Janssen Research & Development

Statistical Analysis Plan

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

Protocol CNTO136COV2001; Phase 2

CNTO136COV2001 (Sirukumab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

AMENDMENT HISTORY

NAP

ABBREVIATIONS

Ab	Antibodies
AE	Adverse event
ALT	Alanine aminotransferase
AST	All subjects treated / Aspartate aminotransferase
BIPAP	Bi-level positive airway pressure
BMI	Body mass index
CI	Confidence interval
CPAP	Continuous positive airway pressure
CRP	C-Reactive protein
CRS	Clinical recovery scale
CTP	Clinical trial protocol
CU	Confirmed undetectability (of viral loads)
DBP	Diastolic blood pressure
DMC	Data monitoring committee
DMID	Division of Microbiology and Infectious Diseases
DPS	Data presentation specifications
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
HR	Heart rate
IA	Interim analysis
ICF	Informed consent form
ICH	International conference on harmonization
ICU	Intensive care unit
IMV	Invasive mechanical ventilator/ventilation
IMG	Immunogenicity
IQR	Interquartile range
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive web response system
KM	Kaplan Meier
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LOQ	Limit of quantification
MedDRA	Medical dictionary for regulatory activities
NGS	Next generation sequencing
NOS	Not otherwise specified
NP	Nasopharyngeal
PK	Pharmacokinetic(s)
PP	Per-protocol
PT	Preferred term
qRT-PCR	Quantitative real time polymerase chain reaction
RAND	Randomized
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure

SD	Standard deviation
SE	Standard error
SOC	Standard of care
SOC-Med	System organ class as per MedDRA
TFL	Tables, figures, and listings
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
VOC	Variant of concern
VOI	Variant of interest

1 INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables and statistical methods for the analysis of efficacy and safety of the investigational compound Sirukumab (**CNTO136COV2001**). A document 'Data Presentation Specifications (DPS)' for mock shells and table of contents for Tables, Figures and Listings (TFLs) is also produced. The SAP is to be interpreted in conjunction with the protocol. The current SAP will cover the primary analysis and the final analysis. Primary analysis will be performed when all randomized participants reach the Day 28 assessment of the study or discontinued earlier. The final analysis will be performed using all data available (including the information from the follow-up visits) after all randomized and/or treated participants reach the end of the study (Week 16) or discontinued earlier. The analysis methods will essentially remain the same for the two analyses.

1.1 Trial Objectives

Primary Objective

The primary objective of the study is to evaluate the clinical response of Sirukumab (administered as a single IV dose) with standard-of-care (SOC) treatment compared to placebo with SOC in confirmed critical COVID-19 disease and as measured by the time to sustained improvement of at least 2 categories relative to baseline on the 6-point ordinal clinical recovery scale (CRS) (up to Day 28).

Secondary Objectives

Objectives	Endpoints
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+ SOC compared to placebo + SOC in confirmed severe or critical COVID-19 disease	• Time to sustained improvement 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	• Incidence of SAEs (up to Day 28)

in confirmed (a) critical and (b) severe or critical COVID-19 disease	• 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)
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 sustained improvement 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 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) • Proportions 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 (as multiple time points up to Day 28)
To evaluate pharmacokinetics following Sirukumab 5 mg/kg treatment	• Sirukumab serum concentration
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

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

1.2 Trial 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, target was to randomly assign 270 participants with confirmed severe or critical COVID-19 in a 2:1 ratio (Sirukumab: placebo) 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 (please also see section 1.4: 'Sample Size Justification' for revised sample size calculations), 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 ('Treatment Phase') and a Post Day 28 'Follow-up Phase' to include 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.

1.3 Statistical Hypotheses for Trial Objectives

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

1.4 Sample Size Justification

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 sustained 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 sustained 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 sustained 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%.

1.5 Randomization and Blinding

Randomization

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 treatment arms in a 2:1 ratio (Sirukumab: placebo) 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 for age (<65 and ≥ 65 years) and IMV (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 participant 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 treatment 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 were disclosed to those authorized and only for those participants included in the IA. Details on the level of unblinding and the parties authorized unblinded during the interim analysis were specified in the IA 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 to return for scheduled evaluations.

In general, randomization codes will be disclosed fully only at the timing of the primary analysis and when the clinical database is closed. However, for the analyses performed for the DMC review or for the interim analysis, the randomization codes and, if required, the translation of randomization codes into intervention and control groups were disclosed to those authorized and only for those participants included in the DMC or interim analysis.

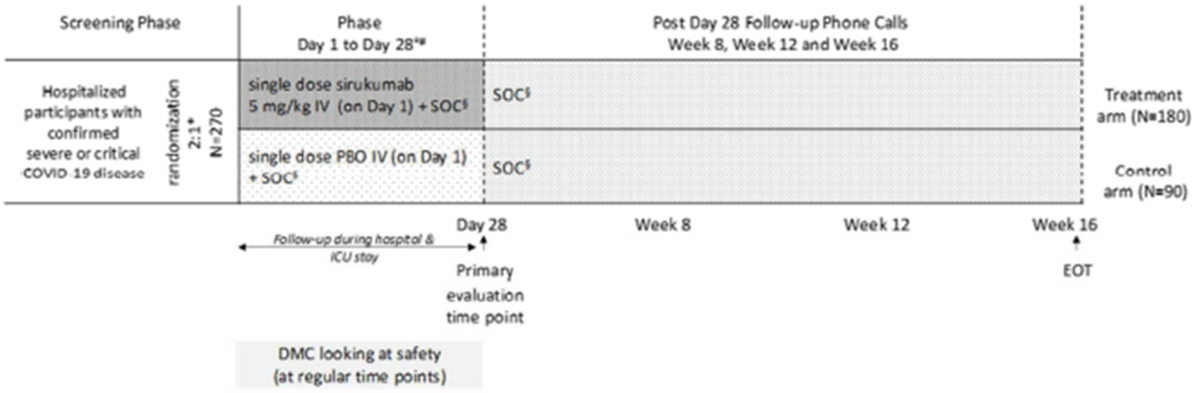
2 GENERAL ANALYSIS DEFINITIONS

All analysis dataset preparations and statistical analyses will be performed using SAS® version 9.4 or higher.

2.1 Visit Windows and Phase Definitions

The study is set up as shown in Figure 1 and Figure 2. The phases will be constructed as shown in Table 1.

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.

° The DMC will review the interim data as soon as the first 30 participants have been dosed and have had at least 7 days of follow-up after study intervention.
An IA for futility will be performed when approximately 20% of the planned number of participants have reached Day 28 or discontinued earlier.

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[a], and pulmonary imaging assessments taken up to 2 days prior to screening will be accepted for screening assessments.

Screening[b] 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.

[a] As of protocol amendment 5

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

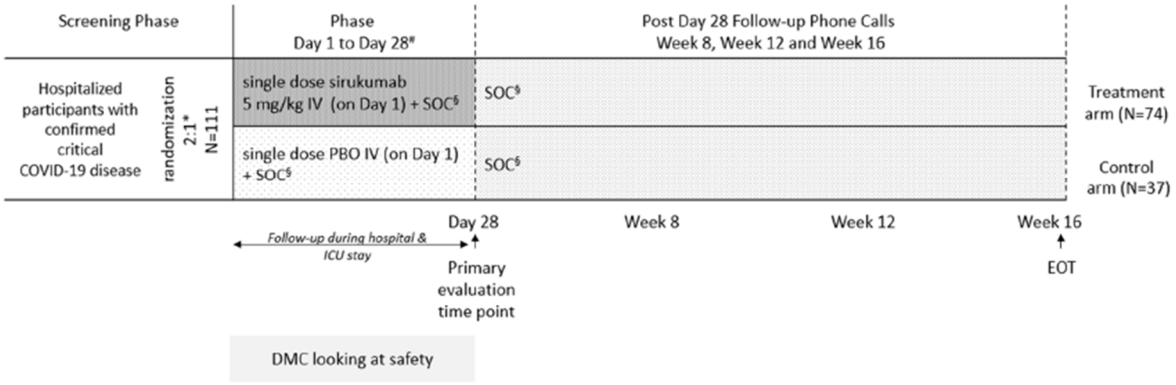
Participants need to receive study intervention preferably within 4 hours but no later than 6 hours after randomization.

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.



2.1.1 Phase Definitions

Table 1: Construction of phases

Study Phase	Start Date/Time	End Date/Time
Screening (phase 1)	The date & time of signing the informed consent[*1]	1 minute before the study drug intake
Treatment (phase 2)	Date & time of study drug administration (Sirukumab or Placebo)[*2]	Minimum of: a. Day 28 Visit at 23.59h or if Discharged earlier phone call Day 28 at 23.59h b. Date of study discontinuation before Day 28[*3] c. Date of death[*3] If a), b) c) did not occur then count 28 days after drug administration at 23.59h
Follow-up (phase 3)	End of the treatment phase +1 minute	Maximum of: a. Date of last contact[3*] b. Date of study discontinuation[3*]

[*1]: if no time is available then impute with 00:00
[*2]: in case the time part of the study drug administration is missing then time part will be imputed by time of randomization
[*3]: Time will be imputed with 23:59

2.2 Analysis Sets

2.2.1 All Randomized (RAND) Analysis Set

The RAND analysis set consists of all participants who were randomized in the study. Analysis based on this analysis set will use the randomized treatment group assigned by IWRS (All randomized analysis set as Randomized).

2.2.2 Intent-to-Treat (ITT) Analysis Set

The ITT analysis set consists of all participants who were randomized and treated in the study. This analysis set will be used for the analysis of efficacy, subject information and virology assessments. Treatment group as randomized will be used for these analyses (ITT analysis set as Randomized).

2.2.3 Primary Analysis Set

The Primary analysis set consists of all participants in the ITT analysis set with confirmed critical COVID-19 disease defined as score of 4 or 5 on the CRS scale at baseline. For more details on CRS score please refer to Section 5: Efficacy. Treatment groups as randomized will be used for the analysis using this analysis set (Primary analysis set as Randomized).

2.2.4 All Subjects Treated (AST) Analysis Set

The AST analysis set consists of all participants who received the study drug. This analysis set will be used to evaluate the safety of drug, using the actual treatment received by a participant (AST analysis set as Treated)

2.2.5 Pharmacokinetics (PK) Analysis Set

The PK analysis set includes all participants in the AST analysis set with no interruption of study medication and who also had at least 1 valid blood sample drawn for PK analysis after dose of Sirukumab. This analysis set will be used to analyze the PK concentration using actual treatment received by a participant (PK analysis set as Treated).

2.2.6 Immunogenicity (IMG) Analysis set

The IMG analysis set consists of participants in AST analysis set who received a dose (full or partial) of Sirukumab during the study and have at least one valid blood sample for immunogenicity analysis after Sirukumab dose. This analysis set will be used to analyze immunogenicity using the actual treatment received by a participant (IMG analysis set as Treated).

2.2.7 Per-Protocol (PP) Analysis Set

The PP analysis set consists of participants in ITT analysis set who don't have any major protocol deviations that could have influenced the efficacy of Sirukumab during the study. This analysis set will be used for exploratory analysis of primary efficacy endpoint if more than 10% of ITT participants have major protocol deviations that could have influenced the efficacy evaluation.

