

AMENDED CLINICAL TRIAL PROTOCOL 04

Protocol title: An adaptive phase 3, randomized, double-blind, placebo-controlled study assessing efficacy and safety of sarilumab for hospitalized patients with COVID-19

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Amendment number: 04

Compound number (INN/Trademark): SAR153191
Sarilumab/Kevzara®

Study phase: Phase 3

Short title: Sarilumab COVID-19

Sponsor name: sanofi-aventis Recherche & Développement

Legal registered address: 1 avenue Pierre Brossolette
91385 Chilly Mazarin Cedex
France

Monitoring Team's Representative Name and Contact Information

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
<i>Amended Clinical Trial Protocol 04</i>	<i>All</i>	<i>11-Jun-2020, version 1 (electronic 4.0)</i>
<i>Amended Clinical Trial Protocol 03</i>	<i>All</i>	<i>29-Apr-2020, version 1 (electronic 3.0)</i>
<i>Amended Clinical Trial Protocol 02</i>	<i>All</i>	<i>08-Apr-2020, version 1 (electronic 2.0)</i>
<i>Amended Clinical Trial Protocol 01</i>	<i>All</i>	<i>26-Mar-2020, version 1 (electronic 1.0)</i>
<i>Original Protocol</i>	<i>All</i>	<i>18-Mar-2020, version 1 (electronic 1.0)</i>

Amended protocol [04] (11-Jun-2020)

This amended protocol 04 (amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of the amendment is to close enrollment into the sarilumab 200 mg IV arm while maintaining the original 2:1 ratio of sarilumab 400 mg IV to placebo. This amendment also clarifies instructions and provides additional guidance to investigators regarding follow-up and reporting of adverse events of special interest (AESI).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 1.2 Schema, Section 2.1 Study Rationale, Section 4.1 Overall Design, Section 4.2 Scientific Rationale for Study Design, Section 4.3 Justification for Dose, Section 6.1. Study Interventions administered (Table 3)	Closed enrollment to the sarilumab 200 mg IV arm	Based on anticipation of a more favorable benefit-risk profile in the 400 mg arm versus the 200 mg arm, enrollment in the 200 mg arm will be closed upon implementation of amended protocol 04.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Urinalysis and urine culture results, serum IL-6, adverse events	The timing of urinalysis, urine culture results, serum IL-6, and adverse events assessments was clarified. No changes were made to the collection schedule.
Section 5.2	E04 was modified to clarify that oral corticosteroids were a type of systemic corticosteroids.	Clarification of definition.
Section 10.3.1 Definition of AE	Events meeting the AE definition: Removed: "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.	This bullet is duplicated in error. The same information is included in the first bullet.
Section 10.3.1 Definition of AE	Events meeting the AE definition: The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.	This bullet is contradictory to the information provided, stating "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE.
Section 10.3.2.1 Recording and follow-up of AE and/or SAE	Added tables for assessment of intensity for infusion related reactions, hypersensitivity reactions, and neutropenia. Added guidance for the follow-up of AESIs of ALT increase and Grade 4 Neutropenia.	Provide guidance to the investigator.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

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

Short title: Sarilumab COVID-19

Rationale: See [Section 2.1](#)

Objectives and endpoints

Objectives

Primary

- To evaluate the clinical efficacy of sarilumab relative to the control arm in adult patients hospitalized with severe or critical COVID-19
-

Secondary

- Evaluate the 28-day survival rate
 - Evaluate the clinical efficacy of sarilumab compared to the control arm by clinical severity
 - Evaluate changes in the National Early Warning Score 2 (NEWS2)
 - Evaluate the duration of predefined symptoms and signs (if applicable)
 - Evaluate the duration of supplemental oxygen dependency (if applicable)
 - Evaluate the incidence of new mechanical ventilation use during the study
 - Evaluate the duration of new mechanical ventilation use during the Study
 - Evaluate the proportion of patients requiring rescue medication during the 28-day period
 - Evaluate need for admission into intensive care unit (ICU)
 - Evaluate duration of hospitalization (days)
 - The 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)
 - Major or opportunistic bacterial or fungal infections in patients with grade 4 neutropenia
 - Grade ≥ 2 infusion related reactions
 - Grade ≥ 2 hypersensitivity reactions
 - Increase in alanine transaminase (ALT) $\geq 3X$ ULN (for patients with normal baseline) or $>3X$ ULN AND at least 2-fold increase from baseline value (for patients with abnormal baseline)
 - Major or opportunistic bacterial or fungal infections
-

Tertiary/exploratory

- Evaluate the virologic changes in the treatment arms compared to the control arm as assessed by nasopharyngeal (NP) and blood quantitative SARS-CoV-2 counts
 - To evaluate the cytokine profile and additional biomarkers that may be associated with efficacy and safety associated with sarilumab treatment
 - To evaluate the incidence of new or worsening laboratory-confirmed serious secondary infections in the treatment arms as compared to the control arm
 - To characterize the concentrations of sarilumab in serum over time
 - Patients will not be recalled after discharge for any missing exploratory assessments.
-

Overall design:

This study is an adaptive, multi-national, multi-center, phase 3, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of sarilumab in hospitalized adults with severe or critical COVID-19. Patients were randomized in a 2:2:1 ratio to sarilumab 400 mg intravenous (IV), 200 mg IV, or matching placebo IV in a stratified manner prior to Amended Protocol 04. The sarilumab 200 mg IV dose arm will be closed for patients enrolled after Amended Protocol 04 is implemented.

Patients will receive a single dose of study drug on Day 1. Patients may receive a second dose with study drug (based on the original treatment group assigned) 24 to 48 hours after the first dose, if they meet prespecified criteria (see [Section 4.1](#)). Randomization will be stratified by severity of illness (severe OR critical) and use of systemic corticosteroids (Yes OR No).

Study duration: An individual patient will complete the study approximately 60 days from screening to follow-up on day 60 \pm 7 days. Patients will not be required to return to the hospital once discharged.

End of study definition: The end of study (EOS) 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: Hospitalized adult (\geq 18 years old) male and female patients with COVID-19.

Disclosure Statement: This is a parallel group treatment study with 3 arms that is participant and Investigator blinded.

Number of participants:

Approximately 400 patients randomized and treated with study medication.

Intervention groups and duration:

Study intervention(s)

Participants who satisfy the inclusion and exclusion criteria will be randomized (2:2:1) to one of the following IMP treatment groups:

- Sarilumab 400 mg IV
- Sarilumab 200 mg IV
- Matching placebo IV

Investigational medicinal product(s)

- Formulation: a 175 mg/ml sarilumab solution in a pre-filled syringe to deliver 200 mg in a 1.14 ml solution
- Route of administration: intravenous (IV)
- Dose regimen:
 - One infusion of sarilumab 400 mg IV, (two sarilumab 200 mg, single dose prefilled syringes (PFS), mixed in ██████████ 0.9% sodium chloride solution for IV use)
 - One infusion of sarilumab 200 mg IV, (one sarilumab, single dose PFS, mixed in ██████████ 0.9% sodium chloride solution for IV use)
 - One infusion of matching placebo ██████████ 0.9% sodium chloride solution for IV use).

For each treatment group, patients will receive a single dose of study drug on Day 1. Patients may receive a second dose with study drug (based on the original treatment group assigned) 24 to 48 hours after the first dose, if they meet prespecified criteria (see [Section 4.1](#)).

Statistical considerations:

Primary endpoint:

The primary endpoint is the time to improvement of 2 points in clinical status assessment from baseline using the 7-point ordinal scale.

The 7-point ordinal scale is an assessment of the clinical status. The scale is as follows:

1. Death;
2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);

6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7. Not hospitalized

Secondary endpoints:

Key secondary endpoint:

- Percent of patients alive at Day 29

The other secondary efficacy endpoints are:

- Proportion of patients with one point improvement from baseline in clinical status assessment at days 4, 7, 15, 21, 29 using the 7-point ordinal scale
- Mean change in the 7-point ordinal scale from baseline to days 4, 7, 15, 21, 29 (or until discharge)
- Time to resolution of fever defined as body temperature ($\leq 36.6^{\circ}\text{C}$ [axilla], or $\leq 37.2^{\circ}\text{C}$ [oral], or $\leq 37.8^{\circ}\text{C}$ [rectal or tympanic]) for at least 48 hours without antipyretics or until discharge, whichever is sooner,
- Time to resolution of fever (as defined above) and improvement in oxygenation (as defined below)
- Days with fever ($>37.4^{\circ}\text{C}$ [axilla], or $>38.0^{\circ}\text{C}$ [oral], or $>38.4^{\circ}\text{C}$ [rectal or tympanic]) based on maximum value observed during a 24-hour period
- Time to change in National Early Warning Score 2 (NEWS2) from baseline
- Time to NEWS2 of <2 and maintained for 24 hours
- Mean change from baseline to days 4, 7, 15, 21, 29 in NEWS2
- Time-to-improvement in oxygenation ($[\text{SpO}_2]/[\text{FiO}_2]$ of 50 or greater) compared to the nadir for at least 48 hours, or until discharge, whichever is sooner
- Alive off supplemental oxygen at day 29
- Days of hypoxemia ($\text{SpO}_2 < 93\%$ on room air, or requiring supplemental oxygen, or mechanical ventilatory support)
- Days of supplemental oxygen use
- Days of resting respiratory rate >24 breaths/min (maximum value if recorded at more than once a day)
- Time to oxygen saturation $\geq 94\%$ on room air
- Ventilator free days in the first 28 days (to day 29)
- Initiation of mechanical ventilation, non-invasive ventilation, or use of high flow nasal cannula (for those not requiring these interventions at baseline)
- Proportion of patients requiring rescue medication during the 28-day period

- ICU status (among those not in an ICU at baseline, record if transferred to the ICU or the need to transfer to the ICU [if the ICU is not available])
- Days of hospitalization among survivors

Safety

The secondary safety endpoints are:

- Incidence of serious adverse events
- The incidence of major or opportunistic bacterial or fungal infections
- The incidence of major or opportunistic bacterial or fungal infections in patients with grade 4 neutropenia
- The incidence of hypersensitivity reactions, infusion reactions, gastrointestinal perforation
- White blood cell count, hemoglobin, platelets, creatinine, total bilirubin, alanine aminotransferase (ALT) on days 1, 4, 7, 15, 21, 29 (if still hospitalized)

Procedures and assessments

Efficacy procedures and assessments include clinical data collection, body temperature, oxygen delivery and oxygenation, resting SpO₂, and National Early Warning Score².

Safety procedures and assessments include laboratory testing, vital signs, targeted physical examination, and concomitant medication review.

Statistical plan

Assuming that accrual duration is 3 months (~90 days) with each patient followed for a period of at least 29 days, the proportions of patients with two points improvement from baseline in clinical status assessment at day 15 are 45% and 70% for placebo and sarilumab, respectively, a total sample size of approximately 400 patients with a 2:2:1 randomization ratio provides at least 90% power for pairwise comparisons between each sarilumab dose (400 mg IV or 200 mg IV; n~160 each) and placebo (n~80), using a log-rank test for superiority at a two-sided significance level of 0.05. Sample size calculation was performed using PASS 14.

The primary analysis is planned when the last patient randomized reaches Day 29 (or planned Day 29 if the patient is discharged or leaves the study early). Final analysis will be performed at study end at Day 60.

