NOVARTIS

Clinical Development

ACZ885/Canakinumab/Ilaris®

CACZ885D2310 / NCT04362813

Phase 3 multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of canakinumab on cytokine release syndrome in patients with COVID-19-induced pneumonia (CAN-COVID)

Statistical Analysis Plan (SAP)

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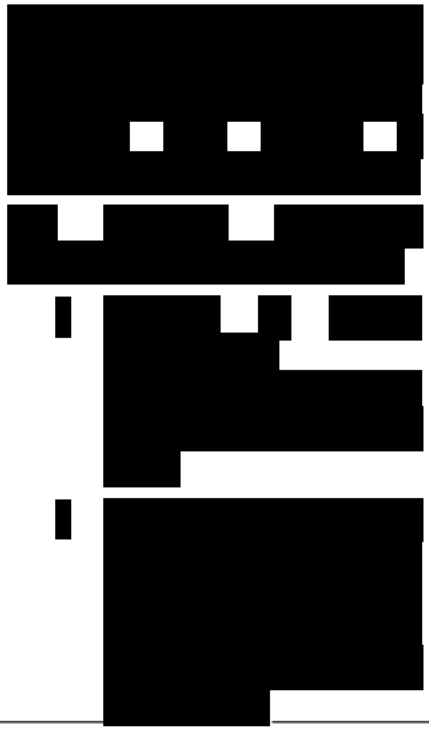
Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
24-Apr-2020	Prior to FPFV	Creation of final version	First version	NA
17-Jun-2020	[redacted]	[redacted]	[redacted]	[redacted]
		Added Hungary and Russia to the region of Europe		2.1 Data analysis general information
		Included misrandomized patients in the FAS per FDA request		2.2 Analysis sets and 5.4 Rule of exclusion criteria of analysis set
		Additional factors for subgroup analyses is added		2.2.1 Subgroup of interest
		The age categories for baseline summary have been updated to break >=65 years to 65-75 and >=75 Added baseline summary on PaO2/FiO2 Deleted Chest x-ray or CT scan interstation since all patients will be abnormal at baseline		2.3 patient disposition, demographics and other baseline characteristics
		Added a supplementary estimand for the primary endpoint per FDA request Specified that early drop outs before Day 3 will be excluded from the analysis on the primary estimand		2.5 Analysis of the primary estimand

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Biomarker parameters will be summarized based on data with LOCF		2.7 Analysis of secondary efficacy objective(s)
		A summary on abnormal liver function parameters is added Summary on SARS-CoV-2 virus test from central lab is added Since the summary tables are added, the listings on the lab data and the virus testing results are deleted		2.8 Safety analysis
				
		Other administrative updates and minor updates for clarifications		
16-Oct-2020	Before Day 29 DBL	Criteria for abnormal liver function parameters are updated per liver safety guidance	Amendment 2	2.8 Safety analysis

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		[redacted]		[redacted]
		Updated the subgroups to align with the evolving SoC and data sharing request		Sections 2.2.1 and 2.9.1
		Other updates to clarify the previously specified analyses, to deal with unexpected data collection issues, or to address the review comments from Dry runs		Various sections
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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List of abbreviations

AE	Adverse event
AESI	AE of Special Interest
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Anatomical Therapeutic Classification
CI	Confidence Interval
CFR	Case Fatality Rate
COVID-19	Coronavirus disease 2019
CRP	C Reactive Protein
CRS	Cytokine Release Syndrome
CSR	Clinical Study report
CV	Coefficient of variation
DBL	Database lock
DMC	Data Monitoring Committee
EoS	End of Study
FAR	First analysis report
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
ICU	Intensive care unit
IV	Intravenous
LDH	Lactate dehydrogenase
LLOQ	lower limit of quantification
LOCF	Last Observation Carry Forward
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MH	Medical History
OR	Odds ratio
PD	Protocol Deviation
[redacted]	[redacted]
PT	Preferred Term
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard deviation
SoC	Standard of Care
SOC	System Organ Class
TFL	Table/Figure/Listing
ULOQ	upper limit of quantification
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of statistical analyses for the Day 29 First Interpretable Results (FIR) and First Analysis Report (FAR) as well as the final report including all the analyses conducted at the Day 29 database lock (DBL) and new analyses including safety follow up data in the final DBL at the end of the study. The analyses to be conducted for FAR or the primary publications at the time of Day 29 will be identified on the Table/Figure/Listing (TFL) shell document.

The SAP should be finalized before the Day 29 DBL after all patients either completed Day 29 assessment or discontinued early from the study before Day 29. Any changes to the SAP after approval will be documented.

The following documents were referenced while writing this SAP:

CACZ885D2310 Clinical Trial Protocol Final version 00 dated 10-April-2020

CACZ885D2310 Clinical Trial Protocol Final version 01 amendment dated on 01-June-2020

Important information is given in the following sections and details are provided, as applicable, in Section 5 Appendix.

