Janssen Research & Development *

Clinical Protocol

Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Sirukumab in Confirmed Severe or Critical COVID-19 Disease

Protocol CNTO136COV2001; Phase 2
AMENDMENT 5

CNTO136 (sirukumab)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

EudraCT NUMBER: 2020-003056-32

Status:	Approved
Date:	17 February 2021
Prepared by:	Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number:	EDMS-ERI-207794964, 13.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	This document
Amendment 4	15 September 2020
Amendment 3	23 July 2020
Amendment 2	17 June 2020
Amendment 1	24 April 2020
Original Protocol	14 April 2020

Amendment 5 (This document)

Overall Rationale for the Amendment: The protocol has been amended to limit the study population to a subset of the currently eligible population, ie, those with confirmed critical COVID-19 disease.

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis 1.2 Schema 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 4.2 Scientific Rationale for Study Design 5.1 Inclusion Criteria 8.1.1 Six-point Ordinal Clinical Recovery Scale 9.1 Statistical Hypotheses 9.2 Sample Size Determination 9.3 Populations for Analysis Sets 9.4.4 Other Secondary Endpoints 9.5 Interim Analysis 10.4.6 Committees Structure	The participants with confirmed severe COVID-19 disease will no longer be eligible for this study as the study population will be limited to participants with confirmed critical COVID-19 disease. Definition of critical COVID-19 is more clearly defined under Sections 5.1 and 8.1.1. The primary objective of this study will evaluate the clinical response of sirukumab (administered as a single IV dose) + SOC compared to placebo + SOC in confirmed critical COVID-19 disease. Sample size and population in scope for the primary and the key secondary objectives have been modified accordingly. Former primary and key secondary objective in confirmed severe or critical COVID-19 disease become additional secondary objectives. All other secondary objectives will be analyzed in the confirmed (a) critical and (b) severe or critical COVID-19 disease.	Based on the rapidly evolving space of COVID-19 therapeutics focusing on the highly impacted population of critical patients together with the results from the interim analysis, the study population will be limited to a subset of the currently eligible population, ie, those with confirmed critical COVID-19 disease.
1.1 Synopsis 9.4.6 Safety Analyses 9.4.7 Other Analyses 10.1 Appendix 1: Abbreviations and Definitions	The increase of ALT or AST combined with increase of bilirubin will be investigated by means of evaluation of drug-induced serious hepatotoxicity (eDISH) plots.	Alignment with Statistical Analysis Plan.
	Update on tables to be generated for the clinical laboratory tests.	
	Removal of analysis of the physical examination.	
	The coefficient of variation (CV) will not be analyzed for the biomarker analysis.	

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
1.2 Schema 1.3 Schedule of Activities (SoA) 5 STUDY POPULATION 8 STUDY ASSESSMENTS AND PROCEDURES 10.3 Appendix 3: Clinical and Laboratory Assessments Described per Day	The ECG assessment has been added in the protocol text for clarification. Footnote g was added to the screening/baseline ECG assessment.	Minor update to allow more flexibility to assess eligibility, based on local standard of care practices.
5.2 Exclusion Criteria	Exclusion criteria based on medical history or on past/current medications are pragmatic criteria. Deviation post randomization from these criteria due to late awareness of medical history and/or comedications are not intended to be qualified as major protocol deviations.	Clarification.
6.1 Study Intervention(s) Administered	Clarify that placebo is to be provided locally and not centrally.	Clarification since the study is not intended to be performed outside of the United States of America.
6.2 Preparation/Handling/Storage/Accountability	To remove details on the preparation, handling, and storage of the study intervention.	To avoid errors on the preparation, handling, and storage of the study intervention, reference is made to the IPPI only.
6.8 Prestudy and Concomitant Therapy	The use of bamlanivimab, and casirivimab plus imdevimab is disallowed during the study.	Per CDC guidelines, monoclonal antibodies are not considered to be standard of care for COVID-19.
	Administration of a COVID-19 vaccine during the study is not allowed at any time between screening and the discharge visit.	Per CDC guidelines, vaccination of persons with known current SARS-COV-2 infection should be deferred until the person has recovered from the acute illness. For the purpose of this study, recovered from acute illness is considered as ready for discharge.
7.3 Lost to Follow-up	Clarify that publicly available vital status information is not to be documented when a participant has withdrawn consent. This participant will be considered lost to follow-up.	Clarification on the rules of data handling consistent with GCP.

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
8.1.1 Six-point Ordinal Clinical Recovery Scale	Edits are made to the 6-point ordinal clinical recovery scale to clarify that: • For participants not hospitalized (category 1), a distinction will be made between participants discharged and in need of (score 1.2) or not in need of (score 1.1) oxygen supplementation as indicated by the investigator on the discharge questionnaire. • Regardless of the device used: – Hospitalized participants with a FiO_2 below 50% corresponds to a category 3. – Hospitalized participants with a FiO_2 of 50% or higher corresponds to a category 4.	Clarification on category 1. Clarifications on categories 3 and 4 to make category 3 fully consistent with category 4, which is using the FiO2 as a threshold and making the allocation to category 3 or 4 independent of the device used.
8.1.4 Supplemental Oxygen Use	Clarify that the use of CPAP at home for obstructive sleep apnea syndrome will not be reported as a need for supplemental oxygen information.	Clarification.
10.1 Appendix 1: Abbreviations and Definitions	Definitions of critical and severe COVID-19 disease have been added to the definitions of terms.	Clarification.
1.1 Synopsis 1.3 Schedule of Activities (SoA) 4.1 Overall Design 10.2 Appendix 2: Clinical Laboratory Tests 10.3 Appendix 3: Clinical and Laboratory Assessments Described per Day	Minor rewording. Corrections for respiratory and vital signs assessments to be performed once weekly after Day 28 if still hospitalized.	Clarification.
Throughout the protocol	Minor formatting and minor updates made.	Minor errors were noted.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Sirukumab in Confirmed Severe or Critical COVID-19 Disease

Sirukumab (also known as CNTO136) is a human anti- IL-6 immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb). Sirukumab binds with high affinity and specificity to human IL-6 and as a result inhibits IL-6-mediated signaling and the biological effects of IL-6.

OBJECTIVES AND ENDPOINTS

The primary and secondary objectives and endpoints are listed below. For the full list of objectives and endpoints see Section 3 OBJECTIVES AND ENDPOINTS.

Objectives	Endpoints
Primary	
To evaluate the clinical response of sirukumab (administered as a single IV dose) + SOC compared to placebo + SOC in confirmed critical COVID-19 disease	• Time to improvement[a] of at least 2 categories relative to Baseline on the 6-point ordinal clinical recovery scale (up to Day 28)
Key Secondary	
To evaluate the clinical response of sirukumab + SOC compared to placebo + SOC in confirmed critical COVID-19 disease	• Proportion of participants with an improvement on Day 28 of at least 2 categories relative to Baseline on the 6-point ordinal clinical recovery scale • Incidence of all-cause mortality (up to Day 28)
Other Secondary	
To evaluate the clinical response of sirukumab (administered as a single IV dose) + SOC compared to placebo + SOC in confirmed severe or critical COVID-19 disease	• Time to improvement[a] of at least 2 categories relative to Baseline on the 6-point ordinal clinical recovery scale (up to Day 28)
To evaluate the clinical response of sirukumab + SOC compared to placebo + SOC in confirmed severe or critical COVID-19 disease	• Proportion of participants with an improvement on Day 28 of at least 2 categories relative to Baseline on the 6-point ordinal clinical recovery scale • Incidence of all-cause mortality (up to Day 28)
To evaluate the safety of sirukumab + SOC compared to placebo + SOC in confirmed (a) critical and (b) severe or critical COVID-19 disease	• Incidence of SAEs (up to Day 28) • Incidence of related AEs (up to Day 28) • Proportion of participants with severe or life-threatening bacterial, invasive fungal, viral or opportunistic infections (other than SARS-CoV-2) (up to Day 28).

[a] The improvement should be sustained until Day 28 (or discharge/discontinuation).

Objectives	Endpoints
	• Incidence of grade 3 and 4 neutropenia and lymphocytopenia (up to Day 28) • Incidence of increased ALT ≥3xULN combined with increased bilirubin >2xULN (up to Day 28)
To evaluate the clinical response of sirukumab + SOC compared to placebo + SOC in confirmed (a) critical and (b) severe or critical COVID-19 disease	• Time to improvement[a] of at least 1 category relative to Baseline on the 6-point ordinal clinical recovery scale (up to Day 28) • Proportion of participants with an improvement on Day 28 of at least 1 category relative to Baseline on the 6-point ordinal clinical recovery scale • Time from study intervention to end of oxygen supplementation (up to Day 28) • Time from study intervention to hospital discharge among the surviving participants (up to Day 28) • Total length of hospitalization among the surviving participants (up to Day 28) • Number of ventilation free days (up to Day 28) • Participant's clinical status at Day 7, 14, 21, 28 (6-point ordinal clinical recovery scale) • Total time on invasive mechanical ventilation • Proportion of participants with a worse[b] category relative to Baseline on the 6-point ordinal clinical recovery scale (up to Day 28) • Proportion of participants on extracorporeal membrane oxygenation (ECMO) over time • Total time on ECMO
To evaluate the safety during follow-up for (a) critical and (b) severe or critical COVID-19 disease	• Proportion of alive participants at Day 28, Week 8, and Week 16 • Proportion of alive participants that required readmission at Week 8 and Week 16 (if previously discharged) • Incidence of SAEs up to Week 16

[a] The improvement should be sustained until Day 28 (or discharge/discontinuation).

[b] Clinical recovery scale score worsened with at least 1 category between Day 5 and Day 28.

Hypothesis

The primary hypothesis of this study is that sirukumab in combination with SOC results in a statistically significant shorter time to improvement (defined as an improvement of at least 2 categories relative to Baseline on the 6-point ordinal clinical recovery scale) versus placebo in combination with SOC, in confirmed critical COVID-19 disease.

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter, interventional Phase 2 study in hospitalized participants with confirmed COVID-19 disease, at risk for progressing to severe ARDS.

Up to protocol amendment 4, a target of approximately 270 participants with confirmed severe or critical COVID-19 disease was to be randomly assigned in a 2:1 ratio to receive 1 of the following 2 treatments:

- Treatment Arm: sirukumab 5 mg/kg IV single dose infusion on Day 1 + SOC treatment
- Control Arm: placebo IV single dose infusion on Day 1 + SOC treatment.

As of protocol amendment 5, the study aims to enroll approximately 111 participants with confirmed critical COVID-19 disease overall in the study. The primary and key secondary analyses will be tested on the participants with confirmed critical COVID-19 disease.

At the time of release of protocol amendment 5, approximately 100 participants with confirmed severe COVID-19 disease had been enrolled. The overall population of participants with confirmed severe or critical COVID-19 disease will be analyzed as part of secondary objectives of the study.

Randomization is stratified by age (<65 and ≥65 years of age) and by use of invasive mechanical ventilation (yes/no) at the time of randomization.

The study will include a Screening Phase, a 'Day 1 to Day 28' Phase and Post Day 28 Follow-up Phase (phone calls on Week 8, Week 12 and Week 16). The entire study duration for each participant will be 16 weeks with daily study assessments up to Day 28 or day of discharge (whichever comes first), and phone call assessments thereafter, ie, at Day 28 in case of discharge prior to Day 28, at Week 8, 12 and 16. The assessment schedule will be on a weekly basis for participants still hospitalized after Day 28. The study is considered completed with the completion of the last study assessment (phone call assessment at Week 16) for the last participant in the study or the discontinuation of the last participant in the study, whichever comes last.

NUMBER OF PARTICIPANTS

A target of approximately 111 participants with confirmed critical COVID-19 disease will be randomized.

At the time of release of protocol amendment 5, approximately 100 participants with confirmed severe COVID-19 disease had been enrolled.

INTERVENTION GROUPS AND DURATION

Description of Interventions

Intervention Name	Sirukumab (CNTO136)
Type	Drug
Dose Formulation	Solution for infusion
Unit Dose Strength(s)	Sirukumab: 100 mg/mL
Dosage Level(s)	Sirukumab: 5 mg/kg single dose
Route of Administration	IV infusion
Use	Intervention
Investigational Medicinal Product (IMP)	Yes
Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)	No
Sourcing	Provided centrally by the sponsor
Packaging and Labeling (Labels will contain information to meet the applicable regulatory requirements.)	Each unit will be labeled with unique medication ID number.
	Not in child resistant packaging
Delivery Instructions	Refer to IPPI for instructions on IV infusion
Food/Fasting Requirement	Regardless of food intake

EFFICACY EVALUATIONS

Efficacy assessments will include 6-point ordinal clinical recovery scale, level of consciousness (Glasgow coma scale), virology assessment, supplemental oxygen use, resting SpO_2, arterial blood gas results, and pulmonary imaging.

SAFETY EVALUATIONS

Safety evaluations will include monitoring of adverse events and serious adverse events, physical examinations, vital sign measurements, electrocardiograms, clinical laboratory tests, pregnancy testing, and checking of vital status.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Serum samples will be used to evaluate the pharmacokinetics of sirukumab, IL-6, as well as antibodies to sirukumab. Serum collected for pharmacokinetic and immunogenicity analyses may additionally be used to evaluate biomarkers, safety or efficacy aspects that address scientific questions relating to sirukumab or SARS-CoV-2 infection.

GENETICS AND PHARMACOGENOMICS

An optional pharmacogenomic (host DNA) blood sample may be collected (preferably at baseline) from those participants who gave consent to allow for host pharmacogenomic research, where local regulations permit. Pharmacogenomic research may include expression quantitative trait locus (eQTL) mapping, single-nucleotide polymorphisms (SNPs) mapping and whole genome sequencing that is related to the IL-6 gene, study intervention, and/or SARS-CoV-2 infection.

BIOMARKER EVALUATIONS

Blood samples will be collected to evaluate biomarkers that may be associated with the safety, efficacy and PK of sirukumab and/or with the SARS-CoV-2 infection. Evaluations may include, but are not limited to, IL-6, procalcitonin, CRP, ferritin, LDH, and D-dimer concentrations. In addition, humoral immunity to SARS-CoV-2 will be evaluated by measuring SARS-CoV-2 specific antibodies.

The study also includes collection of blood samples for exploratory analysis of host biomarkers at the host RNA, protein and cell level. Samples may be analyzed under the supervision of the sponsor and results might be reported separately.

STATISTICAL METHODS

The primary analysis will be done when all participants reached Day 28 or discontinued earlier.

The final analysis will be done when all participants completed the study.

A hierarchical testing strategy will be used for the primary and key secondary endpoints.

First, the primary endpoint will be tested for superiority of sirukumab over placebo at the 2-sided 5% significance level. If superiority is shown on the primary endpoint, then the proportion of participants with a clinical improvement of at least 2 categories at Day 28 will be tested at the 1-sided 5% significance level. If superiority on this endpoint is shown, the mortality by Day 28 will be tested, again at the 1-sided 5% significance level.

The inclusion of a Data Monitoring Committee (DMC) consisting of internal and external members will ensure oversight of patient safety. The DMC will regularly evaluate the cumulative safety data of all participants in the study. As soon as the first 30 participants with confirmed severe or critical COVID-19 disease had received study intervention and had at least 7 days of follow-up after study intervention, the DMC performed an interim data review focused on safety. All data available at the time of the interim data review were included. During this data review enrollment was continued, however, recruitment would have been halted should 60 patients had been enrolled before the outcome of the data review was known. In case recruitment was halted, it would have been resumed upon a positive assessment of results of these interim data by the DMC.

While futility or stopping of the study is to be based on totality of emerging safety data, the DMC has to consider either of the following non-binding futility criteria as recommendation for stopping the study:

- Excess mortality in the treatment arm, beyond the realm of chance (Fisher's Exact test at a 1-sided significance level of 10%).

- Excess in "Worsening by at least 1 category" in the treatment arm, beyond the realm of chance (Fisher's exact test at a 1-sided significance level of 10%).

In addition, an IA was performed by the sponsor on the primary endpoint when approximately 20% of the planned number of participants with confirmed severe and critical COVID-19 disease had reached Day 28 or discontinued earlier (see Synopsis subsection *Interim Analysis* for more details). Results have been discussed with the DMC.

The above DMC set-up and non-binding futility criteria have been implemented in the study for the participants with confirmed severe or critical COVID-19 disease. No additional non-binding futility analyses are planned for the participants with confirmed critical COVID-19 disease in the study.

The efficacy endpoints will be analyzed on the Intent-to-Treat- (ITT) and by randomized treatment. The ITT set consists of all participants who were randomized and treated. These analyses will be performed in the participants with confirmed (a) critical and (b) severe and critical COVID-19 disease.

All safety analyses will be made on the Safety Population. The safety population, consisting of all participants who received study drug, will be analyzed by actual treatment. These analyses will be performed in the participants with confirmed (a) critical and (b) severe and critical COVID-19 disease.

For all participants who receive study drug descriptive statistics will be provided. All demographic characteristics (eg, age, race, ethnicity, height, body weight, body mass index) and other initial participant characteristics (eg, medical and surgical history, concomitant diseases) will be tabulated and analyzed descriptively.

Subgroup analyses will be performed based on the stratification factors (age [<65 and ≥65 years of age] and use of invasive mechanical ventilation [yes/no]) and a selection of the major baseline parameters.

Sample Size Determination

The study was targeted to enroll 270 participants with confirmed severe or critical COVID-19 disease in a 2:1 manner, with approximately 180 participants in the sirukumab treatment arm and approximately 90 participants in the control arm. However, based on the rapidly evolving space of COVID-19 therapeutics focusing on the highly impacted population of critical patients together with the results from the interim analysis, the study population is being limited with protocol amendment 5 to a subset of the currently eligible population, ie, those with confirmed critical COVID-19 disease.

At the time of release of protocol amendment 5 approximately 100 participants with confirmed severe COVID-19 disease had been enrolled.

The study aims to enroll approximately 111 participants with confirmed critical COVID-19 disease overall in the study, with approximately 74 participants in the sirukumab treatment arm and approximately 37 participants in the control arm.

The primary endpoint in this study is the time to improvement of at least 2 categories relative to Baseline on a 6-point ordinal clinical recovery scale, with participants who die prior to Day 28 treated as right censored at Day 28. For the sample size calculation on the primary endpoint, the following assumptions are used for survivors and participants who die prior to Day 28:

- For survivors in the control arm, it is assumed that the log transformed time to improvement (days) follows a normal distribution with mean of log 28 and a standard deviation 0.9. Sirukumab is assumed to reduce the median time to clinical improvement from 28 days to 16.8 days (40% reduction) in the surviving participants, and is assumed to have the same standard deviation of 0.9.
- For the mortality in the control arm, 40% by Day 28 is assumed. Sirukumab is assumed to reduce the mortality with an absolute difference of 20%: from a mortality rate of 40% in the control arm to 20% in the sirukumab arm (50% relative reduction).

Under these assumptions, at least 111 participants with confirmed critical COVID-19 disease are required to have at least 80% power to demonstrate a difference with the log-rank test, at a significance level of 5% two-sided.

The proportion of participants with a clinical improvement of at least 2 categories at Day 28 is a key secondary endpoint. Based on simulations using the above assumptions, the rate with clinical improvement at Day 28 in the control arm is expected to be 30%. The targeted treatment effect is an absolute increase of 25% (from 30% in the control arm to 55% in the sirukumab arm) on this key secondary endpoint. The mortality by Day 28 is considered another key secondary endpoint. The targeted treatment effect is an absolute reduction in mortality by 25% (from 40% in the control arm to 15% in the sirukumab arm). Under

the aforementioned assumptions and with a sample size of 111 participants, at least 80% power is obtained for both key secondary endpoints a 1-sided significance level of 5%.

Analysis of the Primary Endpoint

The primary efficacy analysis will be based on the ITT analysis set restricted to participants with confirmed critical COVID-19 disease and the primary efficacy endpoint is the 'time to improvement of at least 2 categories relative to Baseline on a 6-point ordinal clinical recovery scale'. The improvement should be sustained until Day 28 (or discharge/discontinuation). Time to clinical improvement will be assessed during the 28-day period after study drug administration, with failure to reach clinical improvement or death before Day 28 considered as right-censored at Day 28.

This primary parameter will be analyzed by a stratified log-rank test (using the stratification factors). Kaplan-Meier curves, overall and by stratum will be used to graphically present the primary parameter. The sensitivity analyses will be defined in the statistical analysis plan (SAP).

Analysis of Secondary Endpoints

If superiority is shown on the primary endpoint, then the proportion of participants with a clinical improvement of at least 2 categories at Day 28 will be tested at the 1-sided 5% significance level. If superiority on this endpoint is shown, the mortality by Day 28 will be tested, again at the 1-sided 5% significance level.

The key secondary endpoints will be analyzed using the Cochrane-Mantel-Haenszel (CMH) test for difference in proportions.

Key and other secondary endpoints will be analyzed graphically and descriptively as described in the SAP. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, maximum, and 95% confidence intervals [CIs]) will be calculated. For categorical variables, frequency tables and corresponding 95% CIs will be presented.

The primary and secondary endpoint evaluation will be conducted on the ITT population and on the ITT population restricted to the population with confirmed critical COVID-19 disease. Analyses of qualitative comparison between pre-interim analysis and post-interim analysis for treatment effect in the population with confirmed critical COVID-19 disease will be conducted to check the consistency in the study. This qualitative assessment will be limited to primary and key secondary endpoints only.

Safety analyses

All safety analyses will be made on the Safety Population and on participants with confirmed (a) critical and (b) severe or critical COVID-19 disease.

All reported AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a grade 3 or 4 AE, a serious AE, or an adverse event of special interest (AEOI).

The incidence of participants with SAEs, the incidence of participants with grade 3 or 4 AEs, the incidence of participants with severe or life-threatening, bacterial, invasive fungal, viral or opportunistic infections (other than SARS-CoV-2), the incidence of grade 3 and 4 neutropenia and lymphocytopenia, and the incidence of increased ALT ≥3xULN combined with increased bilirubin >2xULN will be reported. Increase

of ALT or AST combined with increase of bilirubin will be investigated by means of evaluation of drug-induced serious hepatotoxicity (eDISH) plots.

Descriptive statistics will be calculated for clinical laboratory parameters, ECG parameters, and vital signs parameters.

Statistical testing might be applied to the secondary endpoints.

Interim Analysis

A non-binding unblinded IA for futility was performed by the sponsor on the primary endpoint when approximately 20% of the planned number of participants with confirmed severe and critical COVID-19 disease had reached Day 28 or discontinued earlier.

The randomization codes and the translation of randomization codes into treatment and control groups was disclosed to those authorized and only for those participants included in the IA. The following implementation was followed for the non-binding IA for futility while considering the participants with confirmed severe and critical COVID-19 disease in the study.

The futility criterion was based on the conditional power approach for the primary endpoint. The conditional power was calculated for the primary hypothesis using the observed data and assuming a mortality rate of 30% in the control arm versus 21% in the sirukumab arm in the remainder of the study. The effect size and outcomes for the primary endpoint in the survivors was simulated as used for the study sample size calculation. A non-binding futility stopping boundary of 80% for the conditional power was used. Assuming the outcome for the primary endpoint as used for the sample size calculations was true, with a 30% mortality rate in the control arm, the chance of stopping for futility at the time of the IA was 2.5%. Otherwise, if the null hypothesis was true and again with a 30% mortality rate in the control arm, the chance of stopping for futility was 60%. If, at the time of the IA, the probability of a successful study was lower than the futility boundary, the sponsor could have taken the decision to stop for futility after evaluation of all available data. In addition to the conditional power calculations, descriptive analyses of the primary and key secondary endpoints were performed on the available data. The safety outputs planned for the regular DMC safety reviews will be provided too.

No additional non-binding IA for futility is planned for the critical participants to be enrolled in the remainder of the study.

Other Analyses

- SARS-CoV-2 viral load in NP swabs and in endotracheal, blood, and stool samples will be measured by a qRT-PCR assay. These data will be analyzed graphically and descriptively as described in the statistical analysis plan.
- Serum sirukumab concentrations will be summarized using descriptive statistics. The concentrations below the lowest quantifiable sample concentration of the assay will be treated as zero in the summary statistics. All concentrations below the lowest quantifiable sample concentration of the assay or missing data will be labeled as such in the concentration data listing or statistical analysis dataset.
- The incidence of antibodies to sirukumab will be summarized for all participants in the ITT population with appropriate samples for detection of antibodies to sirukumab (ie, participants with at least predose and the Day 28 sample obtained).

- Analysis of the relationship between various blood biomarkers, such as cytokines, and viral parameters, immunogenicity, safety and clinical outcome may be conducted. Descriptive statistics for actual values and (relative) changes from baseline for the different blood biomarkers assessed, will be tabulated for each biomarker

- Statistical approaches to explore correlations between clinical outcome and blood biomarkers vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences between participants.

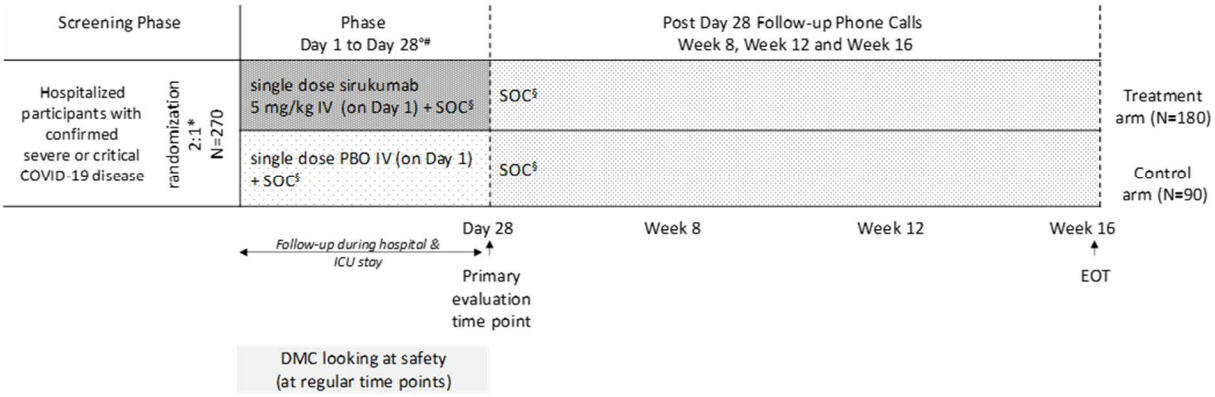
- Associations between baseline levels of biomarkers, immunogenicity tests, PK parameters and clinical response (primary endpoint and a selection of secondary endpoints) will be explored.

- DNA samples will be analyzed if it is hypothesized that this may help resolve issues with the clinical data.

- DNA samples will be used for research related to sirukumab or COVID-19. Pharmacogenomic research may consist of the analysis of one or more candidate genes, of the analysis of genetic markers throughout the genome, or the analysis of the entire genome (as appropriate) to evaluate potential genetic associations with prognosis of clinical outcomes in patients and prediction of responsiveness to active treatment.

1.2. Schema

Figure 1: Schematic Overview of the Study up to Protocol Amendment 4



COVID-19: coronavirus disease 2019; DMC: Data Monitoring Committee, EOT: end of trial, ICU: intensive care unit, IV: intravenous, PBO: placebo, SOC: standard of care

* Randomization will be stratified by age (<65 and ≥65 years of age) and by use of invasive mechanical ventilation (yes/no) at the time of randomization.

\# Up to Day 28 or until hospital discharge or study discontinuation, whichever comes first. If a participant is discharged before Day 28, a phone call visit will be performed at Day 28.

§ SOC treatment (during study treatment and follow-phase) is determined by the investigator based on local practice and consists of supportive care.

SARS-CoV-2 PCR positivity at any time before screening will be accepted. Results from local laboratory, ECG, and pulmonary imaging assessments taken up to 2 days prior to screening will be accepted for screening assessments.

Screening[a] assessments start after signing of the ICF and can continue on the next calendar day, if needed. All screening and baseline assessments may also take place on the same day.

Participants need to receive study intervention preferably within 4 hours but no later than 6 hours after randomization.

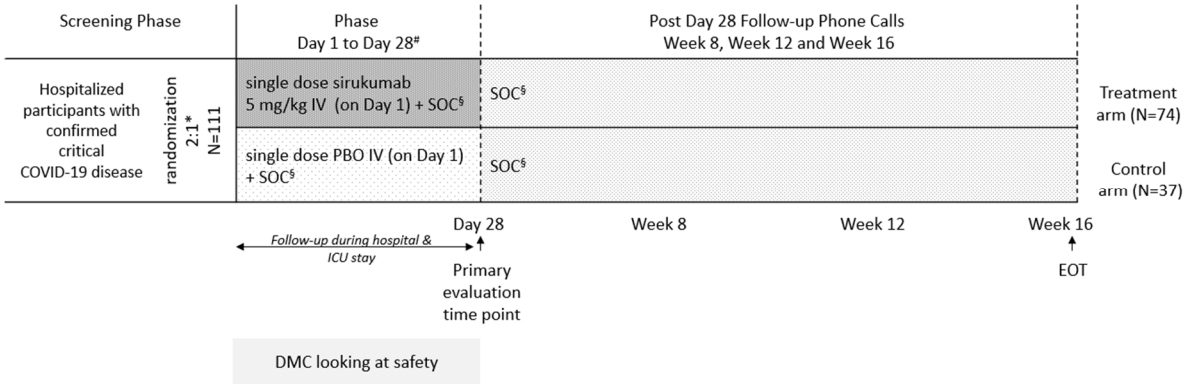
[a] If the participant is on invasive mechanical ventilation or veno-venous ECMO, duration may not be >48 hours at time of screening.