The primary endpoint, which is the time to improvement of 2 points in clinical status assessment from baseline using the 7-point ordinal scale, will be analyzed using a log-rank test stratified by randomization stratum with treatment as a fixed factor in the mITT population. P-value for the pairwise treatment comparison versus placebo will be provided. Estimation of treatment effect of each sarilumab dose will be provided as hazard ratio (sarilumab versus placebo) using Cox proportional hazards model stratified by the randomization stratum with treatment as a covariate,

along with 2-sided confidence intervals. Kaplan-Meier (KM) plot and the median time-to-improvement of 2 points will also be provided.

The key secondary endpoint, which is percent of patients alive at Day 29, will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by randomization stratum in the mITT population. Estimation of treatment effect of each sarilumab dose will be reported as difference in proportion of patients alive at Day 29 (sarilumab - placebo), along with 95% confidence levels. P-value for the pairwise treatment comparison versus placebo will be provided.

For the primary and key secondary endpoints, multiplicity will be controlled via a hierarchical testing procedure in the following order:

1. Primary endpoint sarilumab 400 mg versus placebo
2. Key secondary endpoint sarilumab 400 mg versus placebo
3. Primary endpoint sarilumab 200 mg versus placebo
4. Key secondary endpoint sarilumab 200 mg versus placebo

If one sarilumab dose is discontinued for safety reasons, then all comparisons versus placebo for that dose will be removed and the remaining comparisons will be tested in the order specified above.

An interim analysis is planned to be performed when approximately 50% of total planned number of patients (~200) are randomized. The purpose of the interim analyses is to obtain an understanding of the possible drug effect in the population under study. An administrative alpha of 0.001 will be spent at interim analysis (1).

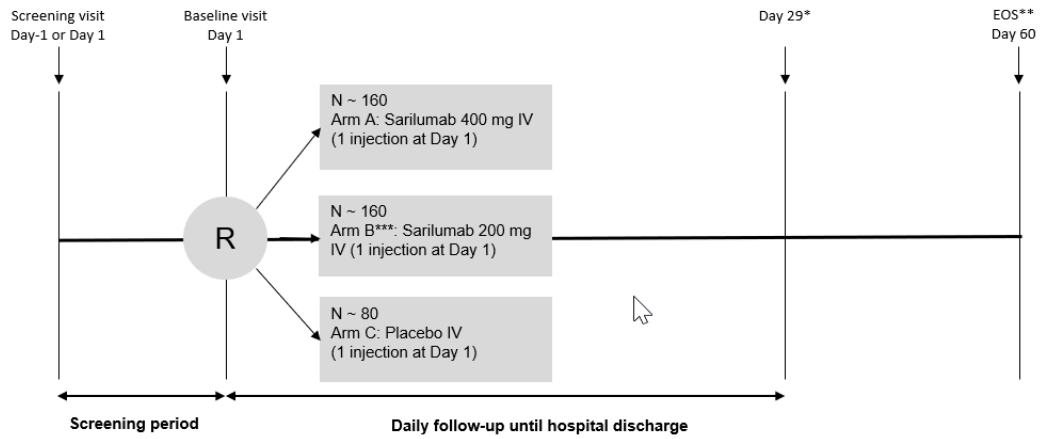
The interim analyses will be performed by an external statistical analysis center and are separated from personnel involved in the trial conduct. The unblinded results can only be viewed by a small group of senior sponsor individuals, who are separate from sponsor personnel involved in the conduct of the study. People involved in the conduct of the study (Patients, Investigators, Study Team, and Project Team) will have no access to the interim analysis results.

Independent Data Monitoring Committee: Yes

An independent data monitoring committee (IDMC) is established to oversee the welfare of patients in the study and to monitor all data to make recommendations to continue the study, to modify the protocol, or to terminate the study. The IDMC members include 2 to 4 independent expert physicians with relevant medical specialist training and 1 statistician.

1.2 SCHEMA

Figure 1 - Graphical study design



* If the patients has been discharged from the hospital before Day 29, the study site staff will contact the patient for a follow-up phone call

** The EOS will be on Day 60 or day of death, whichever comes first. 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

*** Enrollment closed upon implementation of Amended Protocol 04

R: Randomized; EOS: End of study; IV: intravenous; N: number

1.3 SCHEDULE OF ACTIVITIES (SOA)

Study Procedure	Screening Visit ²	Baseline Visit ²	Follow-up Until Hospital Discharge						EO S ³	Discharge Before Day 29 ^{4,5}
			Day	2 or 3	4	7	15	21		
Window (day)									±7	
Screening/Baseline:										
Inclusion/Exclusion For a positive SARS-CoV-2 test qualification, see footnote ¹	X									
Informed Consent	X									
Pharmagenomics Sub-Study Consent	X									
Demographics and Medical History	X									
History of hypercapnic respiratory failure ⁷	X									
Randomization		X								
Treatment:										
Study Drug Administration		X	X ⁶							
Assessments:										
Efficacy										
Body Temperature ⁸	X (4 times a day)		Day 1-3: 4 times a day, Day 4-29: 2 times a day							X
Oxygen Delivery and Oxygenation ⁹	X (4 times a day)		Day 1-3: 4 times a day Day 4-29: record results as assessed							X
Resting SpO ₂ ¹⁰	X (4 times a day)		Day 1-3: 4 times a day Day 4-29: record results as assessed							X
Clinical Daily Assessment (including 7-point ordinal scale) ¹¹	X		Daily until discharge							X
Vital Status (and cause of death)			Daily until discharge						X	X
Arterial blood gas results (as available) ¹²			X							
Vital Signs ¹³ (other than temperature and SpO ₂)	X		Daily until discharge							X
Targeted physical examination	X									

Study Procedure	Screening Visit ²	Baseline Visit ²	Follow-up Until Hospital Discharge						EO S ³	Discharge Before Day 29 ^{4,5}
			Day	2 or 3	4	7	15	21		
Window (day)	-1 or 1	1							±7	
Optional Electrocardiogram (ECG) ¹⁴	X									
Record Concomitant Therapy ¹⁵	X		Daily until discharge							X
Adverse Events ¹⁶	X		Daily until discharge						X	X
Pregnancy Test (WOCBP) ¹⁷	X									
Bacterial infection testing and fungal infection testing (blood)					X	X				
Laboratory Testing Standard-of-Care (Local Laboratories):										
Hematology Results ¹⁸	X	X ²	X ⁶	X	X	X	X	X		X
Blood Chemistry Results ¹⁹	X	X ²	X ⁶	X	X	X	X	X		X
Urinalysis ²⁰	X				X					
Urine Culture Results (if available) ²⁰	X				X					
Optional nasopharyngeal swab for SARS-CoV-2 detection ²¹		X			X	X	X	X		X
PK/Biomarkers (Central Laboratories):										
Serum for PK/Sarilumab Concentration ²²		X ²²	X ²²	X ²²	X	X	X	X ²²		X ²²
ADA		X			X ²³			X		X
Serum IL-6 ²⁴		X		X	X	X	X	X		X
Serum sIL-6R ²⁵		X ²⁵						X		X
Blood for PCR SARS-CoV-2 ²⁶ (Not for determining the inclusion criteria)		X			X	X	X	X		X
Pharmacogenomics (optional genomic study):										
Blood for DNA/RNA ²⁷		X								

ESO: end of study, SpO₂: oxygen saturation, CT-scan: computed tomography ECG: electrocardiogram, WOCBP: women of childbearing potential, PK: pharmacokinetic, ADA: antidrug antibodies, sIL-6R: soluble interleukin 6 receptor, IL: interleukin, PCR: polymerase chain reaction, SARS-Cov-2: Severe acute respiratory syndrome coronavirus 2, DNA: deoxyribonucleic acid, RNA: ribonucleic acid, SAE: serious adverse event, AESI: adverse event of special interest.

1. Laboratory-confirmed SARS-CoV-2 infection (eg by PCR), or other commercial or public health assay in any specimen within 2 weeks prior to randomization and no alternative explanation for current clinical condition is required for inclusion.
2. Screening and baseline may occur within 24 hours. Assessments that are noted for both visits should only be assessed once if the baseline visit is within 24 hours of the screening visit. All baseline samples, if obtained, should be collected before study drug administration at baseline visit except post-infusion PK and sIL-6R samples.
3. Patients will have an end of study (EOS) assessment to collect data on survival, adverse events, and history of hospital re-admission. This assessment may be performed by phone. This visit may be performed earlier if a patients withdraws from the study.
4. Patients discharged prior to Day 29 will have a follow-up phone call on Day 29 to collect data on all adverse events, and history of hospital re-admission.
5. Patients discharged prior to Day 29 should have a sample collected on or before day of discharge. Any sample collected within 24 hours of the day of discharge do not need to be repeated.
6. Patients may receive a second dose with study drug 24 to 48 hours after the first dose, if the patient meets prespecified criteria in [Section 4.1](#). Day 2 or 3 samples are only taken from patients who are administered a second dose of study treatment. They should be drawn prior to administration of the second dose of study drug to aid in benefit/risk assessment.
7. Sites are required to capture the history of chronic hypercapnic respiratory failure.
8. Body temperature is described in [Section 8.1.2](#) (up to 4 times a day at screening). Retrospective temperature within the previous 24 hours can be considered for screening. Body temperature to be reported in the CRF should be the maximum value observed during any time period or window ([Section 8.1.2](#)).
9. Oxygen delivery and oxygenation: refer to [Section 8.1.2](#) of the protocol for details (up to 4 times a day at screening). Retrospective readings within the previous 24 hours can be considered for screening.
10. Must be measured after 5 minutes of rest (sitting or supine), and must be measured simultaneously with oxygen delivery and ventilation data.
11. Clinical Data Assessments (including 7-point ordinal scale, status of intubation, Intensive care unit admission/discharge, CT scan, X-rays, and any other imaging performed during hospitalization, daily consciousness for NEWS2 scoring system [2]): refer to [Section 8.1.1](#) of the protocol for details.
12. Results as reported to be recorded in arterial blood gas results electronic case report form (CRF) (as available).
13. Vital signs include height (screening only), weight (screening only), blood pressure, pulse, and respiration rate, See [Section 8.2.1](#)
14. The ECG is optional. Historical ECG from current hospital admission is acceptable.
15. Concomitant therapy: refer to [Section 6.5](#) of the protocol for details.
16. Adverse events: All AEs will be recorded in CRF. Note: any abnormal physical findings requiring medical or surgical intervention must be recorded as an AE.
17. Pregnancy testing to be performed locally in women of childbearing potential (WOCBP) only. Serum or urine pregnancy test are both acceptable.
18. Hematology: refer to [Table 11](#) for details.
19. Blood Chemistry: refer to [Table 11](#) for details.
20. Urinalysis is performed at screening (if feasible) and should be collected one additional time (optional) during the treatment period.
21. SARS-COV-2 detection will be performed locally. This test is optional.
22. Sarilumab concentration
 - Day 1 sampling: 2 samples with one taken pre dose, and 1 taken within 30 min after the end of infusion; end of infusion sample should be collected from the arm contralateral to that used for IV infusion

- For patients administered a 2nd dose, Day 2 or Day 3 sampling is performed with 2 samples taken on the day of the 2nd dose, with 1 taken pre dose, and 1 taken within 30 min after the end of infusion; end of infusion sample should be collected from the arm contralateral to that used for IV infusion
 - Day 4 (approximately 72 hours post first dose)
 - The Day 29 or Early Discharge PK sample may be used for ADA analysis
23. In the event of any SAE of severe infusion reaction, or any AESI of anaphylactic reaction or systemic allergic reaction that is related to IMP, ADA samples will be collected at or near the onset of the event for any additional analysis.
24. Serum IL-6 samples must be taken pre-dose. Samples are mandatory for baseline/Day 1, Discharge before Day 29 and Day 29. It is optional on Day 4, 7, 15, and 21.
25. Serum sIL-6R:
- Day 1 sample taken pre dose (as close to initiation of treatment as reasonable)
26. Blood collected will be shipped for the central analysis of SARS-CoV-2 viral load and is not for determining the inclusion criteria.
27. Separate consent is required for participation in the optional genomic sub-study and collection of a blood sample for (DNA/RNA). The sample for genomic DNA/RNA should be collected on Day 1 or may be collected at any visit.