1.1 Study design

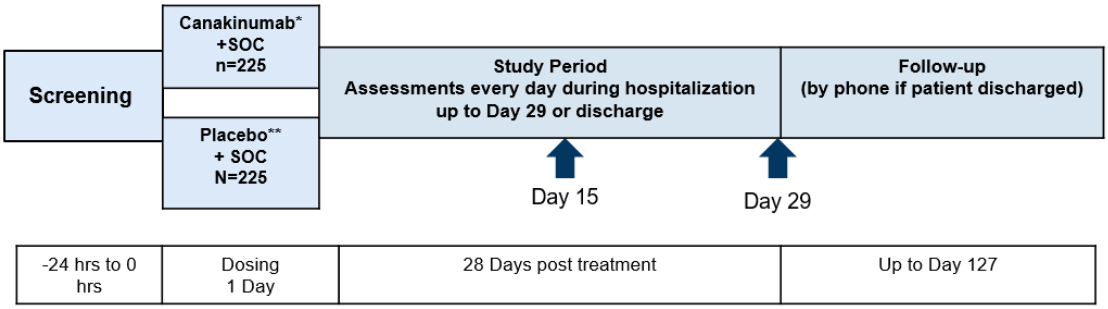
This is a multicenter, double-blind, randomized, placebo-controlled study to assess the efficacy and safety of canakinumab plus standard of care (SoC) compared with placebo plus SoC in adult patients with SARS-CoV-2 virus-induced pneumonia and CRS (Figure 1-1).

The study aims to randomize approximately 450 patients worldwide. Randomization is stratified by country to ensure a balanced allocation of patients to treatment groups within the strata. Enrollment will stop as soon as the target number of randomized patients is reached.

Patients who meet the inclusion/exclusion criteria will be randomized in a 1:1 ratio to either canakinumab + SoC or placebo + SoC and can be dosed immediately after ensuring that the patient has met all eligibility criteria. Patients in the canakinumab arm will be dosed on Day 1 with canakinumab 450 mg for body weight of 40-<60 kg, 600 mg for 60-80 kg or 750 mg for >80 kg) in 250 mL of 5% dextrose infused intravenously (IV) over 2 hours. Patients in the placebo arm will be treated with 250 mL of 5% dextrose infused IV over 2 hours.

Patients who do not meet the criteria for participation in this study (screen failures) will not be re-screened.

Figure 1-1 Study design



Study Treatment:
*Canakinumab 450 mg for body weight 40-<60 kg, 600 mg for 60-80 kg or 750 mg for >80 kg) in 250 mL of 5% dextrose infused IV over 2 hours
** 250 mL of 5% dextrose infused IV over 2 hours

Safety monitoring will be conducted at weekly intervals during the study using a data monitoring committee (DMC). The analysis plan for the DMC will be created separately.

1.2 Study objectives and endpoints

Study objectives and related endpoints pre-specified in the protocol are described in Table 1-1 below.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective To demonstrate the benefit of canakinumab + standard of care (SOC) in increasing chance of survival without ever requiring invasive mechanical ventilation among patients with COVID-19-induced pneumonia and CRS	**Endpoint for primary objective:** Clinical response, defined as survival without ever requiring invasive mechanical ventilation from Day 3 (inclusive) up to Day 29 (inclusive).
Secondary Objective(s) To demonstrate the benefit of canakinumab in reducing 4-week case fatality rate (CFR) among patients with COVID-19-induced pneumonia and CRS regardless of other subsequent clinical interventions	**Endpoint(s) for secondary objective(s):** COVID-19-related death during the 4-week period after study treatment
To evaluate change in clinical serologic measurements related to CRS in COVID-19 patients with pneumonia	Adjusted geometric mean ratio to baseline overtime up to Day 29 in the following clinical chemistry measurements: o C Reactive Protein (CRP) o Serum ferritin o D-dimer
To evaluate safety of canakinumab in patients with COVID-19-induced pneumonia and CRS	Number of participants with Adverse Event (AE), serious adverse events (SAE), clinically significant changes in laboratory measures, and vital signs

Objective(s)	Endpoint(s)
[redacted]	

2 Statistical methods.

2.1 Data analysis general information

For the primary analyses based on Day 29 DBL, efficacy analyses will be based on all data up to and including Day 29. The safety analyses will include all data up to the time of data cut (i.e., including data after Day 29 for those enrolled early in the study) if not otherwise specified.

At the final DBL, summary of all safety data collected from post treatment until end of study will be provided.

Novartis statistical and programming team will be performing the analyses as planned in this document. The Statistical Analysis System (SAS) 9.4 or higher versions will be used. R version 3.6.1 may also be used as appropriate.

Unless if otherwise clarified, descriptive summaries for categorical data will include frequencies and percentages, and continuous data will be presented with mean, standard deviation, median, minimum, and maximum. For selected parameters, geometric mean and geometric coefficient of variation (CV) may also be presented.

Rate differences and odds ratios (OR) for the comparisons between the two treatment arms will be presented with 2-sided 95% confidence interval (CI). P-values will be presented if formal hypothesis test is performed.

The randomization of the study is stratified by country to ensure a balanced allocation of patients to treatment groups within the strata. Statistical models will include adjustments for regions (North America and Europe) by pooling countries to regions. The countries are pooled by regions as follows:

North America: United States

Europe: Italy, France, Germany, Spain, United Kingdom, Hungary, Russia

2.1.1 General definitions

Study treatment

This is a one-time treatment study. Study treatment refers to canakinumab (including patients on any dose as per Table 2-1) in 250 mL of 5% dextrose infused IV over 2 hours or placebo as 250 mL of 5% dextrose infused IV over 2 hours.

