Clinical Study Protocol

AN ADAPTIVE PHASE 2/3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY ASSESSING EFFICACY AND SAFETY OF SARILUMAB FOR HOSPITALIZED PATIENTS WITH COVID-19

Compound:	REGN88 (sarilumab; Kevzara®)
Clinical Phase:	2/3
Protocol Number:	6R88-COV-2040
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Amendment 3 Date of Issue:	28 Mar 2020
Amendment 2 Date of Issue:	Withdrawn and not implemented
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AMENDMENT HISTORY

Amendment 7

The following table outlines the changes made to the protocol and the affected sections:

Change and Rationale	Sections Changed
Based on feedback from the IDMC which noted safety concerns, the following changes have been made to the protocol: • In Phase 3 Cohort 1, only patients receiving mechanical ventilation will be re-dosed. • In Phase 3 Cohort 2, patients will only receive study drug while receiving mechanical ventilation. • In Phase 3 Cohort 3, no additional patients will be enrolled and patients on study will not be re-dosed. All patients will continue to be monitored and complete all assessments per protocol.	Clinical Study Protocol Synopsis: Objectives, Study Design, Treatments, Endpoints, Statistical Plan Section 1 Introduction Section 2.1 Primary Objective Section 2.2 Secondary Objectives Section 3.1 Hypotheses Section 3.2.2 Rationale for Study Design Adaptation Section 3.3 Risk-Benefit for REGN88 (sarilumab, Kevzara®) Section 3.2.4 Rationale for Phase 3 Cohorts 2 and 3 Dose Selection Section 4.1.1 Primary Endpoints Table 4 Phase 3 Efficacy Endpoints Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram for Phase 2 and Phase 3 Section 6.2 Planned Timing of Analysis Section 7.1 Number of Patients Planned Section 7.2.1 Inclusion Criteria #2 Section 7.2.2 Exclusion Criteria Section 8.1 Investigational Treatment Section 8.2.1 Dose Modification Section 8.4 Method of Treatment Assignment Table 5 Schedule of Events Section 9.2.2.4 Clinical Status Assessment (7-Point Ordinal Scale)

	Section 9.2.3.5 Laboratory Testing Section 11 Statistical Plan (including subsections) Table 8 Testing Strategy for Control of Multiplicity in Phase 3 Cohorts 1 and 2 (Overall Type 1 Error in Each Cohort is 0.05 [2-sided])

Amendment 6

The following table outlines the changes made to the protocol and the affected sections:

Change and Rationale	Sections Changed
As part of the Phase 3 adaptation and to explore whether a higher dose could provide further clinical benefit in patients with COVID-19, 2 additional independently powered cohorts were added to evaluate sarilumab 800 mg versus placebo in patients on mechanical ventilation at baseline (Cohort 2) and in patients not on mechanical ventilation but on high-intensity oxygen therapy without mechanical ventilation at baseline (Cohort 3). Each Cohort will be analyzed separately and efficacy endpoints within each Cohort will be tested using a hierarchical testing order.	Clinical Study Protocol Synopsis: Objectives, Study Design, Treatments, Endpoints, Statistical Plan Section 1 Introduction Section 2.1 Primary Objective Section 3.1 Hypotheses Section 3.2.2 Rationale for Study Design Adaptation Table 3 Summary of Phase 3 Adaptations Section 3.2.4 Rationale for Phase 3 Cohorts 2 and 3 Dose Selection Section 4.1.1 Primary Endpoints Table 4 Phase 3 Efficacy Endpoints Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram for Phase 2 and Phase 3 Section 6.2 Planned Timing of Analysis Section 7.1 Number of Patients Planned Section 7.2.1 Inclusion Criteria, #2 Section 8.1 Investigational Treatment Section 8.4 Method of Treatment Assignment Table 5 Schedule of Events Section 9.2.2.4 Clinical Status Assessment (7-Point Ordinal Scale) Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.3.1 Efficacy Analysis Set Section 11.4.3.1 Primary Efficacy Analysis

	Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control of Multiplicity Table 8 Testing Strategy for Control of Multiplicity in Phase 3 Cohorts 1 and 2 (Overall Type 1 Error is 0.05 [2-sided] in Cohort 1, and each stratum of Cohort 2) Section 11.5.1 Interim Analysis in Phase 3
To expedite reporting of key efficacy results, changed the key secondary efficacy endpoint of Day 60 all-cause mortality to Day 29 all-cause mortality.	Clinical Study Protocol Synopsis: Key Secondary Endpoints Table 4 Phase 3 Efficacy Endpoints Section 4.1.3 Exploratory Endpoints Section 11.4.3.2 Secondary Efficacy Analysis Table 8 Testing Strategy for Control of Multiplicity in Phase 3 Cohorts 1 and 2 (Overall Type 1 Error is 0.05 [2-sided] in Cohort 1, and each stratum of Cohort 2)
Surveillance blood cultures for bacteria and fungi should be performed weekly only for patients with sustained ANC <1000/µL for ≥48 hours post-randomization. Previously, surveillance blood cultures were mandatory at Days 7 and 15 regardless of ANC.	Table 5 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events Table, 16 Section 9.2.3.5 Laboratory Testing
Editorial changes made for consistency and clarity based on site feedback, and correction of typographical errors	Section 9.1.1 Footnotes for the Schedule of Events Table Section 11.3.2 Safety Analysis Set

Amendment 5

The following table outlines the changes made to the protocol and the affected sections.

Change and Rationale	Sections Changed
Based on feedback from the IDMC, patients will no longer receive sarilumab 200 mg or be eligible for repeat dosing of 200 mg, and patients in the severe and MSOD strata will no longer receive sarilumab 400 mg or placebo. Patients will continue to be monitored and complete all assessments per protocol. No new safety findings were noted.	Section 2.1 Primary Objective Section 3.2.1 Rationale for Study Design Section 3.3 Risk-Benefit for REGN88 (sarilumab, Kevzara®) Section 8.2.1 Dose Modification
Updated Phase 3 endpoints, sample size, and statistical plan based on interim Phase 2 data.	Section 2.3 Exploratory Objectives Section 3.1 Hypotheses Section 3.2.4 Rationale for Phase 3 Dose Selection Section 4.1.1 Primary Endpoints Section 4.1.2 Secondary Endpoints Section 4.1.2.1 Phase 2 Secondary Endpoints Section 4.1.2.2 Phase 3 Secondary Endpoints Table 4 Phase 3 Efficacy Endpoints Section 4.1.2.3 Safety Endpoints Section 4.1.3 Exploratory Endpoints Section 6.2 Planned Timing of Analysis Section 7.1 Number of Patients Planned Section 11 Statistical Plan Section 11.2 Justification of Sample Size Section 11.4.5.1 Adverse Events Section 11.4.5.3 Treatment Exposure Section 11.4.5.4 Treatment Compliance
Cohort 1 of Phase 3, patients randomized to receive sarilumab 400 mg, sarilumab 200 mg, or placebo, will complete enrollment after	Section 1 Introduction Section 2.1 Primary Objective

approximately 170 patients on a ventilator at baseline have been randomized in the critical stratum. Cohort 2 of Phase 3, in which patients are randomized to receive sarilumab 800 mg or placebo, will start enrolling patients upon the completion of enrollment in Cohort 1. As part of Phase 3 adaptation and to explore whether a higher dose could provide further clinical benefit in patients with COVID-19, an additional cohort (Cohort 2) in 2 strata of patients only was added, to evaluate sarilumab 800 mg versus placebo in patients on mechanical ventilation at baseline and in patients not on mechanical ventilation but on high-intensity oxygen therapy.	Section 2.2 Secondary Objectives Section 3.1 Hypotheses Section 3.2.2 Rationale for Study Design Adaptation Table 1 Interim Phase 2 Results [redacted] Table 3 Summary of Phase 3 Adaptations Section 3.2.4 Rationale for Phase 3 Cohort 2 Dose Selection Section 4.1.1 Primary Endpoints Table 4 Phase 3 Efficacy Endpoints Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria, #2 Section 7.2.2 Exclusion Criteria, #11, #12, #13, #14 Section 8.1 Investigational Treatment Section 8.4 Method of Treatment Assignment Table 5 Schedule of Events Section 11 Statistical Plan Section 11.1 Statistical Hypothesis Section 11.3.1 Efficacy Analysis Sets Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control of Multiplicity Table 8 Testing Strategy for Control of Multiplicity in Phase 3 Cohorts 1 and 2 (Overall Type 1 Error is 0.05 [2-Sided] in each Cohort) Section 11.5.1 Interim Analysis in Phase 3

Removed the surveillance blood cultures as there is no clinically relevant findings based on the Phase 2 database, and this relieves site burden.	Section 9.1 Schedule of Events Section 9.2.3.5 Laboratory Testing
Editorial changes made for consistency and clarity based on site feedback, and correction of typographical errors	Table 5 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events Table, 1, 3, 5, 6, 7, 16, 17 Section 9.2.2.4 Clinical Status Assessment (7-Point Ordinal Scale) Section 9.2.3.5 Laboratory Testing Section 10.1.3 Events that Require Expedited Reporting to Sponsor

Amendment 4

The following table outlines the changes made to the protocol and the affected sections.

Change and Rationale	Sections Changed
Repeat dosing is permitted after 24 hours of dosing if no clinical response is observed. Additionally, repeat weekly dosing is permitted for patients requiring supplemental O_2. This change is justified by a favorable safety profile to date and the potential of increased clearance of the drug in the setting of inflammation associated with COVID pneumonia may lead to lower than effective exposure.	Clinical Study Protocol Synopsis: Study Design, Treatments Section 1 Introduction Section 3.2.3 Rationale for Dose Selection Section 6.1 Study Description and Duration Section 8.1 Investigational Treatment Section 8.2.1 Dose Modification Section 8.2.2 Study Drug Discontinuation Section 9.1 Schedule of Events Section 1.1.1 Footnotes for the Schedule of Events Table Section 11.4.5.4 Treatment Compliance
Additional patients are being included in Phase 2 to allow for adequate estimation of the treatment effect of the potential Phase 3 clinical endpoint.	Clinical Study Protocol Synopsis: Sample Size, Statistical Plan Section 7.1 Number of Patients Planned Section 11.2 Justification of Sample Size
The Sponsor may close enrollment into one or more severity categories at any time to ensure adequate numbers of patients are enrolled into other categories or for other reasons related to safety, futility, or new external information.	Section 6.1 Study Description and Duration
Removing exclusion for immunocompromised patients as the study stratifies for these patients	Section 7.2.2 Exclusion Criteria
Updated drug supply of sarilumab to include distribution of vials to sites	Section 8.7.1 Packaging, Labeling, Storage

Change and Rationale	Sections Changed
Statistical model for primary efficacy analysis was changed to reflect the correct dependent variable in ANCOVA model	Clinical Study Protocol Synopsis: Statistical Plan Section 11.4.3.1 Primary Efficacy Analysis
Editorial changes made for consistency and clarity based on site feedback, and correction of typographical errors	Section 6.1.1.1 Individual Patient Stopping Rules Section 7.2.1 Inclusion Criteria Section 9.2.3.4 Targeted Medication Review Section 8.5 Blinding Section 8.8 Concomitant Medications Section 9.1 Schedule of Events Section 9.2.3.5 Laboratory Testing Section 10.1.2 Reporting Procedure Section 11.4.5.1 Adverse Events

Amendment 3

The following table outlines the changes made to the protocol and the affected sections.

Change and Rationale	Sections Changed
Changed the primary endpoint in Phase 2 to "percent reduction in C-reactive protein (CRP) from baseline to Day 4 in patients with baseline IL-6 levels > ULN". Reduced N of patients for Phase 2 to a total of approximately 200 patients with high IL-6 levels at baseline.	Clinical Study Protocol Synopsis: Primary Endpoint, Secondary Endpoint, Statistical Plan Section 3.1 Hypotheses Section 4.1.1 Primary Endpoint Section 4.1.2 Secondary Endpoints Section 4.1.3 Exploratory Endpoints Section 5.2 Efficacy Variables Section 5.5 Pharmacodynamic and Other Biomarker Variables Section 6.2 Planned Timing of Analysis Section 8.5 Blinding Section 9.2.3.5 Laboratory Testing Section 11.1 Statistical Hypothesis Section 11.4.3.1 Primary Efficacy Analysis
Removed the requirement for documented fever at randomization so patients with pneumonia who are screened and do not have a fever are still eligible for enrollment.	Section 7.2.1 Inclusion Criteria
Removed exclusion criteria which previously prohibited patients who received immunosuppressive therapies from participating in this study. These patients are now included at request of FDA as this could provide useful information on the benefit/risk for this more vulnerable population. Patients who are receiving simultaneous leflunomide and methotrexate are still excluded due to concerns about hepatotoxicity related to this drug combination.	Section 7.2.1 Inclusion Criteria Section 7.2.2 Exclusion Criteria Section 8.4 Method of Treatment Assignment
Updated for consistency with IDMC charter	Section 6.1.1.2 Study Level Stopping Rules

Change and Rationale	Sections Changed
Limitations in clinical site research staff made it challenging to have separate study personnel to not have access to clinical laboratory data.	Section 8.5 Blinding
• Updated to reflect hospital procedures and restrictive infection control measures to minimize staff contact with infected patients. • Added collection (from patients' charts) of temperatures from patient admission to randomization	Section 9.2.2.2 Body Temperature
The Schedule of Events table was updated based on revised primary endpoint of percent change in baseline in CRP for the Phase 2 portion of the study. It was also updated based on site feedback regarding the inability to collect research samples due to lack of personal protective equipment (PPE). Duplicative assessments were also removed.	Clinical Study Protocol Synopsis: Procedures and Assessments Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events Table
Added temporal measurement for assessment of fever. Redefined fever thresholds for resolution of fever endpoint.	Clinical Study Protocol Synopsis: Primary Endpoint, Secondary Endpoint, Statistical Plan Section 4.1.1 Primary Endpoint Section 4.1.2 Secondary Endpoints Section 9.2.2.2 Body Temperature
Editorial changes made for consistency and clarity based on site feedback	Section 6.1 Study Description and Duration Section 7.2.2 Exclusion Criteria Section 8.3.1 Acute Intravenous Infusion Reactions Section 8.4 Method of Treatment Assignment Section 9.2.2.3 Oxygen Administration and Oxygenation Section 9.2.2.4 Clinical Status Assessment (7-Point Ordinal Scale) Section 9.2.2.5 NEWS2 Scoring System

Change and Rationale	Sections Changed
	Section 9.2.3.1 Vital Signs Section 9.2.3.3 Electrocardiogram Section 11 Statistical Plan Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.4.3 Efficacy Analysis Section 11.4.3.1 Primary Efficacy Analysis

Amendment 2 – withdrawn and not implemented

Amendment 1

The following table outlines the changes made to the protocol and the affected sections.

Change and Rationale	**Sections Changed**
Aligned safety objectives and endpoints with adverse events of special interest (AESI) in response to Health Authority feedback	Clinical Study Protocol Synopsis: Study Design Section 2.2 Secondary Objectives Section 4.1.2 Secondary Endpoints
Aligned exploratory objectives with Section 9.2.5 in response to Health Authority feedback	Section 2.3 Exploratory Objectives Section 4.1.3 Exploratory Endpoints
Updated from a 6-point scale to a 7-point scale in response to Health Authority feedback such that no ordinal categories are collapsed after or during data analysis.	Clinical Study Protocol Synopsis: Primary Endpoint, Statistical Plan Section 4.1.1 Primary Endpoint Section 4.1.2 Secondary Endpoints Section 5.2 Efficacy Variables Section 9.2.2.3 Clinical Data Collection Section 11.4.3.1 Primary Efficacy Analysis
Clarified that data reviews will include data, including deaths, for all enrolled study participants, in response to Health Authority feedback	Section 3.2.1 Rationale for Study Design Section 6.2 Planned Timing of Analysis
Included the safety findings of severe neutropenia with sarilumab at the 2 mg/kg IV dose in Study 6R88-RA-0703 in response to Health Authority feedback	Section 3.2.2 Rationale for Dose Selection Section 4.1.2 Secondary Endpoints
Revised the known potential benefits of sarilumab to include a benefit based on data from China and the use of IL-6R antagonists for CAR-T cell-induced cytokine release syndrome (CRS), in response to Health Authority feedback	Section 3.3 Risk-Benefit for REGN88 (sarilumab, Kevzara®)
Nasopharyngeal swab added as an acceptable method to collect virus based on emerging guidelines for SarsCOV-2 testing.	Section 4.1.3 Exploratory Endpoints Table 1 Schedule of Events Section 9.2.3.5 Laboratory Testing

Change and Rationale	Sections Changed
A specific definition of chronic hypercapnic respiratory failure has been added in response to Health Authority feedback	Section 5.1 Demographics and Baseline Characteristics
Updated inclusion criteria to accept a positive PCR result within 2 weeks of randomization, a range typically associated with the disease, to not exclude critical patients as a result of testing delays. In addition, patients develop the severe/critical complications of COVID-19 on average during 2nd week after symptom onset (and PCR testing typically done at that time) and because this is the target population for the study, PCR tests conducted up to 2 weeks from enrollment will be accepted. A sample will be collected at baseline and analyzed to confirm infection but will not be used to determine study inclusion.	Section 7.2.1 Inclusion Criteria (#3)
Patients with a known systemic hypersensitivity to sarilumab or the excipients of the drug product are excluded from the study, per the protocol template.	Section 7.2.2 Exclusion Criteria, #11
The exclusion of patients with a past history of, or current, autoimmune or inflammatory systemic or localized disease(s) other than rheumatoid arthritis was removed as inclusion of these patients does not impact safety or efficacy assessments of these patients in this study population.	Section 7.2.2 Exclusion Criteria, #6
Clarified that patients withdrawn from therapy should continue to be assessed for major outcomes in response to Health Authority feedback	Section 7.3 Premature Withdrawal from the Study Section 9.1.2 Early Termination from the Study
Body temperature will be collected as clinically indicated throughout the study in response to Health Authority feedback	Section 9.1 Schedule of Events
Added Day 1 predose sarilumab concentration collection for ADA analysis	Section 9.1.1 Footnotes for the Schedule of Events Table, Footnote 16

Change and Rationale	**Sections Changed**
Removed serum sIL-6R sample on Day 1 at randomization to reduce site burden	Section 9.1.1 Footnotes for the Schedule of Events Table, Footnote 18
Clarified that any new infection that occurs on study, regardless of organism will be captured, in response to Health Authority feedback	Section 9.2.3.5 Laboratory Testing
Change made in response to Health Authority feedback regarding multiplicity and statistical hypothesis.	Section 11.1 Statistical Hypothesis Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.4 Control of Multiplicity
Editorial changes made for consistency, clarity, and correction of typographical errors	Clinical Study Protocol Synopsis: Procedures and Assessments, Objectives, Secondary Endpoints, Population, Statistical Plan Section 4.1.2 Secondary Endpoints Section 7.2 Study Population Section 7.2.2 Exclusion Criteria (#1, #5, #9, and #10) Section 8.1 Investigational Treatment Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events Table, Footnote 1 Section 9.2.3.4 Target Medication Review Section 9.2.3.5 Laboratory Testing

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CDC	Center for Disease Control
COVID-19	Coronavirus Disease 2019
CMH	Cochran-Mantel-Haenszel test
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EDC	Electronic data capture
EUA	Emergency Use Authorization
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDL	High-density lipoprotein
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee

Abbreviation	Definition
IL-6	Interleukin 6
IRB	Institutional Review Board
ITT	Intention-to-treat
IV	Intravenous
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
mITT	Modified intention-to-treat
MSOD	Multiple System Organ Dysfunction
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NEWS2	National Early Warning Score2
OP	Oropharyngeal
NP	Nasopharyngeal
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PPS	Per Protocol population set
RA	Rheumatoid arthritis
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SC	Subcutaneous
sJIA	Systemic juvenile idiopathic arthritis
SOC	System organ class
SpO_2	Peripheral capillary oxygen saturation
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
WBC	White blood cell

Abbreviation	Definition
WHO	World Health Organization

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	An Adaptive Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study Assessing Efficacy and Safety of Sarilumab for Hospitalized Patients with COVID-19
Site Locations	United States
Principal Investigator	A PI will be identified for this study.
Objectives	**Primary Objective** **Phase 2:** The primary objective of the study is to evaluate the clinical efficacy of sarilumab relative to the control arm in adult patients hospitalized with COVID-19 regardless of severity strata. **Phase 3:** Cohort 1 The primary objective of the study is to evaluate the clinical efficacy of sarilumab 400 mg relative to the control arm in adult patients hospitalized with critical COVID-19 receiving mechanical ventilation at baseline. Cohort 2 The primary objective of the study is to evaluate the clinical efficacy of sarilumab 800 mg relative to the control arm in adult patients hospitalized with COVID-19 receiving mechanical ventilation at baseline **Secondary Objectives** **Phase 2:** The secondary efficacy objectives for the Phase 2 portion of the study are to: 1. Evaluate the clinical efficacy of sarilumab compared to the control arm in all disease severity levels and by clinical severity 2. Evaluate the clinical efficacy of sarilumab compared to the control arm by baseline IL-6 level 3. Evaluate changes in the National Early Warning Score 2 (NEWS2) 4. Evaluate the duration of predefined symptoms and signs (if applicable) 5. Evaluate the duration of supplemental oxygen dependency (if applicable) 6. Evaluate the incidence of new mechanical ventilation use during the study 7. Evaluate the duration of new mechanical ventilation use during the study 8. Evaluate need for admission into intensive care unit (ICU) 9. Evaluate duration of hospitalization (days) 10. Evaluate the 28-day mortality rate