2 INTRODUCTION

This study protocol describes an adaptive Phase 3 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 interleukin-6 receptor (IL-6R) blocker during an acute viral pneumonia.

2.1 STUDY RATIONALE

As there are no treatments with proven efficacy for treatment of patients with severe or critical COVID-19 in the current SARS-CoV-2 pandemic, investigation of novel or repurposed medication is clearly warranted to minimize the impact of COVID-19 on infected patients and society as a whole.

Rationale for Study Design

There are currently no approved treatments for COVID-19. With an increasing amount of people affected by COVID-19 worldwide, it is essential to identify safe treatments quickly. This study utilizes an adaptive phase 3 design aimed at gathering this efficacy data quickly while also closely monitoring safety for all participants. Because the optimal dose regimen of sarilumab IV is unknown for treatment of patients with severe or critical COVID-19, the study includes two dose levels. In addition, a second infusion of sarilumab 200 mg IV, sarilumab 400 mg IV, or placebo can be administered under the conditions specified in [Section 4.1](#). Enrollment to the sarilumab 200 mg IV dose arm will be closed for patients after implementation of Amended Protocol 04 (See [Section 4.3](#)).

As the 2 doses of sarilumab (200 mg IV or 400 mg IV) have not been evaluated formally in a phase 3 clinical trial, the study will have close monitoring by the IDMC. This Phase 3 study utilizes a double-blind to minimize potential for bias on the part of the investigator, patient, or sponsor. Whilst the double-blind is maintained the protocol allows for adaptation of the primary endpoint based on new or emerging information to manage the uncertainties regarding assessment, course and prognosis of pandemic COVID-19.

In the absence of treatments with demonstrated efficacy, a placebo control is warranted to distinguish the safety and tolerability of sarilumab from the background signs and symptoms of COVID-19 infection as well as evaluate its potential to reduce fever, reduce oxygen requirements, and improve clinical outcomes. Due to the severity of COVID-19, in this study 2 patients will be randomized to each sarilumab arm for every 1 patient randomized to placebo in order to minimize the number of patients exposed to placebo.

Because there remains uncertainty regarding appropriate choice of primary endpoint for efficacy trials in hospitalized patients with COVID-19, clinical status represented on a 7-point ordinal scale has been proposed as an endpoint with face-validity and interpretability without regard to the type or target of an investigational treatment. A 7-point ordinal scale clinical assessment has been utilized in a randomized open-label trial of lopinavir-ritonavir in hospitalized adult patients with COVID-19 (3). In this study (3) a 7-point ordinal scale with anchors similar to those included in the current protocol did exhibit sensitivity to change over time and results were

reported in sufficient detail to estimate COVID-19 clinical progression over a 14 to 28-day observation period.

A change in 2 points on the 7-point clinical scale included in the current protocol has face validity as a pragmatic measure of clinical status in hospitalized patients with COVID-19 because it is anchored by the intensity of the intervention needed to support respiration.

The key secondary endpoint is percent of patients alive at Day 29, because patients with severe or critical COVID-19 have elevated risk of non-survival related to conditions not captured in the primary endpoint (eg, myocardial infarction, acute kidney injury, coagulopathy, or secondary infection).

2.2 BACKGROUND

Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a protein-enveloped RNA virus (4) related to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome-related coronavirus (MERS-CoV)(5). COVID-19 presents with influenza-like symptoms (fever, cough, dyspnea, nausea, vomiting, diarrhea) and radiographic features of diffuse pneumonia (5, 6, 7, 8, 9), with more severe cases characterized by neutrophilia, lymphopenia, thrombocytopenia, elevations in acute phase reactants and inflammatory cytokines (8), including IL-6 (9). Over 25% of patients develop acute respiratory distress during the second week of hospitalization (7). Acute, life-threatening respiratory injury induced by coronavirus infection is associated with an over-exuberant cytokine release (also known as “cytokine storm”) (10, 11). Case series of patients afflicted with SARS-Cov and MERS-Cov pneumonia indicate that elevations in IL-6 and other pro-inflammatory cytokines are correlated with clinical and radiographic severity (12, 13) and that in SARS-Cov pneumonia, peak viral load precedes peak IL-6 concentration and subsequent peak radiographic severity (14). As of 14 March 2020, there are many efforts to develop vaccines, anti-virals, and therapeutics against COVID-19, but none have yet demonstrated meaningful efficacy.

Clinical management of hospitalized patients with COVID-19 includes supportive therapy: supplemental oxygen therapy to target SpO₂, empiric antimicrobials, empiric neuraminidase inhibitor for treatment of influenza when there is local circulation, and intensive care as required (WHO, 2020) (15).

Both SARS-CoV-2 (16, 17) and SARS-CoV (18) exploit angiotensin converting enzyme II (ACE2) to infect pulmonary and intestinal epithelial cells (18, 19, 20) and activate NF-kappa B upregulation of proinflammatory cytokines such as IL-6 (21, 22). SARS-CoV infected pulmonary epithelial cells, pneumocytes, and macrophages (M ϕ) produce elevated levels of IL-6, MCP-1, TGF- β 1, and other proinflammatory cytokines and chemokines (23).

SARS-CoV infected human bronchial epithelial cells secrete IL-6, IL-8, and gamma interferon (IFN- γ)-inducible protein 10 (IP-10) which stimulates monocyte-derived M ϕ and dendritic cells (DC) to also produce, IL-6, IL-8, IL-1 β , G-CSF, MIP-1 α/β , and TNF- α . These cytokines from SARS-Cov-infected pulmonary epithelial cells interfere with receptor-mediated endocytosis and DC priming of T cells. In vitro anti-IL-6 or anti-IL-8 antibodies restored DC capacity to prime T cells inhibited by cytokines produced by SARS-Cov-infected pulmonary epithelial cells (24). Excessive pulmonary and systemic cytokine release, sustained, in part by IL-6 signaling,

potentially results in infiltration of activated neutrophils into the alveolar space, followed by a fibroproliferative phase characterized by findings of alveolar hyaline membranes, with varying degrees of interstitial fibrosis, and eventual resolution (25, 26, 27).

These findings related to SARS-CoV support the possibility that systemic inhibition of IL-6 signaling can be used to therapeutic advantage when treating COVID-19.

In the setting of infection, IL-6 is an important mediator of fever induction (28). 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 (29).

During the current COVID-19 outbreak, tocilizumab has been used in 21 patients with severe COVID-19 infection and described in a retrospective study (30). 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. After tocilizumab 15 (75%) lowered oxygen intake after treatment and by Day 3 all patients had SpO₂ >94%, including 1 patient who was breathing without supplemental oxygen.

While evidence of efficacy of tocilizumab in COVID-19 remains unproven, early reports suggested that systemic inhibition of IL6 signaling may have value as a supportive therapy.

Sarilumab (KEVZARA®) is a recombinant human IgG1 kappa monoclonal antibody (mAb) directed against soluble and membrane-bound IL-6 receptor (IL-6R α). Sarilumab, formulated as a solution for subcutaneous (SC) injection at doses of 150 and 200 mg every 2 weeks (q2w), was first approved for the treatment of adult patients with rheumatoid arthritis (RA) in Canada on 12 January 2017, the United States (US) on 22 May 2017, the European Union (EU), Norway, Iceland, and Liechtenstein on 23 June 2017, and Japan on 27 September 2017. Sarilumab is currently approved for the treatment of moderate to severe RA in multiple countries across the globe. Sarilumab inhibition of IL-6 signaling leads to a decrease in concentration of free sIL-6R α and normalization of levels of acute phase proteins and markers of inflammation, such as C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen (31). Because sarilumab inhibits both soluble and membrane bound forms of IL-6R α , thereby suppressing pro-inflammatory signaling by both pulmonary epithelial and immune cells, it has the potential to reduce the severity of pulmonary COVID-19 complications, including respiratory failure. There is no evidence that sarilumab has anti-viral potential.

2.3 BENEFIT/RISK ASSESSMENT

For patients with RA, sarilumab 150 mg and 200 mg every 2 weeks by SC injection has demonstrated clinically meaningful reductions of inflammatory joint swelling and tenderness of RA, improvements in physical function, and reduced progression of joint damage as measured by radiography.

However, in clinical trials of patients with RA sarilumab was associated with an increased risk of infections, including serious infections. As with other immunomodulatory therapies for RA, serious and sometimes fatal infections have been reported on sarilumab.

For this study it is proposed to administer sarilumab IV to patients with a confirmed viral pneumonia for which no antiviral therapy has demonstrated effectiveness. However, the potential benefit of sarilumab for patients with COVID-19 is suppression of the cytokine storm which may be a more important and long-lasting contributor to lung damage than the viral infection itself. One of the features of coronavirus pneumonia is a local and systemic increase in activated neutrophils which function to eliminate the viral infection but also inflict collateral damage to the pulmonary epithelium (26). In this context the dose-related reduction of absolute neutrophil count (ANC) associated with IL-6 α inhibition may help to mitigate the coronavirus-induced neutrophilia.

Uncertainties associated with this study include the route of administration, IV, and the sarilumab 400 mg dose; both intended to increase C_{max} and decrease t_{max} compared to SC route. Given that changes in ANC of antibody-mediated sIL-6 α are dose-dependent, irrespective of route of administration, it is anticipated that sarilumab delivered IV will rapidly suppress ANC. Based on analyses of 7985.5 patient-years of sarilumab exposure collected over 7.3 years from 3358 clinical trial patients with RA, the incidence of infection and serious infection did not increase with increasing severity of neutropenia. ANC values on sarilumab were normal for the majority of infections occurring within 12 weeks after sample collection (3452/3943 [88%] and 370/434 [85%] of patients reporting infections from patients treated with sarilumab plus conventional anti-rheumatic disease-modifying drug and sarilumab monotherapy, respectively. Both observations support the consistent finding that low ANC is not associated with an increased rate of infection for patients treated with sarilumab.

To mitigate the uncertainty around safety and tolerability of sarilumab IV, review of safety data by an independent data monitoring committee (IDMC) after the dosing of the first 12 patients will be required.

Although risks of treatment with sarilumab are established and benefits for patients with COVID-19 are potential, the absence of effective treatments of COVID-19 complications associated with excessive cytokine release during this ongoing pandemic, investigations such as this study are warranted.

A recently published retrospective cohort study (n=191) of hospitalized patients with COVID-19 reports that patients with multi-organ dysfunction (MOD), as quantified using the Sequential Organ Failure Assessment (SOFA) score have a 5.65 odds ratio for non-survival (16). Because the potential benefit is marginal relative to the burden of study-related procedures and established risks of sarilumab, patients with multi-organ dysfunction, along with patients who, in the opinion of the investigator are unlikely to survive after 48 hours will not be included in the study.