Table 2-1 Canakinumab dose by body weight

Patient's weight (kg)	Dose of canakinumab	Volume of 150 mg/mL
> 80	750 mg	5.0 mL
60 to 80	600 mg	4.0 mL
40 to < 60	450 mg	3.0 mL

Study day

Day 1 is defined as the date when the study treatment is started. Study day is defined as the number of days since the date of study treatment (Day 1).

Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after Day 1:

  Study day = Assessment date – Day 1 + 1;

- for dates prior to Day 1:

  Study day = Assessment date – Day 1.

If a patient never took any double-blind treatment, the randomization date will be used as Day 1 .

2.1.1.1 Baseline

The baseline value is defined as the last assessment performed prior to start of study treatment at Day 1.

For patients who are not treated, the baseline is the last assessment scheduled for pre-baseline visit on or before the randomization date, e.g., a 9-point ordinal scale on Day 1 pre-dose visit is considered as baseline.

2.1.1.2 Post-baseline measurement

All data collected after the start of study treatment are defined as post-baseline. For patients who are not treated, the post-baseline is any scheduled post-baseline assessments on or after the randomization visit, e.g., a 9-point ordinal scale on Day 1 or an assessment for early exit visit on the randomization date is considered post-baseline measurement.

The following formula will be used, depending on how the post-baseline endpoint is defined, for each scheduled visit and time-point where baseline and post-baseline values are both available:

Change from baseline = post-baseline value – baseline value.

Percent change from baseline= (post-baseline value – baseline value)/baseline value*100%.

Ratio to baseline= post-baseline value / baseline value.

AEs will be considered as treatment-emergent if the event is starting after the start of double-blind treatment or the event is present prior to start of double-blind treatment but increased in severity after the start of treatment based on preferred term and up to end of study on Day 127.

Details on calculation of post-baseline values are provided in the latter sections.

2.1.1.3 End of study/end of treatment

The end of study (EoS) date is the date when a patient completes or discontinues the study, i.e., the “Disposition Event Date” from the “disposition” CRF form for study disposition.

This is a one-time treatment study and disposition status based on the study treatment is not applicable.

For reporting data by visit in outputs, the discontinuation from study visit will be allocated to the visit number based on the day of EoS if discontinuation is on or before Day 29. For the

assessments that are scheduled on every other day and EoS visit falls on a day without scheduled assessment, the EoS visit will be mapped to next scheduled visit for the corresponding assessment. If the discontinuation from study is after Day 29, the EoS visit will be mapped to the next scheduled visit.

2.1.1.4 Discharge from hospital

Discharge from hospital is not time point specific visit and will be mapped based on the actual day since day 1 if the discharge is on or before Day 29. For the assessments that are scheduled on every other day and discharge falls on a day without scheduled assessment, the discharge visit will be mapped to next scheduled visit for the corresponding assessment.

2.1.1.5 Unscheduled visits

Data collected at unscheduled visits will not be used for analysis by visit, but will be included in analyses based on all post-baseline values such as Last observation carried forward (LOCF) imputation or summary of abnormal findings during the study.

2.1.1.6 Nominal visit of discharge/Day 29

To evaluate the treatment effect at the time of discharge up to Day 29, summary at discharge/Day 29 may be provided based on assessments from

- early discharge visit for those who are discharged from hospital before Day 29 or
- from last available assessment up to Day 29 if not discharged before Day 29

2.1.1.7 Missing and imputable dates

The general approach to handling missing dates is described in Section 5.1.

2.1.1.8 Laboratory results meeting limits of quantification

For observations beyond the limits of quantification, a value of the lower limit of quantification (LLOQ) or the upper limit of quantification (ULOQ) will be used for analysis if not otherwise specified. This rule will be applied to all applicable laboratory values prior to checking against the notable criteria as well as computation of any statistics.

2.2 Analysis sets

The **Full Analysis Set (FAS)** comprises all participants to whom study treatment has been assigned by randomization. An accidental or premature randomization of a patient without providing study medication is considered as a misrandomized patient. Misrandomized patients will be included in FAS. According to the intent to treat (ITT) principle, participants will be analyzed according to the treatment they have been assigned during the randomization procedure.

The FAS will be used for the summary of demography and baseline characteristics as well as for all efficacy analyses.

The **Safety Set** includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received, where treatment

received is defined as the actual treatment if the participant took a treatment different from the assigned treatment.

The Safety Set will be used in the analysis of all safety variables.

Rule of exclusion criteria of analysis sets is provided in Section 5.4.

2.2.1 Subgroup of interest

Subgroup analyses will be conducted to assess consistency of the treatment effect among the subgroups without multiplicity adjustments. The following subgroups will be evaluated for the primary endpoint, i.e. survival without ever requiring invasive mechanical ventilation from Day 3 (inclusive) up to Day 29 (inclusive).