2.3 Study Day 1

Study Day 1 refers to the day/date of the study drug administration (which is the same as the treatment phase start date).

2.4 Imputation of Missing Time Portion of Date/Time Field

Each measurement/observation which is supposed to have date and time associated with it may sometimes have the time portion of date/time as missing. If time is missing, then the measurement/observation is assumed to be at the start of the day (that is, missing time is imputed as 00:00:00 hours/minutes/seconds). Therefore, a measurement/observation with missing time on Day 1 is assumed to be pre-dose unless information on eCRF clearly mentions that it is post-dose.

2.5 Baseline Value

The baseline values for efficacy endpoints are defined in section 5: Efficacy.

For demographics and other measurements during the study, a baseline is defined as the last value/measurement (1) on or after informed consent date/time, **AND** (2) before the date/time of study drug administration.

However, following exceptions apply to define the baseline.

(1) For electrocardiogram (ECG) measurements, for participants who were enrolled before protocol amendment 5, the baseline is defined as the last value/measurement (1) on or after

informed consent date/time, AND (2) before the date/time of study drug administration. For participants who were enrolled based on protocol amendment 5, the baseline may be defined using information from up to 2 days prior to the informed consent date.

(2) Local labs tests (blood chemistry, hematology, coagulation tests), pregnancy tests and chest imaging, the baseline may be defined using the information from up to 2 days prior to the informed consent date.

(3) It is possible that for some biomarkers there are multiple samples taken at the same date/time providing different test results corresponding to the same date/time. In such cases when there are multiple pre-dose measurements exactly on the same date/time that are closest to date/time of study drug administration then average of these measurements is used as baseline value. [Note: Measurements below lower limits of quantification (LLOQ) will be imputed by LLOQ/2 and measurements above upper limits of quantification (ULOQ) by ULOQ prior to taking the average, if required.]

(4) The baseline for viral load may be a post-dose measurement, for more details please see section 6.2: Virology Assessments- Definitions.

(5) If pre-dose height and weight values are not available, then earliest post-dose values on day of study drug administration may be used as the baseline values for height and weight.

[Note: As mentioned in section 2.4, a measurement/observation with missing time on Day 1 is assumed to be pre-dose unless information on eCRF clearly mentions that it is post-dose.]

2.6 Definition of Subgroups

Subgroups used for analyses of different endpoints are defined in the Table 2 below.

Descriptive statistics will be produced for the different subgroups.

Table 2: Subgroup definition

Subgroup	Definition	Endpoints
Age group (years)	• <65 years • ≥ 65 years	- Participants' demographics information, baseline disease characteristics, and disposition information - Selected Efficacy - Safety (selected laboratory test results and AE tables) -
CRS score at baseline[1]	CRS <= 3 CRS <= 4 CRS=4 CRS=5	- Participants' demographics information, baseline disease characteristics, and disposition information - Selected Efficacy - Safety (selected laboratory test results and Adverse events results) -
		○

Subgroup	Definition	Endpoints
Center[2]	• Highest recruiter center (located over 2 sites) • All other centers	- Efficacy (primary and key secondary endpoints)
Interim Analysis	• Included in Interim Analysis • Not included in Interim Analysis	- Efficacy (primary and key secondary endpoints)
Free IL-6 at screening	• <= 33% percentile • > 33 and <= 66% percentile • > 66% percentile	- Efficacy (primary and key secondary endpoints)
CRP at screening	• <= 33% percentile • > 33 and <= 66% percentile • > 66% percentile	- Efficacy (primary and key secondary endpoints)

[1] CRS=5 corresponds to "Use of IMV at the time of randomization". For descriptive statistics, CRS score at baseline with the subgroups as defined will be used. For inferential statistics, the models should include a baseline CRS flag (<=3/> 3) in combination with the stratification factor. Baseline CRS will not be included in the model.

[2] Highest recruiter center (located over 2 sites: US1006 & US10033)

Additional subgroup analysis may be specified in a separate analysis plan and reported separately from the clinical study report. These may include subgroups according to baseline C-Reactive Protein or baseline Albumin values.

2.6.1 Pooling Algorithm for Analysis Centers

As per the information in Table 2, certain analysis will be performed using the participants in the following 2 subgroups of the study centers.

- US1006 and US10033.
- All other centers

3 DATA REVIEW COMMITTEE, INTERIM ANALYSIS

A Data Monitoring Committee (DMC) was established to monitor unblinded data to ensure the continuing safety and well-being of the participants. Also, an interim analysis (IA) was conducted during the study. Details for these are described in the next sections.

3.1 Data Monitoring Committee

A DMC consisting of internal and external members was established to monitor unblinded data to ensure the continuing safety and well-being of the participants enrolled in this study. The DMC regularly evaluated the cumulative safety data of all participants in the study. As soon as the first 30 participants 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. During this data review enrollment was continued, however, it was planned that recruitment would be halted should 60 patients had been enrolled before the outcome of the data review was known. All data available at the time of the interim data review was included. In case recruitment were to be halted, it was planned to resume the enrollment following a positive assessment of results of these interim data by DMC.

The DMC responsibilities, authorities, and procedures are documented in its charter.

3.2 Interim Analyses

A non-binding unblinded interim analysis (IA) for futility was performed by the sponsor on the primary endpoint when approximately 20% of the planned number of participants had reached Day 28 or could have reached Day 28 by the date of data cut-off for the IA. Results have been discussed with the DMC.

The randomization codes and the translation of randomization codes into treatment and control groups were disclosed to those authorized and only for those participants included in the IA. Following this IA, the study was not stopped for futility.

A separate SAP is available for the interim analysis (IA).

4 SUBJECT INFORMATION

4.1 General

Participants' information will be presented using the ITT and Primary analysis sets unless specified otherwise for a specific display. If there is a difference in allocation (>5 participants) between the ITT and the AST sets the disposition information and demographic and baseline disease characteristics will also be provided for the AST.

For continuous data descriptive statistics will be reported (n, mean, SD, median, range, IQR range), for categorical data frequencies and percentages will be displayed.

4.2 Demographics and Baseline Characteristics

The summary tables for demographic characteristics and baseline values will be generated.

Tables summarizing the following demographic characteristics and baseline values for different measurements during the study are planned.

Demographic and baseline parameters:

- Age (years) including categories (<65; ≥65)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple. ('Not Reported' and 'Unknown' for race will be considered as missing)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline weight (kg)
- Baseline height (cm)
- BMI at baseline = Weight at baseline (kg) / (Height at baseline (m))2 (If available in the raw data, BMI will be recalculated from last weight and height measurement before start of treatment) and categories (<18.5, 18.5-25, 25-30, >=30)
- Smoker (No, Yes - Current, Yes - Former)

Baseline disease characteristics:

- Days from Onset of First Symptoms to Randomization
- Level of Hospital Care at Baseline (Hospital inpatient department (ward), Intensive care unit, Step down unit)
- Days from Onset of First Symptoms to First Admission in Hospital (Regardless of Level of Care)
- Days from First Admission in Hospital (Regardless of Level of Care) to screening
- Days from First Admission in ICU to screening
- Days from First Symptoms to IMV and/or ECMO
- Chest Imaging (Normal, Abnormal, Unilateral findings, Bilateral findings)
- Clinical Status at Randomization (Hospitalized - requiring low flow supplemental oxygen, Hospitalized -on non-invasive pressure ventilation or high flow, Hospitalized - on IMV or ECMO)

Use of IMV at baseline (based on eCRF data, if not available on eCRF then on IWRS system) (Yes, No)

Tables summarizing biomarkers and relevant lab tests at baseline will be generated:

- The biomarkers of CRP, D-Dimer, Serum Ferritin, Pro-Calcitonin and Free IL-6 (all from central labs), will be summarized by mean (SD), median, tertiles, IQR, minimum, and maximum. [Note: Measurements below the lower or above the upper limits of quantification (LLOQ, ULOQ) will be imputed as LLOQ/2 or ULOQ, respectively.
- Lab tests of White Blood cell count, Lymphocyte count, Platelets, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and Creatinine (all from local labs) will be summarized as per Division of Microbiology and Infectious Diseases (DMID) grades.
- Lab tests of Lactate Dehydrogenase (LDH), Albumin, Troponin-I, and Troponin-T (all from local labs) will be displayed by n and percentages of participants with values of normal, and high/below normal range.

4.3 Disposition Information

Summary tables for the following information showing number and percentages of participants will be generated.

- Participants 'screened', 'screen failures, 'randomized and treated', 'randomized and not treated', 'not randomized and treated'. The table will include all screened participants (only number of participants will be displayed on the table),
- Participants in different analysis sets (only number of participants will be displayed on the table),
- Participants who are ongoing in study, completed the study, discontinued the study and the reasons for discontinuation.

Participants are randomized by two stratification factors (1) Age categories (< 65, >= 65 years), and (2) Use of IMV at randomization (Yes, No). It is very unlikely but possible that participants are not correctly randomized in the right stratum and that there are discrepancies between IWRS system and information on eCRF pages. A table showing the discrepancies between IWRS system and information on eCRF pages will be generated for participants in RAND analysis set.

4.4 Extent of Exposure and Treatment Compliance

A listing with extent of exposure data (duration of infusion, interruption, and length of interruption) and drug administration information (total calculated dose, participant's weight, total volume prepared, volume added to IV container) will be provided for each treated participant.

A listing of participants randomized will be generated to show the actual treatment received and randomized treatment and the date/time of the treatment received.

4.5 Protocol Deviations

For the participants in the ITT and Primary analysis sets, the number and percentage of participants with major protocol deviations (using coded major protocol deviations) and number and percentage of participants with major protocol deviations that are considered as affecting the efficacy evaluations will be tabulated. A listing will be generated for screened participants with any major protocol deviations and the major protocol deviations affecting the efficacy evaluations will be flagged.

4.6 Prior and Concomitant Medications

Information on prior and concomitant medications will be provided for the ITT and Primary analysis sets.

Medications taken until the end of study will be summarized by treatment group and overall, by preferred term as frequency tables for the prior and concomitant medications separately:

1. Prior medication: medication that started before the date of the first dose of study drug, regardless of the stop date of the medication.

2. Concomitant medication: (1) medication received on or after the date of first dose of study drug, and (2) medication that was received before dosing date and continued after dosing of study drug, or medication with missing stop date.

It should be noted that a medication may be classified both as prior and concomitant medication.

The classification of a medication will be based only on the date of start/end of the medication and the date of start of study dose; and time portion of medication and study dose will not be considered. Therefore, if a medication started on the study dose date then it is considered as a concomitant medication.

If a medication record has missing components of its start and/or stop dates (day and/or month and/or year), the following rules will be used to impute the missing date or its component:

1. In case of partial start or stop date, the concomitant therapy records will be allocated to prior/concomitant using the available partial information, without imputations.
2. In case of a completely missing start date, the prior/concomitant therapy will be considered as having started before the trial.
3. In case of a completely missing end date, the prior/concomitant therapy will be considered as ongoing at the end of the trial.

The analysis of prior/concomitant medications will use the coded terms from the WHO drug dictionary as provided in the clinical database.

The number and percentage of participants with prior and concomitant medications will be summarized by ATC levels 1, 2, 3, and by standardized medication names (coded terms).