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

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives

Primary Objectives
<ul style="list-style-type: none">To evaluate the clinical efficacy of sarilumab relative to the control arm in adult patients hospitalized with severe or critical COVID-19
Secondary Objectives
<ul style="list-style-type: none">Evaluate the 28-day survival rateEvaluate the clinical efficacy of sarilumab compared to the control arm by clinical severityEvaluate changes in the National Early Warning Score 2 (NEWS2)Evaluate the duration of predefined symptoms and signs (if applicable)Evaluate the duration of supplemental oxygen dependency (if applicable)Evaluate the incidence of new mechanical ventilation use during the studyEvaluate the duration of new mechanical ventilation use during the StudyEvaluate the proportion of patients requiring rescue medication during the 28-day periodEvaluate need for admission into intensive care unit (ICU)Evaluate duration of hospitalization (days)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:<ul style="list-style-type: none">Serious adverse events (SAEs)major or opportunistic bacterial or fungal infections in patients with grade 4 neutropeniaGrade ≥ 2 infusion related reactionsGrade ≥ 2 hypersensitivity reactionsIncrease in alanine transaminase (ALT) $\geq 3X$ ULN (for patients with normal baseline) or $>3X$ ULN AND at least 2-fold increase from baseline value (for patients with abnormal baseline)major or opportunistic bacterial or fungal infections
Tertiary/exploratory
<ul style="list-style-type: none">Evaluate the virologic changes in the treatment arms compared to the control arm as assessed by nasopharyngeal (NP) and blood quantitative SARS-CoV-2 countsTo evaluate the cytokine profile and additional biomarkers that may be associated with efficacy and safety associated with sarilumab treatmentTo evaluate the incidence of new or worsening laboratory-confirmed serious secondary infections in the treatment arms as compared to the control armTo characterize the concentrations of sarilumab in serum over timePatients will not be recalled after discharge for any missing exploratory assessments.

Table 2 - Endpoints

Primary Endpoints

The primary endpoint is the time to improvement of 2 points in clinical status assessment from baseline using the 7-point ordinal scale.

The 7-point ordinal scale is an assessment of the clinical status. The scale is as follows:

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

Secondary Endpoints

Key Secondary Endpoint

- Percent of patients alive at Day 29

Other Secondary Endpoints (Efficacy)

- Proportion of patients with one point improvement from baseline in clinical status assessment at days 4, 7, 15, 21, 29 using the 7-point ordinal scale
- Mean change in the 7-point ordinal scale from baseline to days 4, 7, 15, 21, 29 (or until discharge)
- Time to resolution of fever defined as body temperature ($\leq 36.6^{\circ}\text{C}$ [axilla], or $\leq 37.2^{\circ}\text{C}$ [oral], or $\leq 37.8^{\circ}\text{C}$ [rectal or tympanic]) for at least 48 hours without antipyretics or until discharge, whichever is sooner
- Time to resolution of fever (as defined above) and improvement in oxygenation (as defined below)
- Days with fever ($>37.4^{\circ}\text{C}$ [axilla], or $>38.0^{\circ}\text{C}$ [oral], or $>38.4^{\circ}\text{C}$ [rectal or tympanic]) based on maximum value observed during a 24-hour period
- Time to change in NEWS2 from baseline
- Time to NEWS2 of <2 and maintained for 24 hours
- Mean change from baseline to days 4, 7, 15, 21, 29 in NEWS2
- Time-to-improvement in oxygenation ($[\text{SpO}_2]/[\text{FiO}_2]$ of 50 or greater) compared to the nadir for at least 48 hours, or until discharge, whichever is sooner
- Alive off supplemental oxygen at day 29
- Days of hypoxemia ($\text{SpO}_2 < 93\%$ on room air, or requiring supplemental oxygen, or mechanical ventilatory support)
- Days of supplemental oxygen use
- Days of resting respiratory rate >24 breaths/min (maximum value if recorded at more than once a day)
- Time to oxygen saturation $\geq 94\%$ on room air
- Ventilator free days in the first 28 days (to day 29)
- Initiation of mechanical ventilation, non-invasive ventilation, or use of high flow nasal cannula (for those not requiring these interventions at baseline)
- Proportion of patients requiring rescue medication during the 28-day period

- ICU status (among those not in an ICU at baseline, record if transferred to the ICU or the need to transfer to the ICU [if the ICU is not available])
 - Days of hospitalization among survivors
-

Secondary Endpoints (Safety)

The safety endpoints are:

- Incidence of serious adverse events
 - The incidence of major or opportunistic bacterial or fungal infections
 - The incidence of major or opportunistic bacterial or fungal infections in patients with grade 4 neutropenia
 - The incidence of hypersensitivity reactions, infusion reactions, gastrointestinal perforation
 - White cell count, hemoglobin, platelets, creatinine, total bilirubin, ALT on days 1, 4, 7, 15, 21, 29 (if still hospitalized)
-

Tertiary/exploratory

- 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 nasopharyngeal (NP) sample at days 7, 15, 21, and 29
 - Quantitative SARS-CoV-2 virus in the NP sample at days 7, 15, 21, and 29
 - Development of SARS-CoV-2 variants in NP sample at day 7, 15, 21, and 29
 - Quantitative SARS-CoV-2 virus in blood at days 7, 15, 21, and 29
 - To evaluate the cytokine profile and additional biomarkers that may be associated with efficacy and safety associated with sarilumab treatment
 - To evaluate the incidence of new or worsening laboratory-confirmed serious secondary infections in the treatment arms as compared to the control arm
 - To characterize the concentrations of sarilumab in serum over time
 - Patients will not be recalled after discharge for any missing exploratory assessments.
-

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is an adaptive phase 3, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of sarilumab in hospitalized adults with severe or critical COVID-19. The study will be conducted in Europe and other countries except in the United States (US) in up to 100 sites.

Patients will be randomized in a 2:2:1 allocation ratio to sarilumab 400 mg IV, sarilumab 200 mg IV, or placebo. The sarilumab 200 mg IV dose arm will be closed for patients enrolled after Amended Protocol 04 is implemented. Patients enrolled after implementation of Amended Protocol 04 will be randomized in a 2:1 allocation ratio to sarilumab 400 mg IV or placebo ([Section 4.3](#)). All patients will receive a single dose of study drug on Day 1. Patients may receive a second dose with study drug (based on the original treatment group assigned) 24 to 48 hours after the first dose, if

1. The Benefit Risk assessment by the investigator favors the administration of another dose of study drug without compromising safety (e.g., increase in LFTs, neutropenia)

AND

2. And least one of the following criteria is met:
 - Increase in fever or recurrence of fever compared to Day 1 OR
 - Increase or no change in FiO₂ requirement compared to Day 1 OR
 - Requiring vasopressors, ECMO, or development of multi-organ dysfunction

The safety data from approximately the first 12 patients randomized (assuming a total of ~10 patients are dosed on the sarilumab doses of 200 mg IV or 400 mg IV) will be reviewed by an independent data monitoring committee (IDMC) after the last of these patients dosed reaches Day 7. Data on approximately the first 12 and 50 patients (regardless of severity of illness) with at least 7-days follow-up will be reviewed by the IDMC to determine if the study can continue with or without modification. Subsequently, the frequency of IDMC meetings will be determined following the first 2 IDMC meetings. In addition to these specific assessment times, the IDMC will actively monitor interim data to make recommendations about early study closure, changes to study arms, and/or the eligible patient population throughout the course of the study.

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. Serum IL-6 and other markers will be collected and analyzed in a central laboratory. Nasopharyngeal (NP) samples to monitor viral infection and blood samples will be requested on day 1 (pre-dose), 4, 7, 15, 29 (or up until the day of discharge if the patient is discharged from the hospital before day 29).

Randomization will be stratified by:

- Severity of illness
 - Severe disease
 - Critical disease
- Systemic corticosteroids (Yes/No)

The severity categories are:

- Severe disease:
 - Requires supplemental oxygen administration by nasal cannula, simple face mask, or other similar oxygen delivery device
- 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 intensive care unit.

Note: Participants meeting criteria for both severity categories will be stratified according to the more severe category.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Rationale for Study Design

This Phase 3 study utilizes a double-blind to minimize potential for bias on the part of the investigator, patient, or sponsor. Whilst the double-blind is maintained the protocol allows for adaptation of the primary endpoint based on new or emerging information to manage the uncertainties regarding assessment, course and prognosis of pandemic COVID-19.

Because of the novelty of the SARS-CoV-2 pathogen, the ease with which it spreads within a community, the current absence of effective anti-viral therapies or vaccines, and still evolving knowledge regarding course of disease and risk factors for progression, there is no criterion of efficacy validated by health authorities to support authorization for use. An adaptive design is necessary to accommodate these multiple uncertainties during this global health crisis to make most efficient use of valuable participant data and investigator resources in the context of an ongoing pandemic while maintaining the rigor of a double-blind placebo-controlled comparison.

In the absence of treatments with demonstrated efficacy, a placebo control is warranted to distinguish the safety and tolerability of sarilumab from the background signs and symptoms of COVID-19 infection as well as evaluate its potential to reduce fever, reduce oxygen requirements, and improve clinical outcomes.

4.2.1 Participant input into study design

Due to the urgency of the SARS-CoV-2 pandemic potential participants have not been involved in the design of this clinical trial.

4.3 JUSTIFICATION FOR DOSE

Rationale for dose selection

The sarilumab IV doses of 200 mg and 400 mg for this study are based similar pharmacokinetic (PK), pharmacodynamic (PD), and safety profiles between sarilumab and tocilizumab and the dose of tocilizumab 400 mg IV included in (32) mentioned in Xinhua press release dated 7 March 2020 (32) based on a case series of 20 patients treated in China (30). The PK, PD and safety of sarilumab and tocilizumab were compared in several 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. 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 (33). In these single dose 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. 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. 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 (34). Although PK/PD modeling suggested that the higher binding affinity to IL-6R α of sarilumab compared to tocilizumab translates to greater receptor occupancy (35), there is currently no detailed information available on sIL-6R α concentrations in patients with COVID-19. It is possible (perhaps probable) that peak concentrations of sIL-6R α in patients with COVID-19 may greatly exceed what has been measured in patients with RA; therefore, dose-finding above exposures yielded by SC of sarilumab are needed given the urgency to identify useful therapeutics for COVID-19.

Because the optimal dose regimen of sarilumab IV is unknown for treatment of patients with severe or critical COVID-19, the study includes two dose levels. In addition, a second infusion of sarilumab 200 mg IV, sarilumab 400 mg IV, or placebo can be administered under the conditions specified in [Section 4.1](#).

Senior management, who are separate from the blinded team involved in study management and are not involved in any study related activities, reviewed a pre-specified, one time, unblinded interim analysis report ([Section 9.5](#)). Subsequent to this review, a scheduled IDMC reviewed additional unblinded data that is not available to this senior management team ([Section 9.6](#)). Both groups suggested to stop enrollment in the 200 mg arm. Thus, based on anticipation of a more favorable benefit-risk profile in the 400 mg arm versus the 200 mg arm, enrollment in the 200 mg arm will be closed upon implementation of amended protocol 04. The ratio of 2:1 will continue to be maintained for sarilumab 400 mg IV versus placebo after Amended Protocol 04 is implemented.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

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).

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be ≥ 18 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Hospitalized for less than or equal to 7 days (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)

AND meets at least one of the following prior to randomization (patients meeting more than one criterion will be categorized in the most severely affected category).

