A SAP and DMC Charter will be generated with detailed information, including the boundaries of the superiority and futility for the interim analysis.~~ Statistical Analysis Plan (SAP): A detailed (revised) SAP will be signed and submitted to the agencies prior to the interim analysis of 100 subjects.
Section 7.1 Schedule of Assessments	The Schedule of Assessments was revised to clarify the EoS/Early Term assessments. Abbreviations were revised, as needed. Language was added to footnote d to clarify acceptable testing for TB. the event the QuantiFERON Gold assay is not available, and the site performs a different IGRA such as T Spot, then the alternative IGRA will be acceptable for patient screening and enrollment. Enrollment should not be delayed to obtain the QuantiFERON Gold assay in lieu of the IGRA available at the site. If no IGRA test is available, PPD can be used.
Section 7 Study Assessments and Procedures	Language was added to clarify the follow-up conduct for the study. Once a subject is discharged from the hospital every effort MUST be made to ensure visit timepoints listed on the Schedule of Assessments (Table 7-2) are completed via phone or telemed. All visits are required to be completed for every subject unless the subject dies or withdraws consent. If a subject is deemed lost to follow-up every effort should be made to check vital status records at each visit time point to obtain survival status. Proper follow-up and documentation should be completed per GCP/ICH guidelines before deeming a subject lost to follow-up.
Section 13 (References)	New references were added based on text that was added to the protocol.
Appendix 3: Summary of Changes for Protocol Amendments (Section 14.3)	Table 14-3 was added to explain changes made in Protocol Amendment 3.

Table 14-4: Summary of Changes: Amendment 4

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
Global change: Synopsis and throughout	Version and date were updated throughout the entire protocol. Version 4: ~~12 June~~ 2020 Version 5: 17-August-2020
Global change: Synopsis and throughout	Minor edits, including formatting, spelling, and grammar corrections; headers updated throughout.
Medical Contact/Sponsor Information Page	Secondary Medical Monitor name and contact information was updated to reflect staffing change. [redacted]
Synopsis, Study Centers and Countries	The synopsis was updated to reflect the addition of another country and to revise the planned number of sites in the US and potential number of sites in Mexico and to clarify that other countries may be added later. ~~The number of study centers and locations where this study will be conducted are to be determined~~This study will be conducted at approximately 20 centers in the United States and potentially 6 centers in Mexico; other countries may be added, if needed.
Synopsis and Section 5.2 Inclusion Criteria	Inclusion criterion #2 was revised to allow for verbal consent to participate in the study. Inclusion criterion #7 was revised to clarify that FSH only needs to be done to confirm postmenopausal status in women who have not had spontaneous amenorrhea for 12 consecutive months. 2. Subject (or legally authorized representative [LAR]) is able and willing to provide written or verbal informed consent, which includes compliance with study requirements and restrictions listed in the consent form. NOTE: If a subject or LAR must be consented verbally, the site must have a site policy for verbal consent and the consent must be clearly documented in the subject's chart. 7. Postmenopausal defined as 12 months of spontaneous amenorrhea or with follicle stimulating hormone (FSH) confirmation.
Synopsis and Section 5.3 Exclusion Criteria	Exclusion criterion #2 was revised to clarify time of intubation. Exclusion criteria #13 and #14 were revised to match the clarification memos that were sent to sites prior to this amendment. 2. Subject has been intubated for >72 hours. Note: in the event of extubation and re-intubation, the calculation for the number of hours the subject has been intubated begins at the first intubation. 13. Use of any immunomodulatory biologic (e.g., anti-IL-1, anti-IL-6R, anti-TNF, inhibitors of complement signaling), cell therapies (e.g., mesenchymal stem cells), or small molecules (~~e.g.,~~ Janus kinase [JAK]