Medications of interests with COVID-19: The following medication groups of the prior and concomitant medications of interests with COVID-19 will be summarized showing number and percentage of participants by medication groups/coded terms:

- Covid-19 direct antiviral,
- Remdesivir and Glucocorticosteroids,
- Glucocorticosteroids for systemic use,
- Antibacterial for systemic use,
- Antimycotics for systemic use, and
- Antithrombotic agents (excluding antiplatelets)
- Convalescent plasma
- Interleukin Inhibitors
- COVID-19 Vaccine

The above groups and corresponding coded terms will be listed in the DPS.

Duration of medications of interests with COVID-19: The median, range and interquartile range of duration (Days) of treatment with Remdesivir and Glucocorticosteroids during the study will be tabulated.

4.7 Medical history

Medical history for each participant will be collected at screening visit. Summary of medical history will be presented using the ITT and the Primary analysis sets.

General medical history and COVID-19 related medical history are collected on separate pages of the eCRF. COVID-19 related medical history included the following pre-specified symptoms: Fever, Cough, Sour Throat, Rhinorrhea, Wheezing, Chest Pain, Myalgia, Fatigue/Malaise, and Dyspnea. Any other reported COVID-19 related symptoms not pre-specified in the CRF will be presented under 'Other' with subcategories of Gastrointestinal symptoms, loss of taste/smell, headache, and other. General medical history terms are coded using Medical Dictionary for Regulatory Activities (MedDRA).

General medical history will be tabulated by System Organ Classes (SOC-Med) and Preferred Terms (PT) using MedDRA coding, and by splitting them by those 'being currently active' and 'history and not active'. Additionally, a summary table showing only COVID-19 related medical history will be generated.

Relevant comorbidities at screening are defined by ongoing general medical history related to symptoms of Diabetes, Serious Heart Conditions/Coronary Heart Disease, Chronic Obstructive Pulmonary Disease, Chronic Kidney Disease, Cancer, and Obesity (defined as BMI >= 30 kg/m^2 based on height (meter) and weight (kg) at screening). A summary table with number and percentages of participants in each of these comorbidities will be generated. The coded terms (PT) corresponding to comorbidities will be listed in the DPS.

4.8 Physical Examinations and Pregnancy Test Results

For all participants, the targeted physical examinations are performed at screening. Any new findings or worsening of conditions are reported as adverse events (AEs).

For female participants in the AST analysis set, the results of the pregnancy tests at screening/baseline and at Day 28/discharge visits will be listed.

4.9 Results by Sub-groups

As mentioned in the section 2.6, subgroup analysis is planned based on subgroups of (1) age (<= 65 and > 65 years) and (2) CRS score at baseline (<= 3, <= 4, 4, 5) to investigate the disposition of participants during the study, demographic information, and baseline disease characteristics.

5 EFFICACY

Descriptive statistics will be used for all efficacy endpoints and will be tabulated by treatment arm and by the subgroups as specified in table 2.

All efficacy analyses will be performed in the Primary and ITT analysis sets as randomized.

5.1 Analysis Specifications

5.1.1 Level of Significance

The primary endpoint will be tested for superiority of Sirukumab in combination with SOC over placebo in combination with SOC at the 2-sided 5% significance level.

The key secondary endpoints and other secondary endpoints will be tested at the 1-sided 5% significance level.

5.1.2 Stratification Factors

The actual values of the stratification factors will be used for all analyses.

5.2 Primary Efficacy Endpoint(s)

5.2.1 Definitions

Six-point ordinal clinical recovery scale

The 6-point ordinal clinical recovery scale (CRS) provides 6 mutually exclusive conditions ordered from best to worst, and the score reflects the participant's worst situation on the day of the assessment:

1. Not hospitalized
2. Hospitalized, not requiring supplemental oxygen
3. Hospitalized, requiring low flow supplemental oxygen
4. Hospitalized, on non-invasive ventilation, nonrebreather mask or high flow oxygen device
5. Hospitalized, on IMV or ECMO
6. Death

The CRS can be derived from baseline up to and including day 28. The CRS will be missing after trial discontinuation if the participant discontinued the trial for other reason than death. Participants who die before day 28 (before or after discharge from hospital) will be considered to continue the trial up to and including day 28.

The CRS categories are defined below. For ease of categorization, the categories are defined from worst to best. A participant will be evaluated in the same ordering of the categories as below. Once a participant fulfils the criteria for a category, the category is assigned to the participant and the evaluation stops.

6. Death
    - Participant died at any time on the day of assessment or earlier (all-cause mortality).
5. Hospitalized, on IMV or ECMO

- IMV or ECMO is used at any time on the day of assessment, OR
- From a Medical Perspective, the participant should have been on IMV on the day of the assessment

4. Hospitalized, on non-invasive ventilation, nonrebreather mask, or high flow oxygen device
   - The participant is on supplemental oxygen and the worst FiO2 is >=50%.
3. Hospitalized, requiring low flow supplemental oxygen
   - On supplemental oxygen with worst FiO2<50 % and the participant was not able to sustain a blood oxygen saturation of >93% when breathing room air, OR
   - Not on supplemental oxygen and the minimum of all available SpO2 values during the day is <= 93%
2. Hospitalization, not requiring supplemental oxygen
   - Hospitalized according to the status described below
1. Not hospitalized, including subjects on low level of oxygen
   - A distinction will be made between subjects 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.

Hospitalization status

The hospitalization status considered for the definition of the CSR will be defined according to the rules described below. The hospitalization status will be evaluated in the same ordering of rules. Once a participant fulfils the criteria, the hospitalization status is defined and the evaluation stops.

1. If a participant is discharged to the alternate care settings 'different hospital', 'acute care facility', 'subacute care facility' or 'hospice/palliative discharge', the participant will be considered hospitalized until day 28 or trial discontinuation, whichever comes first. The participant will be categorized in the category the participant was in at time of discharge until trial discontinuation.

2. If a participant is discharged 'against medical advice', the participant will be considered hospitalized on the day of discharge and on the day after discharge, unless the participant discontinued the trial. The participant will be categorized in the category the participant was in at time of discharge. The CRS will be considered missing from 2 days after discharge onwards.

3. If a participant is hospitalized although 'ready for discharge' according to the investigator, the participant will be considered hospitalized up to and including the first day on which the participant was considered ready for discharge. The participant will be considered "Not hospitalized" from the day after until day 28 or trial discontinuation, whichever comes first (unless the status changes back to "not ready for discharge").

4. If a participant is discharged although 'not ready for discharge' according to the investigator, the participant will be considered hospitalized up to and including 1 day

after the day of discharge, unless the participant discontinued the trial. The participant will be categorized in the category the participant was in at time of discharge. The participant will be considered non hospitalized from 2 days after the day of discharge onwards until day 28 or trial discontinuation, whichever comes first.

5. If a participant is discharged from the hospital, the day of discharge will be considered as "hospitalized". The participant will be categorized in the category the participant was in at time of discharge. After this day, the participant will be considered "Not hospitalized" until day 28 or trial discontinuation, whichever comes first.

Baseline

The 6-point ordinal CRS at the time of randomization request will be used as the baseline. If the baseline assessment of the CRS is missing, the first available assessment within 12 hours after randomization will be used. If the latter is also missing, the last available assessment prior to baseline will be used.

Sustained Clinical Improvement

Clinical Improvement is obtained if the score on the CRS improved with at least 2 categories with respect to the baseline score.

Sustained clinical improvement is defined as a clinical improvement without documented loss of this clinical improvement up to and including day 28 or until trial discontinuation, whichever comes first.

5.2.2 Primary Estimand

Population: The population of interest are hospitalized patients between ≥18 and <85 years old with confirmed critical COVID-19 disease.

Endpoint: Time to sustained clinical improvement.

Interventions: Received Sirukumab 5 mg/kg (IV single dose infusion on Day 1) and placebo (IV infusion on Day 1), both on top of SOC.

Intercurrent Events:

- Death as intercurrent event is handled in a composite strategy as it is the worst category on the clinical scale.

- The intercurrent event of the use of prohibited medication is handled in a treatment policy strategy: data will be used as observed.

- The intercurrent event of discharge to the alternate care settings 'different hospital', 'acute care facility', 'subacute care facility' or 'hospice/palliative discharge' is handled in a while on treatment strategy: see section 5.2.1

- The intercurrent event of discharge 'against medical advice' is handled in a hypothetical strategy: see section 5.2.1

Population-level summary measure:

Hazard ratio of 'Sustained clinical improvement' for experimental treatment versus placebo, from baseline until day 28.

5.2.3 Analysis Methods

All participants for which the trial is still ongoing at Day 28 and without sustained clinical improvement by Day 28 will be censored on Day 28. Participants that discontinue the study before day 28 will be censored at the last assessment of the CRS, unless they had an event of sustained clinical improvement prior to discontinuation. Participants that died at day 28 or earlier will be censored at day 28, irrespective of whether a clinical improvement occurred prior to death.

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

The primary hypothesis will be evaluated based on the Logrank test, stratified for the stratification factors (age [<65 and ≥65 years] and use of IMV [yes/no]). This test will be performed 2-sided at a 5% significance level. The actual values of the stratification factors will be used, not as randomized.

The hazard ratio of sustained clinical improvement for experimental treatment versus placebo, from baseline until day 28 will be considered as the population-level summary measure of the treatment effect for the primary estimand. The hazard ratio will be estimated in a Cox proportional hazards model stratified for the stratification factors and with treatment as a single covariate. A value larger than 1 indicates the chance of improvement is larger in the experimental treatment group. The 95% Wald confidence interval will be added.

The Log-rank test might generate a different p-value compared to that of the Wald test of the hazard ratio. The Logrank test will be used for formal inference (and not the Wald p-value or CI from the hazard ratio).

Cumulative proportion of patients with clinical improvement, by treatment, will be provided using the complement of the Kaplan Meier curve. The analyses will be completed with the median time to clinical improvement (if reached) and the proportion of participants who had their clinical improvement on day 7, 14, 21 and 28; all per Kaplan Meier method. The complementary log-log transform method is used to calculate the 95% confidence intervals.

As a sensitivity analysis, a Cox proportional hazards model will be estimated that is stratified for the stratification factors, but also adjusted for additional baseline covariates on top of treatment. The covariates are the following: CRS at baseline (<=3 vs > 3), Remdesivir at baseline (yes/no), Glucocorticoids at baseline (yes/no), Number of Comorbidities (0/1/2/≥3), Sex (Male/Female), Race (Asian/Black or African American/White/Unknown or Not reported), Ethnicity (Hispanic or Latino/Not Hispanic or Latino), Free IL-6 at screening, CRP at screening, ferritine at screening, LDH at screening (high/low/normal) and albumin (low/not low) at screening. Each of the additional baseline covariates will be added to the model to estimate the individual effect of these covariates, after which a stepwise selection method will be applied. A covariate will be added to the model if it is significant at the 25% significance level, while the covariate in the model has to be significant at the 0.15% level for it to remain in the model. The hazard ratio will be estimated in the final Cox proportional hazard model.

Comorbidities considered: Obesity (BMI>=30), Diabetes, Serious Heart Condition/Coronary Heart Disease, Chronic Obstructive Lung Disease, Chronic Kidney Disease and cancer.Time to sustained clinical improvement can be considered as a composite of two endpoints: time to improvement in the survivors as well as death by day 28. These two components will therefore also be analyzed separately. That is, the analyses described in the previous paragraph will be repeated in the subgroup of participants that do not die by day 28 and the analyses for the endpoint of death by day 28 are described in section 5.3.