During the period covered up to and including protocol amendment 4:

- The DMC reviewed the interim data as soon as the first 30 participants with confirmed severe or critical COVID-19 disease had been dosed and had had at least 7 days of follow-up after study intervention.
- An IA for futility was performed when approximately 20% of the planned number of participants with confirmed severe or critical COVID-19 disease have reached Day 28 or discontinued earlier.

Figure 2: Schematic Overview of the Study as of Protocol Amendment 5

As of protocol amendment 5, participants with confirmed severe COVID-19 disease are no longer enrolled in the study and the study aims to enroll approximately 111 participants with critical COVID-19 overall in the study. At the time of release of protocol amendment 5, approximately 100 participants with confirmed severe COVID-19 disease had been enrolled.



Footnotes: see Figure 1.

1.3. Schedule of Activities (SoA)

Safety laboratory testing (hematology, chemistry, and coagulation tests) will routinely be performed by local laboratories (refer to Section 10.2 Appendix 2: Clinical Laboratory Tests and Section 10.3 Appendix 3: Clinical and Laboratory Assessments Described per Day).

	Screening Phase[a]	**Phase Day 1 to Day 28**			**Post Day 28 Follow-up Phone Calls**
Day	**Screening**	**Baseline[a] Day 1**	**Day 2 to Day 28[b] or day of discharge from hospital[aa], or study discontinuation, whichever comes first**	**Day 28 Visit if discharged earlier (Phone Call) Day 28 ±3 days**	**Day 56, Day 84, Day 112 ±7 days**
Week	**Week 1**		**Week 1 (Day 2) to Week 4**	**Week 4**	**Week 8, 12, 16**
General Screening/Baseline assessments					
ICF[c]	X				
Inclusion/exclusion criteria	X	X[d]			
Demographics, medical history[e]	X				
Targeted physical exam[h]	X		Any clinically significant findings to be reported		
Treatment administration					
Randomization[i]		X			
Administration of study intervention[i]		X			
Concomitant medication					
Concomitant medication recording	X	X	Throughout the study	X[n]	X[n]
Respiratory function related assessments					
Type of supplemental oxygen	X	X	Once per day		
Resting SpO_2, FiO_2 (if any)[j]	X	X	Minimum 4 times per day		
Arterial pH, PaO_2, $PaCO_2$[j]	As available				
Level of consciousness (Glasgow coma scale score)[k]	X	X	Once per day while in the ICU		
Pulmonary X-ray (or CT imaging or lung ultrasound if X-ray not available)	X[g,bb]		As per SOC, report upon worsening and last available		

	Screening Phase[a]	Phase Day 1 to Day 28			Post Day 28 Follow-up Phone Calls
Day	**Screening**	**Baseline[a] Day 1**	**Day 2 to Day 28[b] or day of discharge from hospital[aa], or study discontinuation, whichever comes first**	**Day 28 Visit if discharged earlier (Phone Call) Day 28 ±3 days**	**Day 56, Day 84, Day 112 ±7 days**
Week	**Week 1**		**Week 1 (Day 2) to Week 4**	**Week 4**	**Week 8, 12, 16**
General safety related assessments					
Standard 12-lead ECG	X[g,bb]		one ECG is to be taken between Day 4 and Day 8		
Vital signs (body temperature, pulse, SBP/DBP, respiratory rate)	X	X	As per SOC, minimum 4 times per day while in the ICU, afterwards once per day		
Any AE	X	X	Throughout the study	X[n]	X[n]
Record discharge from ICU, discharge from hospital			As applicable		
Safety laboratory assessments[dd]					
Hematology[l],	X[g]	X	Day 3, Day 7, Day 14, Day 21, Day 28[cc]		
Chemistry[l] general safety	X[g]	X	Day 3, Day 7, Day 14, Day 21, Day 28[cc]		
Chemistry- Total Cholesterol, LDL, HDL, Triglycerides	X[g]	X	Day of discharge		
Coagulation: PT/INR or aPPT, fibrinogen	X[g,]	X	Day of discharge		
Urine Pregnancy assessment[f]	X[g]	X	Day 28 or at day of discharge		
Bacterial, fungal, viral infection testing (blood, other)[m]	As per local SOC, any new infection is to be reported as AESI				

	Screening Phase[a]	Phase Day 1 to Day 28			Post Day 28 Follow-up Phone Calls
Day	**Screening**	**Baseline[a] Day 1**	**Day 2 to Day 28[b] or day of discharge from hospital[aa], or study discontinuation, whichever comes first**	**Day 28 Visit if discharged earlier (Phone Call) Day 28 ±3 days**	**Day 56, Day 84, Day 112 ±7 days**
Week	**Week 1**		**Week 1 (Day 2) to Week 4**	**Week 4**	**Week 8, 12, 16**
Virology Assessments					
Nasopharyngeal swab for infections testing (PCR quantification of SARS-CoV-2 and multiplex PCR for detection of co-infections)[p,q] If participants are intubated, an endotracheal sample for quantification of SARS-CoV-2 is to be taken in addition to the NP swab[t]	X[r,q]	X[s,•]	Day 3, Day 7, Day 10, Day 14, Day 21, Day 28[u,v,•] Optional: Day 4, Day 5, Day 8[•]		X[v,•]
Stool sample (if feasible)[•]	X[bb]		Day 3, Day 7, Day 10, Day 14, Day 21, Day 28 Optional: Day 4, Day 5, Day 8		
Blood sample for SARS-CoV-2 viremia[•]		X	Day 7, Day 14, Day 28[cc]		
Biomarker/Pharmacology Assessments[dd]					
CRP, Ferritin, D-dimer, Procalcitonin[•]		X	Day 3, Day 5, Day 7, Day 14, Day 21, Day 28[cc]		
Blood samples for cytokines, chemokines[•]		X	Day 5, Day 14, Day 21, Day 28		
Blood samples for various biomarkers[•]		X	Day 5, Day 28		
Blood sample for SARS-CoV-2 specific antibodies[•]		X	Day 14, Day 28		
Blood samples for pharmacology[w,•]		X	Day 14, Day 21, Day 28		
Blood samples for cellular profiling[•]		X	Day 5, Day 28		

	Screening Phase[a]	Phase Day 1 to Day 28			Post Day 28 Follow-up Phone Calls
Day	**Screening**	**Baseline[a] Day 1**	**Day 2 to Day 28[b] or day of discharge from hospital[aa], or study discontinuation, whichever comes first**	**Day 28 Visit if discharged earlier (Phone Call) Day 28 ±3 days**	**Day 56, Day 84, Day 112 ±7 days**
Week	**Week 1**		**Week 1 (Day 2) to Week 4**	**Week 4**	**Week 8, 12, 16**
Exploratory Biomarkers/Pharmacogenomics[•,dd]					
PAXgene blood for RNA profiling[x,•]		X	Day 5, Day 28		
Whole blood for DNA profiling (optional)[y,•]		X[z]			
Phone call assessments					
Record vital status[o]				X[n]	X[n]
Self-reported oxygen needed (yes/no)				X[n]	X[n]
Self-reported pregnancy status				X[n]	X[n]
Record readmission(s) post discharge and reason				X[n]	X[n]

- Laboratory testing to be performed centrally

Note: If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECG, oxygen saturation, vital signs, blood sampling.

Abbreviations: AE: adverse event, AESI: adverse event of special interest; aPPT: activated partial thromboplastin time; CRP: C-reactive protein; CT: computed tomography; DBP: diastolic blood pressure; FiO_2: percentage of inspired oxygen; ECG: electrocardiogram; HDL: low-density lipoprotein; ICF: informed consent form; ICU: intensive care unit; INR: international normalized ratio; LDL: low-density lipoprotein; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressures of oxygen in arterial blood; PCR: polymerase chain reaction; PT: prothrombin time; SAE: serious adverse event; SBP: systolic blood pressure; SOC: standard of care; SpO_2: peripheral capillary oxygen saturation.

Footnotes:

a. Screening assessments start after signing of the ICF and can continue on the next calendar day, if needed. All screening and baseline assessments may also take place on the same day. Screening/Baseline assessments required to verify study eligibility and data collection for assessment of the 6-point ordinal clinical recovery category should take place prior to randomization. All Screening/Baseline procedures should take place prior to study drug administration.

b. The assessment schedule will be on a weekly basis for participants still hospitalized after Day 28. For the required assessments, refer to Section 10.3, Appendix 3: Clinical and Laboratory Assessments Described per Day.

c. Consent to be obtained before the first study-related activity. An exception is in the case of an emergency enrollment in which the informed consent can be obtained as soon as possible.

d. If a participant's clinical status changes after screening but before randomization such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study.

e. Medical history should include collecting onset of COVID-19 symptoms, prior therapy, and date of SARS-CoV-2 diagnosis if available.

f. A urine pregnancy test is to be performed in women of childbearing potential only.

g. Results from the blood chemistry, hematology, and coagulation test, pregnancy test, ECG, and pulmonary imaging, completed as SOC, taken up to 2 days prior to screening will be accepted as screening assessments.

h. Targeted physical examination is to be performed as per local SOC and includes, if feasible, lung auscultation and any examination as indicated by the patient's medical history. Height and body weight are only to be measured at screening if not already available in the participant's chart and if practically feasible. If not feasible, weight for dose calculation can be verbally reported by the participant or a family member.

i. Participants need to receive study intervention preferably within 4 hours but no later than 6 hours after randomization.

j. Supplemental oxygen/percentage of inspired oxygen (FiO_2) use (if any) will be measured (simultaneously with SpO_2, and at any time of arterial blood gas measurements) to monitor the patient's status regarding gas exchange as applicable. The following will be recorded:
   - Oxygen delivery device (eg, nasal cannula, simple face mask, nonrebreather mask, high flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, extracorporeal life support, etc).
   - Oxygen flow rate in liters/min.
   - Record FiO_2 and SpO_2 data 4 times per day, and at any time of arterial blood gas measurements. Record values that are sustained for at least 1 hour.
   - If a patient is using more than one device (eg, extracorporeal life support and invasive ventilation), the worst value of FiO_2 (and the corresponding SpO_2 -and PaO_2 if available-) on the highest level of intervention will be recorded. The worst (highest) value of FiO_2 (and the corresponding SpO_2 -and PaO_2 if available-) on each device will also be recorded separately.

- If a patient does not need oxygen supplementation, this should also be recorded.

k. The final worst score of the Glasgow Coma Scale of the day needs to be recorded in the eCRF. The level of sedation of the participant will be derived from the type of medication entered for indication sedation on the Concomitant Medication page of the eCRF.

l. Laboratory testing to be performed includes:
   - Hematology: hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, RBC indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], % reticulocytes), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils).
   - General safety chemistry: total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, glucose, sodium, potassium, calcium, phosphate, magnesium, chloride, bicarbonate, creatinine, blood urea nitrogen (BUN), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), lactate, and troponin. If ALT or AST >3x ULN or 3x the entry level (if entry levels were >ULN), also provide conjugated bilirubin (direct), unconjugated bilirubin (indirect).

m. Culture results (bacterial, fungal, or viral) including site of infection and specimen source (bronchoalveolar lavage [BAL], tracheal aspirate, sputum, blood, urine, etc.), performed as part of patients' workup for new infections, should be reported. Analyses will be performed by the local laboratory.

n. For participants discharged or who discontinued the study prior to Day 28 and did not withdraw consent, phone calls will be conducted on Day 28 and during the post Day 28 Follow-up Phase to record concomitant medication, the vital status, the occurrence of AEs, self-reported oxygen need, self-reported pregnancy status and the history of readmission since last contact.

o. Whenever possible, vital status will be recorded if the patient is alive. If the participant is deceased, date and cause of mortality should be recorded in the eCRF. Death should be documented as SAE.

p. NP swabs will be used to collect secretions from participants to explore quantification of viral load of SARS-CoV-2. For each participant, NP sampling should be done at approximately the same time (±4 hours) on each sampling day and from the same nostril.

q. If an NP sample for detection of SARS-CoV-2 (local SOC) will be collected on the same day as the NP sample for quantification of SARS-CoV-2 (central lab), only one NP sample should be collected. The sample should be aliquoted and the remaining aliquots of the NP samples should be stored and sent to the central lab for quantification of SARS-CoV-2.

r. SARS-CoV-2 positivity should be documented based on local testing on any specimen, by RT-PCR, any time before randomization. This might require a local test using an NP swab obtained at screening.

s. After randomization, SARS-CoV-2 positivity will be confirmed in a central lab by quantitative RT-PCR. The baseline sample needs to be collected predose, as close as possible to dosing.

t. If the participant is intubated, endotracheal samples need to be taken at the same time as the NP swab. If taking both NP and endotracheal samples is not feasible, the NP sample should be given priority.

u. Lab testing for detection of SARS-CoV-2 on the NP swab at day of hospital discharge. If SARS CoV-2 positive, an additional NP swab will be taken every 7 days, if feasible for the site and tested, until SARS-CoV-2 negative.
v. If viral RNA is detected in NP samples at day of discharge, all possible efforts will be made to follow-up participants and collect samples every 7 days until viral RNA is negative, considering the current pandemic and related logistical challenges. If possible, home visits by a healthcare professional may be conducted to collect samples during the follow-up period.
w. Includes serum samples for measurement of PK, antibodies to sirukumab, and IL-6. On Day 1, a predose and a postdose (within 30 minutes after the end of infusion) sample should be collected. The postdose sample should be collected from the arm contralateral to that used for IV infusion. On Day 1 (predose) and Day 28 the PK, antibodies to sirukumab, and IL-6 will be evaluated. On Day 1 (postdose), Day 14, and Day 21 the PK and IL-6 will be evaluated.
x. PAXgene RNA tubes should always be used last for any blood draw.
y. An optional pharmacogenetics blood sample (DNA) will be obtained from those participants who gave consent (where local regulations permit).
z. Sample can be also taken at any other time point after study drug intervention on Day 1.
aa. For those participants discharged prior to Day 28, all Day 28 assessments should be done at day of discharge. Laboratory, virology, relevant respiratory function related assessments, and biomarker/pharmacology assessments completed maximum 1 day before discharge do not need to be repeated on the day of discharge provided that no clinically relevant changes were noted in the results and the participant was declared 'ready to be discharged' on the day before discharge.
bb. Assessments done at screening do not need to be repeated at baseline.
cc. For participants still hospitalized post Day 28, additional blood sampling should be done every 7 days (±1 day) and at day of discharge.
dd. For all laboratory tests done on Day 21, Day 28, and every week thereafter as needed, a window of ±1 day for all sampling is allowed.

2. INTRODUCTION

Sirukumab (also known as CNTO136) is a human anti- IL-6 immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb). Sirukumab binds with high affinity and specificity to human IL-6 and as a result inhibits IL-6-mediated signaling and the biological effects of IL-6.

For the most comprehensive nonclinical and clinical information regarding sirukumab, refer to the latest version of the Investigator's Brochure (IB) for sirukumab.[29]

The term “study intervention” throughout the protocol, refers to sirukumab or placebo as defined in Section 6.1, Study Interventions Administered.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality.[53] Currently, no treatment of COVID-19 has been established. Many trials (eg, with antivirals) are currently ongoing. While an understanding of the epidemiology and clinical spectrum of COVID-19 is still evolving during the ongoing pandemic, the current knowledge of the disease burden highlights the urgent medical need to develop a treatment. Learnings from SARS-CoV, initial COVID-19 data[17,51] and preclinical mouse model data indicate that IL-6 might be a key driver of the acute lung injury (ALI) and ARDS observed in COVID-19. More severe COVID-19 patients from an initial study in China had elevated levels of IL-6.[67] Tocilizumab (Actemra/roActemra®) is a human mAb that binds the IL-6 receptor (IL-6R) and blocks the IL-6 pathway.[1,52] It is approved to treat cytokine release syndrome (CRS) due to chimeric antigen receptor T (CAR-T) cell therapy and has shown anecdotal preliminary benefit in treating ARDS in patients with COVID-19. Noncontrolled, interim data from patients being treated with sarilumab (Kevzara®, another mAb that binds to IL-6R)[35] also provide some early reports of possible benefit to patients. Sirukumab blocks the IL-6 signaling pathway by binding and neutralizing IL-6, which warrants a study to assess its utility as an additional treatment option for patients with COVID-19-associated ARDS.

2.1.1. Background

SARS-CoV-2 Virology and COVID-19 Disease Burden

SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19), is an enveloped, positive-sense, single -stranded RNA betacoronavirus.[18,75] It was first identified following reports of a cluster of acute respiratory illness cases in Wuhan, Hubei Province, China in December 2019.[39] Epidemiological investigations indicated that the majority of early cases were linked to a seafood market, with patients infected through zoonotic or environmental exposure, followed by the subsequent spread of infection by human-to-human transmission among close contacts.[39] Genomic sequencing was performed on bronchoalveolar lavage fluid samples collected from

patients with viral pneumonia admitted to hospitals in Wuhan, which identified a novel RNA virus from the family *Coronaviridae*.[43,75] Phylogenetic analysis of the complete viral genome revealed that the virus, SARS-CoV-2, is part of the subgenus Sarbecovirus of the genus Betacoronavirus, and is most closely related (approximately 88% identity) to a group of SARS-like coronaviruses previously sampled from bats in China.[43]

SARS-CoV-2 has spread rapidly and globally since its emergence.[15,18,23,39,43,75] The World Health Organization (WHO) declared that the outbreak constituted a public health emergency of international concern on January 30, 2020, and declared the outbreak to be a pandemic on March 11, 2020.[70,72,73,74] As of April 4, 2020, this pandemic has infected over 1,289,380 people with over 70,590 associated deaths worldwide.[34]

Symptoms of infection may appear from 2 to 14 days following exposure, with the spectrum of illnesses ranging from mild symptoms to severe illness or death.[8] Severe clinical presentations have been reported for as many as 20–25% of laboratory-confirmed cases.[25] In a study of 99 patients in a single center in Wuhan with SARS-CoV-2 infection confirmed by real-time reverse-transcriptase polymerase chain reaction (RT-PCR), the most commonly reported clinical manifestations were fever (83%), cough (82%), shortness of breath (31%), and muscle ache (11%).[15] In chest x-rays and CT scans, 75% of patients showed bilateral pneumonia and 14% of patients showed multiple mottling and ground-glass opacities. In a further study of 138 patients with novel coronavirus-induced pneumonia in a single center in Wuhan, common symptoms included fever (98.6%), fatigue (69.6%), and dry cough (59.4%).[66] Lymphopenia occurred in 70.3% of patients, and chest CT scans showed bilateral patchy shadows or ground-glass opacities in the lungs of all patients. Thirty-six patients (26%) were transferred to the intensive care unit (ICU) because of complications, including ARDS, arrhythmia, and shock. Broadly, similar findings were noted in other case studies, eg, in the Seattle region in the US.[6] At present, it appears that individuals aged 65 years or older, especially those with comorbid diseases, are subject to the highest incidence of morbidity and mortality.[10] In contrast, a study of 2,143 children aged <18 years in China with laboratory-confirmed (34.1% of cases) or suspected (65.9% of cases) COVID-19 indicated that the clinical manifestations of the disease may be less severe in children than adults, with approximately 94% of cases being asymptomatic, mild, or moderate.[23] However, young children, particularly infants, were susceptible to severe disease, with the highest proportion of severe and critical cases by age group reported for children aged <1 year (10.6% of cases) and 1-5 years (7.3% of cases). Also, new evidence has emerged from China indicating that a large number of infections do not result in symptoms.[20]

The identification of SARS-CoV-2 follows the emergence of 2 other novel betacoronaviruses capable of causing severe human disease over the past 18 years: SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), which have nucleotide sequence identity with SARS-CoV-2 of approximately 79% and 50%, respectively.[43] The first known cases of SARS occurred in Southern China in November 2002.[74] The etiological agent, SARS-CoV, is believed to be an animal virus that crossed the species barrier to humans followed by human-to-human transmission, leading to SARS cases in >25 countries. The MERS-CoV was isolated from a patient in Saudi Arabia who died of severe pneumonia and multi-organ failure in June 2012.[82] MERS-CoV

is considered to be a zoonotic virus infecting bats and camels capable of non-sustained human-to-human transmission. Since 2012, sporadic cases and community and health-care-associated clusters of infected individuals have been reported in the Middle East.

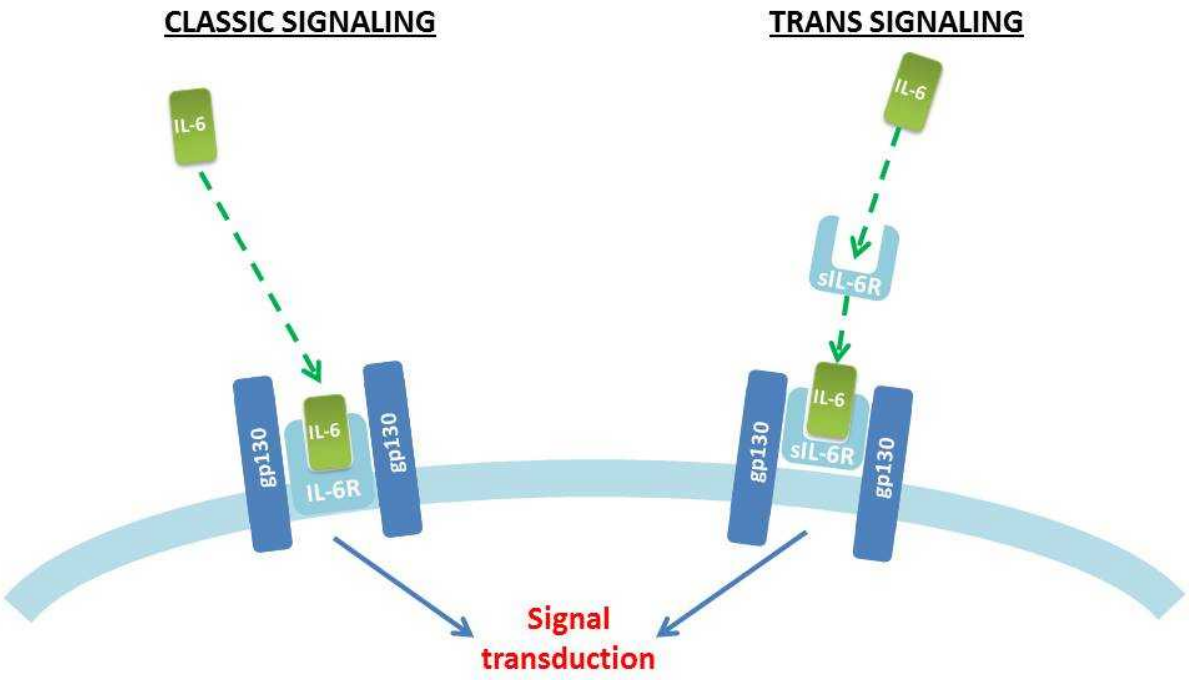
Patients with SARS or MERS present with various clinical features, ranging from asymptomatic or mild respiratory illness to fulminant severe acute respiratory disease with extrapulmonary manifestations.[12,82] Both diseases have predominantly respiratory manifestations, but extrapulmonary features may occur in severe cases. By July 2003, the international spread of SARS-CoV resulted in 8,098 SARS cases and 774 deaths (case-fatality- rate: 10%) with substantial social, economic and health service disruption in some affected countries.[12,74] The case-fatality rate of MERS-CoV infections is estimated to be 35%.[12]

Interleukin-6 as a Key Target of ARDS

IL-6, a biomarker for inflammation and a high-level immune response, is a pleiotropic cytokine that can have multi-faceted effects on multiple cell types and organs.[61,68] There can be both systemic (acute phase response) and local effects in activating and amplifying the immune response. Published studies have demonstrated the involvement of IL-6 in various inflammatory disease processes including asthma, lupus erythematosus, rheumatoid arthritis, anemia of chronic inflammation, insulin resistance, cancer, major depressive disorder, giant cell arteritis and virus-induced ARDS. In addition, IL-6 has been implicated as a central mediator of toxicity in cytokine release syndrome (CRS), a potentially life-threatening, systemic inflammatory response that can be triggered by a variety of factors including viral infections.

IL-6 is a soluble, glycosylated protein expressed by a variety of immune (T-cells, B-cells, macrophages, and microglia) and nonimmune cell types (fibroblasts, endothelial cells, adipocytes, myocytes, and neurons). IL-6 facilitates diverse physiological processes such as T-cell- activation, induction of immunoglobulin secretion, initiation of hepatic acute-phase protein synthesis, and stimulation of hematopoiesis. IL-6 signals via a receptor complex comprising its specific receptor, the IL-6 receptor (IL6R) and glycoprotein (gp) 130, the signal transducing subunit. The IL-6Rα exists in 2 forms; a membrane-bound form and a soluble form. Once a monomer of IL-6 binds a monomer of either form of the IL-6Rα (termed “classic” signaling when using the membrane bound form and “trans” signaling when using the soluble form), the IL-6-IL-6Rα complex is engaged by a gp130 homodimer. While gp130 is present on most if not all cells of the body, the membrane-bound form of the IL-6R is only present on some cells, mainly hepatocytes and several leukocytes, such as monocytes, macrophages, B cells and subtypes of T cells. Cells, which only express gp130 are refractory to IL-6 signals. This facilitates the selective activation of target cells and differentiates between the two different signaling pathways.[68] Activation of IL-6 signal transduction is initiated and mediated by gp130-associated Janus activated kinases (JAKs) and phosphorylation of signal transducer and activator of transcription 3 (STAT-3), resulting in subsequent intracellular signaling (Figure 3).

Figure 3 IL-6 signaling



IL-6 = interleukin 6; IL-6R = IL-6 receptor alpha; sIL-6R = soluble form of IL-6 receptor alpha

While the expression of IL-6 and other cytokines is a component of the normal immune response, excessive expression of cytokines such as IL-6 and the ensuing immune inflammation can lead to disease pathology. This excessive systemic release of proinflammatory cytokines, termed a "cytokine storm", can occur in a number of non-infectious conditions such as graft-versus-host disease (GVHD), CAR-T cell therapy[55], and ARDS as well as several infectious diseases such as sepsis, Ebola and other viral hemorrhagic fevers, avian influenza, and smallpox.[48,59] Actemra/RoActemra® (tocilizumab), an IgG1 mAb that binds to both soluble and membrane-bound IL-6 receptors blocking IL-6 mediated signaling, is indicated for the treatment of adults and children with severe or life-threatening CRS due to CAR-T cell therapy. Approval was based upon a retrospective analysis of pooled outcome data from clinical trials indicating that blocking the IL-6 pathway with tocilizumab resulted in resolution of severe or life-threatening CRS in patients receiving CAR-T cell therapies for hematological malignancies.[1,52]

Coronaviruses, Acute Respiratory Distress, and IL-6

Coronaviruses infect a variety of host species, including humans and several other animal species. In their natural hosts, these viruses predominantly cause respiratory and intestinal tract infections producing a wide range of clinical manifestations. Coronaviruses infecting the respiratory tract have long been recognized as significant pathogens in animals and as the cause of mild and severe respiratory illness in humans. Highly pathogenic human coronaviruses such as SARS-CoV and

MERS-CoV similarly cause a wide spectrum of clinical manifestations in humans. Typically, the majority of patients develop a short period of moderate clinical illness; however, a small but a substantial number of patients develop severe pneumonia often associated with rapid virus replication, massive inflammatory cell infiltration and elevated proinflammatory cytokine/chemokine responses resulting in ALI and ARDS.[13]

It has been well documented for many years that infection by several members of the *Coronaviridae* family both in vitro and in vivo in humans and animals is associated with increases in the production of IL-6.[1,4,22,27,31,38,42,50,60,77,78,81] This induction of IL-6 expression can be caused by productive viral infection, non-productive infection, noninfectious virus-like particles[5], and even individual coronavirus proteins such as the spike or nucleocapsid proteins.[24,47,80,63,64]

Elevated IL-6 levels in the fluid of the lungs have been associated with a poor prognosis for individuals with ARDS.[7,65]

In the case of SARS, increased levels of IL-6 have been reported to be a prognostic indicator associated with more severe pulmonary disease in both animal models[14,19,30,56] as well as in individuals infected with SARS-CoV.[3,32,37,62,69,79] Learnings from SARS-CoV, initial COVID-19 data[17,51] and preclinical mouse model data indicate that IL-6 might indeed be a key driver of the ALI and ARDS observed in COVID-19. More severe COVID-19 patients from an initial study in China had elevated levels of IL-6.[67]

Since blocking the IL-6 pathway in CAR-T induced CRS with tocilizumab is clinically beneficial, it is hypothesized that IL-6 might play a key role in the cytokine storm associated with serious adverse outcomes in COVID-19 patients, and that blocking IL-6 would be a suitable therapeutic target for these patients.[54]

Initial non-peer reviewed results from a single-arm, observational, non-controlled, 21-patient Chinese study showed that COVID-19 participants experienced rapidly reduced fevers and 75% of patients (15 out of 20) reduced their need for supplemental oxygen within days of receiving tocilizumab.[76] The utility of blocking the IL-6 pathway using the IL-6R mAbs tocilizumab (Actemra/roActemra®)[1] and sarilumab (Kevzara®)[35] is now being investigated in an open-label clinical trial (ClinicalTrials.gov Identifier: NCT04322773). The primary outcome measure is the time to independence from supplementary oxygen therapy up to 30 days from enrollment. Secondary outcome measures (30 days from enrollment) include the number of deaths, number of days out of hospital and alive, number of ventilator free days alive and out of hospital, and CRP levels.