Table 14-4: Summary of Changes: Amendment 4

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
	inhibitors) within the past 7 days or within five half-lives (whichever is longer), or planned use of any of these agents from Screening until Day 43 of the study, unless approved by the Medical Monitor. The following will be allowed/disallowed: • Immunomodulatory biologics for COVID-19 treatment are excluded and should not be used until Day 43 unless discussed with the Medical Monitor. Other non-biologic immunomodulators (non-JAK inhibitors), e.g., medicines for previous transplantation, or disease modifying anti-rheumatic drugs (DMARDS) and have had a stable dose for ≥8 weeks are permitted. • Subjects who have been treated with convalescent plasma (CP) prior to enrollment are eligible if the subject continues to meet all inclusion criteria at screening. Ongoing therapy with CP is allowable if clinically indicated in the view of the treating physician or the Investigator. • The use of investigational anti-viral treatment (e.g., remdesivir) is allowed if the subject continues to meet all inclusion criteria at screening. 14. Ongoing c~~C~~hronic (≥4 weeks) use of corticosteroids >10 mg/day of prednisone or equivalent at the time of randomization. A corticosteroid dose that has been tapered to 10 mg or less within 14 days of randomization is also prohibited.
Synopsis, Section 8 (Data Management), and Section 9 (Statistical Considerations and Analyses section)	Revisions were made to reflect that the interim analysis was changed to include stop for superiority as well as mortality at day 43 and to add country instead of site as a stratification factor since another country was added. **Database Locks:** The second interim analysis will be conducted when 100 subjects have completed at least the Day 29 Visit for non-mortality endpoints~~, or~~ and have ~~met~~ the data for the endpoint of mortality (by Day ~~29~~43). **Efficacy Analyses:** The primary analysis of the efficacy endpoint (Mortality by Day 43) will be performed by using logistic regression [Ge, 2011] with treatment, ~~site~~country, and subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]). Adjustment of Multiple Comparisons and Interim Analysis: ~~There is no need to adjust the significance level 0.05 (two-sided) in the analysis since there is only 1 primary endpoint and 1 gimsilumab dose level versus placebo.~~ The interim analysis will be conducted when 60 subjects have been treated and have completed through Day 15; the DMC will review the data for safety and futility and provide their recommendations.

Table 14-4: Summary of Changes: Amendment 4

Section(s) Changed	Description of Changes and Justification Deleted text is indicated as strikethrough, new or moved text is indicated as underlined.
	The second interim analysis will be conducted when 100 subjects have completed at least the Day 29 Visit for non-mortality endpoints~~, or~~ and have ~~met~~ the data for the endpoint of mortality (by Day ~~29~~43). The objectives of the second interim analysis will be to stop the study by superiority, futility, or perform the sample size re-estimation. For controlling overall two-sided alpha of 0.05 overall for the final analysis on the primary endpoint of Mortality Day 43, 0.001 of the alpha will be used for the superiority comparison during the second interim analysis, and 0.049 will be used for the final analysis. ~~And t~~The weighted average of two summary measures by Cui L, Hung HM, Wang [Cui, 1999] will be used, one based on the data collected in the interim analysis, and the other based on the data collected after the interim. **Analyses in General:** All ~~of~~ the continuous variables, including the changes from Baseline, will be summarized by the treatment with the means, SD, medians and the ranges. The Mixed Model with Repeated Measurements (MMRM) /Analysis of Covariance (ANCOVA) model with the treatment, ~~site~~country, subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]), and visit as the model term, and Baseline value as the covariate will be used to test for the significance of the treatment difference. The least square means, standard errors, 95% CIs and p-values will be presented. All the categorical variables will be summarized by the treatment with the numbers and percentages of the subjects, and the treatment difference will be tested by using CMH test stratified by 1) ~~site~~country and 2) subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]). The time to event endpoints will be analyzed by using the Cox Proportional Hazard model with the treatment, ~~site~~country, and subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) as the model term. The hazard ratio of gimsilumab versus placebo will be presented with 95% CI and p-value from the model. The Kaplan-Meier curves of the time to events will be presented for treatments on each endpoint.
Section 4.1 Overall Design	Text was revised to reflect the addition of another country: Randomization will be stratified by ~~site~~country and subject's clinical status at Baseline
Sections 2.2 Dose Rationale, 6.1 Study Treatment, and 6.2 Administration of Study Treatments	Table 6-1 was revised to allow a window for the timing of the infusion given the clinical care setting.