At this moment it is difficult to predict whether prohibited medication will be used, in what frequency in the two treatment arms and what their efficacy might be. Therefore, the impact of prohibited meditation will be explored retrospectively.

Analyses of qualitative comparison between pre-interim analysis and post-interim analysis for treatment effect on the primary endpoint in the population with confirmed critical COVID-19 disease will be conducted to check the consistency in the study.

The primary analysis will be repeated for the ITT population, including the participants with severe confirmed COVID-19 disease.

5.3 Key Secondary Endpoints

5.3.1 Definitions

Similar as for the primary endpoint, the definitions as specified in section 5.2.1 will be used for the key secondary endpoints.

Clinical improvement at Day 28

Clinical Improvement is obtained if the score on the CRS improved with at least 2 categories at Day 28 with respect to the baseline score.

All-cause mortality up to Day 28

All-cause mortality is defined as score 6 on the CRS at Day 28.

5.3.2 Key Secondary Estimands

Clinical improvement at Day 28

Population: The population of interest are hospitalized patients between ≥18 and <85 years old with confirmed critical COVID-19 disease.

Endpoint: Sustained clinical improvement at Day 28 (yes/no)

Interventions: Received Sirukumab 5 mg/kg (IV single dose infusion on Day 1) and placebo (IV infusion on Day 1), both on top of SOC.

Intercurrent Events:

- Death as intercurrent event is handled in a composite strategy as it is the worst category on the clinical scale. Participants that died at Day 28 or earlier will be considered as failure (Sustained clinical improvement at Day 28=no), irrespective of whether a clinical improvement occurred prior to death.
- The intercurrent event of the use of prohibited medication is handled in a treatment policy strategy: data will be used as observed.
- The intercurrent event of discharge to the alternate care settings 'different hospital', 'acute care facility', 'subacute care facility' or 'hospice/palliative discharge' is handled in a while on treatment strategy: see section 5.2.1
- Participants that discontinue the study before Day 28 will be considered as failure (Sustained clinical improvement at Day 28=no), unless they had an event of sustained clinical improvement prior to discontinuation. In the latter scenario it will be considered a success (Sustained clinical improvement at day 28=yes).

Population-level summary measure:

The difference in proportion of participants with of 'Sustained clinical improvement at Day 28' for experimental treatment versus placebo.

All-cause mortality up to Day 28

Population: The population of interest are hospitalized patients between ≥18 and <85 years old with confirmed critical COVID-19 disease.

Endpoint: Death by Day 28 (Yes/No)

Treatment: Sirukumab 5 mg/kg (IV single dose infusion on Day 1) and placebo (IV infusion on Day 1), both on top of SOC.

Intercurrent events:

- The intercurrent event of the use of prohibited medication is handled in a treatment policy strategy: data will be used as observed.
- Participants that discontinue the study before Day 28 with a score > 1 on the CRS will be analyzed according to the composite strategy and will be considered as death on day 28 (Death by day 28=yes).

- Participants whose last score on the CRS was equal to 1 and that were not reported as having died before or at day 28 will be analyzed according to the composite strategy and they will be considered as alive (Death at Day 28=no).

Population level summary measure:

The difference in proportion of participants with 'Death by day 28' for experimental treatment versus placebo.

5.3.3 Analysis Method

The data will be analyzed according to the randomized treatment.

For the key secondary endpoints, the CMH analysis for difference in proportions, adjusted for the stratification factors (age [<65 and ≥65 years] and use of IMV [yes/no]) will be performed. The comparison between treatment groups will be based on CI-estimates and p-values obtained from this analysis.

A positive value on the common proportion (risk) difference using the Mantel-Haenszel method indicates that the proportion of participants with 'Sustained clinical improvement at day 28'/'death by day 28' is larger in the experimental treatment group. The actual values of the stratification factors will be used, not as randomized.

As a sensitivity analysis, a logistic regression model will be estimated that is adjusted for the treatment group, but also adjusted for additional baseline covariates. The covariates are the following: CRS at baseline (<=3 vs > 3), Remdesivir at baseline (yes/no), Glucocorticoids at baseline (yes/no), Number of Comorbidities (0/1/2/≥3), Sex (Male/Female), Race (Asian/Black or African American/White/Unknown or Not reported), Ethnicity (Hispanic or Latino/Not Hispanic or Latino), Free IL-6 at screening, CRP at screening, ferritine at screening, LDH at screening (high/low/normal) and albumin (low/not low) at screening. Each of the additional baseline covariates will be added to the model to estimate the individual effect of these covariates, after which a stepwise selection method will be applied. A covariate will be added to the model if it is significant at the 25% significance level, while the covariate in the model has to be significant at the 0.15% level for it to remain in the model. In the final logistic regression model the treatment difference in proportions will be estimated. This will be done as follows: in each treatment group the proportion of participants with improvement will be estimated using the average value observed the study (across treatment groups) for both the continues and categorical covariates (based on 0/1 coding for categorical). The delta method will be used for the confidence interval.

Comorbidities considered: Obesity (BMI>=30), Diabetes, Serious Heart Condition/Coronary Heart Disease, Chronic Obstructive Lung Disease, Chronic Kidney Disease and Cancer.

Analyses of qualitative comparison between pre-interim analysis and post-interim analysis for treatment effect on the key secondary endpoints in the population with confirmed critical COVID-19 disease will be conducted to check the consistency in the study.

The key secondary analyses will be repeated for the ITT population, including the participants with severe confirmed COVID-19 disease.

5.4 Other Secondary Endpoints

5.4.1 Definitions

CRS (As observed)

The CRS defined for the primary analysis is derived based on a combination of the hospitalization and oxygen supplementation status of the participant. More specifically, the status is considered as the status in which the participant would have been, according to the investigator, in case all circumstances were optimal. As an alternative measure, the CRS (As observed) will be derived using only the information on the actual status of the participant, ignoring alternative choices made because of lack of resources, participants choice and others.

Similar as for the derivation of the CRS, a participant will be evaluated in the same ordering of the categories as below. Once a participant fulfils the criteria for a category, the category is assigned to the participant and the evaluation stops. The actual hospitalization status will be considered in this derivation.

- **Score 6**: Based on the status of the participant on the day of the assessment (based on the date of death).

Based on Type of Oxygen Supplementation page:

- **Score 5**: At least one of the following scores is ticked:
  - IMV
  - Extra Corporeal Membrane Oxygenation
- **Score 4**:
  - Non-invasive mechanical ventilation (CPAP or BIPAP), high-flow nasal cannula, non-rebreather device or OxyMask is used at any time on the day, OR
- **Score 3:**
  - Receiving supplemental oxygen through a face mask, nasal cannula or other
- **Score 2:**
  - Hospitalized as reported
- **Score 1:**
  - Not hospitalized as reported: a distinction will be made between subjects 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 (As observed), for which score 1 will be used in both cases.

Further Definitions for Other Secondary Endpoint

Formulae to be used for derived variables, including data conversions, are provided in the tables below.

Measurement	Formula/Definition
Time to sustained improvement of at least 1 category relative to baseline on the 6-point ordinal CRS (up to Day 28) (days) [Time-to event]	Similar as for the primary endpoint, but with an improvement of 1 category (instead of 2 categories). The parameter name for the analysis will be *"Time to sustained improvement with at least 1 category on the CRS"*
Time to sustained improvement of at least 2 categories relative to baseline on the CRS (As observed) (up to Day 28) (days) [Time-to event]	Similar as for the primary endpoint, but with an improvement of at least 2 categories on the CRS (As observed). The parameter name for the analysis will be *"Time to sustained improvement with at least 2 categories on the CRS (As observed)"*
Time from study intervention to end of oxygen supplementation (up to Day 28) (days) [Time-to event]	The event of end of oxygen supplementation is obtained when a participant reaches a CRS score of 2 or 1.1, provided the event is not followed by a documented deterioration* up to and including day 28 or until trial discontinuation, whichever comes first. Participants who are discharged from hospital but reported as still in need of supplemental oxygen (score 1.2) will be censored on the day after hospital discharge, unless they die at or before day 28. Participants who discharge on score 1.2 and die at of before day 28 will be censored on day 28. Participants who are still hospitalized and on oxygen at day 28 will be censored on day 28. Participants who discontinue the trial before day 28 while still on oxygen will be censored on the day of discontinuation. * In the context of this endpoint, a score of 3,4,5,6 would imply a deterioration with respect to the event. The parameter name for the analysis will be *"Time to end of oxygen supplementation (up to Day 28) (days)"*
Time from study intervention to hospital discharge (up to Day 28) (days) [Time-to event]	Similar as for the primary endpoint, but with a score of 1.1 or 1.2 on the CRS (instead of an improvement of 2 categories). The parameter name for the analysis will be *"Time to discharge (or readiness to discharge) to home (up to day 28)"*

Time from study intervention to hospital discharge (up to Day 28) (days) among the surviving participants [Time-to event]	Similar as for the primary endpoint, but with a score of 1.1 or 1.2 on the CRS (instead of an improvement of 2 categories). This endpoint will be evaluated in the subgroup of participants who were still alive at day 28.
Time to Mechanical Ventilation (up to Day 28) (days) among participants not on mechanical ventilation at Baseline [Time-to event]	Similar as for the primary endpoint, but with a score of 5 on the CRS (instead of an improvement of 2 categories). Participants who did not evolve to score 5 and who die will be censored at the day of death. This endpoint will be evaluated in the subgroup of participants for which the CRS is less than 5 at Baseline.
Time from study intervention to ICU discharge (up to Day 28) among the participants on ICU at baseline (days) [Time-to event]	Subjects who die at or before day 28 will be censored on day 28. Subjects alive on day 28: Only ICU periods with a starting day <= day 28 are taken into account. Missing end dates of ICU periods are imputed with the cut-off date (for ongoing subjects) or the date of study discontinuation/completion - If last ICU stay end date < minimum(date visit day 28, study discontinuation, study completion), -> the subject has an event on the last day in the ICU + 1 day. - If last ICU stay end date >= minimum (date visit day 28, study discontinuation, study completion), -> the subject will be censored on minimum(day 28, day study discontinuation, day study completion).
Total length of hospitalization among the surviving participants (up to Day 28) (days) [Duration]	The total number of days a subject stayed in the hospital during the period from study drug intake until day 28, calculated as sum of the individual hospitalization periods, including re-hospitalizations. This endpoint will be evaluated in the subgroup of participants who were still alive at day 28 The total length of hospitalization will be missing for participants who discontinue the trial for other reason than death before day 28.
Number of ventilation free days in participants on IMV/ECMO at baseline (up to Day 28) (days) [Duration]	Calculated as: Date day 28 – maximum date of day with sore >=5 Participants who die will be considered as being on IMV/ECMO until day 28.