Participants who are with a:

- Severe disease:
Requires supplemental oxygen administration by nasal cannula, simple face mask, or other similar oxygen delivery device (ie. increase in oxygen requirement following COVID infection).
- 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 intensive care unit.

I 03. Laboratory-confirmed SARS-CoV-2 infection (eg, by PCR), or other commercial or public health assay in any specimen within 2 weeks prior to randomization and no alternative explanation for current clinical condition.

I 04. Willing and/or able to comply with study-related procedures/assessments

Sex

I 05. Male and/or female

Contraceptive use by men or women should be consistent with the prescribing information for Kevzara and with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

I 06. Capable of giving signed informed consent as described in Appendix 1 ([Section 10.1](#)) of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions and prior/concomitant therapy

E 01. In the opinion of the investigator, unlikely to survive after 48 hours, or unlikely to remain at the investigational site beyond 48 hours.

Note: Multi-organ dysfunction patients (defined as dysfunction of 2 or more organ systems) and patients requiring extracorporeal life support or renal replacement therapy are excluded.

E 02. Presence of any of the following abnormal laboratory values at screening: absolute neutrophil count (ANC) less than 2000/mm³, AST or ALT greater than 5 x ULN, platelets <50,000 per mm³.

E 03. Any prior (within the defined periods below) or concurrent use of immunosuppressive therapies at screening including but not limited to the following:

- 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 (other than interventional drug).
- Cell-depletion agents (eg, anti CD20) without evidence of recovery of B cells to baseline level.
- Anakinra within 1 week of baseline.
- Abatacept within 8 weeks of baseline.
- Tumor necrosis factor (TNF) inhibitors within 2-8 weeks (etanercept within 2 weeks, infliximab, certolizumab, golimumab, or adalimumab within 8 weeks), or after at least 5 half-lives have elapsed, whichever is longer.
- Alkylating agents including cyclophosphamide (CYC) within 6 months of baseline.
- Cyclosporine (CsA), azathioprine (AZA) or mycophenolate mofetil (MMF) or leflunomide or methotrexate within 4 weeks of baseline.

- Intravenous immunoglobulin (IVIG) within the past 5 months or plans to receive during the study period

Please consult sponsor if the patient has taken any other immunosuppressant therapy not described above within 6 months of screening.

- E 04. Use of systemic chronic (e.g. oral) corticosteroids for a non-COVID-19-related condition in a dose higher than prednisone 10 mg or equivalent per day at screening.
- E 05. Exclusion criteria related to tuberculosis (TB)
- Known active TB or a history of incompletely treated TB
 - Suspected or known extrapulmonary tuberculosis
- E 06. Patients with suspected or known active systemic bacterial or fungal infections within 4 weeks of screening.

Prior/concurrent clinical study experience

- E 07. Participation in any clinical research study, including any double-blind study, evaluating an investigational product or therapy within 3 months and less than 5 half-lives of investigational product prior to the screening visit.

Note: The use of unblinded investigational medications for the treatment of COVID-19 is permitted unless these medications are otherwise prohibited in the protocol.

Other exclusions

- E 08. Patient who withdraws consent during the screening period (following signing of the informed consent form).
- E 09. Any physical examination findings and/or history of any illness 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.
- E 10. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.
- E 11. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.
- E 12. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with section 1.61 of the ICH-GCP Ordinance E6).
- E 13. Any specific situation during study implementation/course that may rise ethics considerations.

- E 14. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

5.3 LIFESTYLE CONSIDERATIONS

No restrictions are required.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a different participant number.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTIONS ADMINISTERED

Table 3 - Overview of study interventions administered

ARM name	Sarilumab 200*	Sarilumab 400	Placebo
Intervention name	Sarilumab	Sarilumab	Placebo
Type	Drug	Drug	Drug
Dose formulation	One single-dose pre-filled syringe containing 200 mg sarilumab in 1.14 ml solution (175 mg/ml) added to ██████ 0.9% sodium chloride for a 1-hour intravenous infusion. Instructions on dose preparation are provided in the pharmacy manual.	Two single-dose pre-filled syringes, each containing 200 mg sarilumab in 1.14 ml solution (175 mg/ml) added to ██████ 0.9% sodium chloride for a 1-hour intravenous infusion. Instructions on dose preparation are provided in the pharmacy manual.	██████ 0.9% sodium chloride for a 1-hour intravenous infusion. Instructions on preparation are provided in the pharmacy manual.
Unit dose strength(s)	200 mg	400 mg	
Dosage level(s)	1 injection	1 injection	1 injection
Route of administration	IV injection	IV injection	IV injection
Use	experimental	experimental	placebo
IMP and NIMP	IMP	IMP	IMP
Packaging and labeling	Study Intervention will be provided in box by the Sponsor. Each box will contain 2 prefilled syringes and will be labeled as required per country requirement. Each box will be stored at the site at a temperature of 2°C to 8°C.	Study Intervention will be provided in box by the Sponsor. Each box will contain 2 prefilled syringes and will be labeled as required per country requirement. Each box will be stored at the site at a temperature of 2°C to 8°C.	NA
Tradename	Kevzara®	Kevzara®	NA

*Enrollment into the sarilumab 200 mg arm will be closed after implementation of Amended Protocol 04.

Instructions on the ancillary supplies needed for IV injection (IV infusion bags, IV infusion sets and IV infusion pumps) are provided in the pharmacy manual.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Detailed instructions are provided for the un-blinded pharmacist in the pharmacy manual.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for DTP shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

RANDOMIZATION

Randomization will occur only after patient has signed informed consent, completed screening procedures, and screening data has been reviewed by the investigator to assess patient eligibility.

Randomization will be performed according to a central randomization scheme using an interactive response technology (IRT).

Once the randomization procedure has been completed, the patient will be considered as randomized, whether or not IMP is administered.

BLINDING

Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved 3rd party, the pharmacist, will be responsible for the reconstitution and dispensation of all study interventions (sarilumab 400 mg, sarilumab 200 mg, or placebo). The pharmacist will endeavor to ensure that there are no differences in time taken to dispense following randomization. Once prepared, the

IMP will be identical in appearance when delivered for infusion. The unblinded pharmacist will be responsible for documentation of treatment as per pharmacy manual.

The study team directly involved with the study conduct will be blinded. In case of an adverse event, if knowledge of study drug is required for treating the patient, emergency unblinding to study drug can be performed. Code breaking can be performed through using the proper module of the IRT and/or by calling any other phone number provided by the Sponsor for that purpose.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.4 STUDY INTERVENTION COMPLIANCE

Measures taken to ensure and document treatment compliance and IMP accountability include:

- As participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision.
- The date and time of each dose administered will be recorded in the source documents and recorded in the CRF.
- All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

6.5 CONCOMITANT THERAPY

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 required to be captured in this trial (All other relevant concomitant medications are recommended to be captured as well, if feasible). The select list of medications that will be assessed from screening to Day 60 (or until day of discharge from hospital if before day 60) include:

- Corticosteroids, NSAIDs, and any other anti-pyretics
- Antivirals (eg. remdesivir), antifungals, antibacterials, antimycobacterials, antiprotozoans, anthelmintics, antimalarials (eg. chloroquine and hydroxychloroquine)
- Interferon beta and convalescent serum.
- Angiotensin converting enzyme and Angiotensin receptor blocking
- Agents that may affect the CYP450 substrate. See CYP substrates below for further detail.
- Any rescue medication that is used during the course of the study.

Information that should be gathered on these medications include:

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

The Sponsor can be contacted if there are any questions regarding concomitant or prior therapy.

CYP Substrates

Interleukin-6 has been shown to reduce cytochrome CYP1A2, 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[®]).

6.6 RESCUE THERAPY

During the course of the study, for patients requiring rescue therapy as per the judgement of the study physician, additional medications may be utilized. The benefit/risk of using additional medications in combination with study medication should be carefully considered. It is recommended that site-specific rescue therapy be identified and reserved for use prior to randomization. Administer rescue medication only 48 hours after the last infusion of study medication.

Rescue medications are defined as the immunosuppressive therapies (described in the exclusion criteria [E 03](#) and [E 04](#)).

6.7 INTERVENTION AFTER THE END OF THE STUDY

No intervention will be provided at the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

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 opt to withdraw from the study may be asked to provide a final blood draw sample for PK analysis before withdrawing from the study.

Patients prematurely discontinued from the study will not be replaced.

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for 60 days. See [Section 1.3](#) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Handling of participants after definitive intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the CRF when considered as confirmed.

7.1.2 Temporary discontinuation

Dose modification for an individual patient is not allowed.

Study drug discontinuation does not apply for this study.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Individual Patient Stopping Rules

For an individual patient, infusion rate should be slowed or stopped if they have a suspected drug-related event of hypersensitivity (Grade 2 or higher) during the infusion. Patients who have an IV infusion stopped for a safety related issue will not continue with dosing nor receive a subsequent dose.

Study Level Stopping Rules

An independent data monitoring committee (IDMC) will actively monitor 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 changes to the study based on the recommendations of the IDMC.

A treatment arm may be discontinued if there is a clinically meaningful imbalance between treatment arms in any of the following safety 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

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).

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early EOS visit should be conducted.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent to the extent allowed by local regulation.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the intervention, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate CRF forms and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant is discharged and cannot be reached by phone for the Day 60 EOS for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 ([Section 10.1](#)).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in [Section 1.3](#). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in [Section 1.3](#), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in [Section 1.3](#).

8.1 EFFICACY ASSESSMENTS

8.1.1 Clinical data collection

Clinical status of patient (7-point ordinal scale) (36) is described below:

1. Death;
2. Hospitalized, on invasive mechanical ventilation or ECMO;
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7. Not hospitalized

Additional clinical assessments that should be collected, if available, and performed as standard-of-care include, but are not limited to:

- Status of intubation
- Intensive care unit admission/discharge
- CT scan, X-rays, and any other imaging performed during hospitalization
- NEWS2 scoring system (2)

Consisting of Physiological Parameters: Respiration rate (per minute), SpO2 Scale 1 (%), SpO2 Scale 2 (%), Air or oxygen, Systolic blood pressure (mmHg), Pulse (per minute), Consciousness, Temperature (°C).

Table 4 - 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	

CVPU: confusion, voice responsive, pain responsive, unresponsive.

Note: Consciousness will be assessed as per the ACVPU scale.

A training document and web-based educational tools to support the implementation of the NEWS in a variety of formats are available at <http://tfnews.ocbmedia.com>. This training is not mandatory. These include additional training modules on hypercapnic respiratory failure and the use of supplemental oxygen, the significance of new confusion, and the importance of the NEWS in the consideration of potential sepsis as a cause for acute clinical deterioration.

Chronic hypercapnic respiratory failure will be 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.

8.1.2 Oxygen Administration and Oxygenation

Supplemental oxygen/FiO₂ use will be measured to monitor the patient's status regarding gas exchange per the schedule in [Section 1.3](#). 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

- FiO2 (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 SpO2 will be measured to assess arterial oxyhemoglobin saturation. SpO2 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. SpO2 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 (PaO2), partial pressure of carbon dioxide in arterial blood (PaCO2), oxyhemoglobin saturation in arterial blood from arterial blood gas analysis (SaO2).

8.1.3 Body temperature

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, or tympanic 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). Temperature will be measured according to timepoints and time period described (or as close as possible) in [Table 5](#). Body temperature measurement will occur before taking antipyretics or more than 4 hours after the last dose of antipyretics. Clinically indicated body temperature measurements between scheduled assessments should be recorded.