Sirukumab is a human anti-IL-6 IgG1κ mAb that binds to human IL-6 with high affinity and specificity. The high affinity binding of sirukumab to IL-6 (equilibrium dissociation constant [Kd] = 0.175 pM) prevents the association of IL-6 with the IL-6R, thereby blocking receptor signaling and biological activities attributed to IL-6 both in vitro and in vivo. In vitro bioassays show that sirukumab neutralizes both cis- and trans-signaling of human IL-6 (mediated via cell surface IL-6R and soluble IL-6R, respectively) in a concentration-dependent manner. Sirukumab also blocks human IL-6-induced expression of the acute phase proteins haptoglobin and serum amyloid A

(SAA) in mice; this effect is sirukumab-specific and dose-dependent. As such, treatment of patients with confirmed COVID-19 severe disease with sirukumab could reduce pulmonary and systemic levels of IL-6 resulting in a clinically meaningful benefit.

Some studies allow for a second (and third) dose of the drug, in case of insufficient response (eg, NCT04320615, NCT04372186, NCT04335071, all with tocilizumab, an IL-6R blocking antibody). IL-6R blocking antibodies bind IL-6R (~2.5 nM for tocilizumab) with similar affinity as IL-6 (0.5-34 nM) and compete with IL-6 for IL-6R binding.[45] At 5 mg/kg IV dose of sirukumab, serum C_{max} is ~125 ug/mL and at Week 4, serum sirukumab concentration is ~10 ug/mL which is substantially higher than the serum IL-6 level in COVID-19 and ARDs patients. In combination with potent affinity of sirukumab for IL-6 (~0.175 pM), it is anticipated that sirukumab levels after a single dose will be sufficiently high to bind circulating IL-6 levels (pg/mL up to ng/mL in ARDS) for at least 4 weeks, and that an additional dose will not be required to block the IL-6 pathway effectively.

Nonclinical Studies

No preclinical studies have been performed to assess the potential activity of sirukumab in SARS-CoV-2 infection.

Sirukumab does not neutralize guinea pig, beagle, rat, or murine-derived IL-6. As such, preclinical testing utilized an analogous mAb that was shown to bind and neutralize murine IL-6. Prophylactic treatment of New Zealand Black/W F1 lupus-prone mice with anti-murine IL-6 mAb reduced anti-dsDNA autoantibody production and suppressed renal damage in a murine model of systemic lupus.[40] Treatment with the anti-murine IL-6 mAb was also effective in reducing the incidence and severity of arthritis and joint histopathology in a mouse model of collagen-induced arthritis.[41]

Pharmacologic Profile

Sirukumab is a human IgG1κ mAb monoclonal antibody with a molecular weight of approximately 150,000 Daltons. Sirukumab binds to and neutralizes human IL-6 and subsequently attenuates IL-6 signaling and the biological effects of IL-6. Sirukumab also binds to and neutralizes cynomolgus monkey IL-6. Because of this, the cynomolgus monkey was selected as a pharmacologically relevant species for the evaluation of the nonclinical pharmacokinetics (PK) and toxicology of sirukumab.

Toxicology

Toxicology results from the 3- and 6-month multiple IV and subcutaneous (SC) dose studies conducted in cynomolgus monkeys showed no adverse effects that were considered related to the administration of sirukumab in clinical signs and measurements and clinical/anatomic pathology parameters. The no-observed-adverse-effect-level (NOAEL) in the related toxicology studies was 50 mg/kg weekly.

Standard genotoxicity studies are generally inappropriate for biotechnology-derived pharmaceuticals and therefore, mutagenesis and carcinogenesis studies have not been conducted. Evaluation of reproductive potential in sexually mature male cynomolgus monkeys by

measurement of testicular volume, sperm count, motility and morphology, and histopathology of male reproductive organs identified no adverse effects. Studies conducted in mice given an anti-mouse IL-6 mAb showed no adverse effects on male or female fertility.

Data from an embryo-fetal developmental toxicity study demonstrated that in the 50 mg/kg group (IV once weekly for 98 days), the abortion/embryo-fetal death ratio was increased, and it was considered that the increased abortion/embryofetal death ratio in this group was possibly sirukumab-related. The NOAEL in dams and fetuses was 10 mg/kg once weekly for a total of 15 administrations.

Pharmacokinetic and Immunogenicity Profile

The PK/toxicokinetics (TK) and immunogenicity of sirukumab have been investigated in cynomolgus monkeys following multiple IV administrations of sirukumab at doses of 10 and 50 mg/kg, and multiple SC administrations of sirukumab at a dose of 50 mg/kg. Please refer to the IB for more information regarding the PK, TK, and immunogenicity of SC sirukumab.[29]

After IV administrations, systemic exposure of sirukumab increased in an approximately dose-proportional manner over the dose range of 10 to 50 mg/kg. The mean terminal half-life ($T_{1/2}$) of sirukumab ranged from 10 to 19 days across all IV dose groups. The mean accumulation ratios were 3.34 and 2.45 for once-weekly IV administrations at 10 and 50 mg/kg, respectively. All animals from all dosing groups tested negative for antibodies to sirukumab.

When administered to pregnant monkeys (IV 10 and 50 mg/kg/week), serum sirukumab concentrations in the maternal animals increased in an approximately dose-proportional manner and sirukumab was also detected in the fetal circulation on the day of cesarean section (during the third trimester). The mean ratios of the fetal to maternal serum sirukumab concentrations were 1.33 (10 mg/kg) and 1.36 (50 mg/kg). All dams who had milk samples collected (n=25) between lactation day (LD) 30 and LD 75 had non-detectable sirukumab concentration samples except 1 monkey in the 50 mg/kg IV group. Sirukumab was also detected in the infant at birth (LD 0-LD 3) with serum concentrations similar to those of the dams; these serum levels were still detected 3 to 6 months post-birth.

Clinical Studies

At time of writing the protocol, 14 interventional studies with administration of sirukumab for the treatment of systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE), lupus nephritis (LN), rheumatoid arthritis (RA), Major Depressive Disorder (MDD) and Giant-cell Arteritis (GCA) were completed.

As of 23 October 2018, overall, 251 healthy participants and an estimated 5,044 participants with RA, 71 participants with lupus, 193 participants with MDD, and 161 participants with GCA have been exposed in the sirukumab clinical program; of these, 3,495 participants have received sirukumab (IV or SC) in company-sponsored interventional clinical trials (227 healthy participants, 3,120 participants with RA, 54 participants with lupus, and 94 participants with MDD) and 111 participants have received sirukumab in business partner-sponsored clinical trials.

Of the total 3,606 participants who have received sirukumab, 272 participants were in the Phase 1 studies, 297 participants were in the Phase 2 studies, and 3,037 participants were in the Phase 3 studies.

Of the participants included in the clinical program, a total of 107 participants received sirukumab IV. Of these, 55 received a dose that was higher than the dose of 5 mg/kg that will be administered in the current study.

Relevant pharmacokinetic and immunogenicity results on IV administration of sirukumab in the clinical program are presented below. More detailed information of all clinical studies performed with sirukumab are described in the IB.[29]

Human Pharmacokinetics and Immunogenicity

The PK of sirukumab has been evaluated in healthy participants following a single IV administration (C0136T01). Sirukumab exhibited linear PK over a dose range of 0.3 to 10.0 mg/kg following a single IV administration to healthy participants. Following a single IV administration of sirukumab 0.3 to 10.0 mg/kg, the mean volume of distribution (V_z) ranged from 121 to 248 mL/kg and the mean total systemic clearance (CL) appeared to be dose independent and ranged from 3.8 to 6.1 mL/day/kg. Mean $T_{1/2}$ values in healthy participants were 15 to 32 days. The mean $T_{1/2}$ at the dose level of 5 mg/kg was estimated to be about 21 days.

In participants with CLE or SLE, following 4 biweekly IV administration of 1, 4, or 10 mg/kg sirukumab, systemic exposure of sirukumab (C_{max} and $AUC_{0\text{-}14d}$) increased in an approximately dose-proportional manner (study C0136T03). Mean $T_{1/2}$ values in participants with CLE or SLE were estimated to be 16 to 23 days.

In participants with LN, following IV administration of sirukumab 10 mg/kg q4w, serum concentrations of sirukumab reached steady-state by Week 12 (study CNTO136LUN2001). The mean trough serum concentration of sirukumab was 20.63 µg/mL at Week 12 and was maintained through Week 24 (22.65 µg/mL). Mean C_{max} and $AUC_{0\text{-}28d}$ values were 239.65 µg/mL and 1421.26 µg*day/mL and 259.47 µg/mL and 1864.92 µg*day/mL following the first and last administrations of 10 mg/kg sirukumab, respectively. Mean accumulation ratios following IV administration of sirukumab 10 mg/kg q4w were 1.08 for C_{max} and 1.24 for $AUC_{0\text{-}28d}$, which indicated minimal drug accumulation. Mean values of CL and volume of distribution at steady-state (V_{ss}) were 5.10 mL/day/kg and 87.03 mL/kg, respectively. Mean $T_{1/2}$ values were comparable between healthy participants (19 to 30 days), and participants with CLE/SLE (16 to 23 days) or participants with LN (16 days) following IV administration.

Immunogenicity of IV sirukumab has been evaluated in 2 Phase 1 and 1 Phase 2 studies as of 16 August 2017, including: studies C0136T01, C0136T03, and CNTO136LUN2001. None of the participants with evaluable serum samples tested positive for antibodies to sirukumab in studies C0136T01 (0/31) and C0136T03 (0/32). In study CNTO136LUN2001, 1 (5.0%) of the 20 sirukumab-treated participants with evaluable samples (5.0%) tested positive for antibodies to sirukumab.

Clinical Efficacy

No efficacy data are available on the use of sirukumab to treat COVID-19 induced ARDS.

In 2016, the sponsor filed a Biologics License Application with the FDA seeking approval for the use of SC sirukumab in the treatment of RA based upon data from the RA clinical development program. During the review of the BLA, the FDA convened an Advisory Committee meeting, held in 2017. While the Advisory Committee felt that sirukumab convincingly demonstrated efficacy in RA, it could not definitely attribute the imbalance in overall mortality to chance or the study design, and given the availability of other drugs for RA, the Advisory Committee did not recommend approval of sirukumab for RA. As a result, the sponsor did not pursue further development of SC sirukumab in RA. Refer to latest version of the IB for a summary the efficacy results in RA and other indications.[29]

Clinical Safety

The clinical safety of sirukumab has been evaluated in 107 participants receiving IV administration (34 participants in C0136T01, 33 participants in C0136T03, 21 participants in CNTO136LUN2001, and 19 participants in CNTO136NAP1003 [Note: 1 participant discontinued participation]) as well as in 3,500 participants who have received sirukumab SC.

Risks associated with sirukumab include infections, hypersensitivity reactions, gastrointestinal perforations, hematologic events such as neutropenia and thrombocytopenia, and changes in lipid profiles and elevations of liver enzymes. These risks are not dissimilar to those observed with other biologics that target the IL-6 pathway such as tocilizumab[1] and sarilumab[35] which also include serious infections, gastrointestinal perforations, and changes in neutrophils, platelets, lipids, and liver function tests. In addition, tocilizumab and sarilumab both have black box warnings for risk of serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections. The utility of blocking the IL-6 pathway using the IL-6R mAbs tocilizumab and sarilumab (KEVZARA®) is now being investigated in several clinical trials (ClinicalTrials.gov Identifiers: NCT04317092, NCT04320615, NCT04310228, NCT04306705, NCT04315480, NCT04322773).

Relevant safety results on IV administration of sirukumab in the clinical program are presented below. More detailed information of all clinical studies performed with sirukumab are described in the IB.[29]

Safety in 3 Phase I studies with IV administration

Study **C0136T01** was a Phase 1, double-blind, placebo-controlled, ascending single-dose study evaluating the safety, PK, and immunogenicity of IV administered sirukumab in healthy participants. A total of 34 participants received a single dose of either 0.3, 1.0, 3.0, 6.0, or 10.0 mg/kg IV sirukumab and 11 participants received placebo.

Sirukumab was generally well tolerated in the 34 healthy participants who received single IV infusions of sirukumab. The most common AE across all sirukumab treatment groups was

pharyngolaryngeal pain (5/34, 14.7%). There was 1 SAE not related to study agent. Thirteen of 34 (38.2%), sirukumab-treated participants had 1 or more AEs considered related to study agent by the investigator. The most common drug-related AE was pharyngolaryngeal pain. No deaths were reported in the study. Overall, there were no dose-related safety concerns.

There were no noteworthy differences among cohorts in mean neutrophils values over time, and the mean values remained within the normal range. However, there was a dose-dependent decrease in median change from baseline in neutrophils in CNTO136-treated participants compared to placebo, with a nadir at Week 4. At Week 4, Cohort 6 (10.0 mg/kg) had the largest decrease from baseline, with a median of –1.8 x109 (approximately -28%).

Of the CNTO136-treated participants, 4 (2 in the 3 mg/kg and 2 in the 6 mg/kg group) had abnormally low lymphocyte values vs one participant in the placebo group. Three treated participants (one each in the 1, 3, and 6 mg/kg group) had abnormally low neutrophil values. These episodes were generally isolated and transient in duration and none were considered by the investigator to be of clinical significance, or were reported as AEs. The participant in the 6.0 mg/kg group, had a low neutrophils count (1.69 x 10^9/L [LLN 1.5 x 10^9/L]) Day –1 prior to dosing. He experienced a marked abnormally low lymphocyte count of 0.81 x 10^9/L at Week 12, which returned to within normal range by Week 16 (2.28 x 10^9/L).

Study **C0136T03** was a 2-part Phase 1 study. Part A was a multicenter/multinational, randomized, double-blind, placebo-controlled, staggered-parallel, 3 ascending-dose cohort study of multiple IV administrations of sirukumab in which 23/31 participants with CLE received either 1, 4, or 10 mg/kg IV sirukumab biweekly over 6 weeks (8/31 participants received placebo). Part B was a multicenter/ multinational, randomized, double-blind, placebo-controlled, single-dose level cohort study of multiple IV administrations of sirukumab in which 10/15 participants with SLE received 10 mg/kg IV sirukumab biweekly (5/15 participants received placebo).

Six SAEs were reported in Part A and 3 SAEs were reported in Part B. The single death in this study, due to a car accident, was considered to be not related to the administration of sirukumab. Two SAEs of infection were reported: pneumonia that was considered to be probably related to sirukumab administration and a bacterial infection of an iatrogenic wound that was considered to be unlikely related to sirukumab administration. Neutropenia and thrombocytopenia were reported more frequently in participants in the sirukumab groups than in the placebo groups in both lupus populations. Compared with the placebo group, participants with CLE in the 1 and 4 mg/kg sirukumab groups reported a relatively higher number of skin-related AEs that were considered to be reasonably related to sirukumab, whereas the 10 mg/kg group did not report any reasonably related skin events.

Participants who received sirukumab showed immediate stable and sustained decreases in WBC, ANC, and platelets at all individual dose levels, while participants in the placebo group showed no change in results. The decreases were not dose dependent. There was little to no clear temporal association between low neutrophil counts and the occurrence of infections. Two participants in the Part B SLE cohort were discontinued from administration because of low ANC and platelet counts, but no immediate apparent clinical symptoms were associated with these low values.

Fasting lipids showed minor elevations of total cholesterol in the cohorts that received sirukumab. Complement C3 and C4 decreased in both CLE and SLE participants in all sirukumab groups, but not in the placebo group. In Part A, WBC, ANC, and platelets showed decreases compared with baseline for the CNTO 136 combined group and at all individual dose levels. Participants in the placebo group showed no changed results for all 3 parameters. For WBC and ANC, some (but not complete) recovery was observed at the Week 22 follow-up visit. For platelets, recovery at the Week 22 follow-up visit was less clear. The decreases were not dose dependent. The effect on platelets and ANC was already seen at Week 2 and the decreases observed during subsequent visits remained of the same order of magnitude. In Part B, median values for WBC, ANC, and platelets showed decreases from baseline for the CNTO 136 group compared with the placebo group. For all 3 parameters, median values reached stable levels upon continued dosing, and there was no clear recovery to baseline values at the Week 22 follow-up visit. The decrease in ANC was observed for most participants after the initial dose administration.

CNTO136NAP1003 was a Phase 1, randomized, open-label, parallel-design study to assess absolute bioavailability and single-dose PK following SC administration of sirukumab delivered by a pre-filled syringe fitted with UltraSafe Passive™ Delivery System (PFS-U) or a SmartJect™ Autoinjector (PFS-AI) in healthy male participants. As a comparator arm, 19/144 participants received a single IV administration of 100 mg sirukumab. Note that 1 of the 19 participants who received IV sirukumab 100 mg terminated study participation early (due to lost to follow-up).

Of the 144 participants who received sirukumab, 68 (47.2%) had at least 1 AE during the study. The incidence of participants with AEs was higher in the IV 100 mg group (11 participants [57.9%]) as compared with the SC treatment groups (50 mg PFS-AI group: 6 participants [31.6%], 50 mg PFS-U group: 9 participants [47.4%], 100 mg PFS-AI group: 22 participants [51.2%], and 100 mg PFS-U group: 20 participants [45.5%]).

Of the 19 participants who received IV 100 mg sirukumab, 11 participants (57.9%) reported 1 or more AEs with no apparent pattern in any system-organ class. None of the participants who received IV 100 mg sirukumab had an SAE or discontinued due to an AE. No deaths occurred.

No infusion reaction AEs were reported after IV infusion of sirukumab 100 mg in any of the participants.

Safety in a Phase II study with IV administration

Study **CNTO136LUN2001** was a randomized, double-blind, placebo-controlled, parallel group, multicenter proof-of-concept study of sirukumab in 25 participants aged between 18 and 70 years (inclusive) with a diagnosis of SLE and a biopsy-proven ISN/RPS Class III or IV LN within approximately 14 months prior to randomization who were not on cyclophosphamide therapy within 3 months of randomization and who were receiving stable maintenance treatment with either mycophenolate mofetil or azathioprine, with or without corticosteroids. Of the 25 participants, 21 participants received sirukumab 10 mg/kg IV and 4 participants received placebo IV. Study treatments were administered every 4 weeks (at Weeks 0, 4, 8, 12, 16, 20, and 24).

The most frequently reported AEs were observed in the System Organ Class of Infections and infestations (17 of 21 participants [81.0%] in the sirukumab group and 2 of 4 participants [50.0%] in the placebo group) and Gastrointestinal disorders (10 of 21 participants [47.6%] in the sirukumab group and 1 of 4 participants [25.0%] in the placebo group. The majority of AEs were mild to moderate in intensity. No participant reported severe AEs in the placebo group whereas, in the sirukumab group 7 participants reported severe AEs, of which 3 participants reported a severe AE of lupus nephritis.

Approximately half of the sirukumab–treated participants (10 of the 21 participants [47.6%]) reported at least 1 SAE. The most frequently reported SAE was lupus nephritis, followed by pneumonia (including pneumonia haemophilus), and cellulitis. No deaths were reported during the study.

No discontinuations due to AEs were reported in the placebo group whereas, 5 of 21 participants (23.8%) in the sirukumab group discontinued due to AEs. The AEs that led to discontinuation were pneumonia haemophilus, hepatic enzyme increased, anaphylactic reaction, neutropenia, and lupus nephritis.

Eight of 21 participants (38.1%) from the sirukumab group and no participant from the placebo group reported treatment–emergent serious infections. All serious infections occurred after patients had received at least 4 doses of sirukumab at Week 12. The most frequently reported treatment-emergent serious infections were pneumonia (3 of 21 participants [14.3%] reported pneumonia and 1 of 21 participants [4.8%] reported pneumonia haemophilus), and cellulitis (2 of 21 participants [9.5%]). In addition, 1 participant had a severe infusion reaction (anaphylactic reaction) following the first administration of sirukumab.

A higher reduction in absolute neutrophils count and WBC count from baseline was observed in the CNTO136 group as compared with the placebo group over time. No noteworthy changes from baseline were observed in other hematology parameters. For neutrophils, there was a 24.88% decrease from baseline at Day 4 and a 27.67% decrease at Week 4. Further decrease varied during the study until Week 40 with a decrease of 31.56%. For neutrophils (decreased), there were no toxicities observed in the placebo group whereas, all toxicities grades were observed in the CNTO136 group: Grade 1 (4 of 21 participants [20.0%]), Grade 2 (8 of 21 participants [40.0%]), Grade 3, and Grade 4 (each observed in 1 of 21 participants [5.0%]). For WBC (decreased), no Grade 4 toxicity was observed in either of the treatment groups. A similar percentage of participants had Grade 1 toxicity (5 of 21 participants [25.0%] in the CNTO 136 group and 1 of 4 participants [25.0%] in the placebo group). No Grade 2 or 3 toxicities were observed in the placebo group whereas, 10 of 21 participants (50.0%) had Grade 2, and 2 of 21 participants (10.0%) had Grade 3 toxicity in the CNTO 136 group. For lymphocytes (decreased), no Grade 4 toxicity was observed in the placebo group whereas, 1 of 21 participants (5.0%) had Grade 4 toxicity in the CNTO 136 group. A higher percentage of participants had Grade 2 and Grade 3 (each observed in 6 of 21 participants [30.0%]) toxicities in the CNTO 136 group whereas, in the placebo group 1 of 4 participants (25.0%) had Grade 2 toxicity and 2 of 4 participants (50.0%) had Grade 3 toxicity. There were few participants in the sirukumab group with elevated toxicity grades for liver function

tests (ALT, AST, and alkaline phosphatase) as compared with no participant with liver toxicity in the placebo group. No clinically relevant changes in vital signs and posttreatment ECGs were observed in the treatment groups during the study.

2.2. Dose Rationale

The sirukumab dose proposed to be evaluated in severely and critically ill participants with confirmed COVID-19 disease is 5 mg/kg administered as a single IV infusion.

It has been demonstrated that a single IV dose of sirukumab at 0.3 to 10 mg/kg was generally well tolerated in healthy participants (C0136T01) without showing evidence of safety concerns. In addition, multiple IV doses of sirukumab at 1, 4 or 10 mg/kg every 2 weeks (q2w) or every 4 weeks (q4w) were investigated in participants with systemic lupus erythematosus or cutaneous lupus erythematosus (n=33, C0136T03), and in participants with lupus nephritis (n=21, CNTO136LUN2001). The proposed IV dose of 5 mg/kg is 2-fold lower than the highest dose (ie, 10 mg/kg IV) evaluated in completed studies of sirukumab. Furthermore, the safety margins at 5 mg/kg as a single-dose IV administration are sufficiently large (~20 based on C_{max} and ~10 based on AUC) compared to the PK exposure at the IV NOAEL dose of 50 mg/kg/week in a 6-month GLP toxicology study in cynomolgus monkeys.

The affinity of sirukumab for IL-6 (0.175 pM) is >1,000-fold higher than that of IL-6R for IL-6 (0.5-34 nM).[6] At 5 mg/kg IV dose of sirukumab, serum C_{max} is predicted to be ~125 µg/mL and at week 4, serum sirukumab concentration is predicted to be ~10 µg/mL, which is substantially higher than the serum IL-6 level in COVID-19 and ARDS patients (in pg/mL magnitude). Molar ratios (serum sirukumab:IL-6) will remain high for at least 4 weeks. In RA patients, a dose at or above 25 mg every 4 weeks inhibited CRP levels for > 4 weeks. For a 70 kg subject, a 5 mg/kg sirukumab dose would translate to 350 mg, which is 14-fold higher than 25 mg (C1377T04). Therefore, even with increased IL-6 levels in COVID-19 as compared to RA, inhibition of IL-6R signaling (read-out by drop in CRP levels) is expected to last at least 4 weeks.

Based on the preliminary findings reported, the baseline blood IL-6 level is significantly elevated to hundreds pg/mL magnitude in severely and critically ill COVID-19 patients[16,76], which is much higher than the baseline IL-6 levels seen in RA participants.[33] In addition, IL-6 levels in bronchoalveolar lavage fluid in patients at risk for ARDS and with established ARDS could raise to thousands pg/mL and remain above the normal range for up to 3 weeks in patients with persistent ARDS.[49] Given the acute nature of the disease for COVID-19 patients, IV administration is considered necessary for sirukumab treatment to rapidly suppress the elevated IL-6 levels in these patients. Subcutaneous absorption of sirukumab would be significantly slower to reach C_{max} compared to IV administration. A 5 mg/kg IV dose of sirukumab is expected to provide sufficient exposure to bind IL-6 efficiently in patients with confirmed severe or critical COVID-19 disease who are at risk of ARDS. A physiologically based pharmacokinetics-pharmacodynamics (PBPK-PD) model predicted treatment with an IV dose of 5 mg/kg sirukumab would suppress elevated IL-6 levels to the normal range (ie, <10 pg/mL) in severely and critically ill COVID-19 patients who are at risk of ARDS.

In summary, sirukumab 5 mg/kg administered as a single IV infusion is expected to be effective with acceptable risks in rapidly suppressing the free IL-6 levels for at least 4 weeks in participants with confirmed severe and critical COVID-19 disease.

2.3. Benefit-Risk Assessment

2.3.1. Risks for Study Participation

Potential risks for participants treated with sirukumab single IV dose are the occurrence of infusion reactions, hypersensitivity, serious infections, liver enzymes increase, and neutropenia/thrombocytopenia (see Section 8.3.6). Of these the most significant risks relate to the complications associated with immunosuppression, essentially bacterial, fungal and viral infections.

The following risk mitigations are in place:

- The study population will be under continuous monitoring in a hospital/intensive care setting.
- The protocol prevents patients with the most severe COVID-19 disease (eg, on invasive mechanical ventilation or veno-venous ECMO for >48 hours) and pre-existing comorbidities (including non-COVID-19-related active infections, severe COPD, steroid dependency, being on renal replacement therapy, chronic liver disease, malignancy), patients ≥85 years of age, from participating.
- To further protect the participants from the immunomodulatory effects of sirukumab that may predispose them to infections, the investigators are referred to the local guidelines for the concomitant use of antibacterials and/or agents that are intended to inhibit SARS-CoV-2 viral activity for management of community acquired pneumonia, COVID-19 pneumonia, or secondary infections. Open-label or off-label use of agents that are intended to inhibit SARS-CoV-2 viral activity, with demonstrated in-vitro effect, as mentioned in the CDC guidelines on Therapeutic Options for patients with COVID-19 are permitted in the study.[6]

The co-administration of convalescent plasma introduces an additional protein load of 2.4 to 8 g/L.[25,35] This may be a concern in patients with renal impairment, however it is noted that the following risk mitigations are in place:

- The exclusion criterion 10 prevents patients with an estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2 or requiring renal replacement therapy from participating.
- The study population will be under continuous monitoring in a hospital/intensive care setting.

The inclusion of a Data Monitoring Committee (DMC) will ensure oversight of patient safety (see Section 10.4.6, Committee Structure).

2.3.2. Benefits for Study Participation

There are currently no established pharmacologic therapies that are effective in the treatment of COVID-19 infection or associated ARDS. The potential benefit of sirukumab is to fulfill an urgent medical need for patients by reducing progression of ARDS and associated mortality.

Additionally, there are potential benefits to global public health in establishing effective therapies with expediency. Given the burden that the COVID-19 pandemic has placed on global health resources in terms of demand for healthcare professionals to treat those hospitalized with COVID-19, the worldwide demand for ventilators, and the overall mortality in those with COVID-19 severe disease, particularly those who are older and have pre-existing comorbidities, sirukumab has the potential to have a positive impact on the COVID-19 pandemic and on the overwhelmed healthcare systems by, eg, reducing duration of mechanical ventilation and of length of stay in ICU/hospital ward.