Phase 3

The secondary efficacy objectives for the Phase 3 portion of the study are to:

Phase 3 Cohort 1:

- Determine whether sarilumab improves respiratory outcomes in patients with critical COVID-19
- Determine whether sarilumab reduces mortality in patients with critical COVID-19
- Determine whether sarilumab shortens hospitalization in patients with critical COVID-19

Phase 3 Cohort 2:

- Determine whether sarilumab improves respiratory outcomes in patients with COVID-19 receiving mechanical ventilation
- Determine whether sarilumab reduces mortality in patients with COVID-19 receiving mechanical ventilation
- Determine whether sarilumab shortens hospitalization in patients with COVID-19 receiving mechanical ventilation

Safety (Phase 2 and 3)

The secondary safety objectives of the study are to evaluate the safety of sarilumab through hospitalization (up to Day 29 if patient is still hospitalized) compared to the control arm as assessed by incidence of:

- Serious adverse events (SAEs)
- Grade 4 neutropenia (ANC<500/mm^3)
- Grade 4 neutropenia (ANC<500/mm^3) with concurrent severe or life-threatening bacterial, invasive fungal, or opportunistic infection
- Grade ≥2 infusion-related reactions
- Grade ≥2 hypersensitivity reactions
- Increase in alanine transaminase (ALT) or aspartate aminotransferase (AST) ≥3X ULN (for patients with normal baseline) or >3X ULN AND at least 2-fold increase from baseline value (for patients with abnormal baseline)
- Invasive bacterial or fungal infections of clinical significance with confirmed diagnosis based on the investigator's assessment with appropriate diagnostic workups and consultations

Study Design

This study is an adaptive Phase 2/3, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of sarilumab in hospitalized adults with COVID-19. The study will be conducted in the United States (US) in up to 150 sites. As part of the Phase 3 adaptation plan, the Phase 3 portion of the study will include 3 cohorts. In Phase 2 and in Cohort 1 of the Phase 3 portion of the study, patients will be randomized in a 2:2:1 allocation ratio to sarilumab 400 mg IV, sarilumab 200 mg IV, or placebo in a stratified manner up to 26 Apr 2020. As of 27 Apr 2020 (as per recommendation of the IDMC), patients will be randomized to sarilumab 400 mg or placebo only in the critical stratum in a 2:1 manner. Enrollment

	into Cohort 1 closed when approximately 170 patients in the critical stratum receiving mechanical ventilation at baseline who were randomized to receive either sarilumab 400 mg or placebo were enrolled. In Cohort 2, patients receiving mechanical ventilation at baseline will be randomized 1:1 to receive sarilumab 800 mg IV or placebo. In the Phase 3 portion of the study, Cohorts 2 and 3 began enrolling patients in parallel when Cohort 1 enrollment completed. Following safety concerns raised by the Independent Data Monitoring Committee (IDMC), the Sponsor determined that the benefit/risk assessment was not favorable in patients who were not receiving mechanical ventilation. Based on this assessment, as of 06 Jun 2020, patients in Cohort 3 will no longer receive study drug. In addition, new patients will no longer be enrolled into Cohort 3. All patients will continue to be monitored and complete all assessments per protocol. Patients receiving mechanical ventilation will receive a single dose of study drug on Day 1. In Phase 3 Cohorts 1 and 2, patients will be re-dosed on Day 2 if the patient is receiving mechanical ventilation and meets 1 of the following criteria: 1. Remains febrile OR 2. Fails to improve gas exchange (eg, as measured by ventilator settings or O2 requirements) OR 3. Is hemodynamically unstable OR 4. Exhibits other objective evidence of clinical worsening (eg, mental status change, etc) Additional doses will be administered weekly only for patients receiving mechanical ventilation at the time of re-dosing and whose ANC is >500/mm^3 and ALT is ≤5x ULN. For Cohort 1, a maximum of 6 doses of study drug in total can be administered during the study. For Cohort 2, a maximum of 4 doses of study drug can be administered during the study. There is no dosing after Day 21 in Cohort 2. Throughout the study, study drug should be withheld if there is a high degree of suspicion of active bacterial or fungal infection. Patients who receive a prohibited medication will not be eligible for re-dosing.
Study Duration	An individual patient will complete the study approximately 60 days from screening to follow-up on Day 60 ±7 days. Patients will not be required to return to the hospital once discharged.
End of Study Definition	The end of study is defined as the date the last patient completes the last study assessment (in the hospital or via a follow-up phone call if the patient was discharged from the hospital before Day 60), withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).
Population	
Target Population:	Hospitalized adult (≥18 years old) male and female patients with COVID-19.

Sample Size:	Total sample size for Phase 2 is expected to be approximately 460 to include patients with all baseline IL-6 levels. Based on results from Phase 2 data, sample size for Phase 3 was re-calculated. For Cohort 1 of the Phase 3 portion of this study, the total sample size will be approximately 1,400 patients. Enrollment into Cohort 1 closed when approximately 170 patients in the critical stratum receiving mechanical ventilation at baseline who were randomized to receive either sarilumab 400 mg or placebo were enrolled. The total sample sizes for Cohort 2 will be approximately 225 patients. The planned sample size for Cohort 3 was 225 patients, however, enrollment ended on 06 Jun 2020 at which time 9 patients enrolled. Cohorts 2 and 3 enrolled in parallel when Cohort 1 enrollment completed.
Treatments	
Study Drug	REGN88 (sarilumab; Kevzara®) or placebo
Dose/Route/Schedule:	200 mg IV or 400 mg IV at single or multiple doses (Phase 2 and Phase 3 Cohort 1) 800 mg IV at single or multiple doses (Phase 3 Cohorts 2 and 3)
Endpoints	Note that for the primary and secondary endpoints, patients will not be required to return to the hospital once discharged. A follow-up phone call will occur on Days 29 and/or 60, depending on when the patient is discharged. All patients will be contacted for an end of study (EOS) follow-up at Day 60.
Primary:	**Phase 2:** The primary endpoint is the percent change from baseline in C-reactive protein (CRP) levels at Day 4 in patients with serum IL-6 levels greater than the upper limit of normal. **Phase 3 Cohort 1:** Proportion of patients with at least a 1-point improvement in clinical status from baseline to Day 22 using the 7-point ordinal scale in patients with critical COVID-19 receiving mechanical ventilation at baseline **Phase 3 Cohort 2:** Proportion of patients with at least a 1-point improvement in clinical status from baseline to Day 22 using the 7-point ordinal scale in patients with COVID-19 receiving mechanical ventilation at baseline Separate analyses of Cohorts 1 and 2 are planned.
Secondary:	The 7-point ordinal scale will be assessed as a secondary endpoint in Phase 2 and will be used for both Primary and Secondary endpoints in Phase 3. The ordinal scale is an assessment of the clinical status. The scale is as follows: • Death; • Hospitalized, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); • Hospitalized, requiring non-invasive ventilation or high flow oxygen devices; • Hospitalized, requiring supplemental oxygen;

- Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)
- Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care
- Not hospitalized

Phase 2:

Key Secondary Efficacy Endpoint

1. Time to improvement (2 points) in clinical status assessment from baseline on the 7-point ordinal scale in severe or critical patients with serum IL-6 level greater than the upper limit of normal
2. Time to improvement (2 points) in clinical status assessment from baseline on the 7-point ordinal scale reporting in severe or critical patients with all IL-6 levels

Other Secondary Endpoints:

Efficacy

1. Time to resolution of fever for at least 48 hours without antipyretics or until discharge, whichever is sooner, in patients with documented fever ≥38°C (oral), ≥38.4°C (rectal or tympanic), or ≥37.6°C (temporal or axillary) at Baseline

   (Resolution of fever is defined as postbaseline body temperature <37.2°C (oral), or <37.6°C (rectal or tympanic) or <36.8°C (temporal or axillary).
2. Time to resolution of fever (defined as above) for at least 48 hours without antipyretics or until discharge, whichever is sooner, in patients defined as above, by clinical severity
3. Time to resolution of fever (defined as above) for at least 48 hours without antipyretics or until discharge, whichever is sooner, in patients defined as above, by baseline IL-6 levels
4. Time to improvement in oxygenation (increase in SpO_2/FiO2 of 50 or greater compared to the nadir SpO_2/FiO2) for at least 48 hours or until discharge, whichever is sooner
5. Time to improvement in oxygenation (increase in SpO_2/FiO2 of 50 or greater compared to the nadir SpO_2/FiO2) for at least 48 hours or until discharge, whichever is sooner, by clinical severity
6. Time to improvement in oxygenation (increase in SpO_2/FiO2 of 50 or greater compared to the nadir SpO_2/FiO2) for at least 48 hours or until discharge, whichever is sooner, by baseline IL-6 level
7. Time to resolution of fever (as defined above) and improvement in oxygenation (as defined above)

8. Mean change in the 7-point ordinal scale from baseline to Days 3, 5, 8, 11, 15, and 29 (or until discharge)
9. Percentage of patients in each clinical status category using the 7-point ordinal scale at Days 3, 5, 8, 11, 15, and 29
10. Time to discharge or to a NEWS2 of ≤2 and maintained for 24 hours, whichever occurs first
11. Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS2
12. Days with fever (≥38°C °C [oral], ≥38.4°C [rectal or tympanic], or ≥37.6°C [temporal or axillary])
13. Proportion of patients alive, off oxygen at Day 29
14. Days of resting respiratory rate >24 breaths/min (recorded at least once each day)
15. Days of hypoxemia (SpO2 ≤93% on room air, or requiring supplemental oxygen, or mechanical ventilatory support)
16. Days of supplemental oxygen use
17. Time to saturation ≥94% on room air
18. Ventilator free days in the first 28 days (to Day 29)
19. Initiation of mechanical ventilation, non-invasive ventilation, or use of high flow nasal cannula (for those not requiring these interventions at baseline)
20. Admission into an ICU (among those not in an ICU at baseline)
21. Days of hospitalization among survivors
22. All-cause mortality

Phase 3:

Key Secondary Efficacy Endpoints

Cohort 1

1. Proportion of patients with at least 1-point improvement in clinical status assessment from baseline to Day 22 in patients with critical COVID-19
2. Proportion of patients who recover (discharged, or alive without supplemental oxygen use or at pre-COVID oxygen use) by Day 22 in patients with critical COVID-19 receiving mechanical ventilation at baseline
3. Proportion of patients who die through Day 29 in patients with critical COVID-19 receiving mechanical ventilation at baseline
4. Proportion of patients who die through Day 29 in patients with critical COVID-19

Cohort 2

1. Proportion of patients who recover (discharged, or alive without supplemental oxygen use or at pre-COVID oxygen use) by Day 22 in patients with COVID-19 receiving mechanical ventilation at baseline
2. Proportion of patients who die through Day 29 in patients with COVID-19 receiving mechanical ventilation at baseline

Other Phase 3 Secondary Endpoints:

Cohort 1

1. Proportion of patients who recover (discharged, alive without supplemental oxygen use, or at pre-COVID oxygen use) by Day 22 in the critical ITT population
2. Proportion of patients who die through Day 29 in the critical ITT population
3. Proportion of patients alive not receiving mechanical ventilation or ECMO at Day 22 in the critical ITT population and in patients receiving mechanical ventilation at baseline
4. Proportion of patients with a 2-point improvement in clinical status on the 7-point ordinal scale from baseline to Day 22 in the critical ITT population and in patients receiving mechanical ventilation at baseline
5. Time to at least 1-point improvement in clinical status assessment from baseline on the 7-point ordinal scale in the critical ITT population and in patients receiving mechanical ventilation at baseline
6. Time to at least a 2-point improvement in clinical status assessment from baseline on the 7-point ordinal scale in the critical ITT population and in patients receiving mechanical ventilation at baseline
7. Proportion of patients receiving mechanical ventilation or ECMO at Day 22 in the critical ITT population and in patients receiving mechanical ventilation at baseline
8. Proportion of patients discharged and alive at Day 22 in the critical ITT population and in patients receiving mechanical ventilation at baseline
9. Time to recovery (discharged, or alive without supplemental oxygen use or at pre-COVID oxygen use) in the critical ITT population and in patients receiving mechanical ventilation at baseline

10. Time to death (all-cause mortality) in the critical ITT population and in patients receiving mechanical ventilation at baseline
11. Number of ventilator free days between baseline and Day 8, 15, 22, and 29 in the critical ITT population and in patients receiving mechanical ventilation at baseline
12. Number of days of hospitalization among survivors up to Day 8, 15, 22, and 29 in the critical ITT population and in patients receiving mechanical ventilation at baseline

Cohort 2

1. Proportion of patients alive not receiving mechanical ventilation or ECMO at Day 22
2. Proportion of patients with a 2-point improvement in clinical status on the 7-point ordinal scale from baseline to Day 22
3. Time to at a least 1-point improvement in clinical status assessment from baseline on the 7-point ordinal scale
4. Time to at least 2-point improvement in clinical status assessment from baseline on the 7-point ordinal scale
5. Proportion of patients receiving mechanical ventilation or ECMO at Day 22
6. Proportion of patients discharged and alive at Day 22
7. Time to recovery (discharged, or alive without supplemental oxygen use or at pre-COVID oxygen use)
8. Proportion of patients who die through Day 60
9. Time to death (all-cause mortality)
10. Number of ventilator free days between baseline and Day 8, 15, 22, and 29
11. Number of days of hospitalization among survivors up to Day 8, 15, 22, and 29

Safety

The secondary safety endpoints for Phase 2 and 3 are:

1. Incidence of serious adverse events
2. Incidence of Grade 4 neutropenia (ANC <500/mm^3)
3. The incidence of severe or life-threatening bacterial, invasive fungal, or opportunistic infection
4. The incidence of severe or life-threatening bacterial, invasive fungal, or opportunistic infection in patients with Grade 4 neutropenia (ANC<500/mm3)

	5. Proportion of patients with hypersensitivity reactions 6. Proportion of patients with infusion reactions 7. Proportion of patients with gastrointestinal perforation 8. White cell count, hemoglobin, platelets, creatinine, total bilirubin, ALT, AST, on Days 1, 4, 5, 8, 11, 15 and 29 (if still hospitalized)
Procedures and Assessments	Efficacy procedures and assessments include serum CRP measurement, body temperature, oxygen administration (FiO2) and oxygenation (SpO_2) clinical data assessment, National Early Warning Score2 (NEWS2), and biospecimens for biomarker analysis and virology. Safety procedures and assessments include laboratory testing, vital signs, limited physical examination, and targeted medication review.
Statistical Plan	For the Phase 2 portion of the study, a total of approximately 460 patients were planned to be randomized (2:2:1) to sarilumab 400 mg IV, sarilumab 200 mg IV or placebo. This sample size was estimated to provide at least 90% power to detect a treatment effect in the Phase 2 endpoint of reduction in CRP levels as well as allow adequate estimation and improve precision for selection of Phase 3 efficacy endpoints. The study analysis plan for Phase 2 is based on the analysis of 2 populations; modified intention-to-treat (mITT) population defined as randomized and treated patients with high baseline IL-6 levels (>ULN) and intention-to-treat (ITT) population defined as all randomized and treated patients. For Phase 3 portion of the study the primary analysis population for efficacy will be the ITT population, unless otherwise specified. Supportive analyses in Phase 3 may also be performed using the per protocol set (PPS) population. For the Phase 2 portion of the study, the primary efficacy analysis will be a pairwise comparison between sarilumab 400 mg IV and placebo with respect to percent change from baseline in CRP levels at Day 4, in patients with COVID-19 disease. Missing values of CRP levels at Day 4 will be imputed by Day 3 or Day 5 levels when available, in this order of priority. Hypothesis test of superiority of sarilumab versus placebo will be done using an analysis of covariance (ANCOVA) model with treatment group, severity of illness and systemic corticosteroid use as fixed effects, and baseline log(CRP) as a covariate. Treatment effect will be reported as difference in mean percent change from baseline in CRP levels at Day 4. P-values will be compared to 0.05 (2-sided) level of significance and 95% confidence levels reported. The data lock point for the first interim analysis of the Phase 2 portion of the study was set at 15 days after the last of the approximately 460 patients in Phase 2 had been randomized. These data were used to determine the adaptations and analysis plan for the Phase 3 portion of this adaptive Phase 2/3 study. Based on the Phase 2 interim results, the sample size for Phase 3 was recalculated using the chosen Phase 3 endpoint of the proportion of patients with at least 1-point improvement in clinical status on the ordinal scale in patients in the critical stratum who were on mechanical ventilation. In the Phase 3 Cohort 1, approximately 450 patients in critical stratum are planned to be enrolled in order to have approximately 170 critical patients who are on mechanical and randomized to receive either sarilumab 400 mg or placebo (sarilumab 400 mg n=113 and placebo n=57). This sample size would provide >99% power to detect a treatment difference of 40% in

sarilumab 400 mg compared to placebo (difference assumed to be similar to that observed in Phase 2).

Additional adaptations were made to Phase 3 to enroll 2 new cohorts in Phase 3 randomized 1:1 to sarilumab 800 mg or placebo. Cohort 2 will enroll patients being treated with using mechanical ventilation. In Cohort 2, a total of 225 patients will be enrolled. This sample size is estimated to provide at least 92% (>99%) power in patients receiving ventilation at baseline to detect a treatment difference of 20% (40%) between sarilumab 800 mg and placebo in Cohort 2. Sample size re-estimation may occur after Phase 3 Cohort 1 results are determined.

The primary hypotheses are to test the superiority of sarilumab 400 mg IV to placebo in Cohort 1 critical patients with mechanical ventilation at baseline and to test the superiority of sarilumab 800 mg IV to placebo in Cohort 2, with respect to the final primary endpoint of proportion of patients with at least 1-point improvement in clinical status on the ordinal scale at Day 22. Interim analysis for the Cohort 1 primary analysis populations will be based on analysis of all patients enrolled up to the date when approximately 110 patients have been enrolled on mechanical ventilation at baseline who are randomized to 400 mg or placebo, with a data lock point 22 days later. The interim analyses will provide for hypothesis testing for the primary endpoint at α=0.005 (2-sided) and the final analysis with data after approximately 170 patients in Cohort 1 on mechanical ventilation at baseline reach Day 22 will be tested at α=0.049 (2-sided). Similar interim analyses are planned for Cohort 2 . Primary endpoint for each comparison will be proportion of patients with a 1-point improvement in clinical status from baseline to Day 22 using the 7-point ordinal scale. Hypothesis tests of superiority of sarilumab (400 or 800 mg dose) versus placebo will be done using the stratified Cochran-Mantel-Haenszel (CMH) test for differences in 2 proportions using stratification factors at randomization. Estimation of the treatment effect will be provided as differences in proportions and confidence intervals calculated using the strata-adjusted CMH method.

Key secondary endpoints will be analyzed similarly as the primary endpoint and testing of key secondary endpoints will be done in a hierarchical order while preserving the overall Type 1 error rate at 0.05 (2-sided) level.

1. INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel enveloped RNA betacoronavirus that emerged in December 2019 in Wuhan, China. The term COVID-19 is the disease caused by SARS-CoV-2 with symptoms that manifest a median of 5 days and up to 14 days after infection. The most frequent clinical presentation of severe COVID-19 is pneumonia with symptoms including fever, cough, and dyspnea. Although fever and cough are the most common presenting symptoms of COVID-19, not all patients with pneumonia present with fever (43%) on admission to the hospital, although the majority will develop fever later in their hospital course. In a report from the Chinese Center for Disease Control and Prevention that included 44,500 confirmed infections, the majority of infections (80%) are mild (with no or mild pneumonia), 14% were severe (defined as dyspnea, hypoxia or >50% lung involvement on imaging) and 5% were critical (respiratory failure, shock, or multiorgan failure) (Wu, 2020). Approximately 20% to 30% of hospitalized patients with COVID-19 and pneumonia have required intensive care for respiratory support (Chen, 2020)(Huang, 2020). In patients with COVID-19, the most common laboratory abnormalities in the peripheral white blood cell counts include lymphopenia (63%), leukocytosis (24-30%) and leukopenia (9-25%). Procalcitonin serum levels are generally not elevated in COVID-19 and were <0.5 in 95% of patients in one study. However, COVID-19 is associated with increases in C-reactive protein (CRP) and CRP levels appears to track disease severity and outcome. In one study of 150 patients with COVID-19 in China, patients who died had a significantly higher serum level of CRP (126.6 vs 34.1 mg/L). The overall case fatality rates can range from 1.0% to 3% with the majority of fatal cases occurring in critically ill patients with advanced age or underlying medical conditions (Guan, 2020)(Young, 2020).

Patients with COVID-19 infection are at risk for the development of pneumonia and the acute respiratory distress syndrome (ARDS). Acute respiratory distress syndrome is a clinical syndrome of severe impairment of gas exchange due to widespread alveolar epithelial cell and pulmonary capillary endothelial injury resulting from a variety of etiologies, including respiratory viral infections. Clinically, ARDS presents with severe hypoxemia (PaO_2/FiO2 ratio <300 mm Hg) evolving over days to a week in combination with bilateral pulmonary infiltrates on chest X-ray (or other lung imaging) not entirely attributable to elevated pulmonary venous pressure (ie, heart failure or fluid overload). ARDS carries a high mortality rate, ranging from 27% for "mild" ARDS to 45% for severe ARDS (defined as a PaO2/FiO2 ratio <100 mm Hg). ARDS is a common complication of severe viral pneumonia, including pneumonia due to highly pathogenic coronaviruses. In one report of 1,099 patients hospitalized with COVID-19, ARDS was reported to occur in 15.6% of patients with severe pneumonia. In a smaller case series of 138 hospitalized patients, ARDS occurred in 19.6% of patients and in 61.1% of patients admitted to an intensive care unit (ICU).