Body temperature to be reported in the CRF should be the maximum value observed during any time period or window.

Table 5 - Body temperature assessment

Assessment period	Time period of a day	Time window as a guide
Screening, Day 1 – Day 3	Morning	Before 10:00
	Noon	10:00 – 14:59
	Evening	15:00 – 19:59
	Bedtime	20:00 and after
Day 4 – Day 29	Morning	Before 12:00
	Evening	18:00 and after

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in [Section 1.3](#).

8.2.1 Vital signs

Vital signs, including height (screening only), weight (screening only), blood pressure, pulse, and respiration rate, will be collected and recorded at the time points according to [Section 1.3](#).

Any new finding or worsening of previous finding should be reported as a new adverse event.

8.2.2 Targeted Physical Examination

A targeted physical examination including lung auscultation and assessment of consciousness will be performed at time points according to [Section 1.3](#). Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

8.2.3 Electrocardiograms

A standard 12-lead ECG will be performed optionally at time points according to [Section 1.3](#). Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (identify QTcB or QTcF) intervals will be recorded in the eCFR. The ECG strips or reports will be retained with the source.

8.2.4 Clinical safety laboratory assessments

See Appendix 2 ([Section 10.2](#)) for the list of clinical laboratory tests to be performed and to [Section 1.3](#) for the timing and frequency. Additional clinical laboratory tests may be performed based on the investigator's clinical judgement.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

A laboratory manual will be provided to study sites with additional information for laboratory parameters assessed centrally.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 60 days of the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Sponsor.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE (see [Section 10.3.1](#)) or SAE ([Section 10.3.2](#)) and remain responsible for following up AEs that are serious, considered related to the study

intervention or study procedures, or that caused the participant to discontinue the study (see [Section 7](#)).

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the time points specified in the SoA ([Section 1.3](#)).

All AE will be collected from the signing of the ICF at the time points specified in the SoA ([Section 1.3](#)).

All SAEs and AESI ([Section 8.3.6](#)) will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 ([Section 10.3](#)). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 ([Section 10.3](#)).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and AESI (as defined in [Section 8.3.6](#)), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in [Section 7.3](#)). Further information on follow-up procedures is provided in Appendix 3 ([Section 10.3](#)).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Adverse events that are considered expected will be specified in the reference safety information (IB and associated addendum).
- Suspected unexpected serious adverse reactions (SUSARs) are reported to regulatory authorities, Investigators, and IRBs/IECs as follows:
 - For SUSARs that are life-threatening or result in death, reporting is no later than 7 days after first knowledge by the Sponsor, with all relevant follow-up information subsequently reported within an additional 8 days
 - For SUSARs, other than those that are life-threatening or result in death, reporting is no later than 15 days after first knowledge by the Sponsor
- An Investigator who receives an Investigator safety report describing a SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and associated addendum and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

It is the responsibility of the investigator to report to the sponsor (or designee), any pregnancy occurring in a female study patient, during the study.

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the outcome of the pregnancy. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 ([Section 10.4](#)).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse event of special interest

Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

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

- **Adverse Events of Special Interest** (AESI; serious and nonserious) include the following:
 - Grade ≥ 2 infusion related reactions (Infusion related reactions are defined as any signs or symptoms experienced by patients who receive IMP within 24 hours of the start of infusion)
 - Grade ≥ 2 hypersensitivity reactions
 - Grade 4 neutropenia (ANC $< 500/\text{mm}^3$)
 - Grade 4 neutropenia with concurrent invasive infection (ANC $< 500/\text{mm}^3$)
 - Increase in alanine transaminase (ALT) $\geq 3\text{X}$ ULN (for patients with normal baseline) or $> 3\text{X}$ 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
 - Symptomatic overdose (serious or nonserious) with IMP
 - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as an increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.

Management of acute reactions is described in [Section 10.3.4](#).

8.3.7 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 TREATMENT OF OVERDOSE

Sponsor does not recommend specific treatment for an overdose. In the event of an overdose, the Investigator should:

1. Contact the Sponsor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until sarilumab can no longer be detected systemically (at least 60 days).
3. Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the Sponsor (determined on a case-by-case basis).
4. Document appropriately in the CRF.

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

8.5 PHARMACOKINETICS

8.5.1 Sampling times

The sampling times for blood collection can be found in the schedule of activities ([Section 1.3](#)).

8.5.2 Sample handling procedure

The sample handling procedure is summarized in [Table 6](#) Special procedures for collection, storage and shipping of serum are described in separate operational manuals.

Table 6 - Summary of handling procedures for samples for sarilumab and sample for anti-sarilumab antibody

	Sarilumab	Anti-sarilumab antibody
Blood Sample Volume	5 mL	5 mL
Anticoagulant	none	none
Handling Procedures	See operation manual	See operation manual

8.5.3 Bioanalytical methods

A brief outline of the bioanalytical assay is given in [Table 7](#). Also, see operational manual.

Table 7 - Summary of bioanalytical method for sarilumab

Bioanalysis	Sarilumab	Anti-sarilumab antibody
Matrix	Serum	Serum
Analytical Technique	ELISA	Electrochemiluminescence
Site of Bioanalysis	Regeneron	Regeneron

8.5.4 Pharmacokinetic parameters

The following pharmacokinetic parameters will be calculated, using a non-compartmental method for serum concentrations of sarilumab after a single dose or two doses. The parameters will include, but may not be limited to, the following listed in [Table 8](#).

Table 8 - List of pharmacokinetic parameters and definitions

C_{max}	Maximum serum concentration observed
t_{max}	First time to reach C_{max}

8.6 PHARMACODYNAMICS

8.6.1 Pharmacodynamic parameters

Pharmacodynamic effects of sarilumab will be assessed through measurement of the following biomarkers: CRP, IL-6, sIL-6R

8.6.2 Assessment methods

The sample handling procedure is summarized in [Table 9](#). Special procedures for collection, storage and shipping of serum are described in separate operational manuals.

Table 9 - Summary of handling procedures for sIL-6 and IL-6

	sIL-6R	IL-6
Blood sample volume	3 mL	3 mL
Anticoagulant	none	none
Handling procedures	refer to Lab Manual	refer to Lab Manual

8.7 GENETICS

Genetics is an optional sub-study. Separate consent is required for participation in the optional genomic sub-study and collection of a blood sample for (DNA/RNA).

A 4 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

For the sub-study, samples will be stored and analysis may be performed on biomarker variants thought to play a role in COVID-19 including, but not limited to, genome-wide analysis for RNA, serum analytes, or tissue biomarkers to evaluate their association with observed clinical responses to demographic and disease characteristics and to sarilumab.

See Appendix 5 ([Section 10.5](#)) for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in central laboratory manual.

8.8 BIOMARKERS

Samples will be tested for IL-6, soluble IL-6R α , and SARS-CoV-2 to evaluate their association with the observed clinical responses (eg, body temperature, clinical status, NEWS2) to sarilumab.

8.9 HEALTH ECONOMICS/MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The hypothesis to be tested are superiority of sarilumab versus placebo with respect to the primary endpoint, which is the time to improvement of two points in clinical assessment from baseline in clinical status assessment using the 7-point ordinal scale. The statistical hypothesis (null H_0 versus alternative H_1) are stated below.

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

where $S_1(t)$ and $S_2(t)$ are the survival probability functions of the primary endpoint for sarilumab and placebo treatment groups, respectively.

9.2 SAMPLE SIZE DETERMINATION

The sample size calculations are performed based on the primary endpoint, the time to improvement of 2 points in clinical status assessment from baseline using the 7-point ordinal scale.

Assuming that accrual duration is 3 months (~90 days) with each patient followed for a period of at least 29 days, the proportions of patients with two points improvement from baseline in clinical status assessment at day 15 are 45% and 70% for placebo and sarilumab, respectively, a total sample size of approximately 400 patients with a 2:2:1 randomization ratio provides at least 90% power for pairwise comparisons between each sarilumab dose (400 mg IV or 200 mg IV; $n \sim 160$ each) and placebo ($n \sim 80$), using a log-rank test of superiority at a two-sided significance level of 0.05. Sample size calculation was performed using PASS 14.

9.3 POPULATIONS FOR ANALYSES

The following populations are defined ([Table 10](#)):

Table 10 - Populations for analyses

Population	Description
Enrolled	All participants who sign the ICF
Randomized	All randomized patients
mITT population:	The modified intention-to-treat (mITT) population includes all randomized patients treated with study medication. 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, as well as for data including (but not limited to) demographics and baseline characteristics.

Population	Description
PPS	The Per Protocol population set (PPS) includes all ITT patients who did not have any relevant major protocol deviations, eg, patients who are randomized and treated, but do not have laboratory-confirmed SARS-CoV-2 infection will be excluded from PPS. The final determination of the exclusion of patients from the PPS will be made prior to the primary database lock. Analysis of the PPS will be done according to the treatment the patient actually received (as treated). The PPS will be used for sensitivity analysis of the primary efficacy endpoint.
Safety	Safety population: The safety population includes all randomized patients treated with study medication. Analysis of the Safety population will be done according to the treatment received (as treated).
PK population	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.

9.4 STATISTICAL ANALYSES

The primary analysis is planned when the last patient randomized reaches Day 29 (or planned Day 29 if the patient is discharged or leaves the study early). Final analysis will be performed at study end (ie, Day 60).

The SAP will be finalized prior to the interim analysis and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General considerations

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 SAP.

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

9.4.2 Primary endpoint(s)

The primary endpoint is the time to improvement of 2 points in clinical status assessment from baseline using the 7-point ordinal scale. Patient who discharged early will be considered as meeting the two points improvement criteria.

The primary endpoint will be analyzed using a log-rank test stratified by randomization stratum with treatment as a fixed factor in the mITT population. P-value for the pairwise treatment comparison versus placebo will be provided. Estimation of treatment effect of each sarilumab dose will be provided as hazard ratio (sarilumab versus placebo) using Cox proportional hazards model stratified by the randomization stratum with treatment as a covariate, along with 2-sided confidence intervals. Kaplan-Meier (KM) plot and the median time-to-improvement of 2 points will also be provided.

Superiority of sarilumab over placebo will be declared if the null hypothesis is rejected at the 5% (2-sided) significance level following the multiplicity control procedure specified in [Section 9.4.3.1](#).

Patients who have an improvement of 2-points in clinical assessment or discharge will be considered as events, while patients who do not experience improvement of 2-points will be censored at the last observation time point. Patients who die or take rescue medication in the study without improvement of 2-points before that will be censored at the earlier date of Day 29 (for the primary analysis) or rescue medication started.

9.4.3 Secondary endpoint(s)

9.4.3.1 Efficacy

Analysis for Key Secondary Endpoint:

The key secondary endpoint is the percent of patients alive at Day 29.

The key secondary endpoint will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by randomization stratum in the mITT population. Estimation of treatment effect of each sarilumab dose will be reported as difference in proportion of patients alive at Day 29 (sarilumab - placebo), along with 95% confidence levels. P-value for the pairwise treatment comparison versus placebo will be provided.

Superiority of sarilumab over placebo will be declared if the null hypothesis is rejected at the 5% (2-sided) significance level following the multiplicity control procedure specified in [Section 9.4.3.1](#).

Analysis for Other Secondary Endpoints:

- Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier estimates and 95% confidence intervals.
- 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).