Improvement at day 28 on the CRS with at least 1 category at day 28 (or at discharge/discontinuation) [Incidence]	CRS improved with at least 1 category at day 28 (or at discharge/discontinuation) when compared to baseline (Yes/No)
Improvement at day 28 on the CRS (As observed) with at least 2 categories at day 28 (or at discharge/discontinuation) [Incidence]	The CRS (As observed) improved with at least 2 categories at day 28 (or at discharge/discontinuation) when compared to baseline (Yes/No)
CRS worsening relative to Baseline (up to Day 28) [Incidence]	CRS worsened with at least 1 category between day 5 and day 28 (Yes/No)
Ventilation free survival at Day of Discharge/Day 28 [Incidence]	CRS score 1, 2, 3 or 4 at Day 28. Participants with a missing score at Day 28 will not be considered
CRS at Day 7, 14, 21 and 28 [Proportions]	See section 5.2.1.

5.4.2 Analysis Methods

The secondary endpoint evaluation will be conducted on the primary and on the ITT population.

Time-to event parameters

The time-to-event parameters will be evaluated based on the log-rank test, stratified for the stratification factors (age [<65 and ≥65 years] and use of IMV [yes/no]). The tests will be performed 1-sided at a 5% significance level. The actual values of the stratification factors will be used, not as randomized.

Cumulative proportion of patients with an event, by treatment, will be provided using the complement of the Kaplan Meier curve. The analyses will be completed with the median time to event (if reached) and the proportion of participants who with an event on day 7, 14, 21 and 28; all per Kaplan Meier method. The complementary log-log transform method is used to calculate the 90% confidence intervals.

Duration parameters

Descriptive statistics of the duration parameters will be shown for all participants that were still alive at day 28.

Total length of hospitalization and number of ventilation free days will be analyzed in the subgroup of participants that were still alive at day 28 by using the Hodges-Lehman approach. Corresponding 90% CIs will be presented as well.

Incidence parameters

For each parameter the number and percentage of participants in each category and subcategory will be tabulated and listed. All participants in the applicable analysis set will be counted for the denominator of the proportion.

The occurrence (yes/no) as described for the incidence parameters will be analyzed using logistic regression as described above (section 5.3).

Proportions: CRS outcome and CRS (As observed) outcome

A tabulation will be made of the CRS and CRS (As observed) outcomes at each day, taking only non-missing values into account (i.e.: the percentages of the six categories per day should sum up to 100%).

A proportional odds model will be used as model to analyze the CRS and CRS (As observed) on days 7, 14, 21 and 28, modeling the common odds ratio of improvement on the ordinal scale of active treatment versus placebo using the 6-point CRS (scores 1.2 and 1.1 will be pooled into a single category 1) The model will include treatment, CRS at baseline (<=3 vs > 3) and the stratification factors. The proportional odds assumption in the treatment effect will be tested in a model that includes both separate slopes and common slopes for treatment. In case the validity of this model is questionable (eg. due to quasi-complete separation of data points), categories on the CRS will be merged (eg. category 2 with category 1). If the assumption of the proportional odds is acceptable, in a first step equal slopes (i.e. proportional odds) for the treatment effect only and unequal slopes for the other covariates, will be modeled. If this model cannot be estimated, a full proportional odds model will be applied, i.e. implying proportional odds for all covariates in the model. The common odds ratio from the final model will be considered as the estimate of the treatment effect. The actual values of the stratification factors will be used for all models, not as randomized. The proportional odds model will be defined in such a way that a common odds ratio smaller than 1 indicates larger improvement in the active treatment group.

If the assumption of the proportional odds would not hold for the treatment effect, the Van Elteren test will be used in a sensitivity analysis and the resulting p-value would be used in the formal testing.

Graphical displays and tabulations will be provided showing the proportion of subjects per CRS category and day. Also, shift tabulations will be provided of the CRS category over time versus the baseline CRS category

6 VIROLOGY ASSESSMENTS

6.1 General

Analysis of viral load is considered an exploratory analysis.

The virology assessments (copies/mL) will be analysed using ITT and Primary analysis sets.

SARS-CoV-2 viral load will be measured during the study by a qRT-PCR assay on Nasopharyngeal (NP) swabs, endotracheal aspirate (if participant is intubated) and on plasma samples.

6.2 Definitions

Baseline Value: For each of the assays, the baseline value of viral load is defined as the last measurement before the intake of the study drug. If no measurements are available prior to the dose of the study drug, then the first measurement obtained up to and including 60 minutes after the study dose will be considered as the baseline.

6.3 Data Handling Rules

In case there are multiple post-dose viral load measurements on a day for the same assay, then the highest value on that day will be used for the analysis.

All analyses on viral loads from central lab (Covance) will be performed after transforming the non-missing viral load measurements to $\log_{10}$ scale. In the database, the missing values are shown as 'Inconclusive', 'Indeterminate' or 'Not done' and will be excluded from the analysis.

The lower limit of quantification (LLOQ) values for assay on nasopharyngeal (NP) swabs and endotracheal aspirate are 1018 copies/mL, and for plasma samples it is 1660 copies/mL. The measurements below LLOQ may or may not be detectable. If the viral load measurements are below the LLOQ then these are imputed as 1 copy/mL if viral load is undetectable, or as LLOQ/2 if it is detectable.

6.4 Analysis Methods

Two summary tables showing N, mean, SE, median, inter-quartile range, minimum and maximum values over time of (1) viral loads ($\log_{10}$ scale) and (2) change from baseline (change in $\log_{10}$ values) will be generated. Over time tables will use all measurements (planned and unscheduled) for the NP assay at Baseline, Day 3, 7, 10, 14, 21, 28.

To compare the two treatment arms for the viral loads (only for assay of NP) over time 3 plots of viral loads ($\log_{10}$ scale) will be generated: (1) Mean values, (+/- SE), (2) Median/IQ values, and (3) Mean Change from baseline (+/- SE). Over time plots will use all (planned and unscheduled) measurements at Baseline, Day 3, 7, 10, 14, 21, 28.

For each participant, a plot showing viral loads ($\log_{10}$ scale) for Nasopharyngeal swabs, endotracheal aspirate and on plasma samples over time (all scheduled and unscheduled measurements) will be generated. To understand the viral load profiles properly, the LLOQs will be shown by horizontal reference lines. Study days of first onset of COVID-19 symptoms, of

discharge from hospital and of death will be shown by vertical reference lines on each plot. The CRS score at baseline will also be shown on the plot.

6.5 Analysis of Undetectability of Viral Load

For the analysis of undetectability of viral load all subjects with at least a post-baseline measurement of viral load by Nasopharynx assay will be considered.

For the primary analysis, all measurements of viral load up to Day 31 of the study (i.e. protocol window: Day 28+3 days) by the NP assay from central lab (central lab) will be used. Plots for individual participants will be generated using data up to Week 16.

Time (Days) to undetectability of virus load will be evaluated using the **First confirmed undetectability (CU)** approach as described below.

First confirmed undetectability (CU)

A participant is said to have (CU) of viral load if (1) participant has two consecutive undetectable viral loads, or (2) if the last viral load in the database is undetectable.

If there is at least one incidence of the CU then the date of the first undetectability among all CUs will be used to find the days from the study dose date to first CU of viral load. If there is no CU until study Day 31 then participant will be censored at date of last viral load assessment until study Day 31.

Following rules will be applied to derive the flags for event (of first CU) or censoring, and to derive the Days to event or censoring.

[For clarity, in the examples below of different cases a detectable viral load is denoted by 'D', and undetectable by 'U', and 'x' will represent any type of load (undetectable or detectable)].

(1) Case when a participant has only 1 viral load measurement in database (therefore it is also the last viral load measurement):

a. If the viral load is undetectable then censor flag = No (same as Event = Yes) [example: U => censor flag = No],

   Days to event = date of last viral load measurement – dose date + 1.

b. Otherwise if the viral load is detectable then censor flag = Yes (same as Event = No),
   [example: D => censor flag = Yes].

   Days to censoring = date of last viral load assessment – dose date + 1.

(2) Case when a participant has more than 1 viral load measurements in the database:

a. if there are no cases of 'CU cases based on 2 consecutive viral loads' then
   i.if last viral load in the database is undetectable then

censor flag = No (same as Event = Yes),
[example: $U_1DDU_2DU_3DU_4$ => censor flag = No],

ii. if last viral load in the database is detectable then
censor flag = Yes (same as Event = No),
[example: $U_1DDU_2DU_3D$ => censor flag = Yes],

In both these cases a(i) and a(ii), the 'Days to event/censoring' will be based on the date of last viral load measurement until study Day 31 in the database.

b. If there are one or more CU cases based on 2 consecutive viral loads then censor flag = No (same as Event = Yes),
and 'Days to event/censoring' will be derived using date of first viral load among the viral loads resulting in CU cases.

[examples: $DU_1D\underline{U_2U_3}D$ or $U_1D\underline{U_2U_3U_4}D\underline{U_5U_6}$ => censor flag = No,
and in both cases 'Days to event/censoring' = Days to U_2).]

Summary and Kaplan-Meier Analysis of Time to Undetectability of Viral Load:

The analysis of time-to first CU of viral load is planned by the Kaplan-Meier (KM) analysis. Days to first CU of viral load will also be summarized using the quartiles (and their confidence intervals). The analysis will be performed for ITT and Primary analysis sets. (Note: As per the inclusion criteria of the protocol all participants in the study are detectable for viral load at baseline. Therefore, all participants in the ITT and Primary analysis sets will be included for these analyses, respectively).

For the primary analysis, non-missing planned and unscheduled measurements will be used to generate the summary tables showing n and percentage (cumulative) of participants with CU by Day 3, 7, 10, 14, 21, 28/31. For the final analysis, table will also include Week 16.

6.6 Analysis of Virus Variants

SARS-CoV-2 viral genome sequence analysis will be performed using Next Generation Sequencing (NGS) using the ARTIC primers/protocol on Illumina platform to evaluate the presence polymorphisms and genetic variations on the amino acid level.

Sequence results will be presented only for the spike protein. The assignment of approximate lineages is based on the predefined set of S amino acid substitutions agreed with the known circulating lineages based on the GISAID database (https://www.gisaid.org/) and the CDC guidelines (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html).
The SARS-Cov-2 Variant of Concern (VOC) and the SARS-Cov-2 variants of Interest (VOI), listed on the timing of database lock, will be included in the analysis.

6.6.1 Time Points and Samples

Samples for viral sequencing are taken throughout the protocol Time&Event schedule, but sequencing is triggered at the discretion of the virologist considering the SARS-CoV-2 viral load levels and the limitations of the sequencing assays. By preference, the screening/baseline sample is selected. If the viral load of this sample is below the limit of detection of the sequencing assay, another sample as close as possible to the baseline timepoint, is selected.

For the statistical analysis, results from all available samples will be considered and data will not be reported by timepoint.

6.6.2 Definitions

Polymorphisms, ie genetic variations, are defined as amino acid changes from the SARS-CoV-2 Wuhan-Hu1 Reference Sequence.

Wild type: If at certain position the amino acid in the participant sequence matches the reference sequence, that is no genetic variation is present at that position, the virus is considered to be wild type at that position.

6.6.3 Parameters to Analyze

The following parameters will be analyzed:

Number (%) of participants with a specific virus variant specific substitution profile.