There are currently no specific treatments for COVID-19. Clinical management of hospitalized patients with COVID-19 includes supportive therapy: supplemental oxygen therapy to target SpO_2, empiric antimicrobials, empiric neuraminidase inhibitor for treatment of influenza when there is local circulation and intensive care as required. The routine use of systemic corticosteroids is not recommended by the World Health Organization (WHO) for the treatment of COVID-19 pneumonia or ARDS, although, in practice, corticosteroids are reported to be used in patients with severe COVID-19 (WHO, 2020a). The median duration of hospitalization for mild cases is 12 to 14 days and approximately 3 to 6 weeks for patients with more severe disease (WHO, 2020b). The decision to discharge patients from a hospital or to discontinue transmission-based precautions is

made on a case-by-case basis but the Center for Disease Control (CDC) recommends waiting until there is resolution of fever without use of antipyretic medication, improvements in illness signs and symptoms and negative results of COVID-19 PCR from 2 consecutive sets of nasopharyngeal and throat swab specimens collected >24 hours apart (Centers for Disease Control and Prevention (CDC), 2020). Among patients who have died, the time from onset of symptoms to death ranges from 2 to 8 weeks.

Data on progression of disease in hospitalized patients are available from a limited number of hospitalized cases. In one report describing 1,099 COVID-19 patients in China, approximately 5% were admitted to the ICU, 2.3% underwent invasive mechanical ventilation and 1.4% died. Among patients with severe disease on admission (defined as pneumonia, hypoxemia and tachypnea), 19% were admitted to the ICU, 38.7% underwent invasive or non-invasive mechanical ventilation, and 8.1% died (Guan, 2020).

Triggers for severe illness with SARS-CoV-2 are not completely understood. The initial inflammatory responses to an infection are rapid and non-specific and regulated by inflammatory mediators including cytokines such as interleukin-6 (IL-6). IL-6 is a chief mediator in the early response to infection including fever (Gabay, 1999). However, IL-6 has been implicated in many pathogenic inflammatory states including the cytokine storm following infection with avian influenza A H5N1, SARS and MERS-CoV infection (de Jong, 2006) (Huang, 2005) (Zhang, 2004). Although the consequences of IL-6 production has been associated with both pro-inflammatory and anti-inflammatory effects, in the setting of infections, IL-6 is an important mediator of fever induction (Evans, 2015). The pyrogenic role of IL-6 was delineated in patients receiving T cell based-immunotherapy (specifically, chimeric antigen receptor-expressing T cells or a CD19/CD3-bispecific antibody) where treatment with the IL-6 receptor antagonist, tocilizumab, quickly reversed the high fevers and other symptoms that developed as part of a cytokine release syndrome (CRS) over several days (Teachey, 2013).

While the majority of patients with COVID-19 have mild infection despite having pneumonia, approximately 20% of patients develop severe disease. Of note, like MERS-COV, in patients with severe COVID-19, the onset of dyspnea, fever and progressive hypoxia can occur late, often during the second week after onset of symptoms suggesting a late pro-inflammatory process associated with the deterioration. For example, in one report, while only 43% of patients had fever on hospital admission, 88% of patients developed fever during hospitalization (Guan, 2020). In another report, dyspnea occurred 8 days (IQR: 5 to 13 days) after onset of symptoms, and ARDS occurred 9 days after onset of symptoms (IQR: 8 to 14 days). The delayed pro-inflammatory clinical presentation of COVID-19 is similar to what has been shown in primary lung epithelial cells infected with MERS-CoV where induction of IL-6 and IL-1b occurs late (30 hours after infection) (Lau, 2013) (Margulis, 2015). Interestingly, MERS-CoV patients who had severe infection, defined as need for oxygen supplementation, had higher IL-6 levels (median 54 pg/mL; range 5 to 228) compared to mild cases (median 3 pg/mL; range 0-44), especially during the 2nd and 3rd week after symptom onset, indicating a delayed pro-inflammatory process associated with severe MERS-CoV infection (Margulis, 2015).

Currently, few data exist on serum IL-6 levels in COVID-19 patients, but a median of 27 ng/L has been reported, and in severely ill patients can range widely (4.58-1182.9 ng/L) (Huang, 2020). In addition, at this time it is not clear how well serum IL-6 levels functions as a prognostic factor for progression of COVID-19. One report from Wuhan, China describe 69 patients with severe COVID-19 (defined as having 1 of the following: shortness of breath, respiratory rate >30/min, O_2sat <93% resting, PaO2/FiO2 ratio <300 mm Hg) and 11 patients with non-severe COVID-19. Baseline serum IL-6 level was increased in the severe COVID-19 cases compared to the non-severe cases (median 35 pg/mL versus <5 pg/mL), as was the (CRP) levels (Liu, 2020).

One hypothesis is that IL-6 is a modifiable driver of progression of disease with COVID-19 among patients with severe COVID-19. A potential therapeutic approach for patients with severe COVID-19 pneumonia therefore would be to temporarily attenuate the localized pulmonary "cytokine storm" in severe patients through blockade of the IL-6 receptor (IL-6R).

Kevzara® (sarilumab) is a human IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6Rs (sIL-6Rα and mIL-6Rα) and has been shown to inhibit IL-6-mediated signaling through these receptors. Sarilumab is formulated for subcutaneous (SC) injection at doses of 150 and 200 mg Q2W and was approved for the treatment of rheumatoid arthritis (RA) in the US on 22 May 2017, EU on 23 Jun 2017, and Japan on 27 Sep 2017. Sarilumab is not currently approved for use in CRS.

Actemra® (tocilizumab) is a humanized monoclonal antibody against the IL-6R and was approved for use in CRS associated with CAR-T cell therapies at a dose of 8 or 12 mg/kg, depending on weight, administered intravenously (IV) alone or in combination with corticosteroids. Symptoms of CRS can include high fevers, hypotension, respiratory and renal insufficiency, cytopenias and coagulopathy, although milder cases of CRS can present with only high fevers and myalgias. Several aspects of the CRS mirror those of severe COVID-19, including fever, respiratory insufficiency, and elevated markers of systemic inflammation, such as CRP. The experience with tocilizumab treated patients with CAR-T cell induced CRS reveals rapid defervescence and hemodynamic stability (Maude, 2014). The pharmacokinetics (PK) of tocilizumab in these patients suggests relatively rapid decline in concentrations following a single 8 mg/kg IV dose. An analysis performed by the FDA shows that C_{max} is about 40% lower in patients with CRS. The analysis indicates a linear clearance of 0.50 L/day and volume of distribution in central compartment of 1.8 L, suggesting half-life of 3 to 4 days in serum. The linear clearance appears faster in patients with CRS than in pediatric patients with systemic juvenile idiopathic arthritis (sJIA) or in adults with RA.

There are currently no known published reports of IL-6R antagonist for infectious sepsis or pneumonia. Because IL-6 contributes to host defense against bacterial and viral pathogens, there is concern that the IL-6R inhibitor drug class, including sarilumab and tocilizumab) may exacerbate infections thus delaying recovery from sepsis. Patients chronically treated with sarilumab are at increased risk for developing serious and opportunistic infections. Most developed infections occur while taking other immunosuppressants with sarilumab. Reported infections include active tuberculosis, invasive fungal infections, bacterial and viral infections. While decreases in absolute neutrophil count is seen in patients treated with sarilumab, they are not reported to be associated with increased incidence of infection or serious infections (Fleischmann, 2017). A clinical study of neutrophil trafficking suggested that this decrease is due to redistribution into the marginating pool, rather than a net decrease in the neutrophil population (Lok, 2017). Other laboratory abnormalities seen with chronic administration of IL-6R antagonists

include thrombocytopenia, elevated liver enzymes and lipid abnormalities. Reports of an increased risk of gastrointestinal perforation has been reported in patients with concurrent diverticulitis, concomitant use of NSAIDS or corticosteroids. Finally, hypersensitivity reactions have been reported with SC administration of IL-6R antagonists.

During the current COVID-19 outbreak, tocilizumab has been used in 21 patients with severe COVID-19 infection and described in a retrospective study (Wu, 2020). Patients were treated between February 5, 2020 and February14, 2020 if they had severe COVID-19 defined as having 1 or more of the following criteria: 1) respiratory rate >30 breaths/min; 2) SpO2 <93% on room air; 3) PaO2/FiO2 <300 mmHg or had critical COVID-19 defined as respiratory failure requiring mechanical ventilation, shock, organ failure or had an ICU admission. Among 21 patients 17 (81%) were severe and 4 (19%) were critical. Eighteen patients received a single dose of tocilizumab and 3 patients received a second dose of tocilizumab 12 hours after the first because of ongoing fever. All patients had fever prior to treatment, baseline mean CRP was 75±66.80 and mean IL-6 level was 132±278 pg/mL. One day after treatment with tocilizumab all patients had normal body temperature. Before treatment, 20 of 21 patients required oxygen therapy through high-flow nasal cannula (n=9), nasal cannula (7), mask oxygenation (1), noninvasive ventilation (1) and invasive ventilation (2). After tocilizumab 15 (75%) lowered oxygen intake after treatment and by Day 3 all patients had SpO_2 >94%, including 1 patient who was breathing without supplemental oxygen. As of March 5, 2020, a larger clinical trial is ongoing in 14 hospitals in Wuhan, China and 272 patients with severe COVID-19 have been treated.

Conducting well-controlled, randomized clinical trials in the setting of an outbreak has previously been found to be feasible and essential to identify safe and efficacious therapeutics for emerging infections like Ebola Virus Disease (Mulangu, 2019). In addition, during a pandemic, drug shortages and resource limitations can hinder the outbreak response, therefore, obtaining high-quality data on multiple therapeutics, even in the same class of drug, against an emerging infection is critical. Sarilumab acts by blocking IL-6R and may constitute a novel therapeutic strategy for severe COVID-19 to control the uncontrolled inflammatory response. If found to be safe and effective as monotherapy, sarilumab could be used in conjunction with future COVID-19-specific antivirals therapeutics. Risk of worsening or new infections associated with chronic use of IL-6R blockers could be mitigated using a single dose that only leads to short-term (<4 weeks) exposure to sarilumab and close monitoring and early treatment of worsening or new infections that may occur during the recovery period from COVID-19.

Study 6R88-COV-2040

This study protocol describes a multi-center, randomized, placebo-controlled trial of sarilumab for the treatment of severe COVID-19 to assess efficacy in reducing time to alleviation of COVID-19 predefined symptoms and safety in administering an IL-6R blocker during an acute viral pneumonia. The study is an adaptive Phase 2/3 study. In the Phase 2 portion of the study and in Cohort 1 of the Phase 3 portion, patients were randomized to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. In the Phase 3 portion of the study, Cohorts 2 and 3 enrolled patients in parallel when Cohort 1 enrollment completed. In Cohort 2, patients receiving mechanical ventilation will be randomized to receive sarilumab 800 mg or placebo. In Cohort 3, patients receiving high-intensity oxygen therapy without mechanical ventilation were randomized to receive sarilumab 800 mg or placebo. . Following safety concerns raised by the Independent Data Monitoring Committee (IDMC), the Sponsor determined that the benefit/risk assessment was not

favorable in patients who were not receiving mechanical ventilation. Based on this assessment, as of 06 Jun 2020, patients in Cohort 3 will no longer receive study drug. In addition, new patients will no longer be enrolled into Cohort 3. All patients will continue to be monitored and complete all assessments per protocol.

2. STUDY OBJECTIVES

2.1. Primary Objective

Phase 2:

The primary objective of the study is to evaluate the clinical efficacy of sarilumab relative to the control arm in adult patients hospitalized with COVID-19 regardless of disease severity strata.

Phase 3 Cohort 1:

The primary objective of the study is to evaluate the clinical efficacy of sarilumab 400 mg relative to the control arm in adult patients hospitalized with critical COVID-19 receiving mechanical ventilation at baseline

Phase 3 Cohort 2:

The primary objective of the study is to evaluate the clinical efficacy of sarilumab 800 mg relative to the control arm in adult patients hospitalized with COVID-19 receiving mechanical ventilation at baseline

2.2. Secondary Objectives

Phase 2:

The secondary efficacy objectives of the study are to:

1. Evaluate the clinical efficacy of sarilumab compared to the control arm in all disease severity levels and by clinical severity
2. Evaluate the clinical efficacy of sarilumab compared to the control arm by baseline IL-6 level
3. Evaluate changes in the National Early Warning Score 2 (NEWS2)
4. Evaluate the duration of predefined symptoms and signs (if applicable)
5. Evaluate the duration of supplemental oxygen dependency (if applicable)
6. Evaluate the incidence of new mechanical ventilation use during the study
7. Evaluate the duration of new mechanical ventilation use during the study
8. Evaluate need for admission into intensive care unit (ICU)
9. Evaluate duration of hospitalization (days)
10. Evaluate the 28-day mortality rate

Phase 3

The secondary efficacy objectives of the study are to:

Phase 3 Cohort 1:

- Determine whether sarilumab improves respiratory outcomes in patients with critical COVID-19

- Determine whether sarilumab reduces mortality in patients with critical COVID-19
- Determine whether sarilumab shortens hospitalization in patients with critical COVID-19

Phase 3 Cohort 2:

- Determine whether sarilumab improves respiratory outcomes in patients with COVID-19 receiving mechanical ventilation
- Determine whether sarilumab reduces mortality in patients with COVID-19 receiving mechanical ventilation
- Determine whether sarilumab shortens hospitalization in patients with COVID-19 receiving mechanical ventilation

Phase 2 and Phase 3:

Safety

The secondary safety objectives of the study are to evaluate the safety of sarilumab through hospitalization (up to Day 29 if patient is still hospitalized) compared to the control arm as assessed by incidence of:

- Serious adverse events (SAEs)
- Grade 4 neutropenia (absolute neutrophil count [ANC]<500/mm^3)
- Grade 4 neutropenia (ANC<500/mm^3) with concurrent severe or life-threatening bacterial, invasive fungal, or opportunistic infection
- Grade ≥2 infusion-related reactions
- Grade ≥2 hypersensitivity reactions
- Increase in alanine transaminase (ALT) or aspartate aminotransferase (AST) ≥3X upper limit of normal (ULN) (for patients with normal baseline) or >3X ULN AND at least 2-fold increase from baseline value (for patients with abnormal baseline)
- Invasive bacterial or fungal infections of clinical significance with confirmed diagnosis based on the investigator's assessment with appropriate diagnostic workups and consultations

2.3. Exploratory Objectives

Phase 2 and Phase 3:

The exploratory objectives of the study are to:

1. Evaluate the virologic changes in the treatment arms compared to the control arm as assessed by:
    - Percent of patients with SARS-COV-2 detectable in oropharyngeal (OP) or nasopharyngeal (NP) sample

- Quantitative SARS-CoV-2 virus in the OP or NP sample
- Development of SARS-CoV-2 variants in OP or NP sample
- Quantitative SARS-CoV-2 virus in blood

2. To evaluate the cytokine profile and additional biomarkers that may be associated with efficacy and safety associated with sarilumab treatment and anti-viral immunity
3. Evaluate the incidence of new or worsening laboratory-confirmed serious secondary infections in the treatment arms as compared to the control arm
4. To characterize the concentrations of sarilumab and sIL-6R in serum over time

Phase 3

1. To characterize the efficacy of sarilumab in severe, MSOD, and immunocompromised patients using the same primary and secondary efficacy endpoints as in the critical patients (Cohort 1 only)
2. To examine the efficacy of sarilumab in patients by serum IL-6 level, CRP level, and neutrophil-to-lymphocyte ratio
3. To determine whether sarilumab improves vital signs (measured by the NEWS2)

Patients will not be recalled after discharge for any missing exploratory assessments.

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Phase 2: Treatment of patients hospitalized with COVID-19 with sarilumab will result in a greater reduction in serum CRP compared to the control.

Phase 3 Cohort 1: Treatment of patients hospitalized with COVID-19 in the critical stratum on mechanical ventilation at baseline with sarilumab 400 mg will result in a greater proportion of patients who improve their clinical status at Day 22 compared to placebo.

Phase 3 Cohort 2: In patients hospitalized with COVID-19 who are on mechanical ventilation, treatment with sarilumab 800 mg will result in a greater proportion of patients who improve their clinical status at Day 22 as compared to placebo.

3.2. Rationale

3.2.1. Rationale for Study Design

Currently, there are no specific COVID-19 treatments. SARS-CoV-2, the betacoronavirus that causes COVID-19, results in a similar acute lower respiratory disease caused by SARS-CoV that was identified in 2002 and the Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV). Many therapeutic agents have been used to treat patients with SARS-CoV and MERS-CoV, including corticosteroids, type 1 IFN agents, convalescent plasma, ribavirin, lopinavir/ritonovir, proteases, and agents targeting viral entry proteins. However, none have been shown to be efficacious in clinical trials. Therefore, the comparator proposed in this study will be placebo.

Randomization is essential for establishing efficacy of sarilumab compared to placebo. Collection of clinical, virologic, and cytokine data using a standardized timeline will provide valuable information on the clinical course of severe COVID-19 and the impact of sarilumab on clinical recovery from COVID-19.

The study utilizes an adaptive Phase 2/3 design that intends to maximize efficiency of identifying early signs of clinical efficacy and to avoid the use of ineffective therapeutics in critically ill patients with COVID-19. Due to the novel nature of the COVID-19 pandemic, efficacy endpoints are not well established, and the standard of care is expected to evolve over time. The adaptive design allows for the assessment of efficacy endpoints in Phase 2 which are then seamlessly confirmed in the Phase 3 portion of the study, as well as evaluating the benefit-risk of multiple doses of sarilumab. This study is therefore intended to allow for multiple adaptations, including dropping of a sarilumab dose arm, modification of the primary endpoints for Phase 3, and sample size re-estimation for Phase 3.

The study will begin enrollment of all patients, as planned. To maximize safety, the Independent Data Monitoring Committee (IDMC) will perform 3 interim data reviews after approximately 12, 25, and 50 patients have been dosed and have had at least 7 days of follow-up to determine if a treatment arm should be discontinued for safety reasons. These data reviews will include all data, including deaths, from all enrolled study participants. Unblinded Regeneron senior physicians who are not directly involved with the study will review data from these 3 interim data reviews independently of the IDMC. The IDMC will also meet regularly throughout the course of the study to review safety data and make recommendations on study conduct.

3.2.2. Rationale for Study Design Adaptation

Adaptations of the Phase 3 portion of the study are based on interim Phase 2 results of this study (Table 1 and Table 2). Sarilumab 400 and 200 mg IV reduced serum CRP by 79% and 77%, respectively, compared to 21% in the placebo arm in the modified intention-to-treat (mITT) population (primary endpoint). Sarilumab did not appear to improve clinical outcomes in patients with severe disease. In patients with critical disease, there were trends toward a benefit of sarilumab 400 mg compared to placebo in the proportion of patients who died or did not require mechanical ventilation, had clinical improvement according to the 7-point ordinal scale, did not require supplemental oxygen, and were discharged (Table 1). Additional analyses did not suggest a benefit in patients in the MSOD group. Based on the IDMC recommendation, as of 27 Apr 2020, the severe and MSOD groups will no longer enroll or receive study drug. The IDMC also recommended that the sarilumab 200 mg arm be discontinued due to lack of benefit.

Table 1: Interim Phase 2 Results

	Placebo	**Sarilumab 200 mg**	**Sarilumab 400 mg**
PRIMARY ENDPOINT (REDUCTION IN C-REACTIVE PROTEIN)			
	(n=77)	(n=136)	(n=145)
% change from baseline in CRP (Patients with high baseline IL-6, where data were available)	-21%	-77%	-79%
EXPLORATORY CLINICAL ENDPOINTS IN THE "CRITICAL" GROUP			
	(n=44)	(n=94)	(n=88)
Died or "On a ventilator"	24 (55%)	43 (46%)	28 (32%)
Died	12 (27%)	34 (36%)	20 (23%)
On a ventilator	12 (27%)	9 (10%)	8 (9%)
2-point clinical improvement on a 7-point scale[1]	18 (41%)	48 (51%)	52 (59%)
Off supplemental oxygen	18 (41%)	40 (43%)	51 (58%)
Discharged	18 (41%)	37 (39%)	47 (53%)

[1] See Section 4.1.2.1 for details of the of the 7-point ordinal scale.
Note: This table is based on the 22 Apr 2020 snapshot

[redacted]

Based on these findings, the following adaptations were made to the Phase 3 portion of this study implemented in Amendment 6, however, as of 06 Jun 2020, Cohort 3 will no longer enroll patients (Table 3).