2.3.3. Benefit-Risk Assessment for Study Participation

The sponsor is of the opinion that the potential benefits of treatment with sirukumab outweigh any associated risks of treatment. This is based upon the following:

- There are no established treatments for COVID-19. The proposed target patient population consists of individuals who have hypoxemia and who are at risk of ARDS. These are the patients with the most urgent medical need who are at the greatest risk of dying. The current mortality due to COVID-19-associated pulmonary complications for hospitalized patients with hypoxemia and pulmonary involvement ranges from approximately 20-50% depending upon the age of the individual and pre-existing comorbidities.
- Access of patients to investigational therapeutics to mitigate the disease is limited in this pandemic setting, and this study will offer the potential to access a therapeutic in the context of a clinical study.
- The proposed dosing is a single IV administration of 5 mg/kg. During the clinical development program, study participants have received up to 10 mg/kg sirukumab IV q2w and no dose-limiting toxicity has been observed. In addition, multiple IV doses of sirukumab at 1, 4 or 10 mg/kg q2w or q4w were administered to lupus patients (C0136T03 and CNTO136LUN2001). In the placebo-controlled trial CNTO136LUN2001, 21 participants (men or women) aged between 18 and 70 years (inclusive) with a diagnosis of SLE and a biopsy-proven LN received sirukumab up to 10 mg/kg IV q4w for 24 weeks. Eight of 21 participants (38.1%) from the sirukumab group and 0/4 participants from the placebo group reported treatment–emergent serious infections. All serious infections occurred after patients had received at least 4 doses of sirukumab at Week 12. In Part A of C0136T03, the first 2 cohorts (1 and 4 mg/kg) consisted of 8 participants each (6 receiving sirukumab and 2 receiving placebo) and the highest dose cohort (10 mg/kg) consisted of 10 participants (8 receiving sirukumab and 2 receiving placebo). A total of 4 doses were to be administered q2w over a 6-week period. In Part B, 15 participants (10 receiving sirukumab and 5 receiving placebo) received 10 mg/kg biweekly over a 6-week period. Two SAEs of infection were reported: pneumonia that was considered to be probably related to sirukumab administration and a bacterial infection of an iatrogenic wound that was considered to be unlikely related to sirukumab administration.
- The risks associated with sirukumab are largely based upon data from studies in immune-mediated diseases which involved chronic repeat dosing over an extended period of time (eg, 1 year).
- The known risks associated with sirukumab are not dissimilar to those of other approved agents that target the IL-6 pathway.

- The study population will be under careful monitoring in the hospital setting with several risk mitigations strategies in place.
- The inclusion of a DMC will ensure oversight of patient safety.

More detailed information about the known and expected benefits and risks of sirukumab can be found in the IB.[29]

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the clinical response of sirukumab (administered as a single IV dose) + SOC compared to placebo + SOC in confirmed critical COVID-19 disease	• Time to improvement[a] of at least 2 categories relative to Baseline on the 6-point ordinal clinical recovery scale (up to Day 28)
Key secondary	
To evaluate the clinical response of sirukumab + SOC compared to placebo + SOC in confirmed critical COVID-19 disease	• Proportion of participants with an improvement on Day 28 of at least 2 categories relative to Baseline on the 6-point ordinal clinical recovery scale • Incidence of all-cause mortality (up to Day 28)
Other Secondary	
To evaluate the clinical response of sirukumab (administered as a single IV dose) + SOC compared to placebo + SOC in confirmed severe or critical COVID-19 disease	• Time to improvement[a] of at least 2 categories relative to Baseline on the 6-point ordinal clinical recovery scale (up to Day 28)
To evaluate the clinical response of sirukumab + SOC compared to placebo + SOC in confirmed severe or critical COVID-19 disease	• Proportion of participants with an improvement on Day 28 of at least 2 categories relative to Baseline on the 6-point ordinal clinical recovery scale • Incidence of all-cause mortality (up to Day 28)
To evaluate the safety of sirukumab + SOC compared to placebo + SOC in confirmed (a) critical and (b) severe or critical COVID-19 disease	• Incidence of SAEs (up to Day 28) • Incidence of related AEs (up to Day 28) • Proportion of participants with severe or life-threatening bacterial, invasive fungal, viral or opportunistic infections (other than SARS-CoV-2) (up to Day 28) • Incidence of grade 3 and 4 neutropenia and lymphocytopenia (up to Day 28) • Incidence of increased ALT ≥3xULN combined with increased bilirubin >2xULN (up to Day 28)

[a]The improvement should be sustained until Day 28 (or discharge/discontinuation).

Objectives	Endpoints
To evaluate the clinical response of sirukumab + SOC compared to placebo + SOC in confirmed (a) critical and (b) severe or critical COVID-19 disease	• Time to improvement[a] of at least 1 category relative to Baseline on the 6-point ordinal clinical recovery scale (up to Day 28) • Proportion of participants with an improvement on Day 28 of at least 1 category relative to Baseline on the 6-point ordinal clinical recovery scale • Time from study intervention to end of oxygen supplementation (up to Day 28) • Time from study intervention to hospital discharge among the surviving participants (up to Day 28) • Total length of hospitalization among the surviving participants (up to Day 28) • Number of ventilation free days (up to Day 28) • Participant's clinical status at Day 7, 14, 21, 28 (6-point ordinal clinical recovery scale) • Total time on invasive mechanical ventilation • Proportion of participants with a worse[b] category relative to Baseline on the 6-point ordinal clinical recovery scale (up to Day 28) • Proportion of participants on extracorporeal membrane oxygenation (ECMO) over time • Total time on ECMO
To evaluate the safety during follow-up for (a) critical and (b) severe or critical COVID-19 disease	• Proportion of alive participants at Day 28, Week 8, and Week 16 • Proportion of alive participants that required readmission at Week 8 and Week 16 (if previously discharged) • Incidence of SAEs up to Week 16
Exploratory	
To evaluate biomarkers that may be associated with response to or complications of sirukumab treatment	Evaluations may include, but are not limited to, IL-6, procalcitonin, C-Reactive protein (CRP), ferritin, LDH and D-dimer serum concentrations (through Day 28)
To explore changes in SARS-CoV-2 viral load and viral genome	• Time to SARS-CoV-2 undetectable viral load by RT-PCR (up to Day 28) • SARS-CoV-2 viral load over time by RT-PCR (up to Day 28)

[a] The improvement should be sustained until Day 28 (or discharge/discontinuation).

[b] Clinical recovery scale score worsened with at least 1 category between Day 5 and Day 28.

Objectives	Endpoints
	• Proportion of participants with undetectable viral load (at multiple time points up to Day 28) • Development of SARS-CoV-2 variants
To evaluate the incidence of SARS-CoV-2 viremia	• Proportion of participants with SARS-CoV-2 viremia (at multiple time points up to Day 28)
To evaluate pharmacokinetics following sirukumab 5 mg/kg treatment	• Sirukumab serum concentrations
To evaluate immunogenicity following sirukumab treatment	• Proportion of participants with sirukumab antibodies (Day 28 or at discharge if discharged after Day 28)
To evaluate SARS-CoV-2 humoral immunity	• Serum levels of SARS-CoV-2 specific antibodies

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

At the time of data analysis, additional endpoints may be considered for analysis in function of the evolution in scientific knowledge on COVID-19.

HYPOTHESIS

The primary hypothesis of this study is that sirukumab in combination with SOC results in a statistically significant shorter time to improvement (defined as an improvement of at least 2 categories relative to Baseline on the 6-point ordinal clinical recovery scale) versus placebo in combination with SOC, in participants with confirmed critical COVID-19 disease.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, multicenter, interventional Phase 2 study in hospitalized participants with confirmed COVID-19 disease, at risk for progressing to severe ARDS.

Up to protocol amendment 4, a target of approximately 270 participants with confirmed severe or critical COVID-19 disease was randomly assigned in a 2:1 ratio to receive 1 of the following 2 treatments:

- Treatment Arm: sirukumab 5 mg/kg IV single dose infusion on Day 1 + SOC treatment
- Control Arm: placebo IV single dose infusion on Day 1 + SOC treatment

More information on the SOC treatment is provided in Section 6.8 Prestudy and Concomitant Therapy.

As of protocol amendment 5, the study aims to enroll approximately 111 participants with confirmed critical COVID-19 disease overall in the study. The primary and key secondary analyses will be tested on the participants with confirmed critical COVID-19 disease.

At the time of release of protocol amendment 5, approximately 100 participants with confirmed severe COVID-19 disease had been enrolled. The overall population of participants with confirmed severe or critical COVID-19 disease will be analyzed as part of secondary objectives of the study.

Randomization is stratified by age (<65 and ≥65 years of age) and by use of invasive mechanical ventilation (yes/no) at the time of randomization.

The study will include a Screening Phase, a 'Day 1 to Day 28' Phase and Post Day 28 Follow-up Phase (phone calls on Week 8, Week 12 and Week 16). The entire study duration for each participant will be 16 weeks with daily study assessments up to Day 28 or day of discharge (whichever comes first), and phone call assessments thereafter, ie, at Day 28 in case of discharge prior to Day 28, at Week 8, 12 and 16. The assessment schedule will be on a weekly basis for participants still hospitalized after Day 28. The study is considered completed with the completion of the last study assessment (phone call assessment at Week 16) for the last participant in the study or the discontinuation of the last participant in the study, whichever comes last. For details, refer to the Schedule of Activities (SoA).

The impact of a single dose treatment with sirukumab on Day 1 + SOC on confirmed critical COVID-19 disease will be evaluated throughout the study. Refer to the Schedule of Activities (SoA) and Section 8, Study Assessments and Procedures for details.

The primary endpoint is the time to improvement of at least 2 categories relative to Baseline on the 6-point ordinal clinical recovery scale (up to 28 days). The improvement should be sustained until Day 28 (or discharge/discontinuation). For details, refer to Section 8.1.1, Six-point Ordinal Clinical Recovery Scale.

The primary analysis will be done when all participants reached Day 28 or discontinued earlier.

The final analysis will be done when all participants completed the study.

The DMC reviewed the interim data after the first 30 participants with confirmed severe or critical COVID-19 disease had been dosed and have had at least 7 days of follow-up after study intervention. Details regarding the DMC are provided in Committees Structure in Section 10.4.6.

A non-binding unblinded IA for futility was performed by the sponsor on the primary endpoint when approximately 20% of the planned number of participants with confirmed severe or critical COVID-19 disease had reached Day 28 or discontinued earlier. Additional IAs on participants with confirmed critical COVID-19 disease are not planned for the study.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

There is currently no treatment for COVID-19. Many drugs are currently under investigation, but none so far have proven efficacy. Current treatment is therefore only supportive, as per SOC.

Sirukumab will be administered on top of SOC, and placebo in combination with SOC will constitute the control group in this Phase 2 exploratory study. Concomitant medications for consideration as part of SOC are provided in Section 6.8, Prestudy and Concomitant Therapy.

Blinded, Controlled, Randomized Study

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention with sirukumab and to characterize the safety profile in this placebo group.

Randomization will be used to minimize bias in the assignment of participants to treatment arms, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment arms, and to enhance the validity of statistical comparisons across treatment arms.

Double blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Stratification will be done by age (<65 and ≥65 years of age) and by use of invasive mechanical ventilation (yes/no) at randomization.

Study Population

The goal is to identify a patient population with confirmed critical COVID-19 disease as defined in Inclusion Criterium 5 (see Section 5.1) who might benefit most from an anti-IL-6 intervention, ie, patients at risk of progressing to severe ARDS.

The initial study design included enrollment of participants with confirmed severe or critical COVID-19 disease. Based on the rapidly evolving space of COVID-19 therapeutics focusing on the highly impacted population of critical patients together with the results from the interim analysis, as of protocol amendment 5, the study population is being limited to a subset of the currently eligible population, ie, those with confirmed critical COVID-19 disease.

At the time of release of protocol amendment 5, approximately 100 participants with confirmed severe COVID-19 disease had been enrolled. The overall population of participants with confirmed severe or critical COVID-19 disease will be analyzed as part of secondary objectives of the study.

DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in response to study intervention and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to evaluate potential genetic associations with prognosis of clinical outcomes in patients and prediction of responsiveness to sirukumab treatment.

Biomarker samples will be collected to evaluate the mechanism of action of sirukumab or to help explain interindividual variability in clinical outcomes, to potentially help identify population subgroups that respond differently to an intervention or to SARS-CoV-2 infection, and/or to characterize markers associated with SARS-CoV-2 infection. The goal of the biomarker analyses is to evaluate the PD of sirukumab and aid in evaluating the intervention-clinical response relationship.

Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants or (legally acceptable representatives) will be fully informed of the risks and requirements of the study and, during the study, participants (or legally acceptable representatives) will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Participants (or legally acceptable representatives) who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

In case of emergency situations due to COVID-19, when patients are incapable of giving their informed consent (eg, under intensive medical care) to enter the study, and the participant's legally acceptable representative is not available (eg, none is in place since the participant had been otherwise healthy before infection with SARS-CoV-2), deferred consent is permitted if in compliance with national law and local regulations. Enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the participant and to ensure compliance with applicable regulatory requirements. The participant or legally acceptable representative should be informed about the study as soon as possible and give consent to continue. In the event the legally acceptable representative is not available, a member of the family can take that role.

Due to the COVID-19 pandemic, alternative procedures to obtain informed consent may be needed, as it is likely that the physical consent form cannot leave the isolation room and is not appropriate as study documentation. In that case, an alternative document (eg, photograph of the signature page) can be filed as a signed consent. For any informed consent that cannot be performed in person (eg, verbal consent by telephone), the process must be documented and confirmed by way of normal consent procedures at the earliest opportunity. An impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign a copy of the ICF (obtained and maintained outside the isolation room) after the oral consent of the participant is obtained.

The primary ethical concerns are that sirukumab may not improve clinical outcomes of a participant with COVID-19 or may worsen clinical outcomes due to the immunosuppressant effect of sirukumab.

The total blood volume to be collected of approximately 275 mL, including the optional sample for pharmacogenomic research, is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross standard blood donation.[2]

4.3. Justification for Dose

Refer to Section 2.2 Dose Rationale.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last scheduled study assessment at Week 16 as shown in the Schedule of Activities for the last participant in the study or the discontinuation of the last participant, whichever comes last. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed assessments at Week 16 or has experienced a clinical endpoint that precludes further continuation in the study (eg, early mortality).

5. STUDY POPULATION

Screening assessments start after signing of the ICF and can continue on the next calendar day, if needed. All screening and baseline assessments may also take place on the same day. Results from the blood test, pregnancy test, ECG, and pulmonary imaging, completed as SOC, taken up to 2 days prior to screening will be accepted as screening assessments. SARS-CoV-2 positivity, as determined locally by real time-PCR, in any specimen at any time prior to randomization is acceptable and this should not be repeated for inclusion in the study. If all eligibility criteria are met at screening then randomization may occur on that same day.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Male or female ≥18 and <85 years of age.
2. Hospitalized.
3. Criterion modified by Amendment 4

   3.1 Has laboratory-confirmed SARS-CoV-2 infection as determined by real time-PCR at any time before randomization.
4. Criterion modified per Amendment 3

   4.1 Evidence of infiltrates by chest X-ray, chest CT, lung ultrasound, or chest auscultation (rales, crackles).
5. Criterion modified per Amendment 2

   5.1 Criterion modified per Amendment 3

   5.2 Criterion modified per Amendment 5

   5.3 Critical COVID-19 disease, defined as:

   Critical disease: Requires supplemental oxygen delivered by nonrebreather mask or high-flow nasal cannula OR use of non-invasive or invasive ventilation OR requiring treatment in an ICU.

   AND,

   corresponding to category 4 on the 6-point ordinal recovery scale (see Section 8.1.1), ie,

   Requires one of the above modalities to sustain a SpO_2 >93%, with an a FiO_2 of 50%[a] or higher. Note, the use of other devices may fit with category 4 if the FiO_2 is 50%[a] or higher.

   OR, corresponding to category 5 on the 6-point ordinal recovery scale, ie,

   PaO_2/FiO_2 ratio <300 mmHg while on invasive mechanical ventilation or veno-venous ECMO for less than 48 hours prior to screening.

   Note: as of protocol amendment 5, patients with confirmed severe COVID-19 disease are no longer eligible in the study. Severe COVID-19 is defined as requiring supplemental oxygen administration by nasal cannula, simple face mask, or other similar oxygen delivery device (ie, above pre-COVID baseline oxygen requirement,

[a] The conversion between the oxygen flow expressed in L/min to the corresponding FiO_2 value in % is the following:

L/min	1	2	3	4	5	6	7	8	9	10
FiO_2 %	24	28	32	36	40	44	48	52	56	60

if any, by the participant) at a FiO_2 less than 50%[a]. This corresponds to category 3 on the 6-point ordinal scale (see Section 8.1.1).

6. Criterion modified per Amendment 1

   6.1 Informed consent must be obtained from the participant (or their legally acceptable representative must sign based on local regulations) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

   Note: In case of emergencies, when participants and their legally acceptable representative are incapable of giving their informed consent (eg, under intensive medical care) to enter the study, the sponsor will adhere to local regulations. Refer to Section 4.2.1 for more information.

For optional DNA research:
Separate informed consent must be obtained from the participant (or their legally acceptable representative) if he or she agrees to provide an optional DNA sample for research (where local regulations permit). The informed consent for the optional DNA research will be obtained in the main study informed consent form (ie, by a tick box).
Refusal to give consent for the optional DNA research sample does not exclude a participant from participation in the study.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Criterion modified per Amendment 2

   1.1 On invasive mechanical ventilation or on veno-venous ECMO for >48 hours at time of screening.

2. Meets local or global criteria to not receive mechanical ventilation or has designated themselves as DNR per a living will.

3. Criterion modified per Amendment 2

   3.1 Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 30 days before the planned dose of study intervention.

   Note: the investigator must ensure that the participant is not enrolled in another COVID-19 study with an investigational intervention (apart from the exception specified below) prior to completion of Day 28 of the current study.

Exceptions: Participation in a single arm study, a non-blinded controlled study, expanded access, compassionate use program or any other program that is not a blinded study is allowed if it is conducted with one of the following:

- agents with demonstrated in vitro-effect against SARS-CoV-2, as mentioned in the CDC guidelines.[6]
- *convalescent plasma.*

4. Criterion modified per Amendment 2

   4.1 Current confirmed or high suspicion for pulmonary embolus, hemodynamic significant pericardial effusion, myocarditis, or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification (Section 10.9, Appendix 9)

   AND/OR

   Current evidence of active cardiac ischemia.

5. Criterion modified per Amendment 1

   5.1 Criterion modified per Amendment 2

   5.2 Currently active clinically significant (eg, causing hemodynamic instability and/or causing hypoxemia) and uncontrolled arrhythmia.

6. Liver function impairment defined as Child Pugh Class B/C based on medical history.

7. Has congenital bleeding diathesis based on medical history.

8. Criterion modified per Amendment 2

   8.1 Has a history of chronic respiratory condition (ie, asthma, chronic obstructive pulmonary disease [COPD], cystic fibrosis, fibrotic lung disease) that requires home oxygen supplementation, supportive non-invasive ventilation, or is status/post lung volume reduction surgery (LVRS)

   Exception: Participants with sleep apnea using supportive non-invasive ventilation (continuous positive airway pressure [CPAP]) at screening may be included.

9. On renal replacement therapy (defined as peritoneal dialysis or hemodialysis)

10. Criterion modified per Amendment 1

    10.1 Criterion modified per Amendment 2

    10.2 Criterion modified per Amendment 3

    10.3 Screening laboratory test result as follows:

    - Absolute neutrophil count (ANC) $<1.0 \times 10^3$ cells/µL (SI: $<1.0 \times 10^9$ cells/L)
    - Platelet count $<50 \times 10^3$ cells/µL (SI: $<50 \times 10^9$ cells/L)

- Estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2
- Bilirubin >2xULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin
- ALT >5xULN
- Prothrombin time (PT)/international normalized ratio (INR) >1.5xULN or activated partial thromboplastin time (aPTT) >1.5xULN related to known coagulopathy or bleeding disorder (the participant can receive anticoagulant therapies for underlying conditions, or as systematic thromboprophylaxis due to COVID-19, or as part of the treatment of complications of COVID-19, but cannot participate in a clinical study with anticoagulants for COVID-19).

11. Criterion modified per Amendment 1

    11.1 Pregnant or breastfeeding, unless in the opinion of the investigator, the benefit outweighs the risks.

12. Has active hepatitis B or C infection, or has HIV/AIDS based on medical history and/or concomitant medication.

13. Criterion modified per Amendment 4

    13.1 Known active or latent TB, history of incompletely treated TB, suspected or known extrapulmonary TB based on medical history and/or concomitant medication.

14. Evidence of active bacterial (including but not limited to bacterial pneumonia), fungal, viral or opportunistic infection (other than SARS-CoV-2).

15. Known allergies, hypersensitivity, or intolerance to sirukumab or its excipients or to other monoclonal antibodies (refer to the IB).[29]

16. Unlikely to be able to complete the study (including but not limited to: likely to be transferred to another hospital, surgery is anticipated to be necessary, in the opinion of the investigator unlikely to survive for >48 hours from screening)

17. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

18. Taken any disallowed therapies as noted in Section 6.8, Concomitant Therapy before the planned dose of study intervention.

19. History of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with minimal risk of recurrence).

20. Organ transplant recipient on immunosuppressant therapy

NOTE:

- Exclusion criteria based on medical history or on past/current medications are pragmatic criteria. Deviation post randomization from these criteria due to late awareness of medical history and/or comedications are not intended to be qualified as major protocol deviations.
- Investigators should ensure that all study enrollment criteria have been met at screening. Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. If a participant's clinical status changes after screening but before randomization such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are noted in Section 10.4, Appendix 4 Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. All requirements must be met during the study as noted in the Inclusion and Exclusion Criteria.

3. Once dismissed from the hospital, female participants should avoid getting pregnant for a period of 4 months after the study intervention.

4. Once dismissed from the hospital, a woman of childbearing potential must practice a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method until 4 months after the study intervention or the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the dose of study intervention. Examples of highly effective methods of contraception are located in Section 10.6, Appendix 6 Contraceptive and Barrier Guidance.

5. A woman must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction for a period of 4 months after the administration of study intervention.

6. Once dismissed from the hospital, a male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person until the end of the study. Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.

7. A male participant must agree not to donate sperm for the purpose of reproduction for a period of 4 months after the administration of study intervention.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant

identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Study intervention administration must be captured in the source documents and the electronic case report form (eCRF).

Sirukumab will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.[29]

Participants need to receive study intervention preferably within 4 hours but no later than 6 hours after randomization.

Description of Interventions

The study intervention will be administered to the participant via an IV infusion using a 5% dextrose[a] IV bag with a total volume of 50 mL.

Sirukumab will be injected into the bag for use in the treatment arm, the volume of the bag will be adjusted so that the total bag volume remains 50 mL.

No substance will be injected in the bag for the placebo arm, and a 5% dextrose[a] 50 mL IV bag will be used as such.[b]

An unblinded pharmacist or qualified staff member will prepare the IV bags before distribution to the clinic.

[a] Dextrose is also commonly known and referred to as glucose.

[b] Placebo will be provided locally by the study site.

Intervention Name	Sirukumab (CNTO136)
Type	Drug
Dose Formulation	Solution for infusion
Unit Dose Strength(s)	Sirukumab: 100 mg/mL
Dosage Level(s)	Sirukumab: 5 mg/kg single dose
Route of Administration	IV infusion
Use	Intervention
Investigational Medicinal Product (IMP)	Yes
Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)	No
Sourcing	Provided centrally by the sponsor
Packaging and Labeling (Labels will contain information to meet the applicable regulatory requirements.)	Each unit will be labeled with unique medication ID number.
	Not in child resistant packaging
Delivery Instructions	Refer to IPPI for instructions on IV infusion
Food/Fasting Requirement	Regardless of food intake

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Sirukumab must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from light.

Refer to the IPPI for additional guidance on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study.

The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention must be available for verification by the sponsor's study site monitor during monitoring visits. The return to the sponsor of unused study intervention will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials containing hazardous liquids, such as used needles, syringes and vials, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by age (<65 and ≥65 years of age) and invasive mechanical ventilation (yes/no) at randomization. The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participants assigned to the active study treatment. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment (ie, preparation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized.

The participants, study-site personnel, and investigators will be blinded to treatment allocation throughout the study, except for the designated pharmacist(s) or independent qualified staff member(s) with primary responsibility for study preparation. These unblinded members will not be part of the team performing the evaluations. The infusion administrator will be blinded and can perform other study evaluations. The sponsor study team will be blinded to study treatment allocation until the database release of the primary analysis.

Under normal circumstances, the blind should not be broken until the database for the primary analysis is locked. However, for the IA, the randomization codes and the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those participants included in the IA. Details on the level of unblinding and the parties

authorized to be unblinded during the interim analysis will be specified in the SAP. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the participant. In such cases, the investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in IWRS, in the appropriate section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded should continue the scheduled evaluations.

6.4. Study Intervention Compliance

Study intervention will be administered as an IV infusion by qualified study-site personnel and the details of each administration will be recorded in the source documentation and in the eCRF (including date, start and stop times of the IV infusion, and volume infused).

6.5. Dose Modification

Not applicable.

6.6. Continued Access to Study Intervention After the End of the Study

No continued access will be proposed for this study as one single dose will be administered by study site personnel.

6.7. Treatment of Overdose

There is no known specific antidote for sirukumab overdose. In the event of an overdose, the participant should be monitored for any signs or symptoms of adverse effects and institute appropriate symptomatic treatment immediately.

6.8. Prestudy and Concomitant Therapy

Sirukumab has immunomodulatory effects that may predispose participants to opportunistic infections. Therefore, all participants are to be managed according to local treatment guidelines, including the latest version of CDC Information for Clinicians on Therapeutic Options for Patients with COVID-19. Open-label or off-label use of agents that are intended to inhibit SARS-Cov-2 viral activity are permitted in the study, but they must have demonstrated in-vitro effect as listed in the CDC guidelines on Therapeutic Options for patients with COVID-19.[6]

Disallowed concomitant medications

- **Conventional synthetic disease-modifying anti-rheumatic drugs/ immunosuppressive agents:**

  - Oral anti-rejection or immunomodulatory drugs (including tocilizumab) are disallowed from 6 months prior to randomization until the end of the study.

  - Treatment with other anti-IL-6, anti-IL6R antagonists, Janus kinase inhibitors, ustekinumab (anti IL-12/23), or anti IL-23 agents (guselkumab) is disallowed within 5 half-lives (Table 1) or from 30 days prior to randomization (whichever is longer) until the end of the study.

Table 1: Treatment Half-life and 5 Half-lives

Drug	Half-life	5 half-lives
tocilizumab IV	21.5 days	107.5 days
siltuximab IV	20.6 days	103 days
sarilumab IV 200 mg	10 days	50 days
sarilumab IV 150 mg	8 days	40 days
ustekinumab IV	19 days	95 days
guselkumab IV	15-18 days	75-90 days
ustekinumab SC	14.9-45.6 days	74.5-228 days
upadacitinib	8-14 hours	40-70 hours
baricitinib	12 hours	60 hours
tofacitinib XR	6-8 hours	30-40 hours

Source: Respective US Prescribing Informations

  - Systemic treatment with disease-modifying anti-rheumatic drugs or immunosuppressive agents including methotrexate, bucillamine, azathioprine, oral cyclosporine A, tacrolimus, mycophenolate mofetil, oral or parenteral gold, and IL-1ra (anakinra) is disallowed from 2 weeks prior to randomization until the end of the study.

    Exceptions: sulfasalazine, hydroxychloroquine and chloroquine

  - The use of cyclophosphamide is disallowed from 12 weeks prior to randomization until the end of the study.

  - Corticosteroids:

    - potential participants on chronic (for >3 months in duration) prednisone in a dose higher than 10 mg/day or other oral corticosteroids at an equivalent dose for any condition are not eligible for the study

  - The use of leflunomide is disallowed from 8 weeks prior to randomization until the end of the study. Potential participants who have undergone standard cholestyramine washout may qualify if it is done at least 4 weeks before randomization: cholestyramine

at a dosage of 8 mg/3 times a day for at least 24 hours, or activated charcoal at a dosage of 50 mg/4 times a day for at least 24 hours.

- **The participants should not have received an investigational intervention** (including investigational vaccines) or used an invasive investigational medical device within 30 days of the planned dose of study intervention and should not receive any investigational medication, other than sirukumab, prior to completion of Day 28.

  Note: *the investigator must ensure that the participant is not enrolled in another COVID-19 study with an investigational intervention (apart from the exception specified below) prior to completion of Day 28 of the current study.*

  Exceptions:
  - *Participation in a single arm study, a non-blinded controlled study, an expanded access, compassionate use program or any other program that is not a blinded study is allowed if it is conducted with one of the following:*
    - *agents with demonstrated in vitro-effect against SARS-CoV-2, as mentioned in the CDC guidelines.*[6]
    - *convalescent plasma.*

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Use of monoclonal antibodies

The use of bamlanivimab, and casirivimab plus imdevimab is disallowed during the study as they are not authorized in hospitalised participants or participants requiring oxygen.

Participants who did receive bamlanivimab or casirivimab plus imdevimab prior to screening are still eligible for the study as long as the administration was stopped before first hospital admission and the participants fulfil all Inclusion/Exclusion criteria of the study.