SARS-Cov-2 Virus Variants:

To classify SARS-CoV-2 S sequences into their most probable lineages the following predefined substitution profiles were used:

Variant Name	Spike Protein Substitutions	First Detected
B.1.526	T95I, D253G, D614G	United States (New York)
B.1.526.1	D80G, Δ144, F157S, L452R, D614G, D950H	United States (New York)
B.1.525	A67V, Δ69/70, Δ144, E484K, D614G, Q677H, F888L	United Kingdom/Nigeria
P.2	E484K, D614G, V1176F	Brazil
B.1.1.7	Δ69/70, Δ144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H	United Kingdom
P.1	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	Japan/Brazil
B.1.351	D80A, D215G, Δ241/242/243, K417N, E484K, N501Y, D614G, A701V	South Africa
B.1.427	L452R, D614G	United States (California)
B.1.429	S13I, W152C, L452R, D614G	United States (California)
B.1.617	L452R, E484Q, D614G	India
B.1.617.1	G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	India
B.1.617.2	T19R, Δ156, Δ157, R158G, L452R, T478K, D614G, P681R, D950N	India
B.1.617.3	T19R, G142D, L452R, E484Q, D614G, P681R, D950N	India

6.6.4 Analysis Methods

Frequencies and percentages will be presented for the variants detected. The denominator is the number of participants with sequencing data. Summaries will be provided by subgroup and intervention arm. Subgroups will be:

- Baseline CRS score (<=3, <=4, 4, 5)
- Center (US10006 and US10033, other)

Tabulation to investigate how the virus variants are spread during the entire study duration will also be provided.

7 BIOMARKERS

7.1 General

The biomarkers will be analysed using AST and Primary analysis sets.

The biomarkers are measured at scheduled visits during the study as mentioned in the protocol.

A table in section 7.2 below provides the list of biomarkers included for the analysis.

7.2 Data Handling Rules

Missing values will not be imputed and not used for the analysis. The measurements below the LLOQ will be imputed as LLOQ/2, and measurements above ULOQ by ULOQ.
In case measurements are not observed exactly on the scheduled days as per protocol, the measurements from adjacent days as shown below (as Measurement Day) may be used for the analysis. The measurement closest to the analysis day will be used. In case there are two measurements equidistant from the analysis day then the later of the two measurements will used for the analysis of different biomarkers, the table below provides the analysis day (target day) and the corresponding study days of measurements to be included in the windows.

Biomarker (Central lab)	**Study Days of Measurements**	**Analysis Day (Target Day)**
CRP D-Dimer Pro-calcitonin Serum Ferritin	2, 3	3
	4, 5, 6	5
	7, 8, 9	7
	12 to 16	14
	19 to 23	21
	26 to 30	28
Cytokines • Interferon Gamma • Interleukin 1 Beta • Interleukin 2 • Interleukin 4 • Interleukin 8 • Interleukin 10 • Interleukin 12p70 (or Interleukin 12) • Interleukin 13 • Tumor Necrosis Factor (or TNF-Alpha) **Chemokines** • Eotaxin-3 (or CCL26) • IP-10 (or IFNGIP10 or CXCL10)	4 to 6	5
	12 to 16	14
	19 to 23	21
	26 to 30	28

Biomarker (Central lab)	Study Days of Measurements	Analysis Day (Target Day)
• Macrophage Inflammatory Protein 1 Alpha (or CCL3) • Macrophage Inflammatory Protein 1 Beta (or CCL4) • Monocyte Chemotactic Protein 1 (or CCL2) • Monocyte Chemotactic Protein 4 (or CCL13) • Macrophage-Derived Chemokine (or CCL22) • TARC (or CCL17)		
Free IL-6 Total IL-6	12 to 16	14
	19 to 23	21
	26 to 30	28
SARS-CoV-2 Ab (IgA, IgG, IgM)	5 to 9	7*
	12 to 16	14
	19 to 23	21*
	26 to 30	28

* No samples are scheduled on these days, but window may include unscheduled visits or final visit.

7.3 Analysis Methods

7.3.1 Analysis of Biomarkers

Over time tables and plots will show the results at target days.

The baseline values of biomarkers will be summarized (see Section 4.1 for more details).

Biomarkers will be summarized over time showing n, Geometric Mean, SE of Geometric Mean, Median, IQR, Minimum, and Maximum. For post-baseline visits, tables will include descriptive statistics (n, Mean, SE, Median, Tertiles, IQR, Minimum, and Maximum) for ratio (visit value/ baseline value). Box plots of values over time will be provided displaying the actual values (using $\log_2$ scale on Y-axis) and presenting the geometric mean values. Box plots for ratio of visit value/baseline value ($\log_2$(visit value / baseline value)) over time will also be generated.

7.3.2 Analysis of SARS-CoV-2 Antibodies (Ab)

For each SARS-CoV-2 antibodies (IgA, IgG, IgM) a stacked bar chart with percentage of subjects with positive, negative or borderline results over time will be presented. Time points will be those as defined in section 7.2.

8 PHARMACOKINETICS (PK) AND IMMUNOGENICITY (IMG)

8.1 General

As mentioned earlier in section 2.2 of the SAP, the Pharmacokinetics (PK) analysis set includes all participants in the AST analysis set with no interruption of study medication and who also had

at least 1 valid blood sample drawn for PK analysis after dose of Sirukumab. The PK analysis will be performed using the PK analysis set and will exclude any participant who received the Placebo. The PK concentration of Sirukumab is evaluated pre- and post-dose on Day 1 and at Day 14, 21 and 28.

Serum samples to evaluate the antibodies to Sirukumab are collected on Day 1 pre-dose and on Day 28. As mentioned in section 2.2 the Immunogenicity (IMG) analysis set consists of participants in AST analysis set who received a dose (full or partial) of Sirukumab during the study and have at least one valid blood sample for immunogenicity analysis after Sirukumab dose, and will exclude any participant who received the placebo. This analysis set will be used to analyze immunogenicity using the actual treatment received by a participant (IMG analysis set as Treated).

8.2 Data Handling Rules

For the analysis of serum Sirukumab concentration, the concentration values below the LLOQ (= 0.1 ug/mL) will be imputed as 0 ug/mL, and all non-missing measurements (planned and unscheduled) will be used.

8.3 Analysis Methods

8.3.1 Analysis Methods for Pharmacokinetics

For participants in PK analysis set, descriptive statistics (n, mean, SD, coefficient of variation, median, range and IQR) of serum Sirukumab concentration (µg/mL) will be tabulated over time. The PK concentrations at scheduled visits (pre- and post-dose on Day 1, Day 14, 21 and 28) will be summarized in a table.

Descriptive statistics will also be tabulated by following baseline subgroups:

(1) By median baseline body weight (kg): <= median, and > median at baseline,
(2) By CRS score at baseline (<=3, 4, 5),
(3) By baseline Free IL-6 (ng/L) tertiles: <= 33%, > 33% and <= 66%, and > 66% percentiles at baseline, and
(4) By baseline CRP (mg/L) tertiles: <= 33%, > 33% and <= 66%, and > 66% percentiles at baseline.

(Note: participants with missing baseline values of subgroup variable will not be used for the subgroup analysis.)

Following plots (Y-axis using scale of $Log_{10,}$ and if mean of values at any visit becomes less than 0 then it will be shown as <0.01 on Y-axis) for serum Sirukumab concentration over time at scheduled visits (post- baseline on Day 1, Day 14, 21 and 28) will be generated:

(1) Mean and SD over time,
(2) Median and IQR over time,
(3) Median and IQR over time by CRS score at baseline (<= 3, 4, 5),
(4) Median and IQR over time by baseline Free IL-6 (ng/L) tertiles: <= 33%, > 33% and <= 66%, and > 66% percentiles at baseline), and

(5) Median and IQR over time by baseline CRP (mg/L) tertiles: <= 33%, > 33% and <= 66%, and > 66% percentiles at baseline).

It is possible that a few participants experienced some interruptions during the infusion of the study drug. If greater than 10 subjects had dose interruption, a sensitivity analysis is planned for the participants in the PK analysis set who did not have any such interruptions. Sensitivity analysis will include the descriptive statistics (n, mean, SD, coefficient of variation, median, range and IQR) of serum Sirukumab concentration (μg/mL) over time.

If data permit, the relationships between serum Sirukumab concentrations and biomarkers or efficacy may be analyzed graphically. If any visual trend is observed, a suitable population PK/PD model may be developed to describe the exposure-response relationship. The results of the population PK/PD analysis will be presented in a separate technical report.

8.3.2 Analysis Methods for Immunogenicity

Analysis of immunogenicity information will be performed using participants in IMG analysis set.

A participant is said to be positive for antibodies to Sirukumab if participant was positive for antibodies to Sirukumab at any time after Sirukumab administration until Day 28 of the study. A participant is classified as negative for antibodies to Sirukumab only if he/she was not positive at any time through Day 28 (that means participant must be negative for antibodies all through Day 28).

For participants who had 1 or more evaluable samples obtained after Sirukumab administration through study Day 28, a table showing number and percent of participants with positive results and negative results for antibodies to Sirukumab will be generated. Number of participants with peak titers will be shown in the table.

For Day 1 (pre- and post-dose), Day 14, 21 and 28 of the study, a table with summary statistics of serum Sirukumab concentrations (n, mean, SD, coefficient of variation, median, min and max) will be provided by participants with negative and positive for antibodies to Sirukumab.

A plot showing median and IQ range of serum Sirukumab concentrations over time by antibody status will be generated. Plots showing median and IQ range of serum Sirukumab concentrations over time by antibody status will be generated by the following subgroups:

(1) Median and IQR over time by baseline Free IL-6 (ng/L) tertiles: <= 33%, > 33% and <= 66%, and > 66% percentiles at baseline), and
(2) Median and IQR over time by baseline CRP (mg/L) tertiles: <= 33%, > 33% and <= 66%, and > 66% percentiles at baseline).

A listing of participants positive for antibodies to Sirukumab any time through Day 28 will be generated.

9 SAFETY

All safety analyses will be performed on the AST and Primary analysis sets.

The safety assessments to be evaluated include AEs, clinical laboratory tests, vital signs, and electrocardiogram (ECG).

Deaths during the study are evaluated as an efficacy endpoint.

9.1 Adverse Events (AE)

9.1.1 General

All adverse events and special reporting situations, whether serious or non-serious, are recorded on eCRF 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 the follow-up of safety.

9.1.2 Definitions

Coding of an AE

The verbatim terms used in the eCRF by investigators to identify AEs will be coded (for system organ class (SOC-Med) and preferred term (PT)) using the Medical Dictionary for Regulatory Activities (MedDRA).

Phase allocation of an AE

AEs will be allocated to different study phases based on their start date/time. (Note: In addition to the date information, time information is also taken into account to allocate AEs to phases.)

In general, the following rule is used to allocate a phase to an AE:

Rule: phase start date/time ≤ AE start date/time ≤ phase end date/time

If the start date/time of an AE is before the start of the treatment phase, then it is allocated to the screening phase. If AE onset is on or after the treatment phase start date/time and prior to follow-up phase start date/time, then AE is allocated to treatment phase. If AE onset date/time is on or after the start of follow-up phase, then AE is allocated to follow-up phase. In case of incomplete AE dates and or times (i.e. time and/or day and/or month and/or year missing) the following conventions are used:

- In case of partial AE start dates and or times, the events are allocated to the phases using the available partial information on start and end datetime; no imputation will be done. If, for instance, for the AE start date only month and year are available, these data are compared to the month and year information of the phases. This rule may result in an AE to be allocated to more than one phase. In case of a completely missing AE start date, the event is allocated to the treatment phase, except if the end date of the AE falls before the start of the treatment phase.
- In case of a completely missing AE end date, the following rules apply:
  - in case the date is identified as unknown then date will remain as missing,

- in case the date is not flagged as unknown the date is assumed to be the cut-off date of the analysis for participants still ongoing in the study, and the end date of the last phase for participants who discontinued or completed the study.