Table 3: Summary of Phase 3 Adaptations

Study Component	Adaptation	Rationale
Phase 3 endpoint	At least a1-point improvement from baseline in clinical status on the 7-point ordinal scale	Phase 2 results
Phase 3 primary analysis population	• Cohort 1: Critical patients receiving mechanical ventilation at baseline • Cohort 2: Patients on mechanical ventilation at baseline • Cohort 3: Patients on high-intensity oxygen therapy without mechanical ventilation at baseline*	Phase 2 results
Dose regimens	• Cohort 1: Primary comparison will be between sarilumab 400 mg and placebo • Cohort 2: Sarilumab 800 mg and placebo • Cohort 3: Sarilumab 800 mg and placebo	Section 3.2.4
Sample size for the Primary Analysis Population in Cohort 1	~170	Section 11.2
Sample Size for Cohort 2	225	Section 11.2
Sample Size for Cohort 3	225	Section 11.2

*High-intensity oxygen therapy is defined as the use of non-rebreather mask with an oxygen flow rate of at least 10 L/min; use of a high flow device with at least 50% FiO_2, or use of non-invasive ventilation (eg, BiPAP™) or CPAP to treat hypoxemia

3.2.3. Rationale for Phase 2 and Phase 3 Cohort 1 Dose Selection

COVID-19 infection can be associated with a degree of pulmonary cytokine release and IL-6 has been shown to be a major contributor to the development of fever and hypoxemia. In the current study, both 200 and 400-mg doses of sarilumab (Kevzara®), an anti-IL-6R mAb, are to be administered by a 1-hour IV infusion. Sarilumab is currently approved for treatment in patients with RA at 200 mg Q2W (SC) [with down dosing to 150 mg Q2W (SC) for certain laboratory changes]. Sarilumab is analogous to tocilizumab and there is reported evidence that IV treatment with 400 mg of tocilizumab (Actemra®), an anti-IL-6R monoclonal antibody (mAb), provides a clinically meaningful improvement in clinical symptoms that are thought to be mediated by cytokine release in patients with severe or critical COVID-19 infection.

There is limited experience in the use of sarilumab by IV infusion and no experience at the doses being studied in this protocol. Sarilumab was initially administered IV in a single dose, dose escalation, safety, pharmacodynamic (PD), and PK study of patients with RA (Study TDU10808/6R88-RA-0703), which was terminated prior to completion due to the occurrence of Grade 4 neutropenia (neutrophil count: 400 per mm^3) in 1 of 2 patients in the 2 mg/kg cohort and the intention to develop the drug for SC dosing in RA patients. Thus, following this first-in-human study, the SC route of administration was used in all subsequent studies. The appropriateness for the use of sarilumab by the IV route in this setting is supported by the high degree of similarity between sarilumab and tocilizumab regarding the clinically observed PK, PD (to include safety and PD endpoints), many of which were assessed in randomized trials. These similarities extend to other clinically observed pharmacology properties, in vitro properties, as well as the physiochemical properties.

The PK/PD strategy in dose selection for a mAb directed against IL-6R, whether it be tocilizumab or sarilumab, is to maintain local and systemic saturation of the target-mediated pathway over an identified duration and thereby ensuring saturation or near-saturation of target binding.

Given the high binding affinity and binding specificity of both tocilizumab and sarilumab, once systemic concentrations of the mAb are sufficient to saturate the target-mediated pathway the pharmacological response in terms of safety, PD, or efficacy associated with further increases in concentration is only increased with respect to the duration of action and, possibly, greater penetration into difficult to reach tissues.

The PK, PD, and safety of sarilumab and tocilizumab were compared in a number of randomized trials. In a single-dose, open-label randomized trial the PK and PD were assessed in patients with RA randomized 1:1:1:1 to either 150 mg or 200 mg (SC) of sarilumab, or 4 mg/kg or 8 mg/kg (IV) of tocilizumab (Study 1309). Also, in a single dose PK/PD study, 150 mg of sarilumab (SC) was compared to 162 mg of tocilizumab (SC) in Japanese patients with RA randomized 1:1 (Study PDY1419) (Huang, 2020). In the multiple-dose double-blind study ASCERTAIN (NCT01768572) the safety and tolerability of sarilumab and tocilizumab were compared in approximately 200 patients with RA randomized 1:1:2 to receive 150 mg Q2W or 200 mg Q2W of sarilumab (SC) or 4 mg/kg Q4W of tocilizumab (IV) for 24 weeks (Emery, 2019).

In the single-dose PK/PD studies, consistent with saturation of the target mediated pathway for sarilumab and tocilizumab, all dose levels regardless of the route of administration demonstrated similar maximal effect in suppression in CRP and ANC lowering. Notably, higher dose levels and the associated higher concentrations, beyond that need to achieve saturation, resulted in a longer duration of the maximal PD response, but did not result in a deeper response. Consistent with the longer duration of saturation following IV administration of tocilizumab, but consistent with the similar PK/PD relationship for sarilumab and tocilizumab, sIL-6R increased in a dose and concentration related manner. Subcutaneous single doses of sarilumab (150 mg) or tocilizumab (162 mg) resulted in similar concentration time profiles and yielded nearly identical PD response in CRP and ANC, as well as changes in sIL-6R and IL-6 over time. In the ASCERTAIN study, similar PD effects were observed with ANC lowering. Additionally, no clinically meaningful differences in treatment-emergent adverse events were observed between sarilumab and tocilizumab. Laboratory changes with sarilumab were within the same range as those with tocilizumab (Emery, 2019).

Consistency in PD effects between tocilizumab and sarilumab are also seen in cross-study comparison of the radiographic studies performed with the 2 products. According to their labeling, the 162 mg Q2W dose of tocilizumab reduced radiographic progression based on the modified total Sharpe score (mTSS) by 50% at 24 weeks; the 150 mg Q2W dose of sarilumab reduced radiographic progression based on the modified total Sharpe score (mTSS) by 68% at 52 weeks.

The best biomarker for PD effect of IL-6R inhibition is decrease in ANC; ANC decreases and remains depressed during the period of receptor blockade and increases after systemic levels of drug fall below those necessary to saturate. Recent publications suggests this lowering in ANC may be a result of neutrophil margination and not a result of clearance of the neutrophils, while the neutrophils maintain their functionality (Lok, 2017). Thus, while a time-dependent increased incidence of infection, including serious infection, due to IL-6 receptor blockade has been noted, this was not related to the decreases in ANC observed with sarilumab (Kevzara [package insert], 2017). It has also been reported that the level of a patient's inflammatory state may result in increased clearance of anti-IL-6R mAb (Le, 2018). Accordingly, patients with CRS may need higher doses of anti-IL-6R antagonist than patients with active RA. Consistent with this, the PD effect of sarilumab as measured by reduction in ANC in RA patients with active inflammation was less pronounced and shorter than in otherwise controlled RA patients. The need to ensure saturation systemically and locally in tissue, together with a shorter time to C_{max} support the use of IV administration over that of SC and support the study of higher doses of sarilumab than approved for the treatment of RA in conditions of cytokine release resulting from COVID-19 infection.

Data from the dose ranging portion of Study EFC11072 (MOBILITY Part A) illustrates the relationship between trough concentrations of sarilumab obtained from 100 mg Q2W, 150 mg Q2W, 200 mg Q2W, and 150 mg QW administration and ANC). These results demonstrate a plateau of ANC decline despite a greater than 2.5-fold increase in trough concentrations with weekly administration. (100 mg QW vs 150 mg QW). This PD effect of IL-6R inhibition on neutrophil suppression is clearly on the plateau of the dose-response curve indicating that higher exposures would not be predicted to yield a further increase in ANC suppression. Furthermore, this expected PD effect on ANC number has not been correlated to an increased risk of infection for either the sarilumab or tocilizumab, nor does it interfere with the phagocytosis, rate of apoptosis, oxidative burst, or other known neutrophil capacity (Lok, 2017). Therefore, the

margination effect of IL-6R inhibition has no known clinical relevance for patients without active bacterial infection.

To date there is a plethora of experience with high doses of tocilizumab; notably it is also approved at dose up to 8 mg/kg IV and has been used in clinical practice at these levels for over a decade in the treatment of RA and more recently higher IV doses of tocilizumab have been used in cytokine release syndrome associated with chimeric antigen receptor T-cell (CART) therapy. Regeneron developed sarilumab for subcutaneous administration and performed a head-to-head study comparing the 150 and 200 mg SC doses of sarilumab with IV tocilizumab at 4 and 8 mg/kg IV (6R88-RA-1309). As expected, the serum concentrations of tocilizumab are substantially higher than those of sarilumab. Yet, despite the higher concentrations of tocilizumab, the magnitude of the PD effects as measured by reduction in ANC and CRP are the same at early timepoints (ie, when drug concentrations of both drugs are at or above those needed to achieve saturation). The only difference between these supra-saturating concentrations of tocilizumab and the lower concentrations of sarilumab is in duration of peak PD effect. It can also be observed with the loss of saturating concentrations there is a temporally rapid decline in these PD effects. These data provide strong evidence that higher doses and higher serum concentrations of either of these anti-IL-6R antibodies beyond those required for saturation do not provide any greater PD effect nor any greater safety concern and these higher doses only serve to extend the duration of the PD effects.

Based on available data, on a per mg basis, tocilizumab and sarilumab behave comparably *in vivo* with respect to potency, PK, PD, efficacy, and safety. Thus, the safety of sarilumab at doses as high as 400 mg IV can be extrapolated from the experience with similar and even higher doses of tocilizumab. Nonetheless, this needs to be verified with actual clinical data. In order to test both lower and higher doses of sarilumab to treat severe COVID-19 pneumonia, 2 doses will be studied: 200 mg IV and 400 mg IV. In the setting of a pandemic where drug supply may become limiting, identifying the minimum dose necessary could increase the supply.

Tocilizumab has been approved for use in patients with CRS as a consequence of CAR-T therapy. During the FDA review of the sBLA for this indication, a comparison of the observed C_{max} in these patients with those for patients with sJIA, indicated that C_{max} in patients with CRS was 40% lower than for patients with sJIA. Pharmacokinetic (PK) modeling was performed by FDA, where clearance (CL) was estimated to be 0.50 L/day (RSE = 10.8%) and central volume of distribution (V_C) was estimated to be 1.8 L (RSE = 11.2%) in patients with CRS. These estimates are higher than CL of 0.17 L/day and V_C of 0.94 L in similar aged patients with sJIA. This analysis indicates that the half-life of the decline in tocilizumab concentrations following IV doses of 8 mg/kg in the patients with CRS (>30kg) is 3 to 4 days.

Assuming a similar PK profile for sarilumab in COVID patients to the tocilizumab data in patients with CRS, a repeat dose of sarilumab at 24 hours should produce approximately the same C_{max} as originally predicted based on the PK in active RA patients. Moreover, assuming the same clearance for sarilumab as observed for tocilizumab, sarilumab levels could fall by 75% within 1 week, which may lead to levels which do not completely block signaling through the IL-6R. Given the similarities in the PK characteristics of sarilumab and tocilizumab, these data suggest that the proposed dosing interval for sarilumab is appropriate.

3.2.4. Rationale for Phase 3 Cohorts 2 and 3 Dose Selection

As discussed above, preliminary, open-label data from the use of tocilizumab, initially at a 400 mg IV dose (Xu, 2020) supported assessment of IL-6R inhibition in patients with severe or critical COVID-19 patients. Subsequent studies with tocilizumab, however, are being conducted at a higher dose: 8 mg/kg up to 800 mg initial dose, with repeat dosing allowed based on clinical criteria. In these studies, benefit has been described in COVID-19 both in ventilated patients and in patients not on a ventilator.

Initial results of the open-label, randomized, controlled Phase 2 study, CORIMUNO-TOCI support the administration of an 8 mg/kg IV dose of tocilizumab. In this study, 129 patients hospitalized for COVID-19 moderate or severe pneumonia and not requiring intensive care upon admission were randomized to standard of care + tocilizumab (8 mg/kg up to a 800 mg maximal dose on Day 1 and if no response, with no decrease of oxygen requirement, a second administration at Day 3; n=65) or to SOC alone (n=64). Data showed that a significantly lower proportion of patients reached ventilation or death at Day 14 in the tocilizumab + SOC arm vs. SOC alone, however, details have not been disclosed (APHP, 2020).

In an interim analysis of the Phase 2 portion of 6R88-COV-2040, based on the prespecified analysis of the combined severe and critical strata, there was no evidence of treatment effect with either the 200- or 400-mg dose. In other prespecified analyses, trends in the number of patients in the critical stratum who achieved a 2-point improvement in clinical status on the 7-point ordinal scale suggested that a single 400 mg dose achieved greater treatment benefit than a single 200-mg dose. [redacted]

These results with sarilumab are not what had been anticipated. Either the results of the previous uncontrolled or small controlled studies with tocilizumab were misleading OR there is a systematic difference in study design between the tocilizumab and sarilumab studies, the most prominent difference being dose. The maximum dose of sarilumab in the Phase 2 and Phase 3 Cohort 1 portion of the current study was 400 mg with repeat dosing allowed based on clinical criteria. With obesity being a risk factor for severe or critical COVID-19, it is not surprising that the mean baseline weight in the 6R88-COV-2040 study, conducted in the US, is ~91 kg. Thus, patients are being dosed at approximately 4.4 mg/kg, significantly less than the dose of tocilizumab in recent studies. And, while sarilumab treatment in the current study readily lowered CRP levels, there has been almost no effect on neutrophil counts, another established pharmacodynamic marker of IL-6R inhibition. Indeed, only 2 patients in the Phase 2 portion of the study had Grade 4 neutropenia.

IL-6 concentration data are consistent with the notion that higher doses of sarilumab are required in COVID-19 than were being administered. Mean baseline IL-6 levels across all treatment arm and disease severity in the Phase 2 portion of the current study was 356 pg/mL and in the critical strata was 373 pg/mL which far exceeds the IL-6 levels observed in the RA studies. For example, in Study 6R88-RA-1309, which evaluated single dose administration of sarilumab SC (150 and 200 mg) and tocilizumab IV (4 mg/kg and 8 mg/kg) in RA patients, the mean baseline IL-6 levels ranged from ~7 to 22 pg/mL.

Taken together, the relatively modest efficacy signal, the absence of trends in the safety data to suggest harm, and the pharmacodynamic data all suggest that effective blockade of IL-6R in

COVID-19 patients may require a higher dose of sarilumab than has been studied. In the absence of a safety signal to suggest otherwise, the dose was increased to sarilumab 800 mg to maximize IL-6R inhibition and determine treatment effects in Phase 3 Cohorts 2 and 3. Therefore, in Cohorts 2 and 3 of Phase 3, an 800-mg dose of sarilumab, with the allowance for repeat dosing based on clinical criteria will be studied to determine if this higher dose results in more robust clinical benefit than has been seen. Risk mitigation strategies, already in place for the protocol were followed including both expedited reporting of adverse events of special interest (AESIs; including Grade 4 neutropenia with or without concurrent invasive infections), and active engagement with the IDMC to provide adequate assurance for patient safety.

This increase in dose was supported by the PK data. In an interim analysis of the preliminary Phase 2 data, following IV administration of a single sarilumab dose, mean (SD) C_{max} was 49.2 (±16.8) mg/L (n=146) for the 200-mg dose and 105 (±46.6) mg/L (n=140) for the 400-mg dose. Based on the central volume for a typical monoclonal antibody the observed C_{max} values are 25% to 30% lower than expected. The subsequent decline in concentrations suggests an initial half-life of sarilumab in serum of about 3 days, indicating that repeat dosing on a weekly interval was not expected to lead to significant accumulation, even at the 800-mg dose. These observations appear to be consistent with the findings for tocilizumab in patients with CRS as a consequence of CAR-T therapy described in Section 3.2.3.

The anticipated mean sarilumab C_{max} following a single 800-mg dose, based on the preliminary interim PK analysis as well as that expected for a typical monoclonal antibody, is about 200 to 250 mg/L. The proposed dosing regimen is supported by the safety and efficacy data observed at 400 mg in patients with COVID-19 and the toxicology data described in Investigator Brochure, where the average C_{trough} at the NOAEL in the monkey following IV dosing ranged from 504 mg/L (40 mg/kg/week in a 5-week study) to 1780 mg/L (50 mg/kg/week in a 26-week study).

3.3. Risk-Benefit for REGN88 (sarilumab, Kevzara®)

Sarilumab is currently approved at 200 mg Q2W (SC) for the treatment of RA in multiple countries. The risks and adverse reactions are described in the approved prescribing information for sarilumab.

There are currently no known published reports of IL-6R antagonists for infectious sepsis or pneumonia. Because IL-6 contributes to host defense against bacterial and viral pathogens, there is a concern that IL-6 inhibition may exacerbate infections thus delaying recovery from sepsis. Patients chronically treated with sarilumab are at increased risk for developing serious and opportunistic infections. Most developed infections while taking other immunosuppressants or disease modifying anti-rheumatic arthritis (DMARDs) with sarilumab. Opportunistic infections, including de novo cases of tuberculosis, disseminated candidiasis and pneumocystis have been infrequently reported with sarilumab. The most frequently reported opportunistic infections were cases of non-disseminated herpes zoster with an incidence similar in sarilumab+DMARD and placebo+DMARD groups. Other serious infections (eg, histoplasmosis, cryptococcus, aspergillus) have not been reported in sarilumab clinical studies but have been reported in patients receiving other immunosuppressive agents. In this study, patients are only receiving corticosteroids if indicated for an acute medical indication, and close monitoring in the hospital or ICU setting to diagnose and treat infections. The risk to subjects is thus minimized.

While decreases in ANC is seen in patients treated with sarilumab, they are reported not to be associated with increased incidence of infection or serious infections in patients with RA (Fleischmann, 2017). A clinical study of neutrophil trafficking suggested that this decrease is due to an redistribution into the marginating pool, rather than a net decrease in the neutrophil population (Lok, 2017).

Treatment with sarilumab in clinical studies has also been associated with a higher incidence of transaminase elevations. These elevations were transient and did not result in any clinically evident hepatic injury in clinical studies. Liver function test monitoring will be performed during the study. In addition, gastrointestinal perforation has been reported in clinical studies, including in patients receiving corticosteroids. Patients will be closely monitoring in the hospital or ICU setting with daily clinically indicated evaluations by health care professionals in detect this event if it occurs.

In the Phase 2 safety population of Study 6R88-COV-2040 (n=457), sarilumab at doses of 200 mg and 400 mg IV were not associated with new safety findings. Transaminase levels were higher in sarilumab patients compared to placebo. Grade 4 neutropenia was rare and clinically significant bacterial and fungal infections were similar in sarilumab-treated groups as compared to placebo. Serious adverse events were generally representative of the underlying patient population.

Additional information on possible risks and adverse drug reactions is provided in the IB.

Sarilumab may or may not improve clinical outcomes of a subject with COVID-19 who is enrolled in this trial. During the current COVID-19 outbreak, tocilizumab (another IL-6R antagonist) has been used in 21 patients with severe COVID-19 infection and described in a retrospective study (Wu, 2020). Data from these patients suggest blockade of the IL-6R may lead to a clinically meaningful improvement in symptoms that are thought to be mediated by cytokine release. Additionally, tocilizumab is approved for use in CRS associated with CAR-T cell therapies (8 or 12 mg/kg, based on weight). Several aspects of the CRS mirror those of severe COVID-19, including fever, respiratory insufficiency, and elevated markers of systemic inflammation, such as CRP.

In critical patients in the Phase 2 portion of the study, sarilumab 400 mg IV was associated with a numerically lower proportion of patients who had died or required mechanical ventilation at Day 21 compared to placebo (32% in sarilumab 400 mg vs. 55% in placebo). There were also numerical differences favoring sarilumab 400 mg IV compared to placebo in the proportion of patients who experienced clinical improvement and who were discharged by Day 21 (Table 1). Among patients receiving mechanical ventilation at baseline, sarilumab 400 mg was associated with a greater proportion of patients who were alive without mechanical ventilation (57% in sarilumab 400 mg vs. 17% in placebo) and a greater proportion of patients who recovered (47% in sarilumab 400 mg vs. 17% in placebo) compared to placebo. [redacted]

Based on review of the Phase 2 data, the IDMC recommended, and the Sponsor agreed, that the benefit/risk assessment supported continued enrollment of only critical COVID-19 patients in Phase 3. These changes were implemented in Protocol Amendment 6.

Based on review of the Phase 3 Cohort 1 data, the IDMC noted a safety concern which led them to recommend no further enrollment or dosing of patients who were not on mechanical ventilation at baseline. The Sponsor's review of the data in patients not on mechanical ventilation at baseline

showed no benefit among those treated with sarilumab compared to placebo, and there were more deaths among the sarilumab-treated patients. The imbalances in mortality observed in this subset of Phase 3 Cohort 1 had not been observed in the smaller Phase 2 400 mg critical patient dataset. Although there had been a small trend in favor of sarilumab 400 mg in the Phase 2 data, no meaningful trends either for efficacy or harm are seen in the combined Phase 2/Phase 3 Cohort 1 data in this subset of patients with critical COVID-19 not on mechanical ventilation. Considering all these data, while it cannot be concluded that there is harm associated with sarilumab treatment in critical COVID-19 patients who were not receiving mechanical ventilation at randomization, there is also no evidence for benefit. Thus, the Sponsor agreed with the IDMC that the benefit/risk assessment is not favorable and continued dosing of sarilumab in this study is not warranted in patients with critical COVID-19 who are not receiving mechanical ventilation. Enrollment will continue in Phase 3 Cohort 2 as the IDMC did not note any safety concerns that precludes enrollment into this cohort. Changes to the Phase 3 planned enrollment are implemented with this protocol amendment.

A risk-benefit statement with respect to the overall development program is provided in the IB.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

Note that for the primary and secondary endpoints, patients will not be required to return to the hospital once discharged. A follow-up phone call will occur on Days 29 and/or 60, depending on when the patient is discharged. All patients will be contacted for an end of study (EOS) follow-up at Day 60.

4.1.1. Primary Endpoints

Phase 2:

Percent change from baseline in CRP levels at Day 4 in patients with serum IL-6 level greater than the upper limit of normal.

Phase 3 Cohort 1:

Proportion of patients with at least a 1-point improvement in clinical status from baseline to Day 22 using the 7-point ordinal scale in patients with critical COVID-19 receiving mechanical ventilation at baseline

Phase 3 Cohort 2:

Proportion of patients with at least 1-point improvement in clinical status from baseline to Day 22 using the 7-point ordinal scale in patients with COVID-19 receiving mechanical ventilation at baseline

Separate analyses of Cohorts 1 and 2 are planned.