- Duration of event (eg, duration of mechanical ventilation) will be summarized according to median days with quartiles.
- Incidence data (eg, incidence of new oxygen use) will be summarized as a percent with 95% confidence intervals.
- 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.
- Categorical data (eg, 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.

Control of multiplicity

Multiplicity will be controlled for the primary analysis (i.e. Day 29), final analysis (i.e. Day 60) will be supportive.

For the primary and key secondary endpoints, multiplicity will be controlled via a hierarchical testing procedure in the following order:

1. Primary endpoint sarilumab 400 mg versus placebo
2. Key secondary endpoint sarilumab 400 mg versus placebo
3. Primary endpoint sarilumab 200 mg versus placebo
4. Key secondary endpoint sarilumab 200 mg versus placebo

If one sarilumab dose is discontinued for safety reasons, then all comparisons versus placebo for that dose will be removed and the remaining comparisons will be tested in the order specified above.

9.4.3.2 Safety

9.4.3.2.1 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 to the last dose of study drug plus 60 days.

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 addition, there will be an end of study (EOS) phone call follow-up to determine the vital status (alive or dead) of the patient and to assess for SAEs and AESI.

Analysis

All AEs 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 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, 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.

9.4.4 Tertiary/exploratory endpoint(s)

Tertiary and exploratory endpoints analyses will be described in the SAP.

9.4.5 Other safety analyse(s)

9.4.5.1 Vital Signs

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

9.4.5.2 Laboratory Tests

Laboratory test results, including but not limited to white blood cell count, hemoglobin, platelets, creatinine, total bilirubin, alanine aminotransferase (ALT), 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 abnormality (PCSA) at any post-randomization time point will be summarized for each clinical laboratory test for all patients and separately for patients in whom the PCSA 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.

9.4.5.3 Assessment of anti- sarilumab antibodies

Anti-sarilumab antibody levels will be listed as negative and positive (titer-based) by patient and visit. Data will also be summarized as number of patients (counts and percents) with negative and positive levels by treatment group.

9.4.6 Pharmacokinetics

9.4.6.1 Analysis of Drug Concentration Data

The concentrations of sarilumab over time and pharmacokinetic parameters, as appropriate, will be summarized using descriptive statistics by treatment group and number of sarilumab doses.

No formal statistical hypothesis testing will be performed.

9.4.6.2 Analysis of Pharmacodynamic and Exploratory Biomarker Data

The concentrations of CRP, IL-6, and sIL-6R over time will be summarized using descriptive statistics by treatment group and number of sarilumab doses.

9.4.7 Other analyse(s)

Treatment Exposure

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

Treatment Compliance

Percentage of compliance is defined as the number of patients who fully completed infusions of the first study drug divided by number who received study drug.

9.5 INTERIM ANALYSES

An interim analysis is planned to be performed when approximately 50% of total planned number of patients (~200) are randomized. The efficacy endpoints will be analyzed using the same methods described in the efficacy analyses section ([Section 9.4](#)). The key secondary endpoint will be modified to be the percent of patients alive at Day 15.

The purpose of the interim analyses is to obtain an understanding of the possible drug effect in the population under study. An administrative alpha of 0.001 will be spent at interim analysis (1). Due to the conservative amount of alpha spent at interim, no alpha adjustment will be made for the primary analysis when the last patient randomized of the whole study reaches Day 29 (or planned Day 29 if the patient is discharged or leaves the study early), or the supportive final analysis at Day 60.

The interim analyses will be performed by an external statistical analysis center and are separated from personnel involved in the trial conduct. The unblinded results can only be viewed by a small group of senior sponsor individuals, who are separate from sponsor personnel involved in the conduct of the study. People involved in the conduct of the study (Patients, Investigators, Study Team, and Project Team) will have no access to the interim analysis results. Sponsor may decide to make changes to the dose and/or alter disease category based on the interim results.

9.6 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An independent data monitoring committee (IDMC) will actively monitor 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 changes to the study based on the recommendations of the IDMC.

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

- Incidence of SAEs
- Incidence of AESIs
- Progression of COVID-19 to more severe, critical or multi-organ dysfunction
- Incidence of clinically significant recurrence of severe or critical disease after clinical improvement

The first analysis of data is planned for safety monitoring when the first approximately 12 patients are randomized and receive study drug. Data on these first 12 patients regardless of severity of illness will be reviewed by an IDMC after the last of these patients dosed reaches Day 7. Data on approximately the first 12 and 50 patients regardless of severity of illness will be reviewed by IDMC to determine if the study can continue with or without modification. Subsequent frequency of IDMC meetings will be determined following the first two IDMC meetings.

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable ICH Good Clinical Practice (GCP) Guidelines
 - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR)
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC Determining whether an incidental finding should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
 - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
 - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
 - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
 - In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as “substantial” (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant’s legally authorized/acceptable representative.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples or new extra samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate consent will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate consent.

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (General Data Protection Regulation).

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study, unless prohibited by local regulation, because these data are required by regulatory agencies (eg, on afro American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- Participant data are intended to be used for the whole drug development program from collection to reimbursement.

10.1.5 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on publically accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, [EU clinicaltrialregister \(eu.ctr\)](http://eu.clinicaltrialregister.eu), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.6 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations)
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the monitoring plan

10.1.8 Study and site start and closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
 - Information on the product leads to doubt as to the benefit/risk ratio
 - Discontinuation of further study intervention development
- For site termination:
 - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
 - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
 - Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.9 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in [Table 11](#) will be performed.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in [Section 5](#) of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing: Pregnancy testing to be performed locally in women of childbearing potential (WOCBP) only. Serum or urine pregnancy test are both acceptable.

Table 11 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit <u>RBC indices:</u> MCV MCH %Reticulocytes <u>White blood cell (WBC) count with differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Blood chemistry ^a	Blood urea nitrogen (BUN) Creatinine Glucose (fasting or nonfasting) Potassium Sodium

Laboratory assessments	Parameters
Routine urinalysis	Calcium Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT) ^a Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT) ^a Alkaline phosphatase Total and direct bilirubin Total protein Ferritin D-dimer C reactive protein (CRP)
Other tests	<ul style="list-style-type: none"> • Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Highly sensitive [Serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)^b • Bacterial and fungal blood culture • PK sarilumab • ADA • Serum IL-6 • Serum sIL-6R • SARS-CoV-2 (Blood sample) • SARS-CoV-2 (NP swab) • Blood for DNA/RNA (optional) • The results of each test must be entered into the CRF.

NOTES:

^a Details of liver chemistry and other follow-up assessments are given in [Section 8.3.6](#).

^b Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
 - Requiring either corrective treatment or consultation, and/or
 - Leading to IMP discontinuation or modification of dosing, and/or
 - Fulfilling a seriousness criterion, and/or
 - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires "a new" inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
 - Allergic bronchospasm
 - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
 - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse
- ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study

10.3.2.1 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor or Representative in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or Representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or Representative.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The severity of neutropenia, hypersensitivity, and infusion related reactions will be graded using the NCI-CTCAE v3 (see [Table 12](#), [Table 13](#), [Table 14](#)).

Table 12 - Grading of infusion related reactions (NCI-CTCAE v3)

Grade	Description
1	Mild reaction; infusion interruption not indicated; intervention not indicated
2	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs
3	Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)
4	Life-threatening; pressor or ventilatory support indicated
5	Death

Table 13 - Grading of hypersensitivity reactions (NCI-CTCAE v3)

Grade	Description
1	Transient flushing or rash; drug fever
2	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)
3	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension
4	Anaphylaxis
5	Death

Table 14 - Grading of neutropenia (NCI-CTCAE v3)

Grade	Description
1	<LLN – 1500/mm ³ or <LLN – 1.5 X 10 ⁹ /L
2	<1500 – 1000 /mm ³ or <1.5 – 1.0 X 10 ⁹ /L
3	<1000 – 500/mm ³ or <1.0 – 0.5 X 10 ⁹ /L
4	<500/mm ³ or < 0.5 X 10 ⁹ /L
5	Death

Adverse events not listed in [Table 12](#), [Table 13](#), [Table 14](#) or in the NCI-CTCAE v5 will be graded according to the following scale ([Table 15](#)):

Table 15 - 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.

An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator’s Brochure (IB) and associated addendum and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or Representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or Representative.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or Representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Sponsor or Representative with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor or Representative within 24 hours of receipt of the information.

Follow-up of AESIs

The following guidance should be considered for patients with AESI of ALT increase and Grade 4 Neutropenia

For AESI of ALT increase:

Inpatient:

- Confirmation of initial AESI by retesting within 24 -72 hours (ALT, AST, ALP, Total bilirubin, etc.).
- Follow up every 24 -72 hours until stabilization (ie, ALT does not continue to increase and/or trends towards baseline).
- If a patient is discharged before Day 29, test for ALT, AST, ALP, Total bilirubin, etc. at discharge.

Outpatient (if possible):

- If not stabilized at discharge, follow up every 24 -72 hours, then every 2 weeks (when possible) until return to baseline and no manifestation of associated signs and symptoms.
- If stabilized, retest every 2 weeks if possible until results return towards baseline assuming no associated signs and symptoms.
- Consider consultation with a hepatologist and additional tests.

For AESI of Grade 4 Neutropenia (absolute neutrophil count less than $<500/\text{mm}^3$):

Inpatient:

- Confirmation of initial ANC within 24 -72 hours. Monitor patients for signs or symptoms of an opportunistic or nosocomial infection. Retest at least twice a week for the first week and then per standard of care until return to baseline or normal.
- If discharged, obtain neutrophil count on day of discharge and recommend follow-up with family doctor.

Outpatient (if possible):

- If the lab result has not stabilized at discharge, continue to monitor at least twice a week for the first week and then twice a month until return to baseline or normal as possible. Monitor patients for signs of infection.

10.3.3 Reporting of SAEs

SAE reporting to the Sponsor (or Representative) via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor or Representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor (or Representative) by fax or email.
- Contacts for SAE reporting can be found in the study manual.

SAE reporting to the Sponsor (or Representative) via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor (or Representative) if electronic data collection tool is not available.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the study manual.

10.3.4 Management of Acute Reactions

10.3.4.1 Acute Intravenous Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in [Section 10.3.1](#) and [Section 10.3.2](#)) and graded using the grading scales as instructed in [Section 10.3.2.1](#).

10.3.4.1.1 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.

10.3.4.1.2 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 (37): 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).

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
 - Documented hysterectomy
 - Documented bilateral salpingectomy
 - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
 - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT before the end of the study.

CONTRACEPTION GUIDANCE:

Contraceptive use by men or women should be consistent with the prescribing information for Kevzara and with local regulations regarding the methods of contraception for those participating in clinical studies.

COLLECTION OF PREGNANCY INFORMATION:

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in [Section 8.3.4](#). While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.5 APPENDIX 5: GENETICS

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to sarilumab or COVID-19 and related diseases. They may also be used to develop tests/assays including diagnostic tests related to sarilumab and or COVID-19 related diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to sarilumab or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on sarilumab and COVID-19 diseases continues but no longer than 15 years or other period as per local requirements.