Examples:

Screening phase: start date: 02JAN2017, end date: 28JAN2017
Treatment phase: start date: 29JAN2017, end date: 12AUG2017

1) Adverse event: start date: JAN2017, end date: 15JUL2017
   As the AE start date only has information about month and year, only this information will be used from the phases and therefore the AE will be assigned to the screening phase as well as to the treatment phase.
2) Adverse event: start date: JAN2017, end date 27JAN2017 As the AE ends before or at the start of the treatment phase, it is only assigned to the Screening phase.

Attributes of an adverse event

For the analysis, the following attributes are assigned to an adverse event:

- Study Phase of an AE (Screening, Treatment and Follow-up phase),
- Verbatim Term, SOC-Med and PT,
- Serious AE (Yes/No), if yes AEs will be listed as well,
- AE grade (Grades 1, 2, 3, and 4),
- Relation to study treatment (related, not related),
- Outcome of AE (Fatal, Recovered/Resolved, not recovered/not resolved, recovering/resolving, unknown),
- AE leading to death (Yes/No),
- AE of special interest (Serious Infections, Hypersensitivity, Hematologic Events, Liver Enzymes).

9.1.3 Analysis Methods

There will be no formal statistical testing for the AEs.

A summary table will be generated for the following attributes of AEs for 2 study phases (treatment phase, follow-up phase):

- any AE,
- serious AEs,
- AEs leading to death,
- AEs with grade >= 3,
- AEs with grade >= 3 and related to study drug,
- AEs related to study drug,
- AEs of special interest,
- AEs of special interest and related to study drug.

AE incidence tables will be generated showing the SOC-Med and PT separately in two phases (treatment and follow-up), in descending order of frequency in Sirukumab treatment arm. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized. The tables will be provided for the following attributes:

- AEs by SOC-Med and PT,
- Serious AEs by SOC-Med and PT,
- AEs of special interest,
- AEs related to study drug,
- AEs with Grade >= 3,
- AEs leading to death.

Separate listings of participants with serious AE, AEs leading to death and AE >=3 grade and AE related to study drug will be generated.

A table showing number of participants with SOC-Med of Infection and Infestation vs Lymphocytopenia Grade 3-4 during treatment phase will be generated.

Subgroup Analysis:

Tables for the following AE attributes will be generated by 2 subgroups: (Age: < 65, >= 65 years, CRS score at baseline: <=3, <=4, 4, 5).

- Serious AEs,
- AEs of special interest, AEs related to study drug,
- AEs with Grade >= 3,
- AEs leading to death.

9.2 Clinical Laboratory Tests

9.2.1 General

The laboratory parameters are measured pre- and post-dose multiple times during the study. Some of these parameters are considered biomarkers for this study and their analyses are described in Section 7 “Biomarkers” of this document. This section describes the analyses of laboratory parameters whose test samples are collected at local labs and are not described under biomarkers.

9.2.2 Data Handling Rules

For lab tests from local labs the local lab reference ranges will be used to determine the lab abnormalities.

Imputations of numerical values expressed as characters

In case a laboratory test result is censored (no numeric value is available, but only a verbatim term), the following rules are applied:

- ‘<x’ or ‘>x’: a numeric value will be imputed by the cut-off value decreased or increased with one unit respectively

- '≤x' or '≥x': imputation by x.

Toxicity grades and abnormalities for laboratory parameters

The laboratory toxicity will be determined according to the criteria specified in the adult toxicity grading table by 'Division of Microbiology and Infectious Diseases' (DMID). In case no toxicity grades are defined for a test, the abnormalities (above/below normal range) will be used.

In determining toxicity grades/abnormalities for each subject the following rules are applied:

- Baseline toxicity grade/abnormality will be based on the baseline value (see section 4.1 for the baseline definition).
- Worst grades/abnormalities during treatment phase are determined over the treatment phase, including all scheduled and unscheduled measurements of that phase.
- The abnormalities "abnormally low" and "abnormally high" are considered equally important, i.e. if a subject has an abnormally low as well as an abnormally high value post-baseline, both abnormalities will be shown in the tables. (This implies that the sum of the percentages can be more than 100%).
- If, for a specific test, the grading list provides distinct limits for abnormally low (=hypo) values as well as for abnormally high (=hyper) values, this test should be repeated for hyper and hypo limits separately in cross-tabulations.

Treatment-emergent definition for toxicity grades and abnormalities

A toxicity grade/abnormality will be considered treatment-emergent if it is worse than the baseline grade/abnormality. If the baseline grade/abnormality is missing, the abnormality is always considered as treatment-emergent. A shift from "abnormally low" at baseline to "abnormally high" post-baseline (or vice versa) is also treatment-emergent.

9.2.3 Analysis Methods

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 a defined toxicity grades) during treatment phase will be generated.

A shift table showing the number and percent of participants with different toxicities at baseline vs treatment phase will be presented for lab tests with defined toxicity grades.

Shift tables showing n and percent of participants with various levels of abnormalities for Troponin-I and -T during treatment phase versus baseline will be generated.

Two eDISH plots showing peak total bilirubin vs peak ALT (and separately for peak AST) measurements during the treatment phase will be generated. Peak values (using $\log_{10}$ scale) on the plot will show the maximum values that occur post-baseline during treatment phase (not necessarily concurrent events). Points on the plot will be distinguished for the two treatment groups. Two reference lines at 2xULN for total bilirubin and at 3xULN for ALT/AST will be shown on the plots. These reference lines will divide the plot into 4 sections showing (1) Hyperbilirubinemia, (2) Hy's Law range, (3) Normal range, and (4) Temple's Corollary range.

A listing of participants with treatment-emergent toxicities/abnormalities will be provided. This listing will include all other timepoints for the corresponding participant/lab test.

A listing of participants with Grade 3 or higher toxicity laboratory values will be provided.

9.3 Vital signs

9.3.1 General

Temperature, pulse rate, respiratory rate, oxygen saturation and blood pressure may be measured once or multiple times during screening/baseline and every day during the treatment phase.

9.3.2 Data Handling Rules

Because of the participants' disease severity, the vital signs may be measured in any position (supine, standing, semi-recumbent, or sitting). For the analysis all measurements irrespective of the position during the assessment will be considered.

All non-missing measurements will be considered for finding the worst abnormalities on a given study day or during the treatment phase.

Vital Signs abnormalities will be determined according to the WHO grading scale boundaries as mentioned in Attachment 1.

For each participant, baseline abnormality will be based on the baseline value (see section 4.1 for the baseline definition). The worst abnormality is determined for the treatment phase. All measurements including all post-baseline scheduled and unscheduled measurements during treatment phase will be used to evaluate worst abnormality during the treatment phase.

An abnormality (based on normal ranges) will be considered treatment-emergent if it is worse than the baseline abnormality. If the baseline abnormality is missing, the abnormality is always considered as treatment-emergent. A shift from "abnormally low" at baseline to "abnormally high" post-baseline (or vice versa) is also considered treatment-emergent.

9.3.3 Analysis Methods

A table showing number and percentage of participants with treatment-emergent worst abnormality during the treatment phase will be generated.

Vital signs data for participants having at least one treatment-emergent abnormality during treatment phase will be listed.

9.4 Electrocardiogram (ECG)

9.4.1 General

ECG measurements (in supine position) for PR interval, QRS interval, Heart Rate (HR) and QTc intervals (using Bazett's correction formula and Fridericia's correction formula) during screening and treatment phases are recorded on the eCRF.

9.4.2 Definitions

Treatment-emergent Abnormalities

ECG abnormalities will be determined according to the boundaries defined in Attachment 2.

For each participant, baseline abnormality (i.e., assessments that are out of normal ranges) will be based on the baseline value (see section 4.1 for the baseline definition). An abnormality during treatment phase will be considered treatment-emergent if it is worse than the baseline abnormality. If the baseline abnormality is missing, the abnormality is always considered as treatment-emergent. A shift from "abnormally low" at baseline to "abnormally high" post-baseline (or vice versa) is also considered treatment-emergent.

9.4.3 Data Handling Conventions

Investigator reported ECG related values (irrespective of the participant's position at ECG evaluation) on the eCRF will be used for analysis without any recalculation. If on a day the ECG is performed multiple times, then for descriptive statistics the mean of the non-missing post-dose ECG evaluations will be used as the value for each specific parameter and study day.

All measurements at scheduled and unscheduled visits during the treatment phase will be considered in determining worst case values during the treatment phase.

9.4.4 Analysis Methods

Number and percent of participants in different categories of worst (and if treatment emergent) ECG abnormalities during treatment phase will be tabulated. The ECG abnormalities based on the change from baseline QTc values will be tabulated. Tables to show the shift from baseline to maximum corrected QT interval (actual values and change from baseline values) during treatment phase will be provided. A table showing shift in frequencies of ECG Interpretations reporting 'ST or T Waves, Ischemia or Infarction' from baseline values (Yes, No, or missing) to post-base values (Yes, No, or missing) will be generated.

Listings of ECG values and Troponin I/T; of participants with Abnormal ST or T Wave, Ischemia, or Infarction; and with ECG abnormalities will be generated.

ATTACHMENTS

ATTACHMENT 1. WHO GRADING SCALE VITAL SIGNS

The following abnormalities are defined for vital signs:

Vital Signs parameter			
Abnormality Code	**Pulse**	**DBP***	**SBP***
Abnormally low	< 45 bpm	≤ 50 mmHg	≤ 90 mmHg
Grade 1 or mild	-	> 90 mmHg - < 100 mmHg	> 140 mmHg - < 160 mmHg
Grade 2 or moderate	-	≥100 mmHg - < 110 mmHg	≥160 mmHg - < 180 mmHg
Grade 3 or severe	-	≥ 110 mmHg	≥ 180 mmHg
Abnormally high	≥ 120 bpm	-	-

* The classification of AEs related to hypotension and hypertension will be done according to the WHO grading scale

Abnormality Code	Vital Signs parameter	
	Temperature (°C/°F)	**Respiratory rate (breaths per minute)**
Grade 1 or mild	> 38.0 -<= 38.6 °C or > 100.4 - <= 101.5 °F	17-20
Grade 2 or moderate	> 38.6 - <= 39.3 °C or > 101.5 - <= 102.7 °F	21-25
Grade 3 or severe	> 39.3 - <= 40.0 °C or > 102.7 - <= 104.0 °F	>25
Grade 4 or potentially life-threatening	>40.0°C or > 104.0°F	

ATTACHMENT 2. ECG ABNORMALITIES

The following abnormalities are defined for ECG:

Abnormality Code	ECG parameter			
	HR	**PR**	**QRS**	**$QT_{corrected}$**
Abnormalities on actual values				
Abnormally low	< 45 bpm	< 110 ms	-	-
Abnormally high	≥ 120 bpm	> 220 ms	≥ 120 ms	-
Borderline prolonged QT (males)	-	-	-	450 ms < QTc ≤ 480 ms
Borderline prolonged QT (females)	-	-	-	470 ms < QTc ≤ 480 ms
Prolonged QT	-	-	-	480 ms < QTc ≤ 500 ms
Pathologically prolonged QT	-	-	-	QTc > 500 ms
Abnormalities on changes from baseline (ΔQTc)				
Normal QTc change	-	-	-	ΔQTc < 30 ms
Borderline QTc change	-	-	-	30 ms ≤ ΔQTc ≤ 60 ms
Abnormally high QTc change	-	-	-	ΔQTc > 60 ms

ATTACHMENT 3. CRS DERIVATION

The CRS categories should be evaluated from 6 to 1. First check if the subject falls in category 6 (has the subject died?) if not then we evaluate category 5, if not 5 then evaluate category 4 and so on.
The CRS is evaluated at baseline and per day, relative to the start of the study drug intake.
The baseline CRS is based on the data obtained at the time of randomization.