4.1.2. Secondary Endpoints

The 7-point ordinal scale will be assessed as a secondary endpoint in Phase 2 and will be used for both Primary and Secondary endpoints in Phase 3. The ordinal scale is an assessment of the clinical status. The scale is as follows:

- Death;
- Hospitalized, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
- Hospitalized, requiring non-invasive ventilation or high flow oxygen devices;
- Hospitalized, requiring supplemental oxygen;
- Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)
- Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care
- Not hospitalized

4.1.2.1. Phase 2 Secondary Endpoints:

Efficacy

Phase 2 Key Secondary Endpoints

1. Time to improvement (2 points) in clinical status assessment from baseline on the 7-point ordinal scale in severe or critical patients with serum IL-6 levels greater than the upper limit of normal
2. Time to improvement (2 points) in clinical status assessment from baseline on the 7-point ordinal scale reporting in severe or critical patients with all IL-6 levels

Other Phase 2 Secondary Endpoints:

1. Time to resolution of fever for at least 48 hours without antipyretics or until discharge, whichever is sooner, in patients with documented fever ≥38°C (oral), ≥38.4°C (rectal or tympanic), or ≥37.6°C (temporal or axillary) at Baseline

   (*Resolution of fever is defined as postbaseline body temperature <37.2°C (oral), or <37.6°C (rectal or tympanic) or <36.8°C (temporal or axillary*).
2. Time to resolution of fever (defined as above) for at least 48 hours without antipyretics or until discharge, whichever is sooner, in patients defined as above, by clinical severity.
3. Time to resolution of fever (defined as above) for at least 48 hours without antipyretics or until discharge, whichever is sooner, in patients defined as above, by baseline IL-6 levels.
4. Time to improvement in oxygenation (increase in SpO_2/FiO2 of 50 or greater compared to the nadir SpO_2/FiO2) for at least 48 hours or until discharge, whichever is sooner.
5. Time to improvement in oxygenation (increase in SpO2/FiO2 of 50 or greater compared to the nadir SpO2/FiO2) for at least 48 hours, or until discharge, whichever is sooner, by clinical severity
6. Time to improvement in oxygenation (increase in SpO2/FiO2 of 50 or greater compared to the nadir SpO2/FiO2) for at least 48 hours, or until discharge, whichever is sooner, by baseline IL-6 level
7. Time to resolution of fever (as defined above) and improvement in oxygenation (as defined above)
8. Mean change in the 7-point ordinal scale from baseline to Days 3, 5, 8, 11, 15, and 29 (or until discharge)
9. Percentage of patients in each clinical status category using the 7-point ordinal scale at Days 3, 5, 8, 11, 15, and 29
10. Time to discharge or to a NEWS2 of ≤2 and maintained for 24 hours, whichever occurs first
11. Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS2
12. Days with fever (≥38°C °C [oral], ≥38.4°C [rectal or tympanic], or ≥37.6°C [temporal or axillary])
13. Proportion of patients alive, off oxygen at Day 29

14. Days of resting respiratory rate >24 breaths/min (recorded at least once each day)
15. Days of hypoxemia (SpO_2 ≤93% on room air, or requiring supplemental oxygen, or mechanical ventilatory support)
16. Days of supplemental oxygen use
17. Time to saturation ≥94% on room air
18. Ventilator free days in the first 28 days (to Day 29)
19. Initiation of mechanical ventilation, non-invasive ventilation, or use of high flow nasal cannula (for those not requiring these interventions at baseline)
20. Admission into an ICU (among those not in an ICU at baseline)
21. Days of hospitalization among survivors
22. All-cause mortality

4.1.2.2. Phase 3 Secondary Endpoints

The Phase 3 secondary endpoints for Cohorts 1 and 2 are outlined in Table 4.

Table 4: Phase 3 Efficacy Endpoints

	Cohort 1: sarilumab 400 mg vs. placebo			Cohort 2: sarilumab 800 mg vs. placebo (receiving mechanical ventilation at baseline)
	Critical ITT	**Critical receiving mechanical ventilation at baseline**	**Critical not receiving mechanical ventilation at baseline[1]**	
Proportion of patients with at least 1-point improvement in clinical status from baseline to Day 22 using the 7-point ordinal scale	Key Secondary	Primary	Descriptive	Primary
Proportion of patients who recover (discharged, or alive without supplemental oxygen use or at pre-COVID oxygen use) by Day 22	Secondary	Key Secondary	Descriptive	Key Secondary
Proportion of patients who die through Day 29	Key Secondary	Key Secondary	Descriptive	Key Secondary
Proportion of patients alive not receiving mechanical ventilation or ECMO at Day 22	Secondary	Secondary	Descriptive	Secondary
Proportion of patients with a 2-point improvement in clinical status on the 7-point ordinal scale from baseline to Day 22	Secondary	Secondary	Descriptive	Secondary
Time to at least 1-point improvement in clinical status assessment from baseline on the 7-point ordinal scale	Secondary	Secondary	Descriptive	Secondary
Time to at least 2-point improvement in clinical status assessment from baseline on the 7-point ordinal scale	Secondary	Secondary	Descriptive	Secondary
Proportion of patients receiving mechanical ventilation or ECMO at Day 22	Secondary	Secondary	Descriptive	Secondary
Proportion of patients discharged and alive at Day 22	Secondary	Secondary	Descriptive	Secondary
Time to recovery (discharged, or alive without supplemental oxygen use or at pre-COVID oxygen use)	Secondary	Secondary	Descriptive	Secondary
Proportion of patients who die through Day 60	Secondary	Secondary	Descriptive	Secondary
Time to death (all-cause mortality)	Secondary	Secondary	Descriptive	Secondary
Number of ventilator free days between baseline and Day 8, 15, 22, and 29	Secondary	Secondary	Descriptive	Secondary
Number of days of hospitalization among survivors up to Day 8, 15, 22, and 29	Secondary	Secondary	Descriptive	Secondary

[1] The main approach in Cohort 1 to the analysis of patients "Critical not receiving mechanical ventilation at baseline" will be through an analysis of a subset of the overall ITT population to assess if an effect observed in the ITT population is observed both in the subset of patients on mechanical ventilation and not on mechanical ventilation at baseline.

4.1.2.3. Safety Endpoints

The secondary safety endpoints for Phase 2 and 3 are:

1. Proportion of patients with serious adverse events
2. Proportion of patients with Grade 4 neutropenia (ANC <500/mm3)
3. Proportion of patients with severe or life-threatening bacterial, invasive fungal, or opportunistic infection
4. Proportion of patients with severe or life-threatening bacterial, invasive fungal, or opportunistic infection in patients with Grade 4 neutropenia (ANC <500/mm^3)
5. Proportion of patients with hypersensitivity reactions
6. Proportion of patients with infusion reactions
7. Proportion of patients with gastrointestinal perforation
8. White cell count, hemoglobin, platelets, creatinine, total bilirubin, ALT, AST, on Days 1, 3, 5, 8, 11, 15, and 29 (if still hospitalized)

4.1.3. Exploratory Endpoints

Phase 2 and 3:

The exploratory endpoints are:

1. Qualitative and quantitative PCR for SARS-CoV-2 in OP/NP swab on Days 1, 4, and 29
2. Time to 2 consecutive negative OP/NP swab PCR results for SARS-CoV-2
3. Qualitative and quantitative PCR for SARS-CoV-2 in blood on Days 1, 4, and 29
4. Change from baseline in circulating cytokines on Days 4, 7, and 29
5. Change from baseline in serum CRP levels
6. Concentrations of sarilumab and sIL-6R in serum

Phase 3 only:

1. Efficacy endpoints specified in Table 4 will be used to characterize the efficacy of sarilumab 200 mg in all disease severity strata (Cohort 1 only)
2. Efficacy endpoints specified in Table 4 will be used to characterize the efficacy of sarilumab 400 mg in severe, MSOD, and immunocompromised patients (Cohort 1 only)
3. Subgroup analysis of proportion of patients with at least 1-point improvement in clinical status from baseline to Day 22 in patients with a baseline IL-6 level ≥230 pg/mL and <230 pg/mL, by CRP tertile, and by neutrophil-to-lymphocyte ratio tertile
4. Subgroup analysis of proportion of patients alive and not receiving ventilation at Day 21 in patients with COVID-19 with baseline IL-6 ≥230 pg/mL compared to those with IL-6 <230 pg/mL

5. Subgroup analysis of proportion of patients who recover (discharged, or alive without supplemental oxygen use or at pre-COVID oxygen use) by Day 22 in patients with a baseline IL-6 level ≥230 pg/mL and <230 pg/mL, by CRP tertile, and by neutrophil-to-lymphocyte ratio tertile
6. Subgroup analysis of proportion of patients who die through Day 29 in patients with a baseline IL-6 level ≥230 pg/mL and <230 pg/mL, by CRP tertile, and by neutrophil-to-lymphocyte ratio tertile
7. Subgroup analysis of proportion of patients who die through Day 60 in patients with a baseline IL-6 level ≥230 pg/mL and <230 pg/mL, by CRP tertile, and by neutrophil-to-lymphocyte ratio tertile
8. Subgroup analysis of proportion of patients alive not receiving mechanical ventilation or ECMO at Day 22 in patients with a baseline IL-6 level ≥230 pg/mL and <230 pg/mL, by CRP tertile, and by neutrophil-to-lymphocyte ratio tertile
9. Subgroup analysis of proportion of patients with a 2-point improvement in clinical status on the 7-point ordinal scale from baseline to Day 22 in patients with a baseline IL-6 level ≥230 pg/mL and <230 pg/mL, by CRP tertile, and by neutrophil-to-lymphocyte ratio tertile
10. Subgroup analysis of proportion of patients receiving mechanical ventilation or ECMO at Day 22 in patients with a baseline IL-6 level ≥230 pg/mL and <230 pg/mL, by CRP tertile, and by neutrophil-to-lymphocyte ratio tertile
11. Subgroup analysis of proportion of patients discharged and alive at Day 22 in patients with a baseline IL-6 level ≥230 pg/mL and <230 pg/mL, by CRP tertile, and by neutrophil-to-lymphocyte ratio tertile
12. Time to discharge or to a NEWS2 of ≤2 and maintained for 24 hours, whichever occurs first

Patients will not be recalled after discharge for any missing exploratory assessments.

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc), disease characteristics, medical history, and medication history for each patient.

The site investigator will assess the patient for a history of chronic hypercapnic respiratory failure (eg, due to chronic obstructive pulmonary disease) at the screening visit. Chronic hypercapnic respiratory failure is defined as the presence of both of the following criteria:

1. Documented current or historical PaCO2 >45 mm Hg (measured from arterial blood gas analysis), and
2. A clinician has documented a history of chronic hypercapnic respiratory failure in the medical record (Note that there are many ways to document this: chronic hypercapnic respiratory failure, CO2 retainer, chronic hypercapnia, chronic alveolar hypoventilation, etc).

5.2. Efficacy Variables

The efficacy variables include serum CRP, body temperature, gas exchange/oxygen requirement, requirement for ventilation support, ICU admissions, days of hospitalization, 7-point ordinal scale score (to assess clinical status), and NEWS2 specified in the study endpoints (Section 4.1.1), survival/mortality status.

5.3. Safety Variables

Safety variables include incidence of AESIs, SAEs, and laboratory safety test results (white cell count including ANC, hemoglobin, platelets, creatinine, total bilirubin, ALT, AST).

5.4. Pharmacokinetic Variables

The PK variable is the concentration of sarilumab and sIL-6R in serum at each time point specified in Table 5.

5.5. Pharmacodynamic and Other Biomarker Variables

Exploratory endpoint variables include measurement of SARS-CoV-2 in OP or NP swabs over time using RT-PCR. Qualitative (positive or negative) or relative quantitation of viral copies may be evaluated. Pharmacodynamic variables may include the time to reach a negative OP or NP RT-PCR result.

Additional biomarker testing may include, but not be limited to, evaluation of inflammatory cytokines in serum, and ANC.

Pharmacodynamic variables may include the time to nadir (or peak), mean and median change from baseline, mean and median percent change from baseline, and area under the curve (AUC) of mean change, median for IL-6 and ANC.

These results may be reported outside the clinical study report (CSR).

6. STUDY DESIGN

6.1. Study Description and Duration

This study is an adaptive Phase 2/3, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of sarilumab in hospitalized adults with severe or critical COVID-19. As part of the Phase 3 adaptation plan, the Phase 3 portion of the study will include 3 cohorts. In Phase 2 and in Cohort 1 of the Phase 3 portion of the study, patients will be randomized in a 2:2:1 allocation ratio to sarilumab 400 mg IV, sarilumab 200 mg IV, or placebo up to 26 Apr 2020. As of 27 Apr 2020 (as per recommendation of the IDMC), patients in Cohort 1 of the Phase 3 portion of the study will be randomized to sarilumab 400 mg or placebo only in the critical stratum in a 2:1 manner. Enrollment into Cohort 1 closed when approximately 170 patients in the critical stratum receiving mechanical ventilation at baseline who were randomized to receive either sarilumab 400 mg or placebo were enrolled. Cohorts 2 and 3 began enrolling patients in parallel when Cohort 1 enrollment completed. In Cohort 2, patients being treated with mechanical ventilation at baseline will be randomized 1:1 to receive sarilumab 800 mg IV or placebo., In Cohort 3, patients receiving high-intensity oxygen therapy without mechanical ventilation were randomized 1:1 to receive sarilumab 800 mg IV or placebo. As of 06 Jun 2020, per recommendation of the IDMC, new patients will no longer be enrolled into Cohort 3. Cohort 2 will continue to enroll. All patients will continue to be monitored and complete all assessments per protocol. The study will be conducted in the United States in up to 150 sites. The Sponsor may close enrollment into one or more severity categories, strata, or dose arms at any time to ensure adequate numbers of patients are enrolled into other categories or for other reasons related to safety, efficacy, futility, or new external information.

Randomization

For Phase 2 and Phase 3 Cohort 1, randomization will be stratified by:

- Severity of illness at enrollment
  - Severe disease
  - Critical disease
  - Multi-system organ dysfunction
  - Immunocompromised
- Systemic corticosteroids (Yes/No)

The severity categories are:

1. **Severe disease**
   - Requires supplemental oxygen administration by nasal cannula, simple face mask, or other similar oxygen delivery device
2. **Critical disease:**
   - Requires supplemental oxygen requiring delivered by non-rebreather mask or high-flow nasal cannula, OR

- Use of invasive or non-invasive ventilation, OR
- Requiring treatment in an ICU

3. **Multi-system organ dysfunction:**
   - Multi-system organ dysfunction**:** use of vasopressors, extracorporeal life support, or renal replacement therapy
4. **Immunocompromised**
   - Immunocompromised patients (or on immunosuppressant treatments)

For Cohort 2, only patients as defined in Section 7.2.1 will be enrolled. Randomization will be stratified by use of a non-IL6/6R therapy under an Emergency Use Authorization (EUA) at randomization (Yes/No) and use of systemic corticosteroids at randomization (Yes/No).

Dosing

Based on the IDMC recommendation, as of 27 Apr 2020, the severe and MSOD groups will no longer enroll or receive study drug. Based on a 2nd IDMC recommendation, as of 06 Jun 2020, patients may only receive study drug while receiving mechanical ventilation. Throughout the study, study drug should be withheld if there is a high degree of suspicion of active bacterial or fungal infection. Patients who received a prohibited medication will not be eligible for re-dosing.

Phase 3 Cohort 1:

Patients will receive a single dose of study drug on Day 1. Patients can be re-dosed at 24 hours (±6 hours) if the patient is receiving mechanical ventilation and meets 1 of the following criteria:

a. Remains febrile OR
b. Fails to improve gas exchange (eg, as measured by ventilator settings or O2 requirements) OR
c. Is hemodynamically unstable OR
d. Exhibits other objective evidence of clinical worsening (eg, mental status change, etc.)

Additional doses may be administered weekly as early as Day 8 only for patients receiving mechanical ventilation at the time of re-dosing whose ANC is >500/mm^3 and ALT is ≤5x ULN. If a patient received a 2nd dose other than Day 2, adjust subsequent weekly doses accordingly. A maximum of 6 doses can be administered**.**

Phase 3 Cohort 2:

In Cohort 2, a maximum of 4 doses in total can be administered during the study. The minimum dosing interval between any 2 doses is 18 hours.

Day 1

Patients will receive a single dose of study drug on Day 1 only if they are receiving mechanical ventilation at the time of dosing.

Day 2 through 7

Patients will be re-dosed on Day 2 if they are receiving mechanical ventilation at the time of re-dosing and meet at least 1 of the following criteria on the day the dose is administered:

a. Remains febrile, OR
b. Fails to improve gas exchange (eg, as measured by ventilator settings or oxygen requirements), OR
c. Is hemodynamically unstable, OR
d. Exhibits other objective evidence of clinical worsening (eg, mental status change, etc.)

If the patient does not meet criteria for dosing on Day 2, study drug administration may be delayed up until Day 7. Study drug should be administered as early as possible between Days 2 and 7 (preferably Day 2) on the earliest day that the patient meets dosing criteria. Study drug should not be administered within 18 hours of the beginning of Day 8 (since scheduled dosing will occur on Day 8). If the patient does not meet criteria for dosing on any day between Days 2 and 7, then no dose will be administered.

Days 8 through 14

A single dose of study drug will be administered on Day 8 if the patient meets all 3 of the following criteria on the day the dose is administered:

a. Requires mechanical ventilation at the time of re-dosing AND
b. ANC >500/mm^3, AND
c. ALT ≤5x ULN

The minimum dosing interval between any 2 doses is 18 hours. If the patient does not meet criteria for dosing on Day 8, study drug administration may be delayed up until Day 14. Study drug should be administered as early as possible between Days 8 and 14 (preferably Day 8) on the earliest day that the patient meets dosing criteria. Study drug should not be administered within 18 hours the beginning of Day 15 (since the scheduled dosing will occur on Day 15). If the patient does not meet criteria for dosing on any day between Days 8 and 14, then no dose will be administered.

Days 15 through 21

A single dose of study drug will be administered on Day 15 if the patient meets all 3 of the following criteria on the day the dose is administered:

a. Requires mechanical ventilation at the time of re-dosing, AND
b. ANC >500/mm^3, AND
c. ALT ≤5x ULN

The minimum dosing interval between any 2 doses is 18 hours. If the patient does not meet criteria for dosing on Day 15, study drug administration may be delayed up until Day 21. Study drug should be administered as early as possible between Days 15 and 21 (preferably Day 15) on the earliest day that the patient meets dosing criteria. If the patient does not meet criteria for dosing on any day between Day 15 and Day 21, then no dose will be administered.

There is no dosing after Day 21.

Phase 3 Cohort 3:

As of 06 Jun 2020, patients in Cohort 3 will no longer be enrolled or continue to receive study drug.

Safety

To maximize safety, the first approximately 12 patients who are randomized and receive the study drug will be monitored for safety (assuming a total of ~10 patients are dosed on the sarilumab doses of 200 mg IV or 400 mg IV). Safety data on these 12 patients will be reviewed by an IDMC after the last of these patients dosed reaches Day 7. Data on the first ~12, ~25, and ~50 patients (regardless of severity of illness) who reach at least Day 7 will be reviewed by the IDMC and Regeneron senior physicians to determine if a treatment arm should be discontinued for safety reasons. Selected treatment groups in the Phase 2 portion may be continued forward in the remainder of the study. In addition to these specific assessment times, the IDMC will actively monitor interim data to make recommendations about early study closure or changes to study arms throughout the course of the study.

Assessments

Patients will be assessed daily while hospitalized. Discharged patients will be contacted by telephone on Day 29 to assess status and occurrence of re-admission to a hospital. Patients will undergo a series of efficacy, safety, and laboratory assessments while in the hospital. Baseline serum IL-6 and other cytokines will be collected and analyzed in a central laboratory. Baseline IL-6 levels will not be used as inclusion criteria or used for stratification at randomization. Oropharyngeal (OP) or NP samples to monitor viral infection and blood samples will be obtained on Day 1 (predose), 3, and 29 (or up until the day of discharge if the patient is discharged from the hospital before Day 29). The study is expected to last up to approximately 1 year, depending on the status of the COVID-19 outbreak.

Figure 1: Study Flow Diagram for Phase 2 and Phase 3

Phase 2

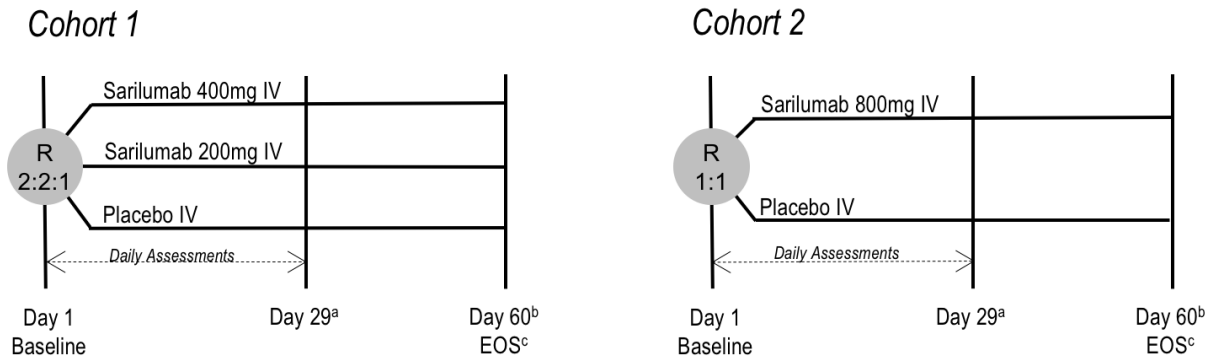
[a] The EOS will be on day 60 or day of death, whichever comes first.