Any co-administration through co-enrolment in a study investigating the effects of bamlanivimab, casirivimab, or imdevimab is not permitted. Similarly, co-enrolment in other clinical studies investigating the effects of other monoclonal antibodies that are specifically directed against the spike protein of SARS-CoV-2 and designed to block the virus' attachment and entry into human cells is not permitted per protocol.

Use of vaccines

Live vaccines should not be given during the study.

Administration of a COVID-19 vaccine during the study is not allowed at any time between screening and the discharge visit.

In case a participant was administered a COVID-19 vaccine outside the hospital prior to the study and becomes infected with COVID-19 the participant can be allowed in the study if all protocol eligibility criteria are fulfilled.

Administration of a COVID-19 vaccine is allowed at the time of the discharge visit, provided there are no contraindications. The administration should be done after the very last blood samplings required per protocol at the discharge visit to avoid potential interference of the COVID-19 vaccine.

Medications to be used with caution as their exposure could be modified by the study medication

Examples include but are not limited to warfarin, theophylline, digoxin, antiepileptics, antiarrhythmics.

Various in vitro studies have shown that cytokines such as IL-6 can affect the expression and activity of multiple cytochrome P450 (CYP) enzymes, such as CYP3A4, CYP2C9, CYP2C19, and CYP1A2. Sirukumab treatment may potentially reverse the effect of IL-6 on CYP enzyme activities in patients with elevated IL-6, which could lead to altered metabolism of drugs that are CYP substrates. The effect of sirukumab on the CYP enzymes may be clinically relevant for CYP substrates with a narrow therapeutic index, where the dose is individually adjusted. Therefore, it is recommended to use these types of drugs with caution until 12 weeks after sirukumab administration (3x half-life); therapeutic monitoring of effect (eg, warfarin) or drug concentration (eg, theophylline) should be performed and the individual dose of the drug adjusted as needed. Caution should be exercised when sirukumab is co-administered with CYP3A4 substrate drugs where a decrease in effectiveness would be undesirable (eg, oral contraceptives). The effect of sirukumab on CYP enzymes may persist for several weeks after stopping therapy. Therefore, female participants using oral contraceptives should use an additional contraceptive method above that required per the Section 5.3 Lifestyle Considerations.

Data collection of concomitant medications

To the extent possible, prestudy therapies administered up to 30 days before obtaining of informed consent must be recorded at screening.

As of obtaining informed consent, concomitant therapies must be recorded in the eCRF throughout the study till 16 weeks after the study intervention. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication.

Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

As this is a single injection study, this section is not applicable.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document.

Withdrawal of Consent

Participants who withdraw consent will be offered an optional Safety Follow-up Visit (call), that will occur the day of consent withdrawal and will consist of the same assessments as at the Day 28 (or day of discharge) visit.

7.2.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research (See Section 10.4.Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF, including the separate consent for optional research samples.

7.3. Lost to Follow-up

Lost to follow-up concerns the Phone Call Visits. A participant will be considered lost to follow-up if he or she is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken:

- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, 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 records.
- Should participants continue to be unreachable, they will be considered to have withdrawn from the study and documented as 'lost to follow-up' in the eCRF.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. If the participant withdrew consent, the vital status information available after consent withdrawal will not be collected in the eCRF and the participant will be considered to have discontinued from the study for consent withdrawal. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (SoA) summarizes the frequency and timing of respiratory function assessments, virology assessments, pharmacology assessments, exploratory biomarkers/pharmacogenomics, and safety measurements applicable to this study.

Screening assessments start after signing of the ICF and can continue on the next calendar day, if needed. All screening and baseline assessments may also take place on the same day.

Results from the blood test, pregnancy test, ECG, and pulmonary imaging, completed as SOC, taken up to 2 days prior to screening will be accepted for screening assessments. SARS-CoV-2 positivity, as determined locally by real time-PCR in any specimen at any time prior to randomization is acceptable and this should not be repeated for inclusion in the study.

Screening/baseline assessments required to verify study eligibility criteria and data collection for assessment of the 6-point ordinal clinical recovery category should take place prior to randomization.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECG, oxygen saturation, vital signs, blood sampling. Blood collections for PK assessments should be kept as close to the specified time as possible.

Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

For those participants discharged prior to Day 28, all Day 28 assessments should be done at day of discharge. Laboratory, virology, relevant respiratory function related assessments, and biomarker/pharmacology assessments completed maximum 1 day before discharge do not need to be repeated on the day of discharge provided that no clinically relevant changes were noted in the results and the participant was declared 'ready to be discharged' on the day before discharge. Leftover samples may be used for exploratory biomarker research.

For all laboratory tests done on Day 21, Day 28, and every week thereafter as needed, a window of ±1 day for all sampling is allowed.

For participants discharged after Day 28, additional assessments to be taken after Day 28 are listed in Schedule of Activities (SoA).

The amount of blood drawn from each participant in this study is approximately 275 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the Schedule of Activities (SoA) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB
- Pharmacy Manual
- Investigational Product Preparation Instructions
- Laboratory Manual
- IWRS Manual
- Sample ICF
- Site Blinding Plan Template

- Contact Information Page(s)
- eDC Manual

8.1. Efficacy Assessments

Efficacy assessments will be done per the Schedule of Activities (SoA) and will include all information necessary for the 6-point ordinal clinical recovery scale, level of consciousness (Glasgow coma scale [GCS]), virology assessment, supplemental oxygen use, resting SpO_2, arterial blood gas results, and pulmonary imaging. Details for selected assessments are provided below.

8.1.1. Six-point Ordinal Clinical Recovery Scale

The 6-point ordinal clinical recovery scale provides 6 mutually exclusive conditions ordered from best to worst, and the score reflects the participant's worst situation **on the day assessed**. The sponsor will assign the ordinal scale category based on the assessment of the participant's clinical status by the investigator. The ordinal clinical recovery scale categories are defined below.

Ordinal Clinical Recovery Scale (and Definitions)[a]

1. Not hospitalized[b]

Any of the following:

- Discharged from the hospital the day of assessment
- Hospitalized at the day of assessment but ready for discharge on the day of assessment, as judged by the investigator (eg, if still hospitalized in case of lack of bed availability in a skilled nursing facility, lack of social support at home).

2. Hospitalization, not requiring supplemental oxygen

[a] Alternate care settings delivering care which would normally be delivered in a hospital setting will be categorized as hospitalized.

If a participant was discharged from the hospital "Against Medical Advice" on the day prior to the day of assessment, the participant will be categorized per the definitions above in the category the participant was in at the moment of discharge "Against Medical Advice". The hospital recovery scale category will be considered missing on subsequent days.

If a participant declines medically-indicated mechanical ventilation, the participant will be categorized according to the care they would otherwise have received on that day.

[b] A distinction will be made between participants discharged and in need of (score 1.2) or not in need of (score 1.1) oxygen supplementation as indicated by the investigator on the discharge questionnaire. This distinction will not be made when calculating improvements on the CRS, for which score 1 will be used in both cases.

3. Hospitalized, requiring low flow supplemental oxygen

- Hospitalized on the day of assessment (including readmittance), and supplemental oxygen is required by the participant.

Requiring supplemental oxygen is defined by:

- Receiving supplemental oxygen for instance through a face mask or nasal cannula, at a FiO_2 < 50%,[a] and not being able to sustain a blood oxygen saturation of >93% when breathing room air.

  OR

- Not receiving supplemental oxygen and having a blood oxygen saturation of ≤93% sustained for 5 minutes.

4. Hospitalized, on non-invasive ventilation, nonrebreather mask, or high flow oxygen device

- On supplemental oxygen, on one of the above modalities, with a FiO_2 (worst of the day) of 50%[a] or higher unless they satisfy a higher category (eg, on invasive mechanical ventilation). Note, the use of other devices may fit with category 4 if the FiO_2 is 50%[a] or higher.

5. Hospitalized, on invasive mechanical ventilation or ECMO

- Any oxygen support requiring intubation or extracorporeal oxygenation.
- Invasive mechanical ventilation is used at any time on the day of assessment.

6. Death

- Participant died at any time on the day of assessment or earlier (all-cause mortality).

In addition, the site will be asked whether or not they are working under (a) restricted material resources for supplemental oxygenation/ventilation and/or (b) changes in hospital discharge policies.

8.1.2. Level of Consciousness

The participant's level of consciousness will be assessed using the GCS. The GCS is a neurological scale ranging from 3 (lowest, corresponds to deep coma or death) to 15 (highest, corresponds to a fully awake person) to assess the state of a person's consciousness. The investigator should record the worst total GCS score once a day in the eCRF, as long as the patient is in ICU.[44]

---

[a] The conversion between the oxygen flow expressed in L/min to the corresponding FiO_2 value in % is the following:

L/min	1	2	3	4	5	6	7	8	9	10
FiO2 %	24	28	32	36	40	44	48	52	56	60

The level of sedation of the participant will be derived from the type of medication entered for indication sedation on the Concomitant Medication page of the eCRF.

The frequency and timing of the assessment can be found in the Schedule of Activities (SoA).

8.1.3. Virology Assessments

Respiratory tract samples

SARS-CoV-2 positivity should be documented based on local testing on any specimen, by RT-PCR any time before randomization. This might require a local test using a NP swab obtained at screening.

In addition, nasopharyngeal swabs will be collected for central testing. An NP swab will be used to collect secretions from patients to explore quantification of viral load of SARS-CoV-2 virus. At baseline, the presence of other respiratory pathogens, using multiplex PCR, will also be tested. Furthermore, sequencing might be performed upon request of the virologist to determine mutations in the viral genome.

For participant who are intubated, endotracheal samples need to be taken at the same time as the NP swabs. If taking both samples is not feasible, the NP should be given priority. Collected samples need to be sent to the central lab to explore quantification of viral load. Sequencing might be performed upon request of the virologist to determine mutations in the viral genome.

Only one sample should be collected if the NP sample for detection and the NP sample for quantification are collected on the same day. This sample should be aliquoted and the remaining aliquots of the NP samples should be stored and sent to the central lab for quantification of SARS-CoV-2.

For each participant, NP sampling should be done at approximately the same time (± 4 hours) on each sampling day and from the same nostril.

Leftover NP swabs and endotracheal samples may be used for exploratory biomarker analyses.

If viral RNA is detected in nasopharyngeal samples at day of discharge, all possible efforts will be made to follow-up subjects and collect samples every 7 days until viral RNA is negative, considering the current pandemic and related logistical challenges. If possible, home visits by a healthcare professional may be conducted to collect samples during the follow-up period.

The frequency and timing of the assessments can be found in the Schedule of Activities (SoA). Details about sample collection, processing, and shipping will be provided in the laboratory manual.

Blood samples

In addition to NP swabs, plasma samples will be collected to assess SARS-CoV-2 viremia. Leftover serum samples may be used for exploratory biomarker analyses.

The frequency and timing of the assessments can be found in the Schedule of Activities (SoA). Details about sample collection, processing, and shipping will be provided in the laboratory manual.

Stool Samples (if feasible)

In addition to respiratory tract and plasma samples, stool samples will be collected to explore quantification of viral load of SARS-CoV-2 virus. The stool collections will only be collected if feasible for the site.

Collected samples need to be sent to the central lab. Leftover stool samples may be used for exploratory biomarker analyses.

The frequency and timing of the assessments can be found in the Schedule of Activities (SoA). Details about sample collection, processing, and shipping will be provided in the laboratory manual.

8.1.4. Supplemental Oxygen Use

Supplemental oxygen/percentage of inspired oxygen (FiO_2) use (if any) will be measured to monitor the patient's status regarding gas exchange as applicable. The following will be recorded:

- Oxygen delivery device (eg, nasal cannula, simple face mask, nonrebreather mask, high flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, extracorporeal life support, etc)
- Oxygen flow rate in liters/min
- Record FiO_2 and SpO_2 data 4 times per day, and at any time of arterial blood gas measurements. Record values that are sustained for at least 1 hour.
- If a patient is using more than one device (eg, extracorporeal life support and invasive ventilation), the worst value of FiO_2 (and the corresponding SpO_2 -and PaO_2 if available-) on the highest level of intervention will be recorded. The worst (highest) value of FiO_2 (and the corresponding SpO_2 -and PaO_2 if available-) on each device will also be recorded.
- If a patient does not need oxygen supplementation, this should also be recorded.

The frequency and timing of the assessment can be found in the Schedule of Activities (SoA).

Note: The use of CPAP at home for obstructive sleep apnea syndrome will not be reported as a need of oxygen supplementation information. Only the information on oxygen supplementation that is COVID-19 related is to be reported.

8.1.5. Resting SpO_2

Resting SpO_2 will be measured to assess arterial oxyhemoglobin saturation. SpO_2 will be measured using a fingertip or similar non-invasive device, while patient is stable, following 5 minutes of rest (inactivity) in supine, semi-recumbent, or sitting position and will only be measured in the presence of a good SpO_2 wave form. SpO_2 must be measured simultaneously with recorded supplemental oxygen/FiO_2 data.

For participants receiving invasive or non-invasive mechanical ventilation, peripheral oxygen saturation should be measured with the ventilatory support in place, and it should be recorded.

The frequency and timing of the assessment can be found in the Schedule of Activities (SoA).

General guidelines for measuring SpO_2 are provided in Section 10.10 Appendix 10: General Guidelines for Measuring Vital Signs and SpO2.

8.1.6. Arterial Blood Gas Test

An arterial blood test will be conducted to assess the following parameters:

- pH: acid-base balance of blood
- PaO_2: partial pressure of oxygen in arterial blood
- $PaCO_2$: partial pressure of carbon dioxide in arterial blood

Supplemental oxygen/FiO_2 and resting SpO_2 must be recorded at the same time as when an arterial blood gas is obtained. Results should be recorded in the eCRF. The frequency and timing of the assessment can be found in the Schedule of Activities (SoA).

8.2. Safety Assessments

Safety and tolerability will be evaluated throughout the study from obtaining informed consent onwards until the last study-related activity.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Section 10.5, Appendix 5 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities (SoA).

8.2.1. Physical Examinations

A targeted physical examination will be performed as indicated in the Schedule of Activities (SoA). A targeted physical examination is to be performed as per local SOC and includes, if feasible, lung auscultation and any examination as indicated by the patient's medical history. Height and body weight are only to be measured at screening if not already available in the participant's chart and if practically feasible. If not feasible, weight for dose calculation can be verbally reported by the participant or a family member.

Clinically significant findings should be documented as AE in the eCRF if they are serious, possibly related to the study drug or correspond to an adverse event of interest.

8.2.2. Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure (SBP/DBP) will be assessed. The frequency and timing for each assessment can be found in the Schedule of Activities (SoA).

Body temperature will be measured 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) and before taking antipyretics or more than 4 hours after the last dose of antipyretics.

Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Confirmatory vital signs measurements can be performed if inconsistent with a prior measurement.

Any clinically relevant abnormalities or changes in severity should be documented as AE in the eCRF if they are serious, possibly related to the study drug or correspond to an adverse event of interest.

General guidelines for measuring vital signs are provided in Section 10.10 Appendix 10: General Guidelines for Measuring Vital Signs and SpO2.

8.2.3. Electrocardiograms

Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If multiple assessments are scheduled for the same time point as ECG recording, the procedures should preferably be performed in the following order: ECG(s), oxygen saturation, vital signs, blood draw.

If an ECG is performed, the following parameters should be collected in the eCRF: Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (identify QT interval corrected for heart rate [QTc] using Bazett's formula [QTcB] or QTc using Fridericia's formula [QTcF]) intervals will be recorded in the eCRF. The ECG strips or reports will be retained with the source and may be requested in case of documentation of a cardiovascular SAE.

The frequency and timing for each assessment can be found in the Schedule of Activities (SoA).

Any clinically relevant abnormalities or changes in severity should be documented as AE in the eCRF if they are serious, possibly related to the study drug or correspond to an adverse event of interest.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Section 10.2, Appendix 2 Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

Any clinically relevant abnormalities or changes in severity should be documented as AE in the eCRF if they are serious, possibly related to the study drug or correspond to an adverse event of special interest (AESI).

8.2.5. Pregnancy Testing

At screening, baseline, and Day 28 (or at discharge, whichever comes first), absence of pregnancy in women of childbearing potential should be confirmed by a urine rapid pregnancy test. The result of a prior serum pregnancy test that occurred within 2 calendar days (as part of SOC) before obtaining consent can be used in lieu of the screening requirement. Self-reported pregnancy status of female participants will be recorded during phone call visits on Day 28 (for participants discharged or who discontinued the study prior to Day 28 and did not withdraw consent) and during the post Day 28 follow-up phase phone call visits. Results should be recorded in the eCRF.

8.2.6. Vital Status

At Day 28 (if discharged before Day 28), and during the post Day 28 follow-up phase (phone call visits), vital status of study participants will be recorded, if the participant is alive. If the participant is deceased, date and cause of mortality should be recorded. Death should be documented as SAE in the eCRF.

8.2.7. Self-reported Oxygen Need

On the Day 28 phone call visit (if discharged before Day 28) and during the post Day 28 follow-up phase (phone call visits) participants will be asked whether they require supplemental oxygen (yes or no). The results should be documented in the eCRF.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and product quality complaints (PQCs), from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported as specified in Section 8.3.1 by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on AEs, SAEs, and PQCs can be found in Section 10.5, Appendix 5 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include phone call contact for follow-up of safety.

Serious Adverse Events

All SAEs, as well as PQCs, occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator through the Week 16 phone call visit, must be reported using a Serious Adverse Event form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically. Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about adverse event occurrence. During the hospital stay, in case participants are non-responsive, investigators will report AEs as specified in Section 8.3.1.

Solicited Adverse Events

Solicited adverse events are predefined local (at the injection site) and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.5, Appendix 5 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using a serious adverse event reporting form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Adverse Events of Special Interest

Adverse events of special interest for the single IV administration of sirukumab (5 mg/kg) are provided below.

Table 2: Events of Interest for a Single IV Dose of Interest

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Serious infections (Bacterial, fungal, and viral infection)	Interleukin-6 stimulates hepatic acute-phase proteins and Ig production and promotes the growth and differentiation of T cells, B cells, and tumor cells. Interleukin-6 is a mediator of inflammation and cellular immune responses in the defense against some intracellular pathogens. Interleukin-6 has been known to serve as a marker of disease severity for infections. Although IL-6 modulates certain physiologic acute-phase responses to infection, a complete lack of IL-6 has not been shown to alter mortality rates in IL-6 knockout mice. Blockage of IL-6 may blunt the acute-phase pyretic response and therefore, fever may be masked in participants receiving sirukumab. Serious, life-threatening infections such as septic shock, some of which have been fatal, have occurred in participants receiving sirukumab.	Inclusion and exclusion criteria; hematologic monitoring; safety evaluation; and supportive treatment.
Hypersensitivity	Reactions observed in humans after IV or SC administration of mAbs include headache, fever, facial flushing, pruritus, urticaria, dermatitis, myalgia, nausea, chest tightness, laryngeal edema, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, Stevens-Johnson syndrome, lightheadedness, hypotension, palpitations, and somnolence.	Inclusion and exclusion criteria; clinical monitoring; safety evaluation; and supportive treatment.
Hematologic Events	Neutropenia and thrombocytopenia have occurred in sirukumab studies, including severe thrombocytopenia associated with bleeding. In the Phase 2 and Phase 3 RA studies, decreases in ANC and platelets occurred in all sirukumab treatment groups. Most patients who developed neutropenia while being treated with sirukumab did not	Inclusion and exclusion criteria; clinical monitoring; safety evaluation; and supportive treatment.

	develop infections, and most patients who developed thrombocytopenia did not report bleeding events. Changes were not observed in participants who received placebo, but did occur after participants crossed over to active treatment. No dose response was observed.	
Liver enzymes	Increases (1 to 3 x ULN, sometimes >5 x ULN) in blood ALT and AST values were observed in participants in completed studies of sirukumab; the majority were transient, asymptomatic, and not associated with an increase in bilirubin	Monitoring of liver parameters (ALT, AST, bilirubin [total, direct and indirect], coagulation factors, alkaline phosphatase)

For information on the adverse events of interest associated with chronic administration of Sirukumab in other disease conditions, such as rheumatoid arthritis, refer to Section 10.7, Appendix 7.

8.4. Pharmacokinetics and Immunogenicity

Serum samples will be used to evaluate the pharmacokinetics of sirukumab, IL-6, as well as antibodies to sirukumab. Serum collected for pharmacokinetic and immunogenicity analyses may additionally be used to evaluate biomarkers, safety or efficacy aspects that address scientific questions relating to sirukumab or SARS-CoV-2 infections. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Details about sample collection, processing, and shipping will be provided in the laboratory manual.

8.4.1. Evaluations

At visits where PK, immunogenicity, and IL-6 will be evaluated (Day 1 predose, Day 28), one venous blood draw will be collected as specified in the Schedule of Activities (SoA). Serum samples will be obtained and split into 3 aliquots (one for sirukumab concentration, one for antibodies to sirukumab, and one for IL-6).

At visits where PK and IL-6 will be evaluated (Day 1 postdose, Day 14, Day 21), one venous blood draw will be collected as specified in the Schedule of Activities (SoA). Serum samples will be obtained and split into 2 aliquots (one for sirukumab concentration and one for IL-6).

Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

8.4.2. Analytical Procedures

Pharmacokinetics

Serum samples will be analyzed to determine concentrations of sirukumab using a validated, specific, and sensitive immunoassay method by or under the supervision of the sponsor.

Immunogenicity

The detection and characterization of antibodies to sirukumab will be performed using a validated immunoassay method by or under the supervision of the sponsor.

8.4.3. Pharmacokinetic Parameters and Evaluations

If feasible, a population PK approach will be used to characterize the disposition characteristics of sirukumab. Total systemic clearance (CL) and volume of distribution (V) after IV administration may be estimated from population PK modeling using nonlinear mixed effects model (NONMEM) approach.

8.4.4. Immunogenicity Assessments

Antibodies to sirukumab will be evaluated in serum samples collected on Day 1 predose and on Day 28.

Serum samples will be screened for antibodies binding to sirukumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to sirukumab and/or further characterize the immunogenicity of sirukumab.

8.5. Genetics and Pharmacogenomics

An optional pharmacogenomic (host DNA) blood sample may be collected (preferably at baseline) from those participants who gave consent to allow for host pharmacogenomic research, where local regulations permit. Pharmacogenomic research may include expression quantitative trait locus (eQTL) mapping, single-nucleotide polymorphisms (SNPs) mapping and whole genome sequencing that is related to the IL-6 gene, study intervention, and/or SARS-CoV-2 infection.

Participant participation in pharmacogenomic research is optional.

8.6. Biomarkers

The frequency and timing of the assessment can be found in the Schedule of Activities (SoA).

Biomarkers for exploratory endpoint evaluation

Blood samples will be collected to evaluate biomarkers that may be associated with the safety, efficacy and PK of sirukumab and/or with SARS-CoV-2 infection. Evaluations may include, but are not limited to, IL-6, procalcitonin, CRP, ferritin, LDH, and D-dimer concentrations. In addition, humoral immunity to SARS-CoV-2 will be evaluated by measuring SARS-CoV-2 specific antibodies.

Biomarker sample collection for research

The study includes collection of blood samples for exploratory analysis of host biomarkers at the host RNA, protein and cell level. Samples may be analyzed under the supervision of the sponsor and results might be reported separately.

Samples can only be used for research related to sirukumab or SARS-CoV-2 infection and/or to develop tests/assays related to sirukumab or SARS-CoV-2 infection. This may include target pathway of IL-6 inhibition, and the impact on pneumonia and respiratory illness associated with SARS-CoV-2 infection.

Analysis of exploratory biomarkers may be conducted at the sponsor's discretion and results may be reported separately from this study. These samples may be stored for up to 15 years after the study completion.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

9.1. Statistical Hypotheses

The primary hypothesis of this study is that sirukumab in combination with SOC results in a statistically significant shorter time to improvement (defined as an improvement of at least 2 categories relative to Baseline on the 6-point ordinal clinical recovery scale) versus placebo in combination with SOC, in participants with confirmed critical COVID-19 disease.

9.2. Sample Size Determination

The study was targeted to enroll 270 participants with confirmed severe or critical COVID-19 disease in a 2:1 manner, with approximately 180 participants in the sirukumab treatment arm and approximately 90 participants in the control arm. However, based on the rapidly evolving space of COVID-19 therapeutics focusing on the highly impacted population of critical patients together with the results from the interim analysis, the study population is being limited with protocol amendment 5 to a subset of the currently eligible population, ie, those with confirmed critical COVID-19 disease.

At the time of release of protocol amendment 5, approximately 100 participants with confirmed severe COVID-19 had been enrolled.

The study aims to enroll approximately 111 participants with confirmed critical COVID-19 disease overall in the study, with approximately 74 participants in the sirukumab treatment arm and approximately 37 participants in the control arm.

The primary endpoint in this study is the time to improvement of at least 2 categories relative to Baseline on the 6-point ordinal clinical recovery scale, with participants who die prior to Day 28

treated as right censored at Day 28. For the sample size calculation on the primary endpoint, the following assumptions are used for survivors and participants who die prior to Day 28:

- For survivors in the control arm, it is assumed that the log transformed time to improvement (days) follows a normal distribution with mean of log 28 and a standard deviation 0.9. Sirukumab is assumed to reduce the median time to clinical improvement from 28 days to 16.8 days (40% reduction) in the surviving participants and is assumed to have the same standard deviation of 0.9.
- For the mortality rate in the control arm, 40% by Day 28 is assumed. Sirukumab is assumed to reduce the mortality with an absolute difference of 20%: from a mortality rate of 40% in the control arm to 20% (50% relative reduction).

Under these assumptions, at least 111 participants with confirmed critical COVID-19 disease are required to have at least 80% power to demonstrate a difference with the log-rank test, at a significance level of 5% two-sided.

The proportion of participants with a clinical improvement of at least 2 categories at Day 28 is a key secondary endpoint. Based on simulations using the above assumptions, the rate with clinical improvement at Day 28 in the control arm is expected to be 30%. The targeted treatment effect is an absolute increase of 25% (from 30% in the control arm to 55% in the sirukumab arm) on this key secondary endpoint. The mortality by Day 28 is considered another key secondary endpoint. The targeted treatment effect is an absolute reduction in mortality by 25% (from 40% in the control arm to 15% in the sirukumab arm). Under the aforementioned assumptions and with a sample size of 111, at least 80% power is obtained for both key secondary endpoints a 1-sided significance level of 5%.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

The efficacy endpoints will be analyzed on the Intent-to-Treat (ITT) and by randomized treatment. The ITT set consists of all participants who were randomized and treated.

The primary and key secondary analyses will be tested on the participants with confirmed critical COVID-19 disease.

All safety endpoints will be evaluated on the Safety Population which consists of all randomized participants who received study intervention and will be analyzed by actual treatment.

Pharmacokinetic data will be evaluated on participants in the ITT set who received sirukumab.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock of the primary 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.

An IA was performed when approximately 20% of the planned number of participants with confirmed severe and critical COVID-19 disease have reached Day 28, or discontinued earlier from the study (refer to Section.9.5).

The primary analysis will be done when all participants reached Day 28 or discontinued earlier.

The final analysis will be done when all participants completed the study.

A hierarchical testing strategy will be used for the primary and key secondary endpoints.

First, the primary endpoint will be tested for superiority of sirukumab over placebo at the 2-sided 5% significance level. If superiority is shown on the primary endpoint, then the proportion of participants with a clinical improvement of at least 2 categories at Day 28 will be tested at the 1-sided 5% significance level. If superiority on this endpoint is shown, the mortality by Day 28 will be tested, again at the 1-sided 5% significance level.

9.4.1. General Considerations

For all participants who receive study drug descriptive statistics will be provided. All demographic characteristics (eg, age, race, ethnicity, height, body weight, body mass index) and other initial participant characteristics (eg, medical and surgical history, concomitant diseases) will be tabulated and analyzed descriptively.

Subgroup analyses will be performed based on the stratification factors (age [<65 and ≥65 years of age] and use of invasive mechanical ventilation [yes/no]) and a selection of the major baseline parameters.

A DMC will be established as noted in Committees Structure in Section 10.4.6 Committees Structure.

9.4.2. Primary Endpoint

The primary efficacy analysis will be based on the ITT analysis set restricted to participants with confirmed critical COVID-19 disease and the primary efficacy endpoint is the 'time to improvement of at least 2 categories relative to Baseline on a 6-point ordinal clinical recovery scale'. The improvement should be sustained until Day 28 (or discharge/discontinuation). Time to clinical improvement will be assessed during the 28-day period after study drug administration, with failure to reach clinical improvement or death before Day 28 considered as right-censored at Day 28.

This primary parameter will be analyzed by a stratified log-rank test (using the stratification factors). Kaplan-Meier curves, overall and by stratum will be used to graphically present the primary parameter. The sensitivity analyses will be defined in the statistical analysis plan.

First, the primary endpoint will be tested for superiority of sirukumab over placebo at the 2-sided 5% significance level. If superiority is shown on the primary endpoint, then the key secondary endpoints will be tested at the 1-sided 5% significance level.