- Age category (< 65, ≥ 65 years)
- Age category (12 - <18; 18 - <40; 40 - <65; 65 - <75; ≥75)
- Baseline clinical status based on 9-point ordinal scale (≤4, ≥5)
- Baseline body Weight (40 kg - <60 kg, 60 kg – 80 kg, >80 kg)
- Baseline BMI categories (≤ 30.0 kg/m^2 and > 30.0 kg/m2)
- Sex (male, female)
- Race (White, Asian, Black, other)
- Ethnicity: Hispanic, non-Hispanic
- Region (North America, Russia, Rest of Europe)
- Active comorbidities based on Medical History
    - Cerebrovascular disease (Yes, No)
    - Chronic heart disease (Yes, No)
    - Hypertension (Yes, No)
    - Diabetes (Yes, No)
    - Asthma (Yes, No)
    - COPD (Yes, No)
    - Chronic kidney disease (Yes, No)
    - Malignant neoplasm (Yes, No)
    - Liver disease (Yes, No)
- [redacted]
- Use of dexamethasone >= 6 mg/day or equivalent or not (Yes, No)
- Use of remdesivir or not (Yes, No)
- Use of convalescent plasma/serum or not (Yes, No)
- Use of hydroxychloroquine or not (Yes, No)
- Use of azithromycin or not (Yes, No)
- Use of JAK inhibitor or not (Yes, No)
- Use of Heparin or not (Yes, No)

- Use of anti-IL6 treatment (Yes, No)

The subgroups based on the use of prior COVID-19-induced pneumonia treatment medication are defined as with/without the given medication that started on or after the onset of the first symptom of COVID-19-induced pneumonia and before the study treatment date (or randomization date if no study treatment is taken).

2.3 Patient disposition, demographics and other baseline characteristics

No inferential testing on the differences in patient disposition, demographics and other baseline characteristics between treatment arms will be performed.

2.3.1 Patient disposition

The number and percentage of patients who were screened but not randomized will be summarized based on all screened patients.

The following disposition status will be summarized based on the FAS:

- The number and percentage of patients who receive study treatment
- The number and percentage of patients who discontinue from study as well as the primary reason for discontinuation on or prior to Day 29
- The number and percentage of patients who discontinue from study as well as the primary reason for discontinuation on or prior to the time of data cut for Day 29 DBL or EoS (for the final DBL)
- The number and percentage of patients who are ongoing up to the time of data cut for Day 29 DBL. This is only applicable for the analysis based on Day 29 DBL

The number of patients included in each analysis set will be tabulated. Patients exclusion from analysis sets will be listed for all patients with reasons for exclusion (i.e. including both protocol and non-protocol deviations).

2.3.2 Demographic characteristics

Demographic characteristics, including gender, race, ethnicity, age, age categories (<18, 18-<65, 65-<75 and ≥ 75 years), body weight, body categories (40 to <60 kg, 60 to 80 kg, >80 kg), body mass index (BMI), BMI categories (≤ 30.0 kg/m^2 and > 30.0 kg/m_2), country and region (North America vs. Europe) will be summarized with descriptive statistics for the FAS by treatment and overall.

2.3.3 Baseline disease characteristics

The summary of the following baseline disease characteristics will be provided by treatment group using the FAS:

- Days from the onset of symptom to randomization as continuous variable
- Days from diagnosis to randomization as continuous variable

[redacted]

- Clinical status based on the 9-point ordinal scale (Score=0, 1, ...8)

[redacted]

- Baseline PaO_2/FiO_2 as continuous variable
- Baseline PaO_2/FiO_2 category (<100 mm Hg, 100–200 mm Hg, > 200 -300 mm Hg, > 300 mm Hg)
- Marker for inflammation as continuous variables: CRP, Serum Ferritin, D-Dimer, LDH

2.3.4 Medical history

Any condition entered on the Medical History (MH) eCRF will be coded using the MedDRA dictionary. Relevant medical history and current medical conditions will be summarized by primary system organ class (SOC), preferred term (PT) and treatment group using the FAS.

The number and percentage of patients with the following comorbidities will also be summarized:

- Cerebrovascular disease
- Chronic heart disease
- Hypertension
- Diabetes
- Asthma
- COPD
- Chronic kidney disease
- Malignant neoplasm
- Liver disease

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

There is only a one-time treatment given on Day 1 of the study. The number and percent of patients discontinued from study treatment, i.e., with an interruption due to adverse event during the 2-hour infusion and never restart the study treatment, will be summarized by treatment arm. The duration from Day 1 to the end of safety follow up will also be summarized based on the Day 29 data cut.

2.4.2 Prior, concomitant and post therapies

Analyses described in this section will be performed on the safety set.

2.4.2.1 Concomitant medication

Records on the Prior and Concomitant Medications eCRF page will be coded using the WHO drug dictionary. All medications will be classified as prior or concomitant medication as follows:

- Prior medications are defined as drugs taken and stopped prior to start of the study medication on Day 1.
- Concomitant medications are defined as drugs taken at least once after the start of the study medication on Day 1

Medications will be categorized into one (and only one) of the two classes based on recorded or imputed start and end dates. When incomplete or missing, dates will be imputed according to Novartis standards (Section 5.1.3).

Medications in one of the two categories will be summarized separately by treatment group, ATC code (ATC class level 3, i.e., therapeutic/pharmacological subgroup) and preferred term.

2.4.2.2 Surgical and medical procedures

Records on the surgical and medical procedures eCRF page will be coded using the MedDRA dictionary. All procedures will be classified as prior or concomitant procedure, in the same way as done for concomitant medications. Surgical and medical procedures in one of the two categories will be summarized separately by SOC, PT and treatment group.

Imputation rules for start and end dates will follow the same rule as for the concomitant medications (section 5.1.4).

2.5 Analysis of the primary estimand

The primary analysis for this study will be conducted on the FAS using treatment policy strategy.

2.5.1 Primary estimand

The primary clinical question of interest is: Does canakinumab + SoC increase the chance of survival without ever requiring invasive mechanical ventilation among patients with COVID-19-induced pneumonia and CRS after start of treatment, regardless of other subsequent clinical interventions?