[b] If the patient has been discharged from the hospital before day 29, the study site staff will contact the patient for a follow-up phone call.

[c] If the patient has been discharged from the hospital before day 60, the study site staff will contact the patient for a follow-up phone call.

EOS: End of study

Phase 3



a. If the patient has been discharged from the hospital before day 29, the study site staff will contact the patient for a follow-up phone call on Day 29 and Day 60.
b. If the patient has been discharged from the hospital before day 60, the study site staff will contact the patient for a follow-up phone call
c. The EOS will be on day 60 or day of death, whichever comes first

EOS: End of study; R: Randomization; IV: intravenous

6.1.1. Study Stopping Rules

6.1.1.1. Individual Patient Stopping Rules

For an individual patient, an investigator should assess potential benefit-risk to determine if study drug should be interrupted or discontinued for suspected drug-related events of infusion-related reactions. Refer to Section 8.3 for details.

6.1.1.2. Study Level Stopping Rules

An independent data monitoring committee (IDMC) will actively monitor interim data to review the ongoing safety of patients and can make recommendations about early study closure or changes to the conduct of the study. The Sponsor may decide to stop or make adaptations to the study based upon the recommendations by the IDMC.

A treatment arm may be dropped if there is a clinically meaningful imbalance between treatment arms in any of the following criteria:

1. Incidence of SAEs
2. Incidence of AESIs
3. Progression of COVID-19 to more severe, critical, or multi-organ dysfunction
4. Incidence of clinically significant recurrence of severe or critical disease after clinical improvement
5. An obvious risk/benefit imbalance based upon any key efficacy endpoint of the study such that one dosing arm appears to be doing substantially better than another with an acceptable safety profile without requiring any specific statistical level of precision

6.1.2. End of Study Definition

The end of study is defined as the date the last patient completes the last study assessment (in the hospital or via a follow-up phone call if the patient was discharged from the hospital before Day 60), withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).

6.2. Planned Timing of Analysis

The first analysis of data is planned for safety and efficacy monitoring when the first approximately 12 patients are randomized, receive a study drug, and have at least 7 days of follow-up. Data, including deaths, on these first 12 patients as well as all patients enrolled in the study at that time regardless of severity of illness will be reviewed by an IDMC and, separately, by unblinded senior physicians at Regeneron. Subsequently, separate reviews of data by the IDMC and Regeneron senior physicians will occur after the first 25 and first 50 patients regardless of severity of illness are enrolled and complete 7 days of follow-up. These analyses will include data, including deaths, from all randomized patients. These analyses will be performed to determine if a treatment arm should be discontinued for safety reasons.

An analysis of the Phase 2 data is also planned when approximately 460 patients with all baseline IL-6 levels are randomized and treated, after which the Sponsor will make any appropriate updates to the Phase 3 study plan.

Separate database locks for Cohorts 1 and 2 of the Phase 3 portion of the study are planned.

Interim analyses may be performed as described Section 11.5.1.

IDMC will continue to monitor the safety of patients throughout the study as specified in the IDMC charter.

A description of the statistical methods to be employed is in Section 11, and blinding implications are discussed in Section 8.5.

6.3. Study Committees

6.3.1. Independent Data Monitoring Committee

An IDMC will actively monitor interim data to review the ongoing safety of patients and can make recommendations about early study closure or changes to the protocol. The IDMC members will include 2 to 4 physicians with relevant medical specialty training and 1 statistician. The operation of the IDMC is governed by a charter describing further details such as frequency of meeting, procedures (including but not limited to periodic safety monitoring) and requirements for reporting its observations to the Sponsor.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

The total sample size for Phase 2 will be approximately 460 to include patients with all baseline IL-6 levels. Based on results from Phase 2 data, sample size for Phase 3 was re-calculated. For Cohort 1 of the Phase 3 portion of this study, the total sample size will be approximately 1,400 patients. Enrollment into Cohort 1 will end when approximately 170 patients in the critical stratum receiving mechanical ventilation at baseline who were randomized to receive either sarilumab 400 mg or placebo are enrolled. The total sample size for Cohort 2 will be approximately 225 patients. The planned sample size for Cohort 3 was 225 patients, however, enrollment ended on 06 Jun 2020 at which time 9 patients enrolled. Cohorts 2 and 3 enrolled in parallel when Cohort 1 enrollment completed.

7.2. Study Population

Hospitalized adult (≥18 years old) male and female patients with COVID-19.

7.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Male or female adult ≥18 years of age at time of enrollment
2. Hospitalized (or documentation of a plan to admit to the hospital if the patient is in an emergency department) with illness of any duration with **evidence of pneumonia** by chest radiograph, chest computed tomography or chest auscultation (rales, crackles), requires supplemental oxygen and/or assisted ventilation and meets 1 of the following criteria:

   Phase 2 and Phase 3 Cohort 1: must meet at **least 1** of the following at baseline (patients meeting more than one criterion will be categorized in the most severely affected category):

   - **Severe disease**
     - Requires supplemental oxygen administration by nasal cannula, simple face mask, or other similar oxygen delivery device (ie, above pre-COVID baseline requirement, if any, by the patient)
   - **Critical disease**
     - Requires supplemental oxygen delivered by non-rebreather mask or high-flow nasal cannula, OR
     - Use of invasive or non-invasive ventilation, OR
     - Requiring treatment in an ICU

- **Multi-system organ dysfunction**
  - Multi-system organ dysfunction**:** use of vasopressors, extracorporeal life support, or renal replacement therapy

    Note: patients receiving vasopressors for reasons other than circulatory shock (eg, related to sedation or mechanical ventilation) may be randomized into the critical stratum
- **Immunocompromised**
  - Immunocompromised patients (or on immunosuppressant treatments)

Phase 3 Cohort 2: Patients must be receiving mechanical ventilation to treat respiratory failure due to COVID-19.

3. Laboratory-confirmed SARS-CoV-2 infection as determined by a PCR result from any specimen (or other commercial or public health assay) within 2 weeks prior to randomization and no alternative explanation for current clinical condition
4. Willing and/or able to comply with study-related procedures/assessments
5. Provide informed consent signed by study patient or legally acceptable representative

7.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. In the opinion of the investigator, not expected to survive for more than 48 hours from screening.
2. Presence of any of the following abnormal laboratory values at screening: ANC less than 2000 mm^3, AST or ALT >5x ULN, platelets <50,000 per mm^3
3. Treatment with anti-IL-6, anti-IL-6R antagonists, or with Janus kinase inhibitors (JAKi) in the past 30 days or plans to receive during the study period
4. Current treatment with the simultaneous combination of leflunomide and methotrexate
5. Exclusion criteria related to tuberculosis (TB)
   a. Known active TB or a history of incompletely treated TB
   b. Suspected or known extrapulmonary TB
6. Patients with suspected or known active systemic bacterial or fungal infections

   Note: Patients with a history of positive bacterial or fungal cultures but on enrollment does not have suspected or known active systemic bacterial or fungal infections may be enrolled.
7. (Placeholder for Case Report Form [CRF]: Exclusion removed per Amendment 4)
8. Participation in a double-blind clinical research study evaluating an investigational product or therapy within 3 months and less than 5 half-lives of investigational product prior to the screening visit.

Exception: The use of remdesivir, hydroxychloroquine, or other treatments being used for COVID-19 treatments in the context of an open-label study, EUA, compassionate use protocol, or open-label use is permitted

9. Any physical examination findings, and/or history of any illness, concomitant medications or recent live vaccines that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study
10. Known systemic hypersensitivity to sarilumab or the excipients of the drug product

Phase 3 Cohort 2 only:

11. Known or suspected history of immunosuppression (eg, due to immunosuppressant medication) or immunodeficiency disorder

    Note: Patients receiving systemic corticosteroids for COVID-19 and patients receiving chronic low dose systemic corticosteroids at a dose less than or equal to 10 mg/day of prednisone (or an equivalent dose of another corticosteroid) may be eligible for inclusion. Well controlled HIV infection with a recent undetectable viral load is not an exclusion criterion
12. Patients who require renal replacement therapy for acute kidney injury at randomization or who required renal replacement therapy within 72 hours prior to randomization

    Note: Patients who have chronic end-stage renal disease on chronic hemodialysis or peritoneal dialysis prior to their hospitalization may be eligible for inclusion.
13. Patients who have circulatory shock requiring vasopressors at randomization or within 24 hours prior to randomization

    Note: Patients who require vasopressors for sedation-related hypotension or reasons other than circulatory shock may be eligible for inclusion.
14. Use of extracorporeal life support (eg, ECMO) or, in the opinion of the investigator, there is a high likelihood that extracorporeal life support will be initiated within 48 hours after randomization

7.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who have taken study drug should be encouraged to remain in the study to allow for the collection of information and biological samples for study purposes. Patients who opt to withdraw from the study may be asked to provide a final blood draw sample for PK analysis before withdrawing from the study (Section 9.1.2) and to allow for re-contact at the end of the trial

(Day 60 follow-up phone call) in order to collect data on survival and history of hospital readmission.

Rules for discontinuation of study treatment are discussed in Section 8.2.2.

7.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational Treatment

In Phase 2 and Phase 3 Cohort 1, all patients randomized and dosed will receive 1 of the following:

- Sarilumab 200 mg IV for 1-hour
- Sarilumab 400 mg IV for 1-hour
- Placebo IV for 1-hour

For Phase 3 Cohort 2, all patients randomized and dosed will receive 1 of the following:

- Sarilumab 800 mg IV for 1-hour
- Placebo IV for 1-hour

Instructions on dose preparation are provided in the pharmacy manual.

8.2. Dose Modification and Study Treatment Discontinuation Rules

8.2.1. Dose Modification

Eligible patients will receive repeat dosing per the criteria outlined in Section 6.1. Per the recommendation of the IDMC, as of 27 Apr 2020, patients will no longer receive sarilumab 200 mg or be eligible for repeat dosing of 200 mg and patients in the severe and MSOD strata will no longer receive sarilumab 400 mg or placebo. As of 06 Jun 2020, based on an IDMC recommendation, only patients receiving mechanical ventilation at the time of dosing will receive study drug (Phase 3 Cohorts 1 and 2), including re-dosing. Patients will no longer be enrolled or receive study drug in Phase 3 Cohort 3. Patients will continue to be monitored and complete all assessments per protocol.

8.2.2. Study Drug Discontinuation

Study drug may be temporarily withheld if ANC $<500/mm^3$ or ALT >5x ULN, or at the discretion of the investigator according to the instructions in Section 6.1. Study drug may be continued if, upon repeat testing, ANC $>500/mm^3$ and ALT ≤5x ULN.

Patients who opt to withdraw from the study may be asked to provide a final blood draw sample for PK and other exploratory PD biomarker analysis before withdrawing from the study (Section 9.1.2).

8.3. Management of Acute Reactions

8.3.1. Acute Intravenous Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All Grade ≥2 infusion-related reactions must be reported as AESIs (see Section 10.1.3 and Section 10.2.4) and graded using the grading scales as instructed in Section 10.2.5.

8.3.1.1. Interruption of the Intravenous Infusion

The infusion should be interrupted if any of the following AEs are observed:

- sustained/severe cough
- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension
- dyspnea (shortness of breath)
- vomiting
- flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

8.3.1.2. Termination of the Intravenous Infusion

The infusion should be terminated and NOT restarted if any of the following adverse events occur:

- anaphylaxis*
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain
- seizure
- severe hypotension
- other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc.)
- any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

8.4. Method of Treatment Assignment

In the Phase 2 study and Cohort 1 of the Phase 3 study, patients will be randomized in a ratio of 2:2:1 to receive sarilumab 400 mg IV, or sarilumab 200 mg IV or placebo, in a stratified manner. In Phase 3, Cohort 2, patients will be randomized in a ratio of 1:1 to receive sarilumab 800 mg IV or placebo IV stratified by the use of systemic corticosteroids and by non-IL6/6R therapy administered under an EUA. Randomization will be performed according to a central randomization scheme using an interactive web response system (IWRS).

Phase 2 and Phase 3 Cohort 1:

Randomization will be stratified by:

- Severity of illness at enrollment
  - Severe disease
  - Critical disease
  - Multi-system organ dysfunction
  - Immunocompromised
- Systemic corticosteroids (Yes/No)

For Cohort 2, only patients meeting criteria as defined in Section 7.2.1 will be enrolled. Randomization will be stratified by use of a non-IL6/6R therapy under an EUA at randomization (Yes/No) and use of systemic corticosteroids at baseline (Yes/No).

While serum IL-6 and cytokines will be measured at a central laboratory predose on Day 1 and periodically after treatment, patients will not be stratified based on serum IL-6 levels. However, analyses will be conducted by baseline IL-6 levels.

For this adaptive Phase 2/3 study, based on the planned analyses (see Section 6.2), the IDMC and Sponsor may decide to drop an arm due to safety reasons. Accordingly, the randomization may be adjusted during the trial.

8.5. Blinding

A pharmacist or qualified personnel at the site, not otherwise associated with the conduct of the study, will reconstitute the drug for IV administration. The drug infusion solution must be provided in identical form for active and placebo treatments, so that they remain indistinguishable to both study personnel and patients. Study patients, the principal investigators, and study site personnel will remain blinded to all randomization assignments throughout the study. The Regeneron Medical/Study Director, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments.

The study team directly involved with the study conduct will be blinded. Selected individuals not involved in the conduct of the study may have access to unblinded data as needed for safety review or other data review. An independent team at Regeneron, including senior physicians/management, will be unblinded and in communication with the IDMC and will make decisions for adaptations to the study during the Phase 2 portion of the study.

Blinding of CRP Assessment Results

The study patients and select Regeneron study team members directly involved in the conduct of the study will remain blinded to post-treatment CRP values.

8.6. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event and when a treatment decision is contingent on knowing the patient's treatment assignment. Study drug will be discontinued for patients whose treatment has been unblinded (Section 8.2.2).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected patients will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient. Unblinding is performed using the IWRS which will notify Regeneron.
  - The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.7. Treatment Logistics and Accountability

8.7.1. Packaging, Labeling, and Storage

Sarilumab for injection, 175 mg/mL will be provided as open-label supplies packaged in boxes. Each box will contain 1 prefilled syringe or vial. Each box will be labeled with a 1-panel, open label printed in black. The product identity and strength, container number, directions for use, route of administration and storage conditions will be indicated.

Open-label study drug will display the product lot number on the label.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

8.7.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed/returned to the sponsor or designee.

8.7.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each patient
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

8.7.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

8.8. Concomitant Medications

Any treatment administered from the first dose of study drug to the final study assessment will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

If the local standard of care per written policies or guidelines includes lopinavir/ritonavir (Kaletra) or other agents, then continuing these during the study is permitted.

CYP Substrates

Interleukin-6 has been shown to reduce cytochrome (CY)P1A2, CYP2C9, CYP2C19, and CYP3A4 enzyme expression in in vitro studies. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as sarilumab, the formation of cytochrome P450 (CYP450) enzymes could be normalized, and as a result drugs that are metabolized by these CYP450 isoforms may have decreased levels when patients start receiving sarilumab. As a precautionary measure, drugs which are metabolized via these cytochromes and with a narrow therapeutic index should be closely monitored and adjusted if needed. Some examples of CYP450 substrates with a narrow therapeutic index requiring monitoring of effect are warfarin; examples of substrates that require monitoring of drug concentration include, but are not limited to, the following: warfarin, CsA, theophylline, digoxin, antiepileptics, such as carbamazepine (Carbatrol®, Tegretol®), divalproex (Depakote®), phenytoin (Dilantin®), or valproic acid (Depakene®); or antiarrhythmics, such as disopyramide (Norpace®), procainamide (Procan®, Pronestyl®), or quinidine (Quinidex®, Quin Release Quin- G®).

Concomitant medications in a hospitalized population change daily and are difficult to collect and attribute to success and failure of therapy and impact on safety. Therefore, only select concomitant medications will be captured in this trial. The select list of medications will be assessed Day 1 to Day 29 (or until day of discharge from hospital if before Day 29) include corticosteroids, remdesivir, lopinavir-ritonavir, chloroquine, hydroxychloroquine, interferon beta, and convalescent serum. Refer to Section 9.2.3.4 for a complete list of concomitant medications that should be collected.

8.8.1. Prohibited and Permitted Medications

Patients may continue their normal regimen of medications and procedures, except for those specified in the exclusion criteria for study enrollment (Section 7.2.2). Patients who receive a prohibited medication will not be eligible for re-dosing of study drug.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

Study assessments and procedures are presented by study period/day in Table 5.

Table 5: Schedule of Events

Study Procedure	**Screening Visit[1]**	**Baseline Visit[1]**	**Daily Follow-up Until Hospital Discharge**					**EOS[2]**
Day	**-1 or 1**	**1**	**2**	**4**	**7**	**8 to 23**	**29 and discharge[3,4]**	**60**
Window							±7 days	±7 days
Screening/Baseline:								
Inclusion/Exclusion	X							
Informed Consent	X							
[redacted]	X							
Demographics and Medical History[1]	X							
Randomization		X						
Treatment:								
Study Drug Administration **(only if receiving mechanical ventilation)**		X	X[5]			X[5]		
Assessments:								
Oxygen administration (FiO_2) and Oxygenation (SpO_2)[6]	X	X	Phase 2 & Phase 3 Cohort 1 - 2 times a day Phase 3 Cohorts 2 and 3 - At least once per day and any time clinical status changes (eg, endotracheal intubation/extubation or requires change in oxygen delivery device)					
Clinical Status Assessment (7-point ordinal scale)[7]		X	Daily until discharge					
NEWS2 Score								
Air or oxygen		X	Daily in the morning until discharge					
Respiratory rate		X	Daily in the morning until discharge					
BP		X	Daily in the morning until discharge					
Pulse		X	Daily in the morning until discharge					
Consciousness		X	Daily in the morning until discharge					
Body temperature before antipyretics or 4 hours after antipyretics[8]		X	Daily in the morning until discharge					
Imaging, microbiology results, and arterial blood gas results (as available)[9]			If available in the medical record					
Limited physical examination (lung auscultation only)	X							

Study Procedure	**Screening Visit[1]**	**Baseline Visit[1]**	**Daily Follow-up Until Hospital Discharge**					**EOS[2]**
Day	**-1 or 1**	**1**	**2**	**4**	**7**	**8 to 23**	**29 and discharge[3,4]**	**60**
Window							±7 days	±7 days
Electrocardiogram (ECG), if feasible[10]	X							
Record Targeted Medications[11]	X		Daily until discharge					
Adverse Events[12]	X		X					
Pregnancy Test (WOCBP)[13]	X							
Follow-up Phone Call							X	X
Laboratory Testing:								
C-Reactive Protein (**mandatory**)	X	X		X	X			
			Order CRP with all routine labs and obtain at the same time Record all results when available in medical chart					
Hematology[14]	X		Must be collected within 48 hours prior to redosing Record all results when available in medical chart					
Blood chemistry (including LFTs and creatinine)[15]	X		Must be collected within 48 hours prior to redosing Record all results when available in medical chart					
Ferritin, LDH, d-dimer		X (**mandatory**)	When available					
Blood cultures for bacteria and fungi[16]					X	X *Weekly culture based on ANC[16]*		
PK/Biomarkers/Research (defer to footnotes for sampling requirements):								
	-1 or 1	**1**	**2**	**4**	**7**	**8 to 23 (Only collect on day of dosing)**	**29 or discharge[3,4]**	**60**
Serum for PK/Sarilumab Concentration[17]		X	X	X	X	X	X	
Serum sIL-6R plus research[17]		X	X	X	X	X	X	
Serum cytokines including IL-6 and biomarker testing[17]		X		X	X	X	X	
Blood for PCR SARS-CoV-2[17,18]	X	X		X			X	
Oropharyngeal or nasopharyngeal swab for SARS-COV-2 detection and sequencing[17,18]	X	X		X			X	
Blood for research plasma[17]		X					X	

Study Procedure	**Screening Visit[1]**	**Baseline Visit[1]**	**Daily Follow-up Until Hospital Discharge**					**EOS[2]**
Day	**-1 or 1**	**1**	**2**	**4**	**7**	**8 to 23**	**29 and discharge[3,4]**	**60**
Window							±7 days	±7 days
[redacted]								
[redacted]		X						

9.1.1. Footnotes for the Schedule of Events Table

1. Screening and baseline may occur on the same day. Assessments that are noted for both visits should only be assessed once. Medical history should include collecting onset of pneumonia symptoms. Body temperature, SpO_2, and FiO_2 must be collected at randomization.
2. Patients will have an end of study (EOS) assessment to collect data on survival and history of hospital re-admission. This assessment may be performed by phone.
3. Patients discharged prior to Day 29 will have a follow-up phone call on Day 29 to collect data on survival and history of hospital re-admission and do not need to be recalled to the hospital for a visit.
4. Patients discharged prior to or after Day 29 should have a sample collected. If day of discharge is not Day 29 and coincides with another visit, the Day 29 assessments should be performed.
5. Patients will be re-dosed according to Section 6.1.
6. Oxygen administration and oxygenation: refer to Section 9.2.2.3 of the protocol for details. SpO_2 must be measured after 5 minutes of rest (sitting or supine) and must be measured simultaneously with oxygen administration and ventilation data. Record oxygen flow rate (L/min) for patients receiving nasal cannula, simple face mask, or non-rebreather mask. Record FiO_2 for patients receiving high flow nasal cannula, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation.
7. Clinical Status Assessment using the 7-point ordinal scale: refer to Section 9.2.2.4 of the protocol for details.
8. Temperature may be measured using the following methods: oral, rectal, tympanic, or temporal according to local hospital protocols and according to the manufacturer's instructions for use of the device. Body temperature should be measured using the same method each time. Temperature should be measured predose after at least 5 minutes of rest (supine or sitting).
9. If available in the medical record, chest CT images will be collected as part of a separate effort related to this study for predictive exploratory analysis and may be provided in a separate study report.
10. ECG only if feasible. Historical ECG from current hospital admission is acceptable.
11. Targeted medications: refer to Section 9.2.3.4 of the protocol for details.
12. Adverse events: Only SAEs and AESIs will be recorded in eCRF.
13. Pregnancy testing to be performed in women of childbearing potential (WOCBP) only. Serum or urine pregnancy test are both acceptable.
14. Hematology: refer to Section 9.2.3.5 of the protocol for details. CBC is required prior to randomization (standard of care labs may be used). After Day 1, CBC will not be performed as a study procedure. When CBC is performed as part of the patient's clinical care, the results will be entered in eCRF.