9.4.3. Secondary Endpoints

Key and other secondary endpoints will be analyzed graphically and descriptively as described in the statistical analysis plan. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, maximum, and 95% confidence intervals [CIs]) will be calculated. For categorical variables, frequency tables and corresponding 95% CIs will be presented.

9.4.3.1. Key Secondary Endpoints

The key secondary endpoints will be analyzed using the Cochrane-Mantel-Haenszel (CMH) test for difference in proportions.

9.4.4. Other Secondary Endpoints

To compare the proportion of participants with an improvement of at least 1 category relative to Baseline on the 6-point ordinal clinical recovery scale relative to Baseline, the proportion of participants with a worse score relative to Baseline on the 6-point ordinal clinical recovery scale, the proportion of participants who progress to mechanical ventilation (for participants not on mechanical ventilation at baseline), and the mortality rates defined as category 6 on the 6-point ordinal clinical recovery scale, the difference in cumulative incidence at Day 28 will be estimated using the same techniques as for the key secondary endpoints.

Total length of hospitalization, total time on invasive mechanical ventilation, number of ventilation free days, and total time on ECMO will be analyzed by the stratified Wilcoxon Rank-Sum test and using the stratification factors. Corresponding 95% CIs will be derived using the Hodges-Lehmann approach.

Time to improvement of at least 1 category and other ‘time to event’ parameters will be analyzed using the stratified log-rank test.

The distribution of outcomes on the 6-point ordinal clinical recovery scale will be described via plots (eg, stacked bar plots representing the proportion of participants in each category, by treatment arm and over time).

A proportional odds model will be used to analyze the 6-point ordinal clinical recovery scale of the clinical status at Days 7, 14, 21 and 28.

Drugs used in the SOC at baseline and changes in the SOC after treatment administration will be tabulated by treatment group.

The primary and secondary endpoint evaluation will be conducted on the ITT population and on the ITT population restricted to the population with confirmed critical COVID-19 disease. Analyses of qualitative comparison between pre-interim analysis and post-interim analysis for treatment effect in the population with confirmed critical COVID-19 disease will be conducted to check the consistency in the study. This qualitative assessment will be limited to primary and key secondary endpoints only.

Other secondary parameters might be added in the SAP.

9.4.5. Exploratory Endpoint(s)

Time to viral negativity will be analyzed analogously to that of the primary efficacy parameter.

SARS-CoV-2 viral load in NP swabs and in endotracheal, blood, and stool samples will be measured by a qRT-PCR assay. These data will be analyzed graphically and descriptively as described in the statistical analysis plan.

Other exploratory parameters might be added in the SAP.

9.4.6. Safety Analyses

All safety analyses will be made on the Safety Population and on participants with confirmed (a) critical and (b) severe or critical COVID-19 disease.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention is considered to be treatment-emergent. All reported AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a grade 3 or 4 AE, a serious AE, or an adverse event of special interest (AEOI).

The incidence of participants with SAEs, the incidence of participants with grade 3 or 4 AEs, the incidence of participants with severe or life-threatening, bacterial, invasive fungal, viral or opportunistic infections (other than SARS-CoV-2), the incidence of grade 3 and 4 neutropenia and lymphocytopenia, and the incidence of increased ALT ≥3xULN combined with increased bilirubin >2xULN will be reported. Increase of ALT or AST combined with increase of bilirubin will be investigated by means of evaluation of drug-induced serious hepatotoxicity (eDISH) plots.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. The laboratory abnormalities will be determined per the criteria specified in the DMID Adult Toxicity Table (Section 10.8, Appendix 8) and in accordance with the normal ranges of the clinical laboratory if no gradings are available. Tables showing n and percent of participants with treatment-emergent worst toxicity grades (for tests with defined toxicity grades) and treatment-emergent worst abnormalities (for tests without defined toxicity grades) during treatment phase will be generated. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

Electrocardiogram

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

Vital Signs

Vital signs including temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

9.4.7. Other Analyses

Pharmacokinetic Analyses

Serum sirukumab concentrations will be summarized using descriptive statistics. The concentrations below the lowest quantifiable sample concentration of the assay will be treated as zero in the summary statistics. All concentrations below the lowest quantifiable sample concentration of the assay or missing data will be labeled as such in the concentration data listing or statistical analysis dataset.

If feasible, population PK analysis of serum concentration-time data of sirukumab may be performed using nonlinear mixed-effects modeling. Data may be combined with other selected studies to support a relevant structural model. Available baseline participant characteristics (eg, demographics, laboratory variables) may be tested as potential covariates affecting PK parameters. The results of the population PK analysis will be presented in a separate report.

Biomarkers Analyses

Analysis of the relationship between various blood biomarkers, such as cytokines, and viral parameters, immunogenicity, safety and clinical outcome may be conducted.

Descriptive statistics for actual values and (relative) changes from baseline for the different blood biomarkers assessed, will be tabulated for each biomarker at each applicable time point specified in the Schedule of Activities (SoA). Statistics include n, mean, SD, geometric mean, median, minimum, and maximum.

Statistical approaches to explore correlations between clinical outcome and blood biomarkers vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences between participants. Analyses will be conducted at the sponsor's discretion and may be reported separately from this study.

Immunogenicity Analyses

The incidence of antibodies to sirukumab will be summarized for all participants in the ITT population with appropriate samples for detection of antibodies to sirukumab (ie, participants with at least predose and the Day 28 sample obtained).

Virology Analyses

SARS-CoV-2 viral load summaries will be presented with descriptive statistics by intervention arm. If the virology endpoint is continuous, the descriptive statistics will include the number of participants, mean, standard deviation (SD), median, and range. If the virology endpoint is binary or categorical, the frequency distribution with the number and percentage of participants in each category will be calculated. For time-to-event variables, a summary table including number of participants included in the analysis, number of participants censored, 25^{th} and 75^{th} percentiles and median time-to event will be shown by intervention arm. Graphic displays will also be used to summarize the data. Comparison between viral load in NP, endotracheal, blood and stool samples might be performed.

Amino acid and/or nucleic acid substitutions in the SARS-CoV-2 genome will be tabulated and described.

Additional exploratory characterization may be performed and reported separately.

Pharmacodynamic Analyses

Associations between baseline levels of biomarkers, immunogenicity tests, PK parameters and clinical response (primary endpoint and a selection of secondary endpoints) will be explored.

More details will be provided in the statistical analysis plan.

Pharmacogenomic Analyses

DNA samples will be analyzed if it is hypothesized that this may help resolve issues with the clinical data.

DNA samples will be used for research related to the IL-6 gene, sirukumab, or SARS-CoV-2 infection. Pharmacogenomic research may consist of the analysis of one or more candidate genes, of the analysis of genetic markers throughout the genome, or the analysis of the entire genome (as appropriate) to evaluate potential genetic associations with prognosis of clinical outcomes in patients and prediction of responsiveness to active treatment.

Results will be presented in a separate report.

9.5. Interim Analysis

A non-binding unblinded IA for futility was performed by the sponsor on the primary endpoint when approximately 20% of the planned number of participants with confirmed severe and critical COVID-19 disease had reached Day 28 or discontinued earlier.

The randomization codes and the translation of randomization codes into treatment and control groups was disclosed to those authorized and only for those participants included in the IA. The following implementation was followed for the non-binding IA for futility while considering the severe and critical participants in the study.

The futility criterion was based on the conditional power approach for the primary endpoint. The conditional power was calculated for the primary hypothesis using the observed data and assuming a mortality rate of 30% in the control arm versus 21% in the sirukumab arm in the remainder of the study. The effect size and outcomes for the primary endpoint in the survivors was simulated as used for the study sample size calculation. A non-binding futility stopping boundary of 80% for the conditional power was used. Assuming the outcome for the primary endpoint as used for the sample size calculations was true, with a 30% mortality rate in the control arm, the chance of stopping for futility at the time of the IA was 2.5%. Otherwise, if the null hypothesis was true and again with a 30% mortality rate in the control arm, the chance of stopping for futility was 60%. If, at the time of the IA, the probability of a successful study was lower than the futility boundary, the sponsor could have taken the decision to stop for futility after evaluation of all available data. In addition to the conditional power calculations, descriptive analyses of the primary and key secondary endpoints were performed on the available data. The safety outputs planned for the regular DMC safety reviews will be provided too.

No additional non-binding IA for futility is planned for the critical participants to be enrolled in the remainder of the study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

AE	adverse event
AEOI	adverse event of interest
AESI	adverse event of special interest
ALI	acute lung injury
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AxMP	Auxiliary Medicinal Product (also known as NIMP)
BAL	bronchoalveolar lavage
BIPAP	bilevel positive airway pressure
BUN	blood urea nitrogen
CAR	chimeric antigen receptor
CDC	Center of Disease Control and Prevention
CI	confidence interval
CMH	Cochrane-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CPK	creatine phosphokinase
CRF	case report form(s) (paper or electronic as appropriate for this study)
CRP	C-reactive protein
CRS	cytokine release syndrome
CRS	cytokine release syndrome
CT	computerized tomography
D	day
DBP	diastolic blood pressure
DMC	data monitoring committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
eDC	electronic data capture
eDISH	evaluation of drug-induced serious hepatotoxicity
EOT	end of trial
eQTL	expression quantitative trait locus
FiO_2	percentage of inspired oxygen
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
GCS	Glasgow coma scale
gG1κ	Immunoglobulin G1 kappa
GGT	gamma-glutamyltransferase
gp	glycoprotein
GVHD	graft-versus-host disease
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
IB	Investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committee
IL	interleukin
IL6R	IL-6 receptor
IMP	Investigational Medicinal Product
IND	Investigational New Drug

INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
JAK	Janus activated kinase
Kd	equilibrium dissociation constant
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East respiratory syndrome coronavirus
MT	mid-turbinate
NIMP	Non-Investigational Medicinal Product
NP	nasopharyngeal
PaCO2	partial pressure of carbon dioxide in arterial blood
PaO_2	partial pressure of oxygen in arterial blood
PBO	placebo
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PT	prothrombin time
PTT	partial thromboplastin time
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RT-PCR	reverse-transcriptase polymerase chain reaction
SAA	serum amyloid A
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV(-2)	severe acute respiratory syndrome coronavirus (2)
SBP	systolic blood pressure
sIL-6R	soluble form of IL-6 receptor
SNP	single-nucleotide polymorphisms
SoA	Schedule of Activities
SOC	standard of care
SpO_2	peripheral capillary oxygen saturation
STAT-3	signal transducer and activator of transcription 3
SUSAR	suspected unexpected serious adverse reaction
US	United States
W	week
WBC	white blood cell

Definitions of Terms

Critical COVID-19 disease	Requires supplemental oxygen delivered by nonrebreather mask or high-flow nasal cannula OR use of non-invasive or invasive ventilation OR requiring treatment in an ICU.
Severe COVID-19 disease	Requires supplemental oxygen administration by nasal cannula, simple face mask, or other similar oxygen delivery device (ie, above pre-COVID baseline oxygen requirement, if any, by the participant).

Study Interventions

Sirukumab (CNTO136)	Sirukumab solution for infusion (100 mg/mL) at a dose of 5 mg/kg injected into a 50 mL dextrose[a] bag (5% dextrose) with the total volume of the bag adjusted to 50 mL.
placebo	50 mL dextrose[i] bag (5% dextrose) without any substance injected in the bag.

[a] Dextrose is also commonly known and referred to as glucose.

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by local laboratories unless specified otherwise.

Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters			Tests to be done by a	
				Local laboratory	Central laboratory
Safety assessments					
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	RBC Indices: MCV MCH % Reticulocytes	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	All tests	
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.				
Blood Chemistry	Sodium Potassium Chloride Bicarbonate Calcium Phosphate Magnesium Blood urea nitrogen (BUN) Creatinine Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic pyruvic transaminase Alkaline phosphatase (ALP) Total bilirubin Conjugated bilirubin (direct)[b] Unconjugated bilirubin (indirect) [b]		Creatine phosphokinase (CPK) Lactic acid dehydrogenase (LDH) Lactate Albumin Total protein Glucose Troponin I or T Total cholesterol LDL HDL Triglycerides	All tests	
Coagulation tests	Prothrombin time (PT) and international normalized ratio (INR) or, activated partial thromboplastin time (aPTT), fibrinogen			All tests	
Arterial blood gases	pH, PaO_2, $PaCO_2$ (as per local SOC, collect if available)			All tests	

Laboratory Assessments	Parameters	Tests to be done by a	
		Local laboratory	Central laboratory
Other Tests			
	• Urine pregnancy testing for all women of childbearing potential (at screening, baseline, and Day 28 or at day of discharge).	All tests	
	• Bacterial, fungal, or viral infection testing (as per local SOC).	All tests	
	• NP swabs to determine SARS-CoV-2 positivity, refer to the Schedule of Activities (SoA) for more details[a].	Any time before randomization	
	• NP swabs for infections testing (PCR quantification of SARS-CoV-2 and multiplex PCR for detection of co-infections).		All time points as from Day 1
	• Endotracheal aspirate (only if intubated) for virology testing (PCR SARS-CoV-2).	Any time before randomization	All time points as from Day 1
	• Stool sample (if feasible) for virology. • Blood samples for SARS-CoV-2 viremia. • Blood samples for cellular profiling. • Blood samples for RNA profiling. • Whole blood for DNA profiling (optional). • Pharmacology samples (including testing for IL-6 and antibodies to sirukumab). • Blood samples to evaluate biomarkers. • Blood samples for SARS-CoV-2 specific antibodies. • CRP, Ferritin, D-dimer, Procalcitonin.		All time points

a. SARS-CoV-2 positivity should be documented based on local testing on any specimen, by RT-PCR any time before randomization. This might require a local test using a NP swab obtained at screening.
b. Only if ALT or AST >3x ULN or if 3x the entry level (if these were >ULN).

10.3. Appendix 3: Clinical and Laboratory Assessments Described per Day

From Screening to Baseline

	Screening Phase[a]	
Day	**Screening**	**1 (Baseline)**
General Screening/Baseline assessments		
ICF[c]	X	
Inclusion/Exclusion criteria	X	X[d]
Demographics, medical history[e]	X	
Targeted physical exam[h]	X	
Treatment administration		
Randomization[i]		X
Administration of study intervention[i]		X
Concomitant medication		
Concomitant medication recording	X	X
Respiratory function related assessments		
Type of supplemental oxygen	X	X
Resting SpO_2, FiO_2 (if any)[j]	X	X
Arterial pH, PaO_2, $PaCO_2$[j]	As available per day	
Level of consciousness (Glasgow coma scale score)[k]	X	X
Pulmonary X-ray (or CT imaging or lung ultrasound if X-ray not available)	X[g,bb]	
General safety related assessments		
Standard 12-lead ECG	X[g bb]	
Vital signs (body temperature, pulse, SBP/DBP, respiratory rate)	X	X
Any AE	X	X
Safety laboratory assessments[dd]		
Hematology[l]	X[g]	X
Chemistry: General Safety[l]	X[g]	X
Chemistry: Total Cholesterol, LDL, HDL, Triglycerides	X[g]	X
Coagulation: PTT/INR or aPTT, fibrinogen	X[g]	X
Pregnancy assessment urine[f]	X[g]	X
Bacterial, fungal, viral infection testing (blood, other)[m]	Per SOC, any infection to be reported as AESI	

	Screening Phase[a]	
Day	**Screening**	**1 (Baseline)**
Virology Assessments		
Blood sample for SARS-CoV-2 viremia		X[●]
Nasopharyngeal swab for infections testing (PCR quantification of SARS-CoV-2 and multiplex PCR for detection of co-infections)[p,q]	X[q,r]	X[●,s]
If participants are intubated, an endotracheal sample for quantification of SARS-CoV-2 is to be taken in addition to the NP swab[t]	X[q,r]	X[●,s]
Stool sample (if feasible)	X[●,bb]	
Biomarker/Pharmacology Assessments[dd]		
CRP, Ferritin, D-dimer, Procalcitonin		X[●]
Blood samples for cytokines, chemokines		X[●]
Blood samples for various biomarkers		X[●]
Blood sample for SARS-CoV-2 specific antibodies		X[●]
Blood samples for pharmacology[w]		X[●predose] / X[●postdose]
Blood samples for cellular profiling		X
Exploratory Biomarkers/Pharmacogenomics[dd]		
PAXgene blood for RNA profiling[x]		X[●]
Whole blood for DNA profiling (optional)[y]		X[●,z]

- ● Laboratory testing to be performed centrally.

Note: If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECG, oxygen saturation, vital signs, blood sampling.

Hospitalization Follow-Up Day 2 until Day 14

	Hospital Follow-Up (Day)												
Day	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week	**1**						**2**						
General Screening/Baseline assessments													
Targeted physical exam[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
	Any clinically significant findings to be reported												
Concomitant medication													
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	X	X
Respiratory function related assessments													
Type of supplemental oxygen	X	X	X	X	X	X	X	X	X	X	X	X	X
	1x per day												
Resting SpO_2, FiO_2 (if any)[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
	Minimum 4x per day												
Arterial pH, PaO_2, $PaCO_2$[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
	As available per day												
Level of consciousness (Glasgow coma scale score)[k]	X	X	X	X	X	X	X	X	X	X	X	X	X
	1x per day in ICU												
Pulmonary X-ray (or CT imaging or lung ultrasound if X-ray not available)	X	X	X	X	X	X	X	X	X	X	X	X	X
	Per SOC, report upon worsening and last available												
General safety related assessments													
Standard 12-lead ECG			Once between Day 4 and Day 8										
Vital signs (body temperature, pulse, SBP/DBP, respiratory rate)	X	X	X	X	X	X	X	X	X	X	X	X	X
	Per SOC, minimum 4x per day in ICU/ 1x per day non-ICU												
Any AE	X	X	X	X	X	X	X	X	X	X	X	X	X
Record discharge from ICU, discharge from hospital	X	X	X	X	X	X	X	X	X	X	X	X	X
	As applicable												
Safety laboratory assessments[dd]													
Hematology[l]		X				X							X
Chemistry general safety[l]		X				X							X
Bacterial, fungal, viral infection testing (blood, other)[m]	X	X	X	X	X	X	X	X	X	X	X	X	X
	Per SOC, any infection to be reported as AESI												

	Hospital Follow-Up (Day)												
Day	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week	**1**						**2**						
Virology Assessments													
Blood sample for SARS-CoV-2 viremia						X●							X●
Nasopharyngeal swab for infections testing (PCR quantification of SARS-CoV-2 and multiplex PCR for detection of co-infections)[p,q]		X●	(X●)	(X●)		X●	(X●)		X●				X●
If participants are intubated, an endotracheal sample for quantification of SARS-CoV-2 is to be taken in addition to the NP swab[t]		X●	(X●)	(X●)		X●	(X●)		X●				X●
Stool sample (if feasible)		X●	(X●)	(X●)		X●	(X●)		X●				X●
Biomarker/Pharmacology Assessments[dd]													
CRP, Ferritin, D-dimer, Procalcitonin		X●		X●		X●							X●
Blood samples for cytokines, chemokines				X●									X●
Blood samples for various biomarkers				X●									
Blood sample for SARS-CoV-2 specific antibodies													X●
Blood samples for pharmacology[w]													X●
Blood samples for cellular profiling				X●									
Exploratory Biomarkers/Pharmacogenomics[dd]													
PAXgene blood for RNA profiling[x]				X●									

● Laboratory testing to be performed centrally.

Note: If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECG, oxygen saturation, vital signs, blood sampling

.Hospitalization Follow-Up Day 15 until Day 28

	Hospital Follow-Up (Day)													
Day	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**[b]
Week	**3**							**4**						
General Screening/Baseline assessments														
Targeted physical exam[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Any clinically significant findings to be reported													
Concomitant medication														
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Respiratory function related assessments														
Type of supplemental oxygen	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	1x per day													
Resting SpO_2, FiO_2 (if any)[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Minimum 4x per day													
Arterial pH, PaO_2, $PaCO_2$[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	As available per day													
Level of consciousness (Glasgow coma scale score)[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	1x per day in ICU													
Pulmonary X-ray (or CT imaging or lung ultrasound if X-ray not available)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Per SOC, report upon worsening and last available													
General safety related assessments														
Vital signs (body temperature, pulse, SBP/DBP, respiratory rate)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Per SOC, minimum 4x per day in ICU, 1x per day non-ICU													
Any AE	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record discharge from ICU, discharge from hospital	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	As applicable													

	Hospital Follow-Up (Day)													
Day	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28[b]**
Week	**3**							**4**						
Safety laboratory assessments[dd]														
Hematology[l]							X							X
Chemistry general safety[l]							X							X
Chemistry:Total Cholesterol, LDL, HDL, Triglycerides														
Coagulation: PTT/INR or aPTT, fibrinogen														
Pregnancy assessment urine[f]														X
Bacterial, fungal, viral infection testing (blood, other)[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Per SOC, any infection to be reported as AESI													
Virology Assessments														
Blood sample for SARS-CoV-2 viremia														X[•]
Nasopharyngeal swab for infections testing (PCR quantification of SARS-CoV-2 and multiplex PCR for detection of co-infections)[p,q]							X[•]							X[•,u,v]
If participants are intubated, an endotracheal sample for quantification of SARS-CoV-2 is to be taken in addition to the NP swab[t]							X[•]							X[•,u,v]
Stool sample (if feasible)							X[•]							X[•]
Biomarker/Pharmacology Assessments[dd]														
CRP, Ferritin, D-dimer, Procalcitonin							X[•]							X[•]
Blood samples for cytokines, chemokines							X[•]							X[•]
Blood samples for various biomarkers														X[•]
Blood sample for SARS-CoV-2 specific antibodies														X[•]
Blood samples for pharmacology[w]							X[•]							X[•]
Blood samples for cellular profiling														X[•]

	Hospital Follow-Up (Day)													
Day	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**[b]
Week	**3**							**4**						
Exploratory Biomarkers/Pharmacogenomics[dd]														
PAXgene blood for RNA profiling[x]														X●

- Laboratory testing to be performed centrally.

Note: If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECG, oxygen saturation, vital signs, blood sampling.

Hospitalization after Day 28, Discharge/Discontinuation Visit after Day 28, and Post-Hospitalization Follow-Up

	Hospital Follow-Up	**Discharge / Discontinuation Visit**		**Post-hospitalization Follow-Up Phone Call**			
Day	**After Day 28[b] (if hospitalized)**	**Discharge up to Day 28[aa]**	**Discharge post Day 28[aa]**	**Day 28 if discharged earlier (±3 days)**	**Day 56 (±7 days)**	**Day 84 (±7 days)**	**Day 112 (±7 days)**
Week	**Every Week (Once on the day of assessment unless specified differently below)**			**Week 4**	**Week 8**	**Week 12**	**Week 16**
General Screening/Baseline assessments							
Targeted physical exam[h]	X	X	X				
	Any clinically significant findings to be reported						
Concomitant medication							
Concomitant medication recording	X	X	X	X[n]	X[n]	X[n]	X[n]
Respiratory function related assessments							
Type of supplemental oxygen	X	X	X				
Resting SpO_2, FiO_2 (if any)[j]	X	X	X				
	Minimum 4x per day on the day of assessment						
Arterial pH, PaO_2, $PaCO_2$[j]	X	X	X				
	As available per day						
Level of consciousness (Glasgow coma scale score)[k]	X (if still in ICU)						
Pulmonary X-ray (or CT imaging or lung ultrasound if X-ray not available)	X	X	X				
	per SOC, report upon worsening and last available						
General safety related assessments							
Vital signs (body temperature, pulse, SBP/DBP, respiratory rate)	X	X	X				
Any AE	X	X	X	X[n]	X[n]	X[n]	X[n]
Record discharge from ICU, discharge from hospital	As applicable	As applicable	As applicable				

	Hospital Follow-Up	Discharge / Discontinuation Visit		Post-hospitalization Follow-Up Phone Call			
Day	**After Day 28[b] (if hospitalized)**	**Discharge up to Day 28[aa]**	**Discharge post Day 28[aa]**	**Day 28 if discharged earlier (±3 days)**	**Day 56 (±7 days)**	**Day 84 (±7 days)**	**Day 112 (±7 days)**
Week	**Every Week (Once on the day of assessment unless specified differently below)**			**Week 4**	**Week 8**	**Week 12**	**Week 16**
Safety laboratory assessments[dd]							
Hematology[l]	X[cc]	X	X				
Chemistry general safety[l]	X[cc]	X	X				
Chemistry[l]: Total Cholesterol, LDL, HDL, Triglycerides		X	X				
Coagulation: PTT/INR or aPTT, fibrinogen		X	X				
Pregnancy assessment urine[f]		X					
Bacterial, fungal, viral infection testing (blood, other)[m]	X per SOC, any infection to be reported as AESI	X	X				
Virology Assessments							
Blood sample for SARS-CoV-2 viremia	X[•]	X[•]	X[•]				
Nasopharyngeal swab for infections testing (PCR quantification of SARS-CoV-2 and multiplex PCR for detection of co-infections)[p,q]	X[•]	X[•,u,v]	X[•,u,v]		X[•,v]	X[•,v]	X[•,v]
If participants are intubated, an endotracheal sample for quantification of SARS-CoV-2 is to be taken in addition to the NP swab[t]	X[•]						
Stool sample (if feasible)	X[•]	X[•]	X[•]				

	Hospital Follow-Up	Discharge / Discontinuation Visit		Post-hospitalization Follow-Up Phone Call			
Day	**After Day 28[b] (if hospitalized)**	**Discharge up to Day 28[aa]**	**Discharge post Day 28[aa]**	**Day 28 if discharged earlier (±3 days)**	**Day 56 (±7 days)**	**Day 84 (±7 days)**	**Day 112 (±7 days)**
Week	**Every Week (Once on the day of assessment unless specified differently below)**			**Week 4**	**Week 8**	**Week 12**	**Week 16**
Biomarker/Pharmacology Assessments[dd]							
CRP, Ferritin, D-diner, Procalcitonin	X●[,cc]	X●	X●				
Blood samples for cytokines, chemokines		X●					
Blood samples for various biomarkers		X●					
Blood sample for SARS-CoV-2 specific antibodies		X●					
Blood samples for pharmacology[w]		X●					
Blood samples for cellular profiling		X●					
Exploratory Biomarkers/Pharmacogenomics[dd]							
PAXgene blood for RNA profiling[x]		X●					
Phone call assessments							
Record vital status[o]				X[n]	X[n]	X[n]	X[n]
Self-reported oxygen needed (yes/no)				X[n]	X[n]	X[n]	X[n]
Self-reported pregnancy status				X[n]	X[n]	X[n]	X[n]
Record readmission(s) post discharge and reason				X[n]	X[n]	X[n]	X[n]

● Laboratory testing to be performed centrally.

Note: If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECG, oxygen saturation, vital signs, blood sampling.

Abbreviations: AE: adverse event, AESI: adverse event of special interest; aPPT: activated partial thromboplastin time; CRP: C-reactive protein; CT: computed tomography; DBP: diastolic blood pressure; FiO_2: percentage of inspired oxygen; ECG: electrocardiogram; HDL: low-density lipoprotein; ICF: informed consent form; ICU: intensive care unit; INR: international normalized ratio; LDL: low-density lipoprotein; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressures of oxygen in arterial blood; PCR: polymerase chain reaction; PT: prothrombin time; SAE: serious adverse event; SBP: systolic blood pressure; SOC: standard of care; SpO_2: peripheral capillary oxygen saturation.

Footnotes:

a. Screening assessments start after signing of the ICF and can continue on the next calendar day, if needed. All screening and baseline assessments may also take place on the same day. Screening/Baseline assessments required to verify study eligibility and data collection for assessment of the 6-point ordinal clinical recovery category should take place prior to randomization. All Screening/Baseline procedures should take place prior to study drug administration.
b. The assessment schedule will be on a weekly for participants still hospitalized after Day 28.
c. Consent to be obtained before the first study-related activity. An exception is in the case of an emergency enrollment in which the informed consent can be obtained as soon as possible.
d. If a participant's clinical status changes after screening but before randomization such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study.
e. Medical history should include collecting onset of COVID-19 symptoms, prior therapy, and date of SARS-CoV-2 diagnosis if available.
f. A urine pregnancy test is to be performed in women of childbearing potential only.
g. Results from the blood chemistry, hematology, and coagulation test, pregnancy test, ECG, and pulmonary imaging, completed as SOC, taken up to 2 days prior to screening will be accepted as screening assessments.
h. Targeted physical examination is to be performed as per local SOC and includes, if feasible, lung auscultation and any examination as indicated by the patient's medical history. Height and body weight are only to be measured at screening if not already available in the participant's chart and if practically feasible. If not feasible, weight for dose calculation can be verbally reported by the participant or a family member.
i. Participants need to receive study intervention preferably within 4 hours but no later than 6 hours after randomization.
j. Supplemental oxygen/percentage of inspired oxygen (FiO_2) use (if any) will be measured (simultaneously with SpO_2, and at any time of arterial blood gas measurements) to monitor the patient's status regarding gas exchange as applicable. The following will be recorded:
    - Oxygen delivery device (eg, nasal cannula, simple face mask, nonrebreather mask, high flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, extracorporeal life support, etc).
    - Oxygen flow rate in liters/min.
    - Record FiO_2 and SpO_2 data 4 times per day, and at any time of arterial blood gas measurements. Record values that are sustained for at least 1 hour.