The justification for this primary estimand is that it captures the clinical outcome of most interest after the canakinumab administration, which reflects also any effects of additional subsequent interventions potentially due to such clinical decision. In the ongoing COVID-19 pandemic with evolving treatment guidelines and healthcare system burdens, this primary estimand is deemed better to reflect actual clinical practices. In addition, the IV delivery of canakinumab is expected to result in a fast decrease in pharmacologically active IL-1β and to reduce L-1β signaling to marginal levels within hours. However, clinical signs or symptoms within the 24 hours after treatment may not necessarily reflect such pharmacological effect yet. Therefore, only clinical status starting from Day 3 will be considered for the primary endpoint.

The primary estimand includes the following components:

Population: Patients with COVID-19-induced pneumonia and CRS.

Endpoint: Clinical response, defined as survival without ever requiring invasive mechanical ventilation (i.e., 9-point ordinal score>=6) from Day 3 (inclusive) up to day 29 (inclusive). A patient will be defined as a non-responder if the worst clinical status at any time from Day3 (inclusive) up to Day 29 (inclusive) is requiring invasive mechanical ventilation or death (category 6, 7 or 8 on the WHO 9-point clinical status ordinary scale (Section 5.1)).

Treatment of interest: The randomized study treatment (canakinumab or placebo) added onto SoC with or without additional subsequent clinical interventions.

Handling of intercurrent events:

The treatment policy strategy will be adopted for primary analysis.

- Clinical interventions (e.g. mechanical ventilator, oxygen, intubation) newly administered as escalated SoCs corresponding to the progression of disease are integrated in efficacy evaluation based on the 9-category ordinal scale.
- Other new or change in strength of concomitant interventions will not be adjusted for primary analysis.
- Early discontinuation from study or lost to follow up before Day 29: A patient will be considered as responder if did not require invasive mechanical ventilation any time on or after Day 3 and meets at least one of the following two criteria:
  - The patient was discharged from hospital with clinical status of 0 or 1
  - The last clinical status was on Day 15 or later and better than baseline

  Patient will otherwise be considered as non-responder.

Summary measure: Odds-ratio comparing response rates in the canakinumab and placebo groups.

2.5.2 Statistical hypothesis, model, and method of analysis

The null hypothesis for the primary analysis is that there is no difference in the response rate

[redacted]

The numbers and percentages of responders will be summarized by treatment groups. The difference in observed response rates between canakinumab and placebo arms will also be presented along with the asymptotic 95% confidence interval.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data due to intercurrent events has been addressed via the handling of intercurrent event under the primary estimand definition.

The primary endpoint is based on clinical status starting from Day 3 (inclusive) post treatment. Patients who died or discontinued from study before Day 3 are excluded from the primary analysis. This is not expected to introduce a bias in favor of either treatment arm since the clinical status is not likely to be affected within two days by the study treatment administered on Day 1.

2.5.4 Sensitivity analysis

2.5.5 Supplementary analysis

Two supplementary analysis will be conducted:

- An analysis will be conducted based on the definition for the primary estimand; however, all data from treatment up to Day 29 will be considered
- An analysis will be conducted based on data from Day 3 to Day 29 but by handling the discontinuation from study or lost to follow up on or before Day 29 as specified below:
  - A patient will be considered as responder if invasive mechanical ventilation is not required any time on or after Day 3 and the last clinical status returning to 0 or 1 before early discontinuation from study or lost to follow up
  - A patient with the last clinical status >1 before early discontinuation from study or lost to follow up will be considered as non-responder

The supplementary analyses will apply the same logistic regression model as for the primary estimand.

2.5.6 Supportive analysis

The subgroup analyses (subgroups defined in Section 2.2.1) will be explored for the primary estimand and by fitting the data from each subgroup to the same logistic regression model as described for the primary analysis. In case of analyses on subgroups with extremely imbalanced sample sizes, the subgroup levels can be combined, if appropriate, while fitting the analysis model. The point estimate and 95% CI for odds ratio for each subgroup will be presented using forest plots.

2.6 Analysis of the key secondary objective

The key secondary efficacy analysis is based on FAS. The inferential testing on the key secondary endpoint specified in this section will be performed if the null hypothesis of the primary endpoint is rejected with a two-sided testing with p-value less than 0.05. This testing procedure controls the overall two-sided type-I error rate to less than 0.05 within the study.

2.6.1 Key secondary estimand

The key secondary clinical question of interest in this study is: Does the administration of canakinumab reduce 4-week mortality among patients with COVID-19-induced pneumonia and CRS, regardless of other subsequent clinical interventions?

The justification for this secondary estimand is that mortality currently represents the main epidemiological and clinical concern for COVID-19 patients and accumulating evidences suggest coexistence of CRS with severe COVID-19-induced pneumonia. Subsequent clinical interventions, including intensive care when a patient become terminally ill, reflect actual clinical practices, whose needs, scope and effectiveness could potentially be related to the earlier decision of canakinumab administration.

The key secondary estimand includes the following components:

Population: Hospitalized patients with COVID-19-induced pneumonia and CRS.

Endpoint: All COVID-19-related deaths (i.e., all deaths caused by study indication) during the 4-week period after study treatment

Treatment of interest: The randomized study treatment (canakinumab or placebo) added onto SOC with or without additional subsequent clinical interventions.