15. Blood Chemistry: refer to Section 9.2.3.5 of the protocol for details. LFTs and creatinine are required prior to randomization (standard of care labs may be used). After Day 1, LFTs and creatinine will not be performed as a study procedure. When chemistries are performed as part of the patient's clinical care, the results will be entered in eCRF.
16. Surveillance blood cultures for bacteria and fungi should be performed weekly for patients who have had a sustained ANC <1000/μL for ≥48 hours post-randomization.
17. All samples should be collected before study drug administration except post-infusion PK and sIL-6R samples:
    - PK and sIL-6R samples collected on dosing days for the initial dose and for the FIRST repeat dose are mandatory. Samples for subsequent doses are requested if sufficient PPE are available:
        - One predose (as close to initiation of treatment as reasonable) and
        - One within 60 minutes after the end-of-infusion (EOI). The EOI sample or flush should be collected from the arm, contralateral to that used for IV infusion, if possible. If not medically feasible, the sample can be drawn from the same arm. If the sample cannot be obtained within 60 minutes of the end of infusion, the time from end of infusion should be provided in the CRF
        - Day 4 samples are mandatory (if PPE and appropriate lab facilities are available).
    - The Day 1 predose sample and Day 29 or Early Termination PK sample may be used for ADA analysis.
18. Swab and tests will be for exploratory analysis only not for inclusion or diagnosis.

[redacted]

9.1.2. Early Termination from the Study

Patients who are withdrawn from the study before the primary endpoint assessment (Day 29) may be asked to provide a final blood draw sample for PK analysis before withdrawing from the study (Table 5) and to allow for re-contact at the end of the trial (Day 60 follow-up phone call) in order to collect data on survival and history of hospital re-admission.

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline characteristics of the study population: demographics, medical history, timing of COVID-19 infection, prior therapy, pregnancy status.

The investigator or sub-investigator will verify that the patient tests positive for SARS-CoV-19 RT-PCR and record the result, specimen type, date of test, and the type of assay in the eCRF.

9.2.2. Efficacy Procedures

9.2.2.1. C-Reactive Protein

Serum CRP will be measured at each site's local laboratory according to the schedule in Table 5. See Section 9.2.3.5 for details.

9.2.2.2. Body Temperature

Body temperature measurement will occur **before taking antipyretics** or more than 4 hours after last dose of antipyretics. Body temperature will be measured to monitor the patient's status regarding fever per the schedule in Table 5. Temperature may be measured using the following methods: axilla, oral, rectal, tympanic, or temporal according to local hospital protocols and according to the manufacturer's instructions for use of the device. Body temperature should be measured using the same method each time. Temperature should be measured after at least 5 minutes of rest (supine or sitting).

9.2.2.3. Oxygen Administration and Oxygenation

Supplemental oxygen/FiO_2 use will be measured to monitor the patient's status regarding gas exchange per the schedule in Table 5. As applicable, the following will be recorded:

- Oxygen delivery device (eg, nasal cannula, simple face mask, non-rebreather mask, high flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, extracorporeal life support, etc)
- Oxygen flow rate in Liters/min (if receiving nasal cannula, simple face mask, non-rebreather mask)
- FiO_2 (if receiving high flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or extracorporeal life support)

If a patient is using more than one device (eg, extracorporeal life support and invasive ventilation), information from both devices will be recorded separately.

Resting SpO_2 will be measured to assess arterial oxyhemoglobin saturation. SpO_2 will be measured using a fingertip or similar non-invasive device following 5 minutes of rest (inactivity) while supine, semi-recumbent, or sitting and will only be measured in the presence of a good SpO2 wave form. SpO_2 must be measured simultaneously with recorded supplemental oxygen/FiO2 data.

Additional data to be collected include (when available from the medical record): arterial pH, partial pressures of oxygen in arterial blood (PaO_2), partial pressure of carbon dioxide in arterial blood ($PaCO_2$), oxyhemoglobin saturation in arterial blood from arterial blood gas analysis (SaO_2).

9.2.2.4. Clinical Status Assessment (7-Point Ordinal Scale)

Cohort 1: A Clinical Status Assessment (7-point ordinal scale) (Peterson, 2017) should be assessed in the morning to consider the worst assessments for the previous day (ie, midnight to midnight; 00:00 – 00:00 [24-hour clock]). If it is the first assessment and 24 hours of data are not available, report status at randomization.

Cohort 2:

- Ordinal Scale will be assessed (1) at the time of randomization and must match the stratum assigned by the investigator in the IRT, and (2) at the time of the administration of the first dose of study drug (which should be administered on Day 1 in most cases). Oxygen delivery device data may be used to calculate the ordinal scale.
- Beginning on Day 3, the Ordinal Scale should be assessed in the morning to consider the worst assessments for the previous day (ie, midnight to midnight; 00:00 – 00:00 [24-hour clock]). Therefore, the Day 3 assessment will reflect the patient's clinical status on Day 2.

The 7-point ordinal scale is:

- Death;
- Hospitalized, requiring invasive mechanical ventilation or ECMO;
- Hospitalized, requiring non-invasive ventilation or high flow oxygen devices;
- Hospitalized, requiring supplemental oxygen;
- Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)
- Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care
- Not hospitalized

9.2.2.5. NEWS2 Scoring System

The NEWS2 scoring system (Table 6) is a composite score derived from respiratory rate (per minute), SpO_2 Scale 1 (%) or SpO_2 Scale 2 (%), Use of air or oxygen (?), Systolic blood pressure (mm Hg), Pulse (per minute), Consciousness, and Temperature (°C).

The NEWS2 score will be assessed daily in the morning.

Table 6: The NEWS2 Scoring System

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

As part of the NEWS2 score**,** the patient's mental status (ACVPU) will be assessed and categorized into one of the following categories:

- **Alert:** A fully awake patient with spontaneous opening of the eyes, response to voice, and has motor function.
- **Confusion:** A patient may be alert but confused or disorientated. It is not always possible to determine whether the confusion is 'new' when a patient presents acutely ill. Such a presentation should always be considered to be 'new' until confirmed to be otherwise. New-onset or worsening confusion, delirium or any other altered mentation should always prompt concern about potentially serious underlying causes and warrants urgent clinical evaluation.
- **Voice**: The patient makes some kind of response when you talk to them, which could be in any of the three component measures of eyes, voice or motor – eg patient's eyes open on being asked 'Are you okay?'. The response could be as little as a grunt, moan, or slight movement of a limb when prompted by voice.
- **Pain**: The patient makes a response to a pain stimulus. A patient who is not alert and who has not responded to voice (hence having the test performed on them) is likely to exhibit only withdrawal from pain, or even involuntary flexion or extension of the limbs from the pain stimulus. The person undertaking the assessment should always exercise care and be suitably trained when using a pain stimulus as a method of assessing levels of consciousness.
- **Unresponsive**: This is also commonly referred to as 'unconscious'. This outcome is recorded if the patient does not give any eye, voice or motor response to voice or pain.

9.2.3. Safety Procedures

9.2.3.1. Vital Signs

Vital signs, including blood pressure, pulse, and respiration, will be collected and recorded at the time points according to Table 5. Predose body temperature should be recorded on the vital signs eCRF.

9.2.3.2. Limited Physical Examination

A targeted physical examination including lung auscultation will be performed at time point according to Table 5. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

9.2.3.3. Electrocardiogram

If feasible, a standard 12-lead ECG will be performed at time points according to Table 5. An historical ECG from the present hospital admission (including ED stay) may be used. The ECG strips or reports will be retained with the source.

9.2.3.4. Targeted Medication Review

The patient's medications will be reviewed and recorded, including but not limited to use of:

- antipyretics, such as aspirin, acetaminophen, ibuprofen, and other non-steroidal anti-inflammatory drugs (NSAIDs)
- warfarin
- cyclosporine A
- theophylline
- digoxin
- antiepileptics, such as carbamazepine (Carbatrol®, Tegretol®), divalproex (Depakote®), phenytoin (Dilantin®), valproic acid (Depakene®);
- antiarrhythmics, such as disopyramide (Norpace®), procainamide (Procan®, Pronestyl®), quinidine (Quinidex®, Quin Release Quin- G®)
- antivirals, antibacterial, and antifungals
- anti-parasitics (chloroquine or hydroxychloroquine)
- interferon beta
- corticosteroids
- convalescent serum
- angiotensin receptor blockers, such as Azilsartan (Edarbi), Candesartan (Atacand), Eprosartan (Teveten), Irbesartan (Avapro), Losartan (Cozaar), Olmesartan (Benicar), Telmisartan (Micardis), Valsartan (Diovan)

- angiotensin converting enzyme inhibitors: benazepril (Lotensin), captopril (Capoten), enalapril (Vasotec), fosinopril (Monopril), lisinopril (Prinivil, Zestril), moexipril (Univasc), perindopril (Aceon), quinapril (Accupril)

9.2.3.5. Laboratory Testing

Serum CRP will be measured at each site's local laboratory according to the schedule in Table 5.

All patients should have white blood cell count, platelet count, AST, and ALT measured prior to randomization (see Section 7.2.2). If these laboratory tests were not performed as part of the patient's clinical care, they may be performed as study procedures in the site's local laboratory.

After randomization, when patients enrolled in this study undergo laboratory testing as part of their standard-of-care, the results of these tests will be provided to the Sponsor, as indicated.

Certain tests that are not necessarily part of the patient's standard-of-care will also be collected as part of this study, as indicated.

Laboratory test results that may be recorded are Table 5. Tests may include:

Blood Chemistry

All patients should have a hepatic function panel, serum ferritin, and serum LDH at baseline prior to administering study drug. The results of blood chemistry testing that is performed as part of the patient's standard-of-care will be shared with the Sponsor. These samples will be analyzed by a local laboratory. LFTs and creatinine are required prior to randomization (standard of care labs may be used). After Day 1, LFTs and creatinine will not be performed as a study procedure. When chemistries are performed as part of the patient's clinical care, the results will be entered in eCRF.

A typical blood chemistry panel is shown below:

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Total cholesterol*
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
Glucose	Alkaline phosphatase	Ferritin
Albumin	Lactate dehydrogenase (LDH)	

*(low-density lipoprotein [LDL] and high-density lipoprotein [HDL])

Hematology/Coagulation

All patients would have a complete blood count with differential and a d-dimer performed at baseline prior to administering study drug. The results of hematology testing that is performed as part of the patient's standard-of-care will be shared with the Sponsor. These samples will be analyzed by a local laboratory. CBC is required prior to randomization (standard of care labs may be used). After Day 1, CBC will not be performed as a study procedure. When CBC is performed as part of the patient's clinical care, the results will be entered in eCRF

A typical hematology panel is shown below:

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Platelet count	Basophils
	Eosinophils

Other Laboratory Tests

Screening:

Patients eligible for study participation will have tested positive for SARS-CoV-19 RT-PCR. This test will be performed as part of standard-of-care and the results will be provided to the Sponsor.

Safety:

Pregnancy testing will be performed using urine or serum samples at screening in women of childbearing potential. A positive pregnancy test is not exclusionary for study participation but will be recorded.

Culture results (bacterial, fungal, or viral) including specimen source (BAL, tracheal aspirate, sputum, blood, urine, etc) performed as part of patients' workup for new infection should be reported to the Sponsor.

Phase 2 and Phase 3 Cohort 1: Surveillance bacterial and fungal blood cultures: Blood samples will be collected on Day 7 and Day 15 for blood cultures. If the patient is discharged before Day 15, blood cultures will be collected on the day of discharge.

Phase 3 Cohort 2: surveillance blood cultures for bacteria and fungi should be performed weekly for patients who have had a sustained ANC <1000/µL for ≥48 hours post-randomization.

Biomarkers/Research Samples:

Serum samples will be collected to measure cytokines and biomarkers such as IL-6, soluble IL-6R and will be analyzed by a central laboratory.

Nasopharyngeal (NP)/oropharyngeal (OP) swabs will be used to collect secretions from patients to determine presence or absence of SARS-CoV-2 virus and to explore relative quantitation of viral load as an exploratory measure. In addition to RT-PCR to quantify viral load, viral sequencing may be performed if sufficient sample is available to determine the sequence and variations. Detailed instructions for blood/OP and NP swab sample collections are in the laboratory manual provided to study sites.

9.2.4. Drug Concentration and Measurements

Samples for measurement of sarilumab and sIL-6R in serum will be collected at visits listed in Table 5. These samples will be analyzed either by the Sponsor or a central laboratory.

[redacted]

9.2.5. Pharmacodynamic and Exploratory Biomarker Procedures

In this study, research assessments will be performed to explore how sarilumab may modify the clinical manifestations and pathology associated with COVID-19 and how the IL-6 signaling pathway may be modulated.

Biomarker samples will be collected at time points according to Table 5. PD marker/Biomarker measurements will be performed to determine the target pathway of IL-6 inhibition and the impact on pneumonia and respiratory illness associate with viral infection and pathology. Relative quantitation of viral load and viral sequencing may be evaluated using methodologies that include but may not be limited to RT-PCR and sequencing. Additional biomarkers related to anti-viral immunity, including but not limited to neutralizing antibodies may also be measured.

[redacted]

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all serious clinical events and AESIs occurring during the study data collection, from the time of signing the ICF to the end of study. Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history.

Throughout the study, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. The Investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of study) that the Investigator assesses as related to study drug should also be reported.

All serious adverse events (SAEs), AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All SAEs and AESIs (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the blinded study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the AE CRF and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**.
- **Adverse Events of Special Interest** (AESI; serious and nonserious)**:** Adverse events of special interest for this study include the following:
  - Grade ≥2 infusion-related reactions
  - Grade ≥2 hypersensitivity reactions
  - Grade 4 neutropenia (ANC <500/mm^3)
  - Grade 4 neutropenia with concurrent invasive infection (ANC <500/mm^3)
  - Invasive bacterial or fungal infections of clinical significance with confirmed diagnosis based on the investigator's assessment with appropriate diagnostic workups and consultations
  - Increase in alanine transaminase (ALT) or aspartate aminotransferase (AST) ≥3X ULN (for patients with normal baseline) or >3X ULN AND at least 2-fold increase from baseline value (for patients with abnormal baseline)
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female study patient, during the study or existing at the time of signing the informed consent form. Any complication of pregnancy affecting a female study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient re-**hospitalization** (readmission after discharge) or **prolongation of existing hospitalization**. In-patient hospitalization is defined as a hospital re-admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

10.2.4. Infusion Reactions

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 2 hours after the infusion is completed.

10.2.5. Severity

The severity of AEs will be graded using the NCI-CTCAE v5. Adverse events not listed in the NCI-CTCAE v5 will be graded according to the following scale:

Table 7: Grading System for Adverse Events Not Listed in NCI-CTCAE

Grade	Severity	Description
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 ADL*.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life–threatening	Life-threatening consequences; urgent intervention indicated.
5	Death	Death related to AE

* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.2.6. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

For double blinded studies using an active comparator, the investigator should consider all study drugs in determining event causality.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset versus time drug was administered
- Nature of the reactions: immediate versus long term
- Clinical and pathological features of the events
- Existing information about the drug and same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study or its class of drugs or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol specified procedure and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance; Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Board, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, IRBs, and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers using the active study drug (sarilumab), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB unless delegated to the sponsor.

[redacted].

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and IRB as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plans (SAPs) for the study. There will be 2 separate SAPs for this study; one will be for Phase 2 and second for Phase 3. The SAPs will be revised prior to the end of each portion of the study (Phase 2 or Phase 3) to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAPs will be issued before the first database lock in each portion of the study (Phase 2 or Phase 3).

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

This adaptive Phase 2/3 study is intended to allow for adaptations such as follows: dropping of a treatment group for safety reasons; confirmation or modification of the endpoints for Phase 3; and sample size re-estimation in Phase 3. Therefore, treatment groups in Phase 3 and analyses for Phase 3 portion will depend on the final endpoints and treatment groups selected based on Phase 2 results.

The Phase 3 portion will be powered and analyzed independently of the Phase 2 portion, in order to ensure that the Phase 3 portion is confirmatory and to avoid inflating the Type I error rate of the Phase 3 portion of the study.

As mentioned in Section 3.2.2, the adaptations to the Phase 3 cohorts include: 1) dropping of the sarilumab 200-mg dose group, 2) modification of the Phase 3 endpoints, 3) addition of Cohorts 2 and 3, ie, new cohorts of patients randomized to sarilumab 800 mg or placebo, and 4) justification of sample size for Cohort 1 and establishing sample sizes for Cohorts 2 and 3.

11.1. Statistical Hypothesis

Phase 2 Portion of the Study

For the Phase 2 portion of the study, the hypothesis to be tested is the superiority of sarilumab versus placebo with respect to the primary endpoint of percent change from baseline in CRP levels at Day 4 (Section 4.1.1 and Section 11.4.3.1).

The statistical hypotheses (null H_0 vs. alternative H_1) for the primary endpoint are:

$$H_0: \mu_1 = \mu_2 \quad \text{versus} \quad H_1: \mu_1 \neq \mu_2$$

where μ_1 and μ_2 are mean percent changes from baseline in CRP-levels at Day 4 (based on natural logarithm scale) in the 2 treatment groups.

The statistical hypotheses (null H_0 vs. alternative H_1) for the Phase 2 key secondary efficacy endpoint of time-to-improvement (2 points) in clinical status from baseline using the 7-point ordinal scale, time-to-resolution of fever and time-to-improvement in oxygenation (Section 4.1.2) are stated below.

$$H_0: S_1(t) = S_2(t) \text{ for all time } t \quad \text{versus} \quad H_1: S_1(t) \neq S_2(t) \text{ for some time } t$$

where $S_1(t)$ and $S_2(t)$ are the survival probability functions of the above endpoints.

Phase 3 Portion of the Study (Prior to Adaptation)

For the Phase 3 portion, the study is intended to allow for adaptation of the primary endpoint based on results from the Phase 2 data, ie, confirmation or modification of the primary endpoint. Hence the final endpoint may be different. The currently specified primary endpoint for Phase 3 is time-to-improvement (2 points) in clinical status from baseline on the 7-point ordinal scale (Section 4.1.1). The statistical hypotheses for this endpoint are the same as stated above for Phase 2 time-to-event endpoint.

Phase 3 Portion of the Study (Post-Adaptations)

Based on the adaptations to the Phase 3 study design, the null hypotheses to be tested (separately) in each of the 3 Phase 3 Cohorts corresponding to the final primary endpoint are:

Cohort 1

H_{10}: Sarilumab 400 mg IV is not different than placebo in terms of proportion of patients with at least a 1-point improvement in clinical status from baseline to Day 22 using the 7-point ordinal scale in patients with critical COVID-19 receiving mechanical ventilation at baseline.

Cohort 2

H_{20}: Sarilumab 800 mg IV is not different than placebo in terms of proportion of patients with at least a 1-point improvement in clinical status from baseline to Day 22 using the 7-point ordinal scale in patients with COVID-19 receiving mechanical ventilation at baseline.

The statistical hypotheses (null H_0 vs. alternative H_1) for each of these can be stated as:

$$H_{10}: p_1^{(1)} = p_0^{(1)} \quad \text{versus} \quad H_{11}: p_1^{(1)} \neq p_0^{(1)}$$

$$H_{20}: p_1^{(2)} = p_0^{(2)} \quad \text{versus} \quad H_{21}: p_1^{(2)} \neq p_0^{(2)}$$

where $p_1^{(1)}\left(p_1^{(2)}\right)$ and $p_0^{(1)}\left(p_0^{(2)}\right)$ are the proportions of responders in the sarilumab and placebo treatment groups within Cohorts 1 and 2, respectively.

11.2. Justification of Sample Size

For the Phase 2 portion of the study, approximately 200 patients (80 in each of the 2 sarilumab dose groups and 40 on placebo) are required in all disease severity strata with high baseline IL-6 levels to test for superiority of sarilumab versus placebo with respect to percent change from baseline CRP levels at Day 4. This sample size will provide 90% power using a 2-sample t-test to detect an effect size (ie, difference/SD) of 0.633 at the 0.05 (2-sided) significance level. The effect size of 0.633 assumes that the mean treatment difference in percent change from baseline using natural logarithm of CRP levels (sarilumab minus placebo) would be -6.6% with a standard deviation of 10.43% (percent change from baseline in sarilumab is estimated to be mean = -45.98% and SD=10.43% based on tocilizumab data from China study in COVID-19; See Figure 2 in (Xu, 2020). If the effect in the placebo group is assumed to be negligible (~0%) and variability in CRP is high, then the power could be much greater than 90% for larger effect sizes (eg, treatment difference = -50% and SD = 30%, effect size = 1.667). Total sample size for Phase 2 is expected to be larger than 200 to include patients with all baseline IL-6 levels.