Notes:

- The CRS scores will be calculated up to day 28 for subjects who are still in the trial at day 28. Participants who die before they discontinued the trial before day 28 will be considered to continue the trial up to and including day 28.
- If the subject has different types of oxygen supplementation on a single day, the worst type will be considered to derive the score.
- In case the subject withdrew from the study for other reason than death, the CRS will not be calculated from the next day onwards. A record indicating this type of missing scores should be foreseen in the ADAM data sets.
- Intermittent missing values can occur (eg. Due to incomplete supplementary oxygen information). For intermittent missing values, a record should be foreseen in the adam dataset. It should be possible to make the distinction between this type of missing values and the missing values due to trial discontinuation.

Hospitalized and Not Hospitalized
Rules will be applied in the order as described below. The first rule fulfilled by a subject will be considered.

1. If a subject is discharged to the alternate care settings “2. Different hospital”, “3. Acute Care Facility”, “4. Subacute care facility” or “7. Hospice/Palliative Discharge”, the subject will be considered hospitalized until day 28 or until trial discontinuation. The subject will be categorized in the category the subject was in at the moment of discharge.

2. If a subject is discharged ‘against medical advice’, the subject will be considered hospitalized on the day of discharge and on the day after discharge (unless the subject discontinued the trial). The subject will be categorized in the category the subject was in at the moment of discharge. The CRS will be considered missing on subsequent days.

3. If a subject is hospitalized, but is ‘ready for discharge’ according to the investigator, the subject will be considered hospitalized up to and including the first day on which the subject was considered ready for discharge. The subject will be considered “Not hospitalized” from the day after until day 28/trial discharge (unless the status changes back to “not ready for discharge”).

4. If a subject is discharged, but is ‘not ready for discharge’ according to the investigator, the subject will considered hospitalized up and including 1 day after the day of discharge or until trial discontinuation. The subject will be categorized in the category the subject was in at the moment of discharge. The subject will be considered non hospitalized from 2 days after the day of discharge onwards until day 28/trial discontinuation.

5. If a subject is discharged from the hospital, the day of discharge will be considered as “hospitalized”. The subject will be categorized in the category the subject was in at the moment of discharge. After this day, the subject will be considered “Not hospitalized” until day 28/trial discontinuation.

CRS Derivation

The Ordinal Clinical Recovery Scale can be derived from Baseline up to and including Day 28, or until trial discontinuation. Participant who died before day 28 (before or after hospital discharge, but before trial discontinuation) will be considered to continue the trial up to and including day 28.

For the derivation, we will start with the highest score.

If the subject didn't fall into this category, we will check for the next highest score.

- **Score 6**: Based on the status of the participant on the day of the assessment (based on the date of death).

Based on Type of Oxygen Supplementation page:

- **Score 5**: At least one of the following scores is ticked:
  - IMV
  - Extra Corporeal Membrane Oxygenation
  - The question "Is the subject on Mechanical Ventilation" is answered "No", and the question "From a Medical Perspective, should the patient be on IMV?" is answered "Yes". (on Subject Status Form)*

* To comply with the note: "*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"*

- **Score 4**:
  - Subject is on supplemental oxygen and the FiO2 is >=50%.
- **Score 3:**
  - Hospitalized & **requiring low flow supplemental oxygen, defined as**
    - Receiving supplemental oxygen (through a face mask, nasal cannula, high flow nasal canula or other where FiO2 is < 50%) & the patient was not able to sustain a blood oxygen saturation of >93% when breathing room air:
      - If assessed for blood oxygen saturation when breathing room air, SpO2 value should be <=93%
      - If not assessed for blood oxygen saturation when breathing room air (for any reason), SpO2 value is assumed to be <=93

    OR
    - Not on supplemental oxygen and the minimum of all measured SpO2 values during the day <= 93% (as this will be measured at least 4 times/day)
- **Score 2:**
  - Hospitalized according to hospitalization rules as discussed earlier.
- **Score 1:**
  - Not hospitalized, including subjects on low level of oxygen.

A distinction will be made between subjects 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.

Some examples

Case 1: Discharged from hospital on Day 6 (Rule 5)

Case 1	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 to Day 28
Against medical advice?				--/NO		
Status (SS*)	hospitalized	hospitalized	hospitalized	Discharged		
Discharged to**				1/5/..		
ready (SS*)	--/Not ready	--/Not ready	--/Not ready	--/Ready		
CRS	>1	>1	>1	>1	1	1

Case 2: Alternate care setting (rule 1): hospitalized until Day 28

Case 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 to Day 28
Against medical advice?				--/NO/YES		
Status(SS*)	Hospitalized	hospitalized	hospitalized	Discharged		
Discharged to**				2/3/..		
ready (SS*)	--/Not ready	--/Not ready	--/Not ready	--/Ready/ Not ready		
CRS	>1	>1	>1	>1	>1	>1

Case 3: Against medical advice (rule 2): hospitalized on Day 6 and 7, missing thereafter

Case 3	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 to Day 28
Against medical advice?				YES		
Status(SS*)	hospitalized	hospitalized	hospitalized	Discharged		
Discharge to**				1/5/..		
ready (SS*)	--/Not ready	--/Not ready	--/Not ready	--/Ready/ Not ready		
CRS	>1	>1	>1	>1	>1	Missing

*SS = Subject Status
1= not hospitalized; > 1 = hospitalized
** 1=Patient's Home; 2=Different Hospital; 3=Acute Care Facility;4=Subacute care facility
5=Long-Term Facility; 6=Rehab Facility; 7=Hospice/Palliative Discharge; 8=Other

Case 4: Ready for discharge at Day 5 (rule 3)

Case 4	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 to Day 28
Against medical advice?					--/NO	
Status(SS*)	hospitalized	hospitalized	hospitalized	hospitalized	Discharged	
Discharge to**					1/5/..	
ready (SS*)	--/Not ready	--/Not ready	Ready	--/Ready	--/Ready	
CRS	>1	>1	>1	1	1	1

Case 5: Discharged from hospital on Day 6, but not ready for dicharge (Rule 4)

Case 5	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 to Day 28
Against medical advice?				--/NO		
Status(SS*)	hospitalized	hospitalized	hospitalized	Discharged		
Discharged to**				1/5/..		
ready (SS*)	--/Not ready	--/Not ready	--/Not ready	Not ready		
CRS	>1	>1	>1	>1	>1	1

Case 6: Ready for discharge at Day 5, Not ready for discharge at Day 6 (rule 3) Discharged from hospital on Day 7 (Rule 5)

Case 6	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 to Day 28
Against medical advice?					--/NO	
Status(SS*)	hospitalized	hospitalized	hospitalized	hospitalized	Discharged	
Discharge to**					1/5/..	
ready (SS*)	--/Not ready	--/Not ready	Ready	Not ready	--/Ready	
CRS	>1	>1	>1	>1	>1	1

*SS = Subject Status
1= not hospitalized; > 1 = hospitalized
** 1=Patient's Home; 2=Different Hospital; 3=Acute Care Facility;4=Subacute care facility
5=Long-Term Facility; 6=Rehab Facility; 7=Hospice/Palliative Discharge; 8=Other

Case 7: Ready for discharge at Day 4, Not ready for discharge at Day 5 (rule 3) Discharged from hospital on Day 6, but not ready for discharge (Rule 4)

Case 7	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 to Day 28
Against medical advice?				--/NO		
Status(SS*)	hospitalized	hospitalized	hospitalized	Discharged		
Discharge to**				1/5/..		
ready (SS*)	--/Not ready	Ready	Not ready	Not ready		
CRS	>1	>1	>1	>1	>1	1

Case 8: Ready for discharge at Day 4, Not ready after ready at Day 6 (Rule 3) Discharged from hospital on Day 6, but not ready (Rule 4)

Case 8	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 to Day 28
Against medical advice?				--/NO		
Status(SS*)	hospitalized	hospitalized	hospitalized	Discharged		
Discharge to**				1/5/..		
ready (SS*)	Not ready	Ready	--/Ready	Not ready		
CRS	>1	>1	1	>1	>1	1

Case 9: Ready for discharge at Day 5 (rule 3)

Case 9	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 to Day 28
Against medical advice?					--/NO	
Status(SS*)	hospitalized	hospitalized	hospitalized	hospitalized	Discharged	
Discharge to**					1/5/..	
ready (SS*)	--/Not ready	--/Not ready	Ready	--	--/Ready	
CRS	>1	>1	>1	1	1	1

*SS = Subject Status
1= not hospitalized; > 1 = hospitalized
** 1=Patient's Home; 2=Different Hospital; 3=Acute Care Facility;4=Subacute care facility
5=Long-Term Facility; 6=Rehab Facility; 7=Hospice/Palliative Discharge; 8=Other

Case 10: Rule 3 (ready at day 6)

Case 10	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 to Day 28
Against medical advice?					--/NO	
Status(SS*)	hospitalized	hospitalized	hospitalized	hospitalized	Discharged	
Discharge to**					1/5/..	
ready (SS*)	Not ready	Not ready	Not ready	Ready	--/Ready	
CRS	>1	>1	>1	>1	1	1

Case 11: Not ready after ready (Rule 3)
Discharged while not ready on Day 6 (Rule 4)

Case 11	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 to Day 28
Against medical advice?				--/NO		
Status(SS*)	hospitalized	hospitalized	hospitalized	Discharged		
Discharge to**				1/5/..		
ready (SS*)	Not ready	Not ready	Ready	Not ready		
CRS	>1	>1	>1	>1	>1	1

Case 12: Ready for discharge at Day 5 (rule 3)
Alternate care setting (rule 1): hospitalized until Day 28

Case 12	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 to Day 28
Against medical advice?				--/NO		
Status(SS*)	hospitalized	hospitalized	Hospitalized	Discharged		
Discharge to**				2/3/..		
ready (SS*)	--/Not ready	Ready	--	--/Ready		
CRS	>1	>1	1	>1	>1	>1

*SS = Subject Status
1= not hospitalized; > 1 = hospitalized
** 1=Patient's Home; 2=Different Hospital; 3=Acute Care Facility;4=Subacute care facility
5=Long-Term Facility; 6=Rehab Facility; 7=Hospice/Palliative Discharge; 8=Other