Handling of remaining intercurrent events:

The treatment policy strategy will be adopted for this key secondary analysis.

- Effect of other subsequent clinical interventions will not be adjusted
- Early study discontinuation or lost to follow-up before Day 29: a patient will be considered as survivor if the last clinical status of 0 or 1; otherwise, the patient will not be included in this key secondary analysis (note: this include deaths which are not marked as caused by study indication).

Summary measure: Odds-ratio comparing 4-week CFR in the canakinumab and control groups.

2.6.2 Statistical hypothesis, model, and method of analysis

The null hypothesis for the key secondary analysis is that there is no difference in the COVID-19 related death rate (i.e. CFR) in patients treated with canakinumab compared to patients on placebo. The alternative hypothesis is that there is a difference between the two treatment groups.

The superiority of canakinumab over placebo will be concluded if the odds ratio <1 for the COVID-19 related death between canakinumab and placebo and the null hypothesis can be rejected at the two-sided significance level of 0.05.

The test of the hypothesis will be based on a logistic regression model with study treatment, region (North America vs. Europe), baseline clinical status based on the 9-point ordinal scale (≤4, ≥5) as factors. Model-based estimates of the CFR and their 95% confidence intervals (CIs), estimate of the odds ratio and 95% CI, and p-value for comparing canakinumab vs. placebo will be provided. In case of model converge problem caused by separability, Firth's penalized maximum likelihood estimation will be performed based on the same logistic regression model. The estimated odds ratio, p-values and 95% CI (all computed by penalized profile likelihood) will be presented.

The number and percent of patients with COVID-19 related death during the 4-week period will also be summarized by treatment arms. The difference in observed response rates between canakinumab and placebo arms will also be presented along with the asymptotic 95% confidence interval.

2.6.3 Handling of missing values/censoring/discontinuations

Missing data due to intercurrent events has been address via the handling of intercurrent event under the key secondary endpoint estimand definition.

2.6.4 Sensitivity analysis

As a sensitivity analysis, the between group difference will also be assessed by rate difference using the marginal standardization method, for which the rate difference will be derived from the predicted rate for every patient as if they had received the study treatment or the placebo using a logistic regression model. The model will be adjusted by treatment, region (North America vs. Europe), and baseline clinical status based on the 9-point ordinal scale (≤4, ≥5) as factors. The rate within each treatment arm along with the 95% CI, rate difference along with the 95% CI and p-value will be presented.

2.6.5 Supplementary analysis

A supplementary analysis will be implemented, for which all patients who discontinued from study or lost to follow up will be considered non-survivors in the analysis.

The supplementary analysis will apply the same logistic regression model as for the key secondary analysis.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

The secondary efficacy endpoints include the clinical serologic measurements on markers of inflammation related to CRS in COVID-19 patients with pneumonia:

- ratio to baseline overtime up to Day 29 in CRP
- ratio to baseline overtime up to Day 29 in Serum ferritin
- ratio to baseline overtime up to Day 29 in D-dimer

The ratio to baseline and post baseline value will be summarized by mean, SD, median, Q1, Q3, and geometric statistics (geometric mean, geometric CV, 95% CI of the geometric mean) by treatment arm and visit. The summary is based on data with last observation carry forward

(LOCF) as well as observed data. Only post-baseline observations can be used for LOCF, i.e., for patients without post-baseline observation, baseline should not be used to impute missing data at post-baseline time points.

2.7.2 Statistical hypothesis, model, and method of analysis

No hypotheses will be tested for the secondary efficacy endpoints listed above and no p-values for the treatment comparisons will be provided.

2.7.3 Handling of missing values/censoring/discontinuations

The summary is based on data with LOCF for missing data imputation.

For patients who are discharged from hospital before Day 29, biomarker data are not likely to be available after discharge. [redacted]

2.8 Safety analyses

There are no formal safety hypotheses in this study. All safety analyses will be descriptive and performed based on observed data using the safety set. According to the definition of the safety set, patients will be grouped by the actual treatment received.

The safety analyses will include all treatment-emergent data, i.e., data collected after the start of the study treatment up to the time of database cutoff date for the analyses based on Day 29 DBL or up to EoS for the final DBL after the end of the safety follow up at Day 127. A subset of outputs based on safety data in the first 29 days of treatment will also be created at the time of Day 29 DBL. The applicable outputs will be specified in TFL shell document.

2.8.1 Adverse events (AEs)

A treatment-emergent adverse event (TEAE) is defined as any adverse event that develops on or after start of the study treatment or any event already present that worsens following exposure to the study treatment.

Adverse events will be coded using the MedDRA dictionary and presented by system organ class (SOC) and preferred term (PT). The MedDRA version used for reporting the study will be described in a footnote on AE related outputs.

The number (and percentage) of patients with TEAE will be summarized by treatment and presented by the SOCs in alphabetical order and the PTs in descending incidence in the canakinumab treatment arm. A patient with multiple adverse events within a given category is only counted once for summary purposes. AE, regardless of study drug relationship, will be summarized in the following ways:

- by treatment and preferred term
- by treatment, preferred term and maximum severity.
- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Summaries by primary system organ class and preferred term will be provided for serious adverse events.