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	Infuse the entire contents of the IV bag via the intravenous route over a [redacted] Flush the line with 0.9% saline to ensure the entire contents is administered.
Section 7.1 Schedule of Assessments	The Schedule of Assessments footnotes were revised to clarify the following: screening serology and TB test results do not need to be received prior to enrollment, physical examinations and vital signs measurements performed as standard of care may not need to be repeated, local laboratory values must be documented in the eCRF, and DoD assessments can be performed one day prior to discharge if the subject has been labelled as "ready for discharge.". Abbreviations were revised, as needed.
Section 7.4.2.1 Physical Examinations	Language was added to clarify that physical examinations performed as standard of care may not need to be repeated. Note: If a physical examination is performed as standard of care by appropriate personnel the same day that consent is signed or the same day of any scheduled study visit, results from that examination may be used if personal protective equipment (PPE) is not available or if study site staff consider additional examinations are unwarranted due to already having been performed as standard of care.
Section 7.4.2.2 Vital Signs	Language was added to clarify that vital signs measurements performed as standard of care may not need to be repeated. Note: If vital signs measurements are performed as standard of care by appropriate personnel the same day that consent is signed or the same day of any scheduled study visit, results from that examination may be used if PPE is not available or if study site staff consider additional measurements are unwarranted due to already having been performed as standard of care.
Section 7.4.2.4 Follicle Stimulating Hormone (FSH), Viral Serology, and Tuberculosis Assessments	This section was added to allow for clarifying text to be included in the main body of the protocol. Follicle stimulating hormone (FSH) will be performed at screening, for women only, to confirm postmenopausal status in women who have not had 12 months of spontaneous amenorrhea. A blood sample will be collected at Screening as specified in the Schedule of Assessments (Table 7-2), for viral serology and TB testing, but enrollment can continue without receiving the results first. HCV testing can be RNA or Ag, only to confirm suspected infection. If a subject is diagnosed with latent TB (positive QuantiFERON Gold or purified protein derivative [PPD]), hepatitis B or C, or HIV during the study, the

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	Investigator must discuss this with the medical monitor and a decision will then be made concerning the second dose of gimsilumab, if applicable. In the event the QuantiFERON Gold assay is not available, and the site performs a different IGRA such as T Spot, then the alternative IGRA will be acceptable for patient screening and enrollment. Enrollment should not be delayed to obtain the QuantiFERON Gold assay in lieu of the IGRA available at the site. If no IGRA test is available, PPD can be used. If TB testing and viral serology is missed during screening it must be completed and results received prior to the second dose of study drug. If not completed or unable to obtain results further discussions with the medical monitor will be required.
Section 9.2 Randomization	Text added to reflect the addition of another country. The central stratified randomization will be used to assign subjects into 1 of the 2 study treatment arms with an equal randomization ratio (1:1) with the stratification factors of subject's clinical status at Baseline ([lung injury/mild ARDS] or [moderate/severe ARDS]) and country.
Appendix 3: Summary of Changes for Protocol Amendments (Section 14.3)	Text was revised to reflect the new Amendment. The original Protocol (Version 1.0) was approved on 22-March-2020, and has been amended ~~3~~4 times; Protocol Amendment 1 (Version 2.0) was approved on 05-April-2020, Protocol Amendment 2 (Version 3.0) was approved on 06-May-2020, ~~and~~ Protocol Amendment 3 (Version 4.0) was approved on 12-June-2020, and Protocol Amendment 4 (Version 5) was approved on 17-August-2020. Summaries of changes are presented in Table 14-1 for Amendment 1, Table 14-2 for Amendment 2, ~~and~~ Table 14-3 for Amendment 3, and Table 14-4 for Amendment 4. Table 14-4 was added to explain changes made in Protocol Amendment 4.