Additional patients are being included in Phase 2 to allow for adequate estimation and improve precision of the treatment effect using the Phase 3 clinical endpoint—time to improvement (2 points) in clinical status (7-point ordinal scale)—prior to making adaptations to Phase 3 study design. The total sample size for Phase 2 is updated to be approximately 460 patients, to include patients with all baseline IL-6 levels.

Phase 3 Portion of the Study (Prior to Adaptations)

Sample size calculations for the Phase 3 portion of the study prior to adaptations were based on the Phase 3 primary endpoint of time-to-improvement (2 points) in clinical status from baseline on the 7-point ordinal scale, using the log-rank test of superiority. Median time-to-improvement (2 points) in clinical status was assumed to follow an exponential survival distribution with difference between sarilumab and placebo median times assumed to be 2 days (5 days in placebo and 3 days in sarilumab group).

With a 2:2:1 randomization ratio (sarilumab 400 mg IV:sarilumab 200 mg IV:placebo) and assuming that accrual duration is 1 year (~365 days) with each patient followed for a period of at least 29 days, the Phase 3 portion of the study would require a total of approximately 300 patients in the severe and critical strata with high baseline IL-6. For a pairwise comparison between each sarilumab dose (400 mg IV or 200 mg IV) and placebo using a log-rank test, a sample size of approximately 123 on sarilumab and 61 on placebo (184 total) will provide 90% power at a 2-sided significance level of 0.05.

This study plans to enroll approximately 400 patients in Phase 3 Cohort 1 (across all IL-6 levels and severity of illness) in order to have 300 patients in the severe and critical strata to test the primary hypothesis in high IL-6 patients. The number of patients enrolled may be revised based on the observed distribution of baseline IL-6 levels in Phase 2.

Due to the novel nature of the COVID-19 pandemic, the ordinal scale primary efficacy endpoint planned in Phase 3 is not well established and will require confirmation based on Phase 2 data. At the end of the Phase 2 portion, power calculations will be reassessed, and Phase 3 sample size may be re-estimated.

Phase 3 Portion of the Study (Post-Adaptations)

Sample size calculations for the Phase 3 portion of the study after the adaptations are based on the Phase 3 primary endpoint of the percentage of patients who were on mechanical ventilation at baseline and had at least a 1-point improvement in the ordinal scale (ie, alive and off of ventilation). In Cohort 1, the hypothesis is tested only in patients in the critical stratum, first in the subgroup of patients on mechanical ventilation at baseline and then, as an enrichment strategy, in the overall critical stratum (ITT). In the Phase 2 portion of the study, approximately 17% of patients treated with placebo (ie, standard of care) and 57% of patients treated with sarilumab (on top of standard of care) achieved at least 1-point improvement by Day 22.

Cohort 1: With a 2:1 randomization ratio (sarilumab 400 mg IV: placebo), an effect size the same as that observed in Phase 2, and 170 patients in the critical stratum on mechanical ventilation, then the pairwise comparison between sarilumab 400 mg (n~113) and placebo (n~57) would have >99% power. Assuming the response rate on placebo is 17% and the rate on sarilumab 400 mg is 37% (ie, a difference in proportions is one-half that observed in Phase 2), then the sample size of 170 would provide approximately 80% power to detect this reduced difference. These calculations assume alpha=0.045, allowing for an interim analysis at the 0.005 level (see Section 11.5.1. Therefore, this study plans to enroll approximately 450 critical patients in order to have approximately 170 patients within the critical stratum who are on mechanical ventilation and randomized to 400 mg or placebo. Note that the total number of patients enrolled in Phase 3 Cohort 1 is larger than that to account for the patients who had been randomized to the severe stratum, MSOD stratum, or to the 200-mg dose group before the IDMC decision to discontinue further enrollment into those strata and dose groups.

Cohort 2: With a 1:1 randomization ratio (sarilumab 800 mg IV: placebo), an effect size the same as that observed in Phase 2 for 400 mg, and 225 patients total, then the pairwise comparison between sarilumab 800 mg (n=113) and placebo (n=112) would have >99% power to detect the difference observed in Phase 2, and would have 92% power if the effect were half of that observed in Phase 2 (ie, 20% difference). These calculations assume alpha=0.045, allowing for an interim analysis at the 0.005 level. A sample size re-estimation may occur after Phase 3 Cohort 1 results are determined.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

ITT population: The intention-to-treat (ITT) population includes all randomized patients who received at least one dose of the study drug. Analysis of the ITT population will be done according to the initial treatment assigned to the patient (as randomized). ITT population will be used for sensitivity analysis of the efficacy endpoints in Phase 2, as well as for analysis of data including (but not limited to) demographics and baseline characteristics. ITT population will be the primary analysis population for the Phase 3 Cohorts 1 and 2. For Cohort 1, the specific primary population will be the subset of patients on mechanical ventilation at baseline.

mITT population: The modified intention-to-treat (mITT) population includes all randomized patients who received at least one dose of the study drug and have high baseline IL-6 levels. Analysis of the mITT population will be done according to the initial treatment assigned to the

patient (as randomized). The mITT population will be the primary population for analysis of primary and secondary efficacy endpoints in Phase 2, as well as for data including (but not limited to) demographics and baseline characteristics.

PPS: The per protocol population set (PPS) includes all ITT patients who did not have any relevant major protocol deviations. A relevant major protocol deviation is one that may affect the interpretation of study efficacy results. The final determination of the definition of PPS will be made prior to the first database lock. Analysis of the PPS will be done according to the treatment the patient actually received (as treated). Determination of "as treated" will be based on the actual study drug received on Day 1. The PPS will be used only in Phase 3 Cohorts 1 and 2for sensitivity analysis of the primary efficacy endpoints.

11.3.2. Safety Analysis Set

Safety population: The safety population includes all randomized patients who received at least one dose of the study drug. Analysis of the Safety population will be done according to the treatment received (as treated). Determination of "as treated" will be based on the actual study drug received on Day 1.

11.3.3. Pharmacokinetic Analysis Sets

The PK analysis population includes all patients who received any study drug and who had at least 1 non-missing result following the first dose of study drug.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Subgroups will be defined by key baseline factors (eg, demographics, disease characteristics). Subgroup analyses will be performed on efficacy endpoints and safety endpoints, as needed. Details will be described in the Statistical Analysis Plan (SAP).

Statistical analyses will be performed using Statistical Analysis Software (SAS) Version 9.4 or higher.

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who discontinued from study treatment, and the reasons for discontinuation

- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation
- The ITT population, mITT population, and PPS (defined in Section 11.3.1)
- The Safety population (defined in Section 11.3.2)

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined.

11.4.3. Efficacy Analyses

The study analysis plan is based on the analysis of 2 populations, an mITT and an ITT population, within specific strata or combinations of strata. Supportive analyses may also be performed using the PPS population.

11.4.3.1. Primary Efficacy Analysis

Phase 2 portion of study (COVID-19 patients in all disease severity strata):

For the Phase 2 portion of the study, the primary efficacy analysis will be a pairwise comparison between sarilumab 400 mg IV and placebo with respect to the primary endpoint of percent change from baseline in CRP levels (natural logarithm scale) at Day 4.

Percent change from baseline in CRP levels is estimated using the natural log-transformed data. Missing values of CRP levels at Day 4 will be imputed by Day 3 or Day 5 levels when available, in this order of priority. CRP levels measured by local labs will be used to compute the primary endpoint. If local lab data is missing, then data from central labs will be used. Sensitivity analysis will be conducted using the CRP data from central labs. Additional details on missing data handling will be specified in the SAP.

Hypothesis test of superiority of sarilumab versus placebo will be done using an ANCOVA model with change from baseline in CRP at Day 4 as dependent variable; treatment group, severity of illness and systemic corticosteroid use as fixed effects, and ln(Baseline CRP) as covariate.

Estimation of treatment effect will be provided in terms of percent change from baseline in CRP levels at Day 4 along with 2-sided 95% confidence intervals. P-values will be compared to the 2-sided 5% significance level.

To determine the success of the Phase 2 portion of the trial, first the data in patients with high baseline IL-6 will be analyzed (mITT). If the treatment difference is statistically significant, similar analysis will be done between sarilumab 400 mg IV and placebo on the data for the full Phase 2 ITT population (that is, without regard to baseline IL-6 levels). In addition, the key secondary endpoint, time to improvement (2 points) in clinical status from baseline on the 7-point ordinal scale, will also be analyzed as below using Phase 2 data. These analyses will be used to inform selection of the primary endpoint for Phase 3 portion. Comparison between sarilumab 200 mg IV and placebo will also be performed descriptively.

Phase 3 portion of the study (COVID-19 patients in Cohort 1 critical disease severity stratum; and COVID-19 patients in Cohort 2):

Post adaptations to the Phase 3 study design, the primary efficacy analyses will be 2 separate pairwise comparisons, namely:

1. One in Cohort 1 critical patients with mechanical ventilation at baseline comparing sarilumab 400 mg IV versus placebo, and
2. Second in Cohort 2 patients receiving mechanical ventilation at baseline comparing sarilumab 800 mg IV versus placebo.

Primary endpoint for each comparison will be proportion of patients with a 1-point improvement in clinical status from baseline to Day 22 using the 7-point ordinal scale. Hypothesis tests of superiority of sarilumab (400 mg or 800 mg-dose) versus placebo will be done using the stratified Cochran-Mantel-Haenszel (CMH) test for 2 proportions. For Cohort 1, the stratification factor will be use of corticosteroids (yes/no). For Cohort 2, the stratification factors will be use of non-IL-6/6R therapies administered under an EUA at baseline (yes/no) and use of corticosteroids (yes/no).

Estimation of the treatment effect will be provided as differences in proportions and confidence intervals calculated using the strata-adjusted confidence intervals from CMH method (Zhang, 2016). Stratification factors are as mentioned above.

For each cohort, p-values and confidence intervals will be reported with overall Type 1 error controlled at 0.05 (2-sided).

11.4.3.2. Secondary Efficacy Analysis

Analysis for Phase 2 Key Secondary Endpoints:

The key secondary endpoint of time-to-improvement (2 points) in clinical status assessment with 7-point ordinal scale will be analyzed for Phase 2 similarly as described above for the Phase 3 primary endpoint in COVID-19 patients (all disease severity strata) with high baseline IL-6 (ie, mITT) as well as in the ITT population of all baseline IL-6 levels.

Testing of the key secondary endpoint for the Phase 2 portion of the study will be done at the significance level of 0.05 (2-sided). P-values for other secondary endpoints will also be reported and compared with 0.05 (2-sided) significance level for descriptive purpose.

Analysis for Phase 3 Key Secondary Endpoints:

The following key secondary endpoints in Phase 3 will be tested similarly as the Phase 3 primary endpoint described in Section 11.4.3.1. See Table 4 for details for secondary endpoints.

Cohort 1

1. Proportion of patients with at least 1-point improvement in clinical status assessment from baseline to Day 22 in patients with critical COVID-19

2. Proportion of patients who recover (discharged, or alive without supplemental oxygen use or at pre-COVID oxygen use) by Day 22 in patients with critical COVID-19 receiving mechanical ventilation at baseline
3. Proportion of patients who die through Day 29 in patients with critical COVID-19 receiving mechanical ventilation at baseline
4. Proportion of patients who die through Day 29 in patients with critical COVID-19

Cohort 2

1. Proportion of patients who recover (discharged, or alive without supplemental oxygen use or at pre-COVID oxygen use) by Day 22 in patients with COVID-19 receiving mechanical ventilation at baseline
2. Proportion of patients who die through Day 29 in patients with COVID-19 receiving mechanical ventilation at baseline

Key secondary endpoints for the Phase 3 portion of the study will be tested sequentially in a hierarchical manner, while preserving the overall significance level at 0.05 (2-sided).

Analysis for Other Secondary Endpoints (Phase 2 and Phase 3):

1. Differences in time-to-event endpoints by treatment (eg, time to a one category improvement in ordinal scale, and other time-to-event endpoints) will be summarized with Kaplan-Meier estimates and 95% confidence intervals on medians will be reported. P-values and confidence intervals for hazard ratios comparing treatment groups will also be reported using Cox proportional hazards model with stratification factors mentioned earlier. Cumulative incidence rates will be plotted with comparisons between groups descriptively tested using log-rank test.
2. Change in ordinal scale at specific time points will be summarized by proportions (eg, proportion who have a 1-, 2-, 3-, or 4-point improvement or 1-, 2-, 3-, 4-point worsening).
3. Duration of event (eg, duration of mechanical ventilation, ventilator-free days, days of hospitalization) will be summarized through descriptive statistics including mean, standard deviation, and median days with quartiles. P-values using 2-sample t-test and 95% confidence intervals using normal approximation will also be reported.
4. Continuous endpoints and their changes from baseline will be summarized through descriptive statistics including mean, standard deviation, median and quartiles, and 95% confidence intervals of means, as needed.
5. Categorical data (eg, 28-day mortality or ordinal scale by day) will be summarized according to proportions with confidence intervals on the difference or odds ratios for a binary or multiple category scale, respectively.

Missing data procedures will be described in the SAP.

11.4.4. Control of Multiplicity

Phase 2 Portion of the Study (Prior to Adaptations)

For the Phase 2 portion of the study, hypothesis test will be conducted for the Phase 2 primary endpoint of percent change from baseline in CRP levels at Day 4 in patients across all disease severity strata in mITT population (ie, high baseline IL-6). If there is substantial overlap between mITT (eg, ≥95%, then ITT will be the primary population). Otherwise, ITT population will be tested sequentially.

The key secondary endpoint of time-to-improvement (≥2 points) in clinical status assessment will only be descriptively analyzed in Phase 2. P-values will be reported for descriptive purpose.

Overall Type 1 error will be controlled at 0.05 level (2-sided) in Phase 2.

Based on Phase 2 results, adaptations may be made to Phase 3, such as to change Phase 3 endpoints and re-estimate the size of the Phase 3 portion of the study. The final Phase 3 analyses will be independent from Phase 2 and possess an independent 5% significance level.

Phase 3 Portion of the Study (Post-adaptations):

Primary analyses in Cohorts 1 and 2 will be conducted separately. Overall type 1 error will be controlled within each cohort at 0.05 (2-sided) level.

Multiplicity adjustment will be made for interim looks and significance level will be adjusted for final analysis of the primary endpoint within each cohort. Overall type 1 error for testing primary and key secondary endpoints within each cohort will be controlled using a hierarchical testing order as shown in Table 8.

Table 8: Testing Strategy for Control of Multiplicity in Phase 3 Cohorts 1 and 2 (Overall Type 1 Error in Each Cohort is 0.05 [2-sided])

Order	Timing of Analysis	Type of Endpoint	Endpoint	Population	Example Nominal Significance level, α
Cohort 1					
1	Final	Primary	Proportion of patients with a 1- point improvement in clinical status from baseline to Day 22	Critical COVID-19 patients receiving mechanical ventilation at baseline	0.049†
2	Final	Key Secondary	Proportion of patients with a 1- point improvement in clinical status assessment from baseline to Day 22	All Critical stratum COVID-19 patients (including ventilated or ECMO or not ventilated at baseline)	0.049†
3	Final	Key Secondary	Proportion of patients who recover (discharged, or alive without supplemental oxygen use) by Day 22	Critical COVID-19 patients receiving mechanical ventilation at baseline	0.049†
4	Final	Key Secondary	All-cause mortality at Day 29	Critical COVID-19 patients receiving mechanical ventilation at baseline	0.049†
5	Final	Key Secondary	All-cause mortality at Day 29	All Critical stratum COVID-19 patients (including ventilated or ECMO or not ventilated at baseline)	0.049†
Cohort 2					
1	Final	Primary	Proportion of patients with a 1- point improvement in clinical status from baseline to Day 22	COVID-19 patients receiving mechanical ventilation at baseline	0.049‡
2	Final	Key Secondary	Proportion of patients who recover (discharged, or alive without supplemental oxygen use) by Day 22	COVID-19 patients receiving mechanical ventilation at baseline	0.049‡
3	Final	Key Secondary	All-cause mortality at Day 29	COVID-19 patients receiving mechanical ventilation at baseline	0.049‡

Order	Timing of Analysis	Type of Endpoint	Endpoint	Population	Example Nominal Significance level, α

† If the interim analysis results for primary endpoint are statistically significant, then the Sponsor may decide to stop the cohort earlier for efficacy and the alpha used at interim will be reallocated to test the key secondary endpoints at the full α=0.05 (2-sided). If the interim analysis on the primary endpoint is not significant, the Sponsor will continue the follow-up of cohort and any interim results on the secondary endpoints will be exploratory. The Sponsor may present nominal p-values for key secondary endpoints at the interim without formal testing at interim.

‡ Interim analyses for Cohort 2. In case of interim analyses, similar alpha spending and alpha re-allocation rules will be used for Cohort 2.

11.4.5. Safety Analysis

11.4.5.1. Adverse Events

Definitions

For safety variables, the following observation period is defined:

- The on-treatment period is defined as the day from first dose of study drug (Day 1) to study Day 29 (patients who are discharged prior to Day 29 will receive a follow-up phone call to collect data on SAEs (if any), survival and history of hospital re-admission).

Treatment-emergent adverse events (TEAEs) are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period. In this study, only SAEs and AESIs are collected. As such TEAEs will reflect this data.

In addition, there will be an end of study (EOS) phone call follow-up to collect data on survival and history of hospital re-admission.

Analysis

All SAEs and AESIs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all reportable TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.5), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

11.4.5.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test for all patients and separately for patients in whom the PCSV criterion was normal or missing at baseline.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

11.4.5.3. Treatment Exposure

Exposure to study drug will be examined for each patient. The total number of doses administered to each patient and exposure related parameters (eg, duration of IV infusion, total volume of drug administered etc.) will be analyzed and summarized using descriptive statistics by treatment group in the Safety population.

11.4.5.4. Treatment Compliance

Treatment compliance in a given patient for this study is defined as the number of fully completed infusions of study drug divided by number of doses administered (applicable, both, to patients who receive only single dose or multiple doses since protocol amendment #4).

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

The concentrations of sarilumab and sIL-6R over time and selected PK parameters, as appropriate, will be summarized using descriptive statistics.

No formal statistical hypothesis testing will be performed.

11.4.7. Analysis of Pharmacodynamic and Exploratory Biomarker Data

The concentrations of exploratory PD/Biomarkers over time will be summarized using descriptive statistics and may be reported separately from the CSR.

11.5. Timing of Analysis

The timing of the analyses for this study are detailed in Section 6.2.

11.5.1. Interim Analysis in Phase 3

Because of the unmet medical need for effective medicines in this global COVID-19 pandemic situation, interim analyses are planned for efficacy in the Phase 3 portion of the study. The timing of the first interim analysis will be determined once approximately 110 patients in the Phase 3 Cohort 1 critical stratum receiving mechanical ventilation at baseline and randomized to 400 mg or placebo are enrolled, with a data lock point 22 days later. Interim analysis for this data lock will be conducted in all critical Phase 3 Cohort 1 patients who were enrolled until the first dose date of the last 110th patient in Cohort 1 critical stratum randomized to sarilumab 400 mg or placebo who was on a ventilator at baseline.

To preserve the overall Type 1 error at 0.05 in the Phase 3 Cohort 1, the primary efficacy endpoint will be tested at interim analysis at the 0.005 level (2-sided), leaving the remaining significance level of 0.049 (2-sided) for the final analysis should the interim results not be statistically significant. The information fraction at this first interim analysis will be 65% (ie, 110 patients out of 170 at final). Under the Hwang-Shih-DeCani alpha spending function (Hwang, Shih, DeCani, 1990, Anderson 2020 [gsDesign R package]) (assume gamma family with parameter $\gamma = -6.5$), if the interim analysis is not significant, then the nominal significance level for testing the final analysis of primary endpoint will be 0.049 (2-sided).

Should the interim analysis be positive, the alpha from the interim analysis will be recycled and added to the alpha for the planned key secondary endpoints which will allow them to be tested at a significance level of 0.05. Similar interim analyses are planned for the Phase 3 Cohort 2 and will be specified in the SAP in more detail.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (Sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, SAEs, baseline findings, medication, medical history, etc) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC) Medidata Rave.

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

The study monitor and/or designee will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate, and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (CRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRF that will be provided to the sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB. A copy of the IRB -approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patients Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board

An appropriately constituted IRB, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB approval letter with a current list of the IRB members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: An adaptive phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study Assessing Efficacy and Safety of Sarilumab for Hospitalized Patients with COVID-19 and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study Title: An Adaptive Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study Assessing Efficacy and Safety of Sarilumab for Hospitalized Patients with COVID-19

Protocol Number: 6R88-COV-2040

Protocol Version: 6R88-COV-2040 Amendment 7

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00114290 v1.0

ESig Approval	[redacted] 10-Jun-2020 22:09:57 GMT+0000
ESig Approval	[redacted] 10-Jun-2020 22:23:47 GMT+0000
ESig Approval	[redacted]ment 10-Jun-2020 22:39:29 GMT+0000
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ESig Approval	[redacted] 11-Jun-2020 14:36:25 GMT+0000

Signature Page for VV-RIM-00114290 v1.0 Approved