- If a patient is using more than one device (eg, extracorporeal life support and invasive ventilation), the worst value of FiO_2 (and the corresponding SpO_2 -and PaO_2 if available-) on the highest level of intervention will be recorded. The worst (highest) value of FiO_2 (and the corresponding SpO_2 -and PaO_2 if available-) on each device will also be recorded separately.
- If a patient does not need oxygen supplementation, this should also be recorded.

k. The final worst score of the Glasgow Coma Scale of the day needs to be recorded in the eCRF. The level of sedation of the participant will be derived from the type of medication entered for indication sedation on the Concomitant Medication page of the eCRF.

l. Laboratory testing to be performed includes:
   - Hematology: hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, RBC indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], % reticulocytes), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils).
   - General safety chemistry: total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, glucose, sodium, potassium, calcium, phosphate, magnesium, chloride, bicarbonate, creatinine, blood urea nitrogen (BUN), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), lactate, and troponin. If ALT or AST >3x ULN or 3x the entry level (if entry levels were >ULN) also provide conjugated bilirubin (direct), unconjugated bilirubin (indirect).

m. Culture results (bacterial, fungal, or viral) including site of infection and specimen source (bronchoalveolar lavage [BAL], tracheal aspirate, sputum, blood, urine, etc.), performed as part of patients' workup for new infections, should be reported. Analyses will be performed by the local laboratory.

n. For participants discharged or who discontinued the study prior to Day 28 and did not withdraw consent, phone calls will be conducted on Day 28 and during the post Day 28 Follow-up Phase to record concomitant medication, the vital status, the occurrence of AEs, self-reported oxygen need, self-reported pregnancy status and the history of readmission since last contact.

o. Whenever possible, vital status will be recorded if the patient is alive. If the participant is deceased, date and cause of mortality should be recorded in the eCRF. Death should be documented as SAE.

p. NP swabs will be used to collect secretions from participants to explore quantification of viral load of SARS-CoV-2. For each participant, NP sampling should be done at approximately the same time (±4 hours) on each sampling day and from the same nostril.

q. If an NP sample for detection of SARS-CoV-2 (local SOC) will be collected on the same day as the NP sample for quantification of SARS-CoV-2 (central lab), only one NP sample should be collected. The sample should be aliquoted and the remaining aliquots of the NP samples should be stored and sent to the central lab for quantification of SARS-CoV-2.

r. SARS-CoV-2 positivity should be documented based on local testing on any specimen, by RT-PCR any time before randomization. This might require a local test using an NP swab obtained at screening.

s. After randomization, SARS-CoV-2 positivity will be confirmed in a central lab by quantitative RT-PCR. The baseline sample needs to be collected predose, as close as possible to dosing.
t. If the participant is intubated, endotracheal samples need to be taken at the same time as the NP swab. If taking both NP and endotracheal samples is not feasible, the NP sample should be given priority.
u. Lab testing for detection of SARS-CoV-2 on the NP swab at day of hospital discharge. If SARS CoV-2 positive, an additional NP swab will be taken every 7 days, if feasible for the site and tested, until SARS-CoV-2 negative.
v. If viral RNA is detected in NP samples at day of discharge, all possible efforts will be made to follow-up participants and collect samples every 7 days until viral RNA is negative, considering the current pandemic and related logistical challenges. If possible, home visits by a healthcare professional may be conducted to collect samples during the follow-up period.
w. Includes serum samples for measurement of PK, antibodies to sirukumab, and IL-6. On Day 1, a predose and a postdose (within 30 minutes after the end of infusion) sample should be collected. The postdose sample should be collected from the arm contralateral to that used for IV infusion. On Day 1 (predose) and Day 28 the PK, antibodies to sirukumab, and IL-6 will be evaluated. On Day 1 (postdose), Day 14, and Day 21 the PK and IL-6 will be evaluated.
x. PAXgene RNA tubes should always be used last for any blood draw.
y. An optional pharmacogenetics blood sample (DNA) will be obtained from those participants who gave consent (where local regulations permit).
z. Sample can be also taken at any other time point after study drug intervention on Day 1.
aa. For those participants discharged prior to Day 28, all Day 28 assessments should be done at day of discharge. Laboratory, virology, relevant respiratory function related assessments, and biomarker/pharmacology assessments completed maximum 1 day before discharge do not need to be repeated on the day of discharge provided that no clinically relevant changes were noted in the results and the participant was declared 'ready to be discharged' on the day before discharge.
bb. Assessments done at screening do not need to be repeated at baseline.
cc. For participants still hospitalized post Day 28, additional blood sampling should be done every 7 days (±1 day) and at day of discharge.
dd. For all laboratory tests done on Day 21, Day 28, and every week thereafter as needed, a window of ±1 day for all sampling is allowed.

10.4. Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

10.4.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)

- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.4.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations 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.

Refer to Required Prestudy Documentation (above) and contracts for details on financial disclosure.

10.4.3. Informed Consent Process

Consent of each participant (or legally acceptable representative based on local regulations) must be obtained according to local requirements after the nature of the study has been fully explained. The informed consent (s) must be obtained before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants or their legally acceptable representative (based on local regulations) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. They will be informed that participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations.

For more information on emergency situations due to COVID-19, see also Section 4.2.1.

By obtaining the informed consent the participant or legally acceptable representative (based on local regulations) is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant or legally acceptable representative (based on local regulations) will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the participant's or his or her legally acceptable representative (based on local regulations) personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Where local regulations require, separate consent needs to be obtained for the optional DNA component of the study.

If the participant or legally acceptable representative (based on local regulations) is unable to read or write, or consent is given verbally by phone, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant or legally acceptable representative (based on local regulations) is obtained.

When prior consent of the participant is not possible and the participant's legally acceptable representative (based on local regulations) is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the participant and to ensure compliance with applicable regulatory requirements. The participant or legally acceptable representative (based on local regulations) must be informed about the study as soon as possible and give consent to continue.

10.4.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant or his or her legally acceptable representative (based on local regulations) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source

data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory pharmacogenomic and biomarker research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.4.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand sirukumab, to understand COVID-19, to understand differential intervention responders, and to develop tests/assays related to sirukumab and COVID-19. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

10.4.6. Committees Structure

Data Monitoring Committee (DMC)

A DMC will be established to actively monitor interim data to review the ongoing safety of the participants in this study and to make recommendations about early study closure or changes to the conduct of the study. This committee will consist of sponsor personnel not directly involved in the conduct of the study and who have expertise in clinical study conduct, at least one medical expert in the relevant therapeutic area, at least one statistician and a safety expert. In addition, at least 2 external experts, are also included in this DMC. The committee will convene regularly at the discretion of the DMC chair during the study conduct, according to their charter, to evaluate the cumulative safety data of all participants in the study. The study responsible physician will inform the DMC of any AE of concern.

As soon as the first 30 participants with confirmed severe and critical COVID-19 disease had received study intervention and had at least 7 days of follow-up after study intervention, the DMC performed an interim data review focused on safety. All data available at the time of the interim data review was included. During this data review enrollment was continued, however, recruitment would have been halted should 60 patients had been enrolled before the outcome of the data review

was known. In case recruitment was halted, it would have been resumed upon a positive assessment of results of these interim data by DMC.

While futility or stopping of the study will be based on totality of emerging safety data, the DMC will consider either of the following non-binding futility criteria as recommendation for stopping the study.

- Excess mortality in the treatment arm, beyond the realm of chance (Fisher's Exact test at a 1-sided significance level of 10%).

- Excess in "Worsening by at least 1 category" in the treatment arm, beyond the realm of chance (Fisher's exact test at a 1-sided significance level of 10%).

A non-binding unblinded IA for futility was performed by the sponsor on the primary endpoint when approximately 20% of the planned number of participants with confirmed severe and critical COVID-19 disease had reached Day 28 or discontinued earlier (see Interim Analysis Section 9.5). Results have been discussed with the DMC.

The DMC is also instructed to use their assessment of individual cases to evaluate even if data do not meet the criteria.

10.4.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding sirukumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of sirukumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of PK, pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.4.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRF for accuracy and completeness during monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.4.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

10.4.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and

date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data may be recorded directly into the eCRF and may be considered source data:

- Race
- History of all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination
- Investigator-completed scales and assessments

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history may include:

- Referral letter from treating physician
- Complete history of medical notes at the site
- Discharge summaries
- Hospital admission records

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

10.4.11. Monitoring

The sponsor will use a combination of monitoring techniques, ie central, remote, and/or on-site monitoring to monitor this study.

The sponsor will conduct monitoring activities as frequently as necessary. The first post-initiation visit will be made as soon as feasible. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records), if possible. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

If possible, given the current pandemic, direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.4.12. Audits

Representatives of the sponsor's clinical quality assurance department may conduct an audit remote and/or on-site (when feasible) at any time during or after completion of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.4.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.4.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor 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 the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.5. Appendix 5 : Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.5.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH][28])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events as of time of obtaining consent, as specified in Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information.

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also 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 intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For sirukumab, the expectedness of an adverse event will be determined by whether or not it is listed in the IB. For SOC treatment with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the local product information.

10.5.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the Investigator. The following selection should be used to assess all adverse events (AE).

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.5.3. Severity Criteria

An assessment of severity grade will be made by the investigator using the general categorical descriptors outlined in the Microbiology and Infectious Diseases (DMID) toxicity table (see Section 10.8, Appendix 8 DMID Table).

10.5.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)

- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

10.5.5. Procedures

All Adverse Events

Adverse events, collected as specified in Section 8.3.1, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The participant, once discharged, will be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as a serious adverse event.

The cause of death of a participant in a study, whether or not the event is expected or associated with the study intervention, is considered a serious adverse event.

Information regarding serious adverse events will be transmitted to the sponsor using a serious adverse event reporting form and safety report form of the eCRF, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted in a secure manner electronically. Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.5.6. Product Quality Complaint Handling

Definition

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.5.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.6. Appendix 6 : Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria 5.3, Lifestyle Considerations. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Section 10.5, Appendix 5 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

- premenarchal
  A premenarchal state is one in which menarche has not yet occurred.
- postmenopausal
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- permanently sterile (for the purpose of this study)
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the lifestyle considerations.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT (preferable) **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion

• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.7. Appendix 7: Risks Associated with Sirukumab

Note: the below listed risks associated with sirukumab are largely based upon data from studies in immune-mediated diseases which involved chronic subcutaneous repeat dosing over an extended period of time (eg, 1 year).

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk
Serious infections	Interleukin-6 stimulates hepatic acute-phase proteins and Ig production and promotes the growth and differentiation of T cells, B cells, and tumor cells. Interleukin-6 is a mediator of inflammation and cellular immune responses in the defense against some intracellular pathogens. Interleukin-6 has been known to serve as a marker of disease severity for infections. Although IL-6 modulates certain physiologic acute-phase responses to infection, a complete lack of IL-6 has not been shown to alter mortality rates in IL-6 knockout mice. Blockage of IL-6 may blunt the acute-phase pyretic response and therefore, fever may be masked in participants receiving sirukumab. Serious, life-threatening infections such as septic shock, some of which have been fatal, have occurred in participants receiving sirukumab.
Hypersensitivity	Reactions observed in humans after IV or SC administration of mAbs include headache, fever, facial flushing, pruritus, urticaria, dermatitis, myalgia, nausea, chest tightness, laryngeal edema, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, Stevens-Johnson syndrome, lightheadedness, hypotension, palpitations, and somnolence.
Gastrointestinal Perforation	Events of gastrointestinal (GI) perforation have been reported in clinical studies with sirukumab, primarily as a complication of peptic ulcer disease or diverticulitis in RA patients. Most patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory drugs, corticosteroids, and/or MTX. The relative contribution of these concomitant medications versus sirukumab to the development of GI perforations is not known.
Hematologic Events	Neutropenia and thrombocytopenia have occurred in sirukumab studies, including severe thrombocytopenia associated with bleeding. In the Phase 2 and Phase 3 RA studies, decreases in ANC and platelets occurred in all sirukumab treatment groups. Most patients who developed neutropenia while being treated with sirukumab did not develop infections, and most patients who developed thrombocytopenia did not report bleeding events. Changes were not observed in participants who received placebo, but did occur after participants crossed over to active treatment. No dose response was observed.
Lipids	Increases in blood total cholesterol, LDL, HDL, and triglycerides have occurred in sirukumab treated participants. No dose response was observed.

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk
Liver enzymes	Increases (1 to 3 x ULN, sometimes >5 x ULN) in blood ALT and AST values were observed in participants in completed and ongoing studies of sirukumab; the majority were transient, asymptomatic, and not associated with an increase in bilirubin
Drug-drug interactions	Inflammatory cytokines, including IL-6, are known to down-regulate activity and expression of multiple CYP enzymes. Hypothetically, IL-6 inhibition in a patient with an inflammatory condition will restore the CYP enzyme activity, and, in turn, increase the hepatic metabolism and clearance of drugs that are substrates for those enzymes.
Geriatric patients (>65 years of age)	Of the 2,926 participants treated with sirukumab in RA studies, 498 were 65 years and older. The incidence of serious infections among elderly participants (65 years and older) treated with sirukumab was higher than participants younger than 65 years.
Pediatric patients (<18 years of age)	The safety of sirukumab in children has not been studied.
Renal impairment/hepatic dysfunction/failure	There is no experience with the use of sirukumab in patients with hepatic insufficiency.
Pregnancy	It is not known whether sirukumab can cause fetal harm when administered to a pregnant woman or affect reproductive capacity.
Nursing	Sirukumab was not detectable in most cynomolgus monkey milk samples. It is not known whether sirukumab is excreted in human milk.
Acute and subacute toxicity	No information is available on acute and subchronic toxicity in humans.

10.8. Appendix 8: DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE[45] – NOVEMBER 2007

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1 **Mild** Transient or mild discomfort (< 48 hours); no medical intervention/therapy required

GRADE 2 **Moderate** Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

GRADE 3 **Severe** Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible

GRADE 4 **Life-threatening** Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization [WHO]) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol-specific grading criteria, which will supersede the use of these tables for specified criteria.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1,000-1,500/ mm^3	750-999/ mm^3	500-749/ mm^3	<500/ mm^3
Absolute Lymphocyte Count, Low[a] *aged >5 years* *(not HIV-infected)*	600 to <650 / mm^3 *0.600×10^9 to $<0.650\times10^9$*	500 to <600 / mm^3 *0.500×10^9 to $<0.600\times10^9$*	350 to <500 / mm^3 *0.350×10^9 to $<0.500\times10^9$*	<350 / mm^3 *$<0.350\times10^9$*
Platelets	75,000-99,999/ mm^3	50,000-74,999/ mm^3	20,000-49,999/ mm^3	<20,000/ mm^3
WBCs	11,000-13,000/ mm^3	13,000-15,000 / mm^3	15,000-30,000/ mm^3	>30,000 or <1,000 / mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ mL	41-50 mcg/ mL	51-60 mcg/ mL	> 60 mcg/ mL
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

[a] Added by the sponsor, based on Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, version 2.1, July 2017.[21]

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/ L	123-129 mEq/ L	116-122 mEq/ L	< 116 mEq/ L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/ L	151-157 mEq/ L	158-165 mEq/ L	> 165 mEq/ L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/ L	2.5 - 2.9 mEq/ L	2.0 - 2.4 mEq/ L or intensive replacement therapy or hospitalization required	< 2.0 mEq/ L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/ L	6.1 - 6.5 mEq/ L	6.6 - 7.0 mEq/l	> 7.0 mEq/ L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/d L	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life-threatening arrhythmia or tetany

CHEMISTRIES (continued)				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/d L	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life-threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/ L	1.1 - 0.9 mEq/ L	0.8 - 0.6 mEq/ L	< 0.6 mEq/ L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/d L	>15.0 mg/d L
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	>6 x ULN or dialysis required

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or >3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR RBC casts	obstructive or required transfusion

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase >20 mm/ Hg; no treatment	recurrent, chronic increase > 20mm/ Hg /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral flu id treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/ moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; >3 units transfused

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV1 of peak flow	requires treatment; normalizes with bronchodilator; FEV1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV1 25% - 50% of peak flow; or retractions present	cyanosis: FEV1 <25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring oxygen therapy

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV flu ids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last <1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink flu ids; requires IV fluids

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, eg, vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, eg, vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (ie, upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELATEL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint destruction
Myalgia	Myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	erythema; pruritus	diffuse, maculopapular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	<15mm	15-30 mm	>30mm	
Erythema	<15mm	15-30 mm	>30mm	
Edema	<15mm	15-30 mm	>30mm	
Rash at Injection Site	<15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy

10.9. Appendix 9: The New York Heart Association Classification System

Class	New York Heart Association functional classification
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

10.10. Appendix 10: General Guidelines for Measuring Vital Signs and SpO_2

Variability in the measurement of vital signs and SpO_2 is to be expected due to a number of reasons; therefore, general guidelines for measuring vital signs and SpO_2 have been developed to have a more consistent approach across sites and countries related to the methodology for measuring these clinical parameters.

Parameter	General Instructions
Blood Pressure	• While participant is hospitalized, if possible, use the same blood pressure measurement methodology for all patients enrolled at the site. • Prior to the measurement, participant needs to be rested for at least 5 minutes and preferably 10 minutes in a quiet setting without distractions. • Participant can be in either a sitting or supine position. In the sitting position, the participant should be comfortably seated, with the legs uncrossed. When measurements are taken in the supine position, the arm should be supported with a pillow. • Blood pressure measurements should preferentially be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. • If an automated device is not available, a properly maintained mercury sphygmomanometer is preferred over aneroid and hybrid sphygmomanometers. When using a mercury sphygmomanometer, the mercury column should be deflated at 2 to 3 mm/s, and the first and last audible sounds should be taken as systolic and diastolic pressure. The column should be read to the nearest 2 mm Hg. • Preferentially, the standard location for blood pressure measurement is the upper arm, with the stethoscope at the elbow crease over the brachial artery (with manual technique). Clothing that covers the arm should be removed prior to the placement of the cuff.
Heart Rate	• While participant is hospitalized, if possible, use the same heart rate measurement methodology for all patients enrolled at the site. • Prior to the measurement, participant needs to be rested for at least 5 minutes, and preferably 10 minutes in a quiet setting without distractions. • Participant can be in either a sitting or supine position. • Heart rate measurements should preferentially be assessed with a completely automated device. • Manual techniques will be used only if an automated device is not available. • If manual measurement, auscultation of the heart or pulse (radial, brachial) determination is considered acceptable. • If manual measurement, 30 seconds (minimum) or 1 minute (preferred) counts are considered acceptable.
Respiratory Rate	• While participant is hospitalized, if possible, use the same respiratory rate measurement methodology for all patients enrolled at the site.

	• Prior to the measurement, participant needs to be rested for at least 5 minutes, and preferably 10 minutes in a quiet setting without distractions. • Participant can be in either a sitting or supine position. • Respiratory rate measurements can be assessed with an automated device or with manual measurement (no preference). • If manual measurement is used, inspection (preferred) or auscultation of the lungs (alternative) are considered acceptable. • If manual measurement, 30 seconds (minimum) or 1 minute (preferred) count are considered acceptable.
Temperature	• While participant is hospitalized, if possible, use the same type of temperature measurement methodology for all participants enrolled at the site. • Electronic devices (tympanic, oral) are preferred over traditional mercury thermometers (for oral temperature). • Tympanic (preferred) or oral (alternative) temperature measurements are considered acceptable. Axillary temperature should be avoided since it provides the worst estimate of core temperature and it is largely influenced by environmental conditions.
SpO_2	• While participant is hospitalized, if possible, use the same type of probe for all patients enrolled at the site. • Prior to the measurement, participant needs to be rested for at least 5 minutes, and preferably 10 minutes in a quiet setting without distractions. • Participant can be in either a sitting or supine position. • Pulse oximetry measurements using finger, toe, earlobe or frontal sensors are considered acceptable. If using the digits, assess for warmth and capillary refill, since adequate arterial pulse strength is necessary for obtaining accurate SpO_2 measurements. • Avoid placing the sensor on sites distal to indwelling arterial catheters, blood pressure cuffs, or venous engorgement (eg, arteriovenous fistulas, blood transfusions). • For hospitalized participants receiving supplemental O_2, the measurement should be performed after 5 minutes on room air. • If it is determined by the investigator that it is unsafe to remove the participant's supplemental O_2 for assessment of O_2 saturation (eg, participant is on high-flow mask), then it should be recorded in the source documentation as not assessed and the reason should be documented.

10.11. Appendix 11: Protocol Amendment History

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

Amendment 4 (15 September 2020)

Overall Rationale for the Amendment: The protocol has been amended to allow for an Interim Analysis (IA) to be performed when approximately 20% of the planned number of participants have reached Day 28 or discontinued earlier.

Activation of sites outside the US is delayed until availability of the IA results.

In addition, to accommodate for feedback received from investigators about the challenges when using a central laboratory, the safety laboratory assessments (hematology, chemistry, coagulation tests) will be performed by local laboratories.

Further, to accommodate for feedback received from investigators, the sponsor has optimized the mandatory laboratory tests to be performed.

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis 1.2 Schema 4.1 Overall Design 6.3 Measures to Minimize Bias: Randomization and Blinding 9.5 Interim Analysis 10.4.6 Committees Structure	A non-binding unblinded Interim Analysis (IA) for futility will be performed by the sponsor on the primary endpoint when approximately 20% of the planned number of participants have reached Day 28 or discontinued earlier.	In view of the mixed results of emerging clinical data with IL-6 receptor inhibitors, the purpose of this IA is to perform a futility analysis to determine further study conduct.
1.3 Schedule of Activities (SoA) 5.1 Inclusion Criteria 8 STUDY ASSESSMENTS AND PROCEDURES 8.1.3 Virology Assessments 10.2 Appendix 2: Clinical Laboratory Tests 10.3 Appendix 3: Clinical and Laboratory Assessments Described per Day	Only PCR-based tests are allowed for detection of SARS-CoV-2 infection.	To prevent possible false positive results by using a rapid antigen test at time of screening.
1.3 Schedule of Activities (SoA) 10.2 Appendix 2: Clinical Laboratory Tests	The required use of a central laboratory for the safety laboratory assessments (hematology, chemistry, coagulation tests) is no longer in place.	To limit changes in the laboratory safety assessments and allow fast availability of laboratory results.
1.3 Schedule of Activities (SoA) 8 STUDY ASSESSMENTS AND PROCEDURES 8.2.5 Pregnancy Testing	The mandatory laboratory tests to be performed have been optimized.	To accommodate for feedback received from investigators.
10.3 Appendix 3: Clinical and Laboratory Assessments Described per Day	The assessments as described in the Schedule of Activities have now also been described per day in a protocol appendix.	To add clarity and be more user-friendly.
5.2 Exclusion Criteria	Exclusion criterion 13 has been reworded.	To accommodate for feedback from investigators.

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 3 (23 July 2020)

Overall Rationale for the Amendment: The protocol has been amended to state that all clinical laboratory tests are to be performed by the central laboratory, except for screening visit assessments, and to allow flexibility concerning the sourcing of placebo as the study has been extended from a single-country trial to a global trial. The frequency of Data Monitoring Committee (DMC) review has been adapted to allow for flexibility in alignment with recruitment rates. A separate sample for SARS-CoV-2 specific antibodies testing has been added. Furthermore, clarifications, minor updates and corrections have been made throughout the protocol.

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
1.3 Schedule of Activities (SoA) 8.3.6 Adverse Events of Special Interest 10.2 Appendix 2: Clinical Laboratory Tests	Hematology, chemistry, coagulation and pregnancy tests will be done by the central laboratory instead of the local laboratory, with exception of the tests that are performed during the screening visit.	As the study is extended to become a global trial, central laboratory testing is being implemented.
1.1 Synopsis 1.2 Schema 10.1 Appendix 1: Abbreviations and Definitions 10.3.6 Committees Structure	The DMC review frequency has been changed from weekly to regularly.	Allow for flexibility in alignment with recruitment rates.
6.1 Study Intervention(s) Administered	Footnote has been added to clarify that placebo will be provided locally by the study site or centrally by the sponsor.	Allow flexibility concerning the sourcing of placebo based on local regulations in participating countries.
1.3 Schedule of Activities (SoA) 8.2.5 Pregnancy Testing 10.2 Appendix 2: Clinical Laboratory Tests	Pregnancy assessment has been added to the baseline visit. Furthermore, it has been clarified that urine pregnancy testing is only acceptable for the screening visit (in emergency situations).	Allow for pregnancy testing by central laboratory at baseline.
1.3 Schedule of Activities (SoA)	A separate sample for SARS-CoV-2 specific antibody testing has been added to the baseline, Day 14, and Day 28 visit.	Allow flexibility on the type of assays to be performed on these samples.

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
1.3 Schedule of Activities (SoA)	Hematology, chemistry and coagulation testing has been added to the baseline visit and footnote dd has been removed for the screening visit. The statement 'preferred daily testing if per local standard of care, otherwise as a minimum on' has been removed. Furthermore, footnote l and footnote ee have been reworded.	Allow for hematology, chemistry and coagulation testing by the central laboratory at baseline and at specific time points between Day 2 and discharge.
	Optional time points for collection of blood samples for biomarker research have been removed. In addition, footnote v has been removed for the Day 28 visit and footnote x has been reworded.	Separate sample for central procalcitonin testing no longer required between Day 2 and Day 28.
	Footnote cc has been edited to clarify that the relevant respiratory function assessments, completed maximum 1 day before discharge do not need to be repeated on the day of discharge provided that no clinically relevant changes were noted in the results and the participant was declared 'ready to be discharged' on the day before discharge.	Clarification
1.1 Synopsis 1.3 Schedule of Activities (SoA) 8.6 Biomarkers 10.2 Appendix 2: Clinical Laboratory Tests	The words 'sample collection' have been removed from the subtitle to clarify that multiple samples will be used for the assessment of the exploratory biomarkers. Furthermore, the description of the type of biomarker parameters to be evaluated in the biomarker blood samples has been removed.	Clarification.
1.3 Schedule of Activities (SoA) 5.1 Inclusion Criteria #4	Lung ultrasound has been added as an option for the assessment of inclusion criterion 4 and to the SoA if a pulmonary assessment with X-ray would not be available.	Allow flexibility to assess eligibility based on local standard of care practices.
5.1 Inclusion Criteria #5	The requirement of supplemental oxygen to sustain a SpO_2 >93% is to be documented by an SpO_2 of ≤93% on room air or on supplemental oxygen.	Clarification
5.2 Exclusion Criteria #10	Participants can receive anticoagulant therapies for underlying conditions, or as systematic thromboprophylaxis due to COVID-19, or as part of the treatment of complications of COVID-19, but cannot participate in a clinical study with anticoagulants for COVID-19. This has been added to exclusion criterion 10.	Broadening of the eligible patient population.

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
6.1 Study Intervention(s) Administered 6.2 Preparation/Handling/Storage/Accountability 10.1 Appendix 1: Abbreviations and Definitions	Footnote has been added to clarify that dextrose is commonly known and referred to as glucose.	Clarification.
6.3 Measures to Minimize Bias: Randomization and Blinding	It has been specified that the interactive web response system (IWRS) will assign a unique intervention code for the participants assigned to the active study treatment.	Clarification.
8.1.3 Virology Assessments	Stool sample collection post hospital discharge has been removed.	Correction.
Throughout protocol	Minor updates, corrections or additions have been made.	Correction, clarification and consistency.

Amendment 2 (17 June 2020)

Overall Rationale for the Amendment: Following investigator feedback and given the evolving COVID-19 landscape, the protocol has been amended to allow enrollment of a broader patient population into the study. In addition, incidence of all-cause mortality has been elevated to be a key secondary endpoint. Furthermore, clarifications, minor updates and corrections have been made throughout the protocol.