In addition, AE (and SAE) suspected to be related to study medication, AE requiring additional therapy, AE requiring discontinuation of study treatment will be summarized by treatment, primary system organ class and preferred term

Serious AEs and study medication related AEs will be listed separately

2.8.1.1 Adverse events of special interest / grouping of AEs

The number (and proportion) of patients with the adverse events that fulfill the risk search terms (listed below as defined in the case retrieval sheet) will be summarized by risk name, PT, and treatment:

- Infections
- Interactions with vaccines
- Opportunistic infections
- Drug induced liver injury
- Immunosuppressants combination therapy toxicity
- Macrophage activation syndrome

In the summary table, risk names will be sorted alphabetically and, within each risk name, the PTs will be sorted in descending order of frequency in the canakinumab arm. If a patient reported more than one adverse event with the same PT, the AE will be counted only once. If a patient reported more than one AE within the same risk, the patient will be counted only once at that risk.

SAEs of special interest, AEs of special interest suspected to be related to study treatment, and SAEs of special interest suspected to be related to study treatment, will also be summarized by risk name, PT and treatment group.

A list of the risk search terms used for the selection of AE of special interest will be provided.

2.8.1.2 Deaths

Adverse events leading to death will be summarized with number and percentage by treatment and primary AE (SOC and PT). Similar summary on adverse events leading to death that is suspected to be related to study treatment will also be provided. Listing of death will also be provided.

2.8.1.3 Adverse events reporting for CT.gov and EudraCT

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 2% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set including all data up to EoS based on the final DBL.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2 Laboratory data

Laboratory tests will be conducted by local lab. Clinically significant abnormal results will be reported as adverse events and included in the AE summaries; however the following liver enzyme testing results will be entered into the clinical database:

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total bilirubin (TBIL) / Direct bilirubin
- Alkaline phosphatase (ALP)

Number (%) of newly occurring liver enzyme abnormalities, as listed below, at any time during post-treatment will be provided. A newly occurring event is when a patient not meeting a given criterion at baseline but meeting the corresponding criterion during post-baseline.

- ALT or AST > 3.0x, 5.0x, 10.0x, 20.0x ULN
- ALP>1.5xULN
- TBIL > 1.5x, 2.0x ULN
- ALT or AST > 3.0x ULN & TBIL > 1.5x ULN
- ALT or AST > 3.0x ULN & TBIL > 2.0x ULN

The last two criteria on the list are based on the maximum post-baseline ALT, AST, and TBIL.

An eDISH plot on the maximum post-baseline ALT value relative to the ULN and TBIL value relative to the ULN will also be provided at log-log scale.

Hematology parameters

The hematology parameters include absolute neutrophil count, monocytes, lymphocytes measured from local lab. The post baseline value and the percent change from baseline at post baseline are summarized by mean, SD, median, Q1, and Q3. The summary is based on the observed data.

2.8.3 Other safety data

2.8.3.1 SARS-CoV-2 Virus test

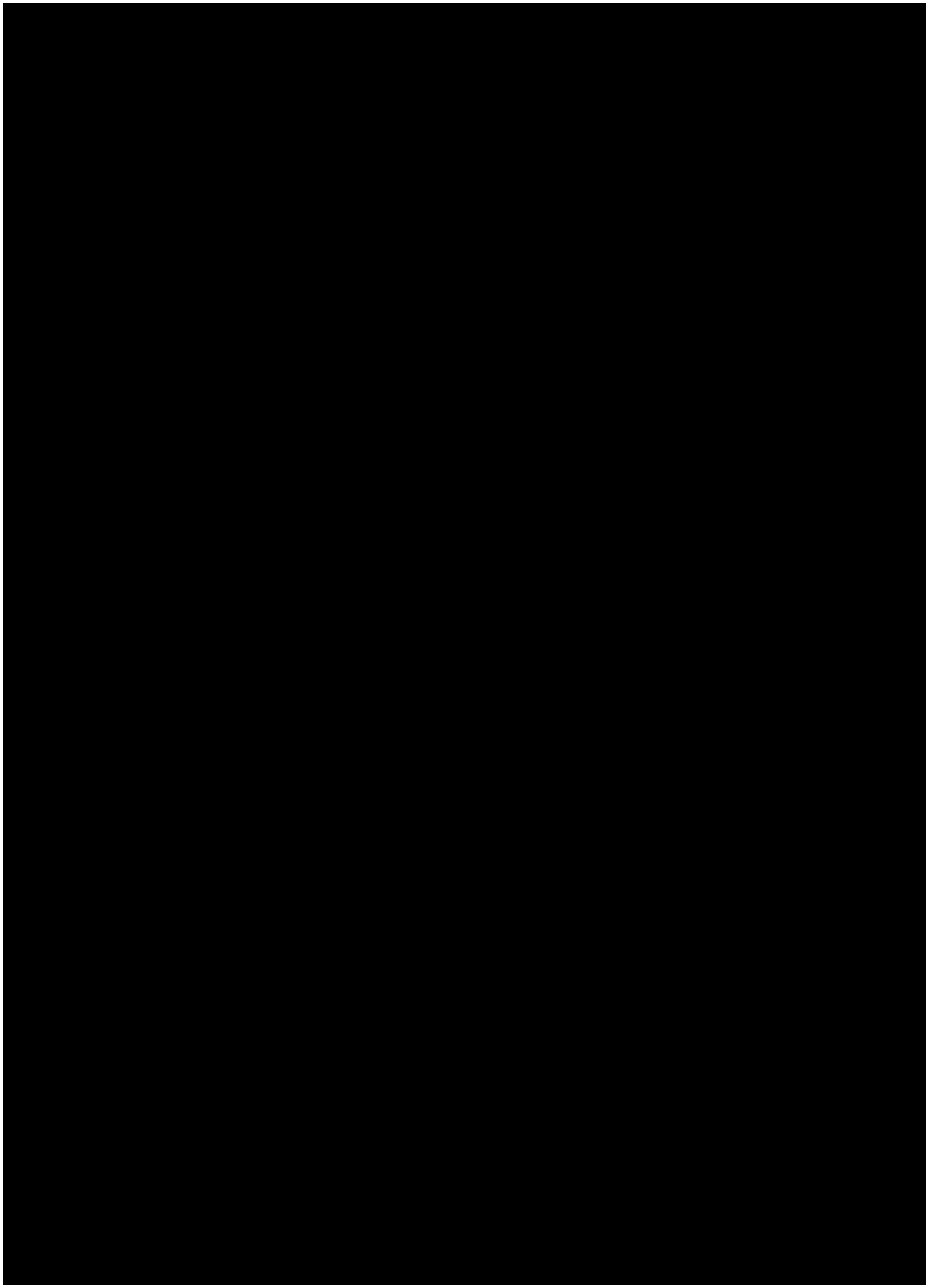
The presence of SARS-CoV-2 virus will be tested by central lab based on nasopharyngeal samples taken at baseline and at discharge from hospital/Day 29 if not discharged.