10.6 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.7 APPENDIX 9: ABBREVIATIONS

ADA Anti-drug antibody
AE Adverse event
AESI Adverse event of special interest
ALT Alanine aminotransferase
ANC Absolute neutrophil count
ARDS Acute respiratory distress syndrome
AST Aspartate aminotransferase
BUN Blood urea nitrogen
CDC Center for Disease Control
CMH Cochran-Mantel-Haenszel
COVID-19 Coronavirus Disease 2019
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
FAS Full analysis set
FDA Food and Drug Administration
FiO₂ fraction of inspired oxygen
GCP Good Clinical Practice
HDL High-density lipoprotein
ICF Informed consent form
ICH International Council for Harmonisation
ICU Intensive care unit
IL-6 Interleukin 6
IRB Institutional Review Board
IV Intravenous
KM Kaplan-Meier
LDH Lactate dehydrogenase
LDL Low-density lipoprotein
MOD Multi-organ dysfunction
NCI-CTCAE National Cancer Institute-Common Terminology Criteria for Adverse Events
NEWS2 National Early Warning Score2
NP Nasopharyngeal
PCSA potentially clinically significant abnormality
PK Pharmacokinetic(s)
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
SOC System organ class
SOFA Sequential Organ Failure Assessment
SpO₂ Oxygen saturation
SUSAR Suspected unexpected serious adverse reaction
TEAE Treatment-emergent adverse event
WBC White blood cell
WHO World Health Organization

10.8 APPENDIX 10: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.8.1 Amended protocol [01] (26 March 2020)

This amended protocol (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 9.4.3 Secondary Endpoints	Clarified statistical analysis for the control of multiplicity	Provided in response to Health Authority recommendation
Section 1.1 Synopsis and Section 3 Objectives and Endpoints	Phase 2 primary endpoint changed to: The primary endpoint is the time to resolution of fever for at least 48 hours without antipyretics or until discharge, whichever is sooner	Clarified primary endpoint collection
Section 1.1 Synopsis and Section 3 Objectives and Endpoints	Phase 3 Primary endpoint: Added the timepoint as Day 15 for the primary endpoint of Phase 3	Provided to clarify description of Phase 3 default primary endpoint
Section 1.1 Synopsis and Section 3 Objectives and Endpoints	Phase 2 and Phase 3 endpoints: Added an endpoint to evaluate the proportion of patients requiring rescue medication during the 28-day period	Added to accommodate analysis of rescue medication use
Section 1.1 Synopsis Overall Design	Added that screening will be limited to severe patients until approximately 100 patients have reached Day 15, after which screening can be considered for patients of the same or greater severity.	Clarifies time point at which patients with critical disease or multi-system organ dysfunction can be considered for screening
Section 1.1 Synopsis Overall Design	Stratification changed to systemic corticosteroids (Yes, No).	Broadened scope to include systemic corticosteroid use for any reason
Section 1.1 Number of patients and Section 9.2 Sample size determination	Modified to: Sample size may be re-estimated for Phase 3 based on results from Phase 2	Clarification of potential impact of Phase 2 analyses on Phase 3 sample size.
Section 1.1 Statistical Plan and Section 9.2 Sample size determination	Modified accrual duration to 3 months (~90 days)	Adapted accrual duration to account for change in accelerated rates of local transmission of SARS-CoV-2

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Statistical Plan	For phase 2 the primary analysis of time-to-fever-resolution will be conducted on data from patients with fever within the 24 hours prior to randomization	Clarification of starting time for time-to-fever-resolution analysis
Section 1.1 Statistical Plan and Section 9.2 Sample size determination	Added details for the Phase 2 analyses cut-off. Clarified control of multiplicity for Phase 2	Clarification in response to health authority comment
Section 1.3 Schedule of Activities	Clarified the inclusion criteria for a positive SARS-CoV-2 test.	Allowed for inclusion based on positive SARS-CoV-2 test recorded prior to screening visit
Section 1.3 Schedule of Activities	Clarified that the blood is collected for the central analysis of SARS-CoV-2 viral load.	Clarify that the blood is collected for the central analysis of SARS-CoV-2 viral load and is not for determining the inclusion criteria.
Section 1.3 Schedule of Activities	Clarified patients who discontinue early should complete the End of Study Visit, if possible.	Operational clarification
Section 1.3 Schedule of Activities	Clarified that All AEs will be recorded in CRF. Note: any abnormal physical findings requiring medical or surgical intervention must be recorded as an AE.	Operational clarification
Section 1.3 Schedule of Activities And Section 8.1.1 Body Temperature	Clarified that the body temperature to be reported in the CRF should be the maximum value observed during any time period or window.	Operational clarification
Section 2.3 Benefit/Risk Assessment	The review of safety data by an independent data monitoring committee (IDMC) after the dosing of the first 12 patients will not be required prior to enrolling additional patients and through the duration of the study	Modified in response to accelerated pace of local transmission
Section 5.1 Inclusion Criteria	Fever has been removed as a necessary criterion for definition of pneumonia	Because body temperature may be altered by anti-pyretic medication, fever may not be evident in patients with pneumonia
Section 5.1 Inclusion Criteria	Laboratory-confirmed SARS-CoV-2 infection (eg by PCR), or other commercial or public health assay in any specimen within 2 weeks prior to randomization and no alternative explanation for current clinical condition	Modified to account for regional variability in SARS-CoV-2 testing recommendations
Section 5.2 Exclusion Criteria	Modified E01 to: In the opinion of the investigator, unlikely to survive after 48 hours, or unlikely to remain at the investigational site beyond 48 hours.	Clarification
Section 6.3 Blinding	Added code breaking rules	Operational clarification
Section 6.6 Rescue Therapy	Added: Administer rescue medication only 48 hours after the initial infusion of study medication. Rescue medications are defined as the immunosuppressive therapies (described in the exclusion criteria E 03 and E 04).	Added to mitigate risk of potential lack of benefit from investigational intervention

Section # and Name	Description of Change	Brief Rationale
Section 8.2.2 Limited Physical Examination	Changed to 8.2.2 Targeted Physical Examination Added: assessment of consciousness	Added to ensure assessment. Necessary to complete NEWS2 score
Section 9.2 Sample size determination	Detailed sample size determination of the primary endpoint of Phase 3	Provided in response to Health Authority recommendation
Section 9.4.2 Primary Endpoint(s)	Added: The primary endpoint of time to fever resolution will be performed on patients with fever (defined as temperature > 37.4°C [axilla], or > 38.0 °C [oral], or >38.4°C [rectal or tympanic]) documented in the medical record, within the 24 hours prior to randomization.	Clarification of definition of fever for analysis of time to fever resolution.
All sections	Minor edits	Minor corrections, corrections and formatting of bibliography

10.8.2 Amended protocol [02] (08 April 2020)

This amended protocol 02 (amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The unanticipated and rapid enrollment into this study for COVID -19 patients renders a staged approach to analysis unfeasible; consequently the Phase 2 analysis will not be performed.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title and throughout the protocol	An adaptive phase 3, randomized, double-blind, placebo-controlled study assessing efficacy and safety of sarilumab for hospitalized patients with COVID-19.	The unanticipated and rapid enrollment into the study renders a staged approach to analysis unfeasible; consequently the Phase 2 analysis will not be performed.
Section 1.1 Synopsis Section 3 Objectives and Endpoints Section 9 Statistical Considerations	The primary endpoint is the time to improvement of 2 points in clinical status assessment from baseline using the 7-point ordinal scale.	The 7-point clinical status scale has face validity and a two point change in status is considered large enough to demonstrate a meaningful difference between treatment groups.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 3 Objectives and Endpoints Section 9 Statistical Considerations	The key secondary endpoint is percent of patients alive at Day 29.	Captures non pulmonary mortality.
Section 1.1 Synopsis Section 3 Objectives and Endpoints Section 9 Statistical Considerations	A secondary endpoint is the proportion of patients with one point improvement from baseline in clinical status assessment at days 4, 7, 15, 21, 29 using the 7-point ordinal scale.	The 7-point clinical status scale has face validity and a one point change in status will demonstrate a meaningful difference between treatment groups.
Section 1.1 Synopsis Overall Design	Removed that screening will be limited to severe patients until approximately 100 patients have reached Day 15, after which screening can be considered for patients of the same or greater severity.	100 patients comprised the initial phase 2 cohort. This is removed as phase 2 analysis will not be performed.
Section 1.1 Synopsis Overall Design Section 4.1 Overall Design	Added that patients may receive a second dose of study treatment if they meet prespecified criteria.	Optimal dose of sarilumab IV for patients with severe or critical COVID-19 is unknown.
Section 1.1 Synopsis Overall Design Section 4.1 Overall Design Section 5.1 Inclusion Criteria	Removed the severity category of multi-system organ dysfunction, and removed stratification by multi-system organ dysfunction.	Clarified which patients can be considered for screening.
Section 1.1 Synopsis Overall Design Section 4.1 Overall Design Section 9.5 Interim Analysis	An interim analysis has been specified when approximately 50% of total planned number of patients (~200) would have reached Day 15.	Obtain an understanding of the possible drug effect in the population under study.
Section 1.3 Schedule of Activities	Separated urinalysis from urine culture results.	Clarify that urinalysis is required for all patients, and urine culture results are only requested if available.
Section 5.1 Inclusion Criteria	Added:	Further clarify Exclusion Criterion 01.

Section # and Name	Description of Change	Brief Rationale
	Note: patients requiring extracorporeal life support, vasopressors, or renal replacement therapy are excluded.	
Section 6.6 Rescue Therapy	Removed sarilumab as rescue therapy. Specified that rescue therapy may be given 48 hours after the last infusion of study treatment.	Clarify time for the administration and type of rescue therapy.
Section 8.3.6 Adverse event of Special Interest	Added: Infusion related reactions are defined as any signs or symptoms experienced by patients who receive IMP within 24 hours of the start of infusion.	Provide a definition for Infusion related reactions.
Section 10.3.2 Definition of SAE	Modified: Requires inpatient hospitalization or prolongation of existing hospitalization To: Requires a "new" inpatient hospitalization or prolongation of existing hospitalization.	Clarified SAE, as patients enrolled are hospitalized patients.
	Added the list of medically important events intended to serve as a guideline for determining which condition has to be considered as a medically important event.	Clarification for the Investigator.
Protocol Amendment history	Removed that the use of immunosuppressive therapy following infusion of study drug, besides corticosteroids and anti-malarial medication, is not permitted for Section 6.5 Concomitant therapy.	Correction.
All sections	Minor edits	Minor corrections, corrections and formatting of bibliography.

10.8.3 Amended protocol [03] (29 April 2020)

This amended protocol 03 (amendment 03) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

To clarify language regarding interim analysis.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 10.2: Clinical Laboratory Tests	Remove requirement that the interim analysis requires data up to Day 15.	Clarifies the scope of adaptations the Sponsor may make based on the interim analysis results
1.3 Schedule of Activities (SoA)	Clarified PK sample collection for Day 2 and Day 3. Removed 'optional' for the serum sIL-6R.	Provided clarity on PK and serum sIL-6R collection
Section 2.3 Benefit/Risk Assessment	Changed multisystem organ dysfunction to multi-organ dysfunction	Corrected to align with the publication where it is described (16)
Section 4.1 Overall design	Clarified that IDMC will actively monitor interim data, and also make recommendations pertaining to the eligible population throughout the course of the study.	Clarification
Section 5.2 Exclusion criteria	Removes the use of vasopressors as a factor to be considered for selection criterion E01.	Vasopressors are also used by critical patients and not primarily patients with multi organ disease (who are excluded).
And Section 9.5 Interim analysis	Specify the type of modifications that the Sponsor may make based on the interim analysis results.	Clarifies the scope of adaptations the Sponsor may make based on the interim analysis results

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