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis 1.3 Schedule of Activities (SoA) 3 OBJECTIVES AND ENDPOINTS 8.6 Biomarkers	IgG and IgM are no longer specified as SARS-CoV-2 specific antibodies to evaluate the humoral immune response to SARS-CoV-2. The humoral immune response assays are still to be determined.	Allow flexibility as the immunity assays are still to be determined.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 9.2 Sample Size Determination 9.4 Statistical Analyses 9.4.2 Primary Endpoint 9.4.3.1 Key Secondary Endpoints 9.4.4 Other Secondary Endpoints	Incidence of all-cause mortality (up to Day 28) has been elevated to be a key secondary endpoint (instead of othher secondary endpoint). A hierarchical testing strategy will be used for the primary and key secondary endpoints. For the mortality rate in the control arm, a range from 30% to 50% is considered for the sample size determination. For the considered absolute difference in mortality rate, a power of at least 80% is retained for this range and the power will be higher in case the mortality rate in the control arm will be near the lower end of the considered range.	Updated to be able to assess the mortality rate as a key secondary analysis.
	A stratified log-rank test (instead of a Gehan-Wilcoxon test) will be used in the analyses of the primary parameter. Key secondary endpoints will be analyzed using the Cochrane-Mantel-Haenszel test for difference in proportions. A graphical presentation over time to analyze the 6-point ordinal clinical recovery scale of the clinical	Update on statistical tests to be used

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
	status has been added to the protocol. The proportional odds model has been updated from each day up to Day 28 to Days 7, 14, 21 and 28.	
1.1 Synopsis 1.2 Schema 4.1 Overall Design 9.4 Statistical Analyses 9.5 Interim Analysis 10.3.6 Committees Structure	The Data Monitoring Committee (DMC) interim data review will focus on safety data. Therefore, the DMC details have been removed from the interim analysis sections.	Clarification
1.1 Synopsis 9.3 Populations for Analysis Sets 9.4.2 Primary Endpoint 9.4.7 Other Analyses	The ITT (Intent-to-Treat) population will be used for statistical analyses instead of the ITT-i (or ITT-infected, defined as the population with a central laboratory confirmed SARS-COV-2 test at baseline). The ITT population comprises all study participants; all participants are required to have a local laboratory-confirmed SARS-CoV-2 infection prior to randomization per inclusion criterion 3.	Update of the population to be used for statistical analyses
1.3 Schedule of Activities (SoA)	Footnote added to clarify that in participants still hospitalized post Day 28 additional blood sampling for hematology, chemistry and coagulation should be done per SOC with a minimum of every 7 days and at Day of discharge.	Clarification
	Footnote clarifying that, for participants discharged prior to Day 28, assessments completed maximum 1 day before discharge do not need to be repeated on the day of discharge.	Clarification
	Footnote clarifying that pulmonary X-ray, 12-lead ECG, hematology, chemistry, coagulation sample, and stool sample do not need to be repeated at baseline if done at screening. Screening and baseline cells in SoA have therefore been merged.	Clarification
	Stool sample collection post Day 28 has been removed in the SoA as this sample cannot be collected at home due to safety reasons.	Removal of stool sample collection post Day 28 due to non-feasibility for safety reasons
1.2 Schema 1.3 Schedule of Activities (SoA) 5 STUDY POPULATION 8 STUDY ASSESSMENTS AND PROCEDURES	Further clarifying text on timing of screening and/or baseline assessments to be conducted prior to randomization has been added.	Clarification
1.3 Schedule of Activities (SoA) 5 STUDY POPULATION 5.1 Inclusion Criteria #3 8 STUDY ASSESSMENTS AND PROCEDURES 8.1.3 Virology Assessments	It has been added that the any other commercial or public health assay that could be used to determine SARS-CoV-2 positivity, must be approved or authorized for (emergency) use.	Clarification
2.1.1 Background 2.2 Dose Rationale 11 REFERENCES	Additional information regarding sirukumab IL-6 affinity and serum concentrations has been added to	Clarification

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
	clarify the expected free IL-6 suppression for at least 4 weeks.	
1.3 Schedule of Activities (SoA) 5.1 Inclusion Criteria #5	Participants not receiving supplemental oxygen and having a blood oxygen saturation ≤93% sustained for 5 minutes have been added as being eligible. The required supplemental oxygen flow rate of ≥6 L/min has been removed. The limitation of the invasive mechanical ventilation to <24h at screening has been extended to <48h. Furthermore, it has been added that participants on veno-venous ECMO <48h are also allowed. The note concerning the requirement of supplemental oxygen at ≥6 L/min has been removed.	Broadening of the eligible patient population
1.2 Schema 1.3 Schedule of Activities (SoA) 2.3.1 Risks for Study Participation 5.2 Exclusion Criteria #1	Participants on veno-venous ECMO for >48 hours at time of screening are excluded.	Clarification
2.3.1 Risks for Study Participation 5.2 Exclusion Criteria #3 6.8 Prestudy and Concomitant Therapy 11 REFERENCES	Administration of agents with demonstrated in vitro-effect against SARS-CoV-2 (as mentioned in the CDC guidelines) or convalescent plasma within 30 days prior to the planned study intervention or during the study is allowed provided it is not via a blinded clinical study. The risk of an additional protein load associated with co-administration of convalescent plasma has been added to the Benefit-Risk Assessment.	Broadening of the eligible patient population and of the accepted concomitant therapies
5.2 Exclusion Criteria #4	Exclusion criterion #4 is now limited to: Current confirmed or high suspicion for pulmonary embolus, hemodynamic significant pericardial effusion, myocarditis, or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification AND/OR Current Evidence of active cardiac ischemia.	Broadening of the eligible patient population
5.2 Exclusion Criteria #5	Exclusion criterion #5 is now limited to: Currently active clinically significant (eg, causing hemodynamic instability and/or causing hypoxemia) and uncontrolled arrhythmia.	Broadening of the eligible patient population
5.2 Exclusion Criteria #8	Exclusion criterion #8 is now limited to: Has a history of chronic respiratory condition (ie, asthma, chronic obstructive pulmonary disease [COPD], cystic fibrosis, fibrotic lung disease) that requires home oxygen supplementation, supportive non-invasive ventilation, or is status/post lung volume reduction surgery (LVRS). Participants with sleep apnea using a supportive non-invasive ventilation (continuous positive airway pressure [CPAP]) at screening may be included. This has been added as exception to exclusion criterion 8.	Broadening of the eligible patient population
5.2 Exclusion Criteria #10	Absolute neutrophil count (ANC) values have been adjusted from $<2.0 \times 10^3$ cells/µL to $<1.0 \times 10^3$ cells/µL (SI: $<1.0 \times 10^9$ cells/L).	Broadening of the eligible patient population

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
	Platelet count values have been adjusted from $<100 \times 10^3$ cells/μL to $<50 \times 10^3$ cells/μL (SI: $<50 \times 10^9$ cells/L). Transaminase values have been adjusted from ALT/AST > 5x ULN to ALT > 5x ULN.	
6.8 Prestudy and Concomitant Therapy	Participants on chronic (for >3 months in duration) prednisone in a dose higher than 10mg/day or other oral corticosteroids at an equivalent dose for any condition are not eligible for the study.	Clarification
Throughout protocol	Minor updates, corrections or additions have been made.	Correction, clarification and consistency

Amendment 1 (24 April 2020)

Overall Rationale for the Amendment: Following Health Authority, Data Monitoring Committee and investigator feedback, the protocol has been amended to allow enrollment of a diverse patient population into the study (by removing the requirement for participants to understand English), to also allow enrollment of breastfeeding women if the benefit outweighs the risk, to ensure that at least one 12-lead ECG is taken after study intervention and to simplify the requirements for nasopharyngeal swabs and other specimens (by making one more time point optional). Furthermore, clarifications, additions and corrections have been made throughout the protocol.

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis 1.2 Schema 2.3.1 Risks for Study Participation 2.3.3 Benefit-Risk Assessment for Study Participation 4.1 Overall Design	A Data Monitoring Committee (DMC) instead of a Data Review Committee will be established in this study.	Correction on terminology
6.3 Measures to Minimize Bias: Randomization and Blinding 9.4 Statistical Analyses 9.4.1 General Considerations 9.5 Interim Analysis 10.1 Appendix 1: Abbreviations and Definitions 10.3.6 Committees Structure	It has been added that the DMC will also weekly evaluate the accumulating safety data of all participants in the study.	Clarification
1.1 Synopsis 9.4.3.1 Key Secondary Endpoint 9.4.4 Other Secondary Endpoints	The difference in cumulative incidence at Day 28 will be estimated using the Nelson-Aalen estimator of the cumulative hazard in each treatment group. This has been added instead of a logistic regression model.	Update on more appropriate statistical test to be used
1.1 Synopsis 9.4.7 Other Analyses	Details addressing the statistical analysis on the SARS-CoV-2 viral loads have been added.	Clarification, for completeness.
1.3 Schedule of Activities (SoA) 8.1.6 Arterial Blood Gas Test 10.2 Appendix 2: Clinical Laboratory Tests	SaO_2 has been removed as blood gas parameter to be assessed, as it is not captured in the CRF. In addition, blood gas has been specified as arterial.	Correction For completeness and consistency

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
1.3 Schedule of Activities (SoA)	It has been added that one ECG is to be taken between Day 4 and Day 8, as a minimum.	To ensure that at least one 12-lead ECG is taken after study intervention
1.3 Schedule of Activities (SoA)	The Day 5 nasopharyngeal swab, endotracheal sample and stool sample have been made optional.	Decrease sampling burden for participants and the sites
1.3 Schedule of Activities (SoA) 8.1.3 Virology Assessments	Stool samples will only be collected if feasible for the site. 'Optional' has been removed and replaced by 'if feasible'.	Clarification
1.3 Schedule of Activities (SoA) 8 STUDY ASSESSMENTS AND PROCEDURES	Clarifying text on which screening or baseline assessments are to be conducted prior to randomization (ie, those to verify study eligibility criteria and those allowing baseline assessment of the 6-point ordinal clinical recovery category) has been added.	Clarification
1.3 Schedule of Activities (SoA) 5.2 Exclusion Criteria	Text regarding exclusion of a participant from study participation if he or she no longer meets eligibility criteria due to clinical status changes occurring after screening but before the study intervention is given has been corrected to before randomization.	Correction
1.3 Schedule of Activities (SoA) 8.2.1 Physical Examinations	Targeted physical examinations are to be performed as per local standard of care.	Clarification
	It has been added, that if body weight cannot be measured at screening or is not already available in the participant's chart, weight for dose calculations can be verbally reported.	Clarification
1.3 Schedule of Activities (SoA) 8.1.4 Supplemental Oxygen Use	Wording has been added to clarify that if more than one device is being used for supplemental oxygen delivery, the worst (highest) FiO_2 value measured on the highest level of intervention will be recorded as well as the worst recording on each device separately.	Clarification and consistency
1.3 Schedule of Activities (SoA) 10.2 Appendix 2: Clinical Laboratory Tests	Following lab parameters also need to be tested and have thus been added: conjugated bilirubin (direct), unconjugated bilirubin (indirect), and international normalized ratio (INR).	For completeness and consistency
1.3 Schedule of Activities (SoA) 8.1.3 Virology Assessments	The possibility of home visits by health care professionals during follow-up period, has been added.	Allow health care professional home visits during follow-up
1.3 Schedule of Activities (SoA) 8 STUDY ASSESSMENTS AND PROCEDURES	A statement has been added as footnote 'ee' to clarify that for those participants discharged prior to Day 28, all Day 28 assessments should be done at day of discharge.	Clarification
2.3.1 Risks for Study Participation 6.8 Prestudy and Concomitant Therapy	It has been added that antivirals must have 'demonstrated in-vitro effect', as mentioned in the CDC Guidelines to be allowed as concomitant medication.	For completeness and consistency
5.1 Inclusion Criteria	The requirement to understand English language has been removed from the inclusion criterion 6.	To increase participant diversity in this clinical study

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
	The informed consent for the optional DNA research will be obtained in the main study informed consent form (ie, by a tick box) instead of through a separate informed consent form.	Clarification
5.2 Exclusion Criteria	Participants with currently active uncontrolled arrhythmia will be excluded if 'clinically significant'. Clinically significant has been added.	Clarification and consistency across the section
	Participants with prothrombin time/international normalized ratio >1.5xULN or (instead of 'and') activated partial thromboplastin time >1.5xULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder) screening laboratory test results will be excluded.	Correction
	It has been added that breastfeeding women should be excluded unless, in the opinion of the investigator, the benefits outweigh the risks.	Clarification
6.2 Preparation/Handling/Storage/ Accountability	The IV infusion rate has been changed from 100mL/min to 100 mL/h.	Correction
6.4 Study Intervention Compliance	The weight of IV infusion bag, including the infusion line before and after the completion of the IV infusion does not need to be recorded and has thus been removed.	Correction
6.8 Prestudy and Concomitant Therapy	Leflunomide has been removed from the list of drugs disallowed from 2 weeks prior to randomization, as it is later stated that leflunomide is disallowed from 8 weeks prior to randomization until the end of the study. It has also been adjusted that prestudy therapies must be recorded if taken up to 30 days before obtaining informed consent (instead of drugs taken up to 30 days before study intervention having to be recorded).	Consistency across the section Correction
8.1.1 Six-point Ordinal Clinical Recovery Scale	Text regarding declining care that requires an ICU level of intervention, has been removed from the footnote (as ICU stay is not part of the 6-point ordinal scale).	Correction
8.1.6 Arterial Blood Gas Test	Supplemental oxygen/FiO2 'and resting SpO_2' must be recorded at the same time as when an arterial blood gas is obtained. Resting SpO_2 has been added.	Consistency across the section
8.2.3 Electrocardiograms	It has been added that ECG strips or reports may be requested in case of documentation of a cardiovascular SAE.	Clarification
8.2.6 Vital Status	Vital status recording at Day 28 if discharge occurred before Day 28, has been added.	Clarification and consistency
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Spontaneously reported SAEs through the Week 16 visit instead of within 30 days after the last dose of study intervention, must be reported using an SAE form.	Clarification and consistency
9.4.4 Other Secondary Endpoints	Clarifications on the analyses are provided. It has also been added that drugs used in the SOC at baseline will also be tabulated by treatment group.	Clarification

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
9.4.5 Exploratory Endpoint(s)	In addition to NP swabs, SARS-CoV-2 viral load will also be measured in endotracheal, blood, and stool samples.	Clarification and consistency
6.2 Preparation/Handling/Storage/ Accountability 10.3.8 Data Quality Assurance 10.3.11 Monitoring 10.3.12 Audits	Language on on-site monitoring visits and on-site audits has been updated to allow flexibility during the COVID-19 pandemic.	Allow flexibility regarding on-site visits and audits.
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities (SoA) 2.2 Dose Rationale 3 OBJECTIVES AND ENDPOINTS 6.3 Measures to Minimize Bias: Randomization and Blinding 6.8 Prestudy and Concomitant Therapy 8.1 Efficacy Assessments 8.1.1 Six-point Ordinal Clinical Recovery Scale 8.1.2 Level of Consciousness 8.1.3 Virology Assessments 8.2.7 Self-reported Oxygen Need 9.3 Populations for Analysis Sets 9.4.4 Other Secondary Endpoints 9.5 Interim Analysis 10.1 Appendix 1: Abbreviations and Definitions 10.2 Appendix 2: Clinical Laboratory Tests 10.3.6 Committees Structure	Minor corrections or additions have been made.	Correction, clarification and consistency

11. REFERENCES

1. Actemra® USPI. Revised August 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s114lbl.pdf. Accessed 29 March 2020.
2. American Red Cross Blood donor eligibility requirements. Available from: http://www.redcrossblood.org/learn-about-blood/blood-facts-and-statistics. Accessed 28 March 2020.
3. Baas T, Taubenberger JK, Chong PY, Chui P, Katze MG. SARS-CoV virus-host interactions and comparative etiologies of acute respiratory distress syndrome as determined by transcriptional and cytokine profiling of formalin-fixed paraffin-embedded tissues. J Interferon Cytokine Res. 2006;26(5):309-317.
4. Banerjee S, Narayanan K, Mitzutani T, Makino S. Murine coronavirus replication-induced p38 mitogen-activated protein kinase activation promotes interleukin-6 production and virus replication in cultured cells. J Virol. 2002;76(12):5937-5948.
5. Bai B, hu Q, hu H, et al. Virus-like particles of SARS-like coronavirus formed by membrane proteins from different origins demonstrate stimulating activity in human dendritic cells. PLoS One. 2008;3(7):e2685.
6. Baran P, Hansen S, Waetzig GH, et al. The Balance of Interleukin (IL)-6, IL-6·soluble IL-6 Receptor (sIL-6R), and IL-6·sIL-6R·sgp130 Complexes Allows Simultaneous Classic and Trans-Signaling. J Biol Chem. 2018;293(18):6762-6775. doi: 10.1074/jbc.RA117.001163.
7. Bhatraju PK , Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically Ill Patients in the Seattle Region — Case Series. NEJM March 30, 2020 DOI: 10.1056/NEJMoa2004500
8. Butt Y, Kurdowska A, Allen TC .Acute lung injury: a clinical and molecular review. Arch Pathol Lab Med. 2016;140(4):345-350.
9. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19) Symptoms and Complications. Available at: https://www.cdc.gov/coronavirus/2019-ncov/about/symptoms.html. Accessed: 27 March 2020.
10. Centers for Disease Control and Prevention. Transcript - CDC Media Telebriefing: Update on COVID-19. Available at: https://www.cdc.gov/media/releases/2020/t0309-covid-19-update.html. Accessed on: 27 March 2020.
11. Centers for Disease Control and Prevention. Transcript - CDC Media Telebriefing: Update on COVID-19. Available at: https://www.cdc.gov/media/releases/2020/t0309-covid-19-update.html. Accessed on: 27 March 2020.
12. Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen KY. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. Clin. Microbiol. Rev. 2015; 28:465–522.
13. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin immunopathol. 2017;39(5):529-539.
14. Chen J, Lau YF, Lamirande EW, et al. Cellular immune responses to severe acute respiratory syndrome coronavirus (SARS-CoV) infection in senescent BALB/c mice: CD4+ T cells are important in control of SARS-CoV infection. J Virol. 2010;84(3):1289-1301.
15. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.
16. Chen X, Zhao B, Qu Y, et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely associated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. MedRxiv. 2020. Available at doi: https://doi.org/10.1101/2020.02.29.20029520. Accessed 30 Mar 2020.
17. Conti P, Ronconi G, Caraffa A. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents. 2020;34(2). pii: 1.
18. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020 Mar 2. doi: 10.1038/s41564-020-0695-z. [Epub ahead of print]

19. Day CW, Baric R, Cai SX, et al. A new mouse-adapted strain of SARS-CoV as a lethal model for evaluating antiviral agents in vitro and in vivo. Virology. 2009;395(2):210-222.

20. Day M. Covid-19: four fifths of cases are asymptomatic, China figures indicate. BMJ 2020;369:m1375 doi: 10.1136/bmj.m1375 (Published 2 Apr 2020)

21. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events. Corrected Version 2.1, July 2017. Available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. Accessed: 6 April 2020.

22. Dominquez SR, Travanty EA, Qian Z, Mason RJ. Human coronavirus HKU1 infection of primary human type II alveolar epithelial cells: cytopathic effects and innate immune response. PLoS One. 2013;8(7): e70129.

23. Dong Y, Mo X, Hu Y, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. Pediatrics. 2020 Mar 16. pii: e20200702. [Epub ahead of print]

24. Dosch SF, Mahajan SD, Collins AR. SARS coronavirus spike protein-induced innate immune response occurs via activation of the NF-kappaB pathway in human monocyte macrophages in vitro. Virus Res. 2009;142(1-2):19-27.

25. Eske J. What to know about the protein test and results. MedicalNewsToday, May 29, 2019. Available at: https://www.medicalnewstoday.com/articles/325320. Accessed 12 June 2020.

26. European Centre for Disease Prevention and Control. Factsheet for health professionals on coronaviruses. Available at: https://www.ecdc.europa.eu/en/factsheet-health-professionals-coronaviruses. Accessed: 15 Feb 2020.

27. Grun JL, Lublin FD, Knobler RL. Interleukin-6 induction in vitro in mouse brain endothelial cells and astrocytes by exposure to mouse hepatitis virus (MHV-4, JHM). J Neuroimmunol. 1993;42(1):47-52.

28. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline E14: Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. ICH 12 May 2005.

29. Investigator's Brochure: CNTO136 (sirukumab) Edition 13. Janssen Research & Development, April 2020.

30. Ishii K, Hasegawa H, Nagata N, et al. Neutralizing antibody against severe acute respiratory syndrome (SARS)-coronavirus spike is highly effective for the protection of mice in the murine SARS model. Microbiol Immunol. 2009;53(2):75-82.

31. Jacques A, Bleau C, Turbide C, Beauchemin N, Lamontagne L. Macrophage interleukin-6 and tumour necrosis factor-alpha are induced by coronavirus fixation to Toll-like receptor 2/heparan sulphate receptors but not carcinoembryonic cell adhesion antigen 1a. Immunology. 2009; 128(1 Suppl):e181-192.

32. Jiang Y, Xu J, Zhou C, et al. Characterization of cytokine/chemokine profiles of severe acute respiratory syndrome. Am J Respir Crit Care Med. 2005;171(8):850-870

33. Jiang X, Zhuang Y, Xu Z, Wang W, Zhou H. Development of a Physiologically Based Pharmacokinetic Model to Predict Disease-Mediated Therapeutic Protein–Drug Interactions: Modulation of Multiple Cytochrome P450 Enzymes by Interleukin-6. The AAPS Journal. 2016;18(3)767-776.

34. Johns Hopkins CSSE. Coronavirus COVID-19 Global Cases. Available at: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6. Accessed: 6 Apr 2020.

35. Joyner MJ, Wright RS, Fairweather D, et al. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients. MedRxiv preprint doi: https://doi.org/10.1101/2020.05.12.20099879, May 2020. Available at: https://www.medrxiv.org/content/10.1101/2020.05.12.20099879v1.full.pdf. Accessed 12 June 2020.

36. Kevzara® USPI. Revised May 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761037s000lbl.pdf. Accessed 29 March 20202.

37. Lam CW, Chan MH, Wong CK. Severe acute respiratory syndrome: clinical and laboratory manifestations. Clin Biochem Rev. 2004;25(2):121-132.

38. Li Y, Chen M, Cao H, Zhu Y, Zheng J, Zhou H. Extraordinary GU-rich single-strand RNA identified from SARS coronavirus contributes an excessive innate immune response. Microbes Infect. 2013;15(2):88-95.

39. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020 Jan 29. doi: 10.1056/NEJMoa2001316. [Epub ahead of print].

40. Liang B, Gardner DB, Griswold DE, Bugelski PJ, Song XY. Anti-interleukin-6 monoclonal antibody inhibits autoimmune responses in a murine model of systemic lupus erythematosus. Immunology. 2006;119:296-305.

41. Liang B, Song Z, Wu B, Gardner D, et al. Evaluation of anti-IL-6 monoclonal antibody therapy using murine type II collagen-induced arthritis. J Inflamm. 2009;6(10).

42. Liao Y, Wang X, Huang M, Tam JP, Liu DX. Regulation of the p38 mitogen-activated protein kinase and dual-specificity phosphatase 1 feedback loop modulates the induction of interleukin 6 and 8 in cells infected with coronavirus infectious bronchitis virus. Virology. 2011; 420(2):106-116.

43. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Jan 30. pii: S0140-6736(20)30251-8.

44. McNarry AF, Bateman DN. Simple bedside assessment of level of consciousness: comparison of two simple assessment scales with the Glasgow Coma scale. Anaesthesia. 2004;59:34–37.

45. Mihara M, Kasutani K, Okazaki M, etal. Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family. International Immunopharmacology. 2005(5);1731–1740.

46. National Institute of Allergy and Infectious Diseases. Division of Microbiology and Infectious Diseases (DMID) Adult toxicity tables. November 2007 (draft). Available at: https://www.niaid.nih.gov/sites/default/files/dmidadulttox.pdf. Accessed on 2 April 2020.

47. Nieto-Torres JL, DeDiego ML, Verdiá-Báguena C, et al. Severe acute respiratory syndrome coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis. PLoS Pathog. 2014;10(5):e1004077.

48. Paessler S and Walker DH. Pathogenesis of the viral hemorrhagic fevers. Annu Rev Pathol. 2013; 8:411-440.

49. Park WY, Goodman RB, Steinberg KP, et al. Cytokine Balance in the Lungs of Patients with Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2001;164:1896–1903.

50. Priestnall SL, Mitchell JA, Brooks HW, Brownlie J, and Erles K. Quantification of mRNA encoding cytokines and chemokines and assessment of ciliary function in canine tracheal epithelium during infection with canine respiratory coronavirus (CRCoV). Vet Immunol Immunopathol. 2009;127(1-2):38-46.

51. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol. 2020;38(1):1-9.

52. roActemra® SmPC. Revised 25 September 2013. Available at: https://www.ema.europa.eu/en/documents/product-information/roactemra-epar-product-information_en.pdf. Accessed 3 Apr 2020.

53. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on analysis of data of 150 patients from Wuhan China. Intensive Care Med. 2020. doi: 10.1007/s00134-020-05991-x. [Epub ahead of print]

54. Shi Y, Wan Y, Shao C, et al. COVID-19 infection: the perspectives on immune responses. Cell Death Differ 2020. doi: 10.1038/s41418-020-0530-3. [Epub ahead of print].

55. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. J Immunother Cancer. 2018 15;6(1):56. doi: 10.1186/s40425-018-0343-9.

56. Smits SL, van den Brand JM, de Lang A, et al. Distinct severe acute respiratory syndrome coronavirus-induced acute lung injury pathways in two different nonhuman primate species. J Virol. 2011;85(9):4234-4245.

57. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med 2020; 383: 2333-44.

58. The REMAP-CAP Investigators, Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report, medRxiv preprint. Available at: doi: https://doi.org/10.1101/2021.01.07.21249390. Accessed on 8 February 2021.

59. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, and Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biol Rev. 2012;76(1):16-32.

60. Tseng CT, Peronne LA, Zhu H, Makino S, Peters CJ. Severe acute respiratory syndrome and the innate immune responses: modulation of effector cell function without productive infection. J Immunol. 2005;174(12):7977-7985.

61. Unver N, McAllister F. IL-6 family cytokines: key inflammatory mediators as biomarkers and potential therapeutic targets. Cytokine Growth Factor Rev. 2018;41:10-17.

62. Wang WK, Chen SY, Liu IJ. Temporal relationship of viral load, ribavirin, interleukin (IL)-6, IL-8, and clinical progression in patients with severe acute respiratory syndrome. Clin Infect Dis. 2004;39(7):1071-1075.

63. Wang W, Ye L, Ye L, et al. Up-regulation of IL-6 and TNF-alpha induced by SARS-coronavirus spike protein in murine macrophages via NF-kappaB pathway. Virus Res. 2007;128(1-2):1-8.

64. Wang SF, Tseng SP, Yen CH, et al. Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. Biochem Biophys Res Commun. 2014;451(2):208-214.

65. Wang Y, Wang H, Zhang C, et al. Lung fluid biomarkers for acute respiratory distress syndrome: a systematic review and meta-analysis. Crit Care. 2019;23(1):43.

66. Wang D, Hu B, Hu C. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb 7. doi: 10.1001/jama.2020.1585. [Epub ahead of print].

67. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease in 2019 in Wuhan China. Clin Infect Dis. 2020. pii: ciaa272

68. Wolf J, Rose-John S, and Garbers C. Interleuking-6 and its receptors: highly regulated and dynamic system. Cytokine. 2014;70(1):11-20.

69. Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol. 2004;136(1):95-103.

70. World Health Organization (WHO). Global surveillance for COVID-19 caused by human infection with COVID-19 virus. Interim guidance 20 March 2020. Available at: https://apps.who.int/iris/bitstream/handle/10665/331506/WHO-2019-nCoV-SurveillanceGuidance-2020.6-eng.pdf?sequence=1&isAllowed=y. Accessed 14 Apr 2020.

71. World Health Organization (WHO). Clinical management of severe acute respiratory infection when COVID-19 is suspected. Interim guidance 13 March 2020. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. Accessed 14 Apr 2020.

72. World Health Organization. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). Available at: https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov). Accessed 14 Apr 2020.

73. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed 12 Mar 2020.

74. World Health Organization. WHO guidelines for the global surveillance of severe acute respiratory syndrome (SARS). Updated recommendations, October 2004. Available at: https://www.who.int/csr/resources/publications/WHO_CDS_CSR_ARO_2004_1/en/. Accessed: 15 Feb 2020.

75. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265-269.

76. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. chinaXiv:202003.00026v1.

77. Yoshikawa T, Hill T, Li K, Peters CJ, and Tseng CT. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. J Virol. 2009; 83(7):3039-3048.

78. Yu D, Zhu H, Liu Y, Cao J, and Zhang X. Regulation of proinflammatory cytokine expression in primary mouse astrocytes by coronavirus infection. J Virol. 2009;83(23):12204-12214.

79. Zhang Y, Li J, Zhan Y. Analysis of serum cytokines in patients with severe acute respiratory syndrome. Infect Immun. 2004;72(8):4410-5.

80. Zhang X, Wu K, Wang D et al. Nucleocapsid protein of SARS-CoV activates interleukin-6 expression through cellular transcription factor NF-kappaB. Virology. 2007;365(2):324-335.

81. Zhou J, Chu H, Li C, et al. Active replication of Middle East respiratory syndrome coronavirus and aberrant induction of inflammatory cytokines and chemokines in human macrophages: implications for pathogenesis. J Infect Dis. 2014;209(9):1331-1342.

82. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses - drug discovery and therapeutic options. Nat Rev Drug Discov. 2016;15(5):327-347.

INVESTIGATOR AGREEMENT

CNTO136 (sirukumab) Clinical Protocol CNTO136COV2001
AMENDMENT 5

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Magda Opsomer

Institution: Janssen Research & Development

Signature: PPD _____ Date: PPD
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 148
Status: Approved, Date: 17 February 2021