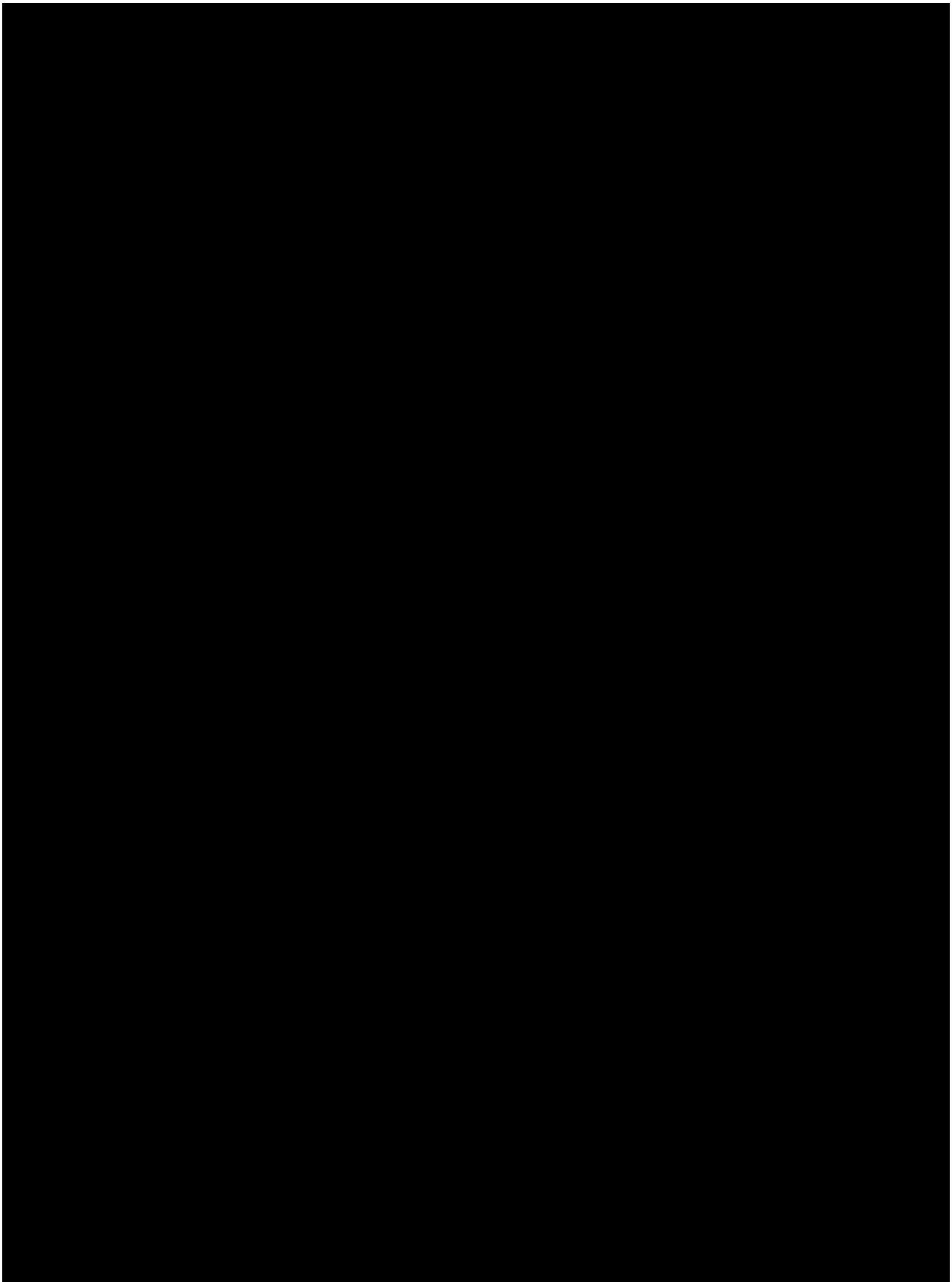
A summary on viral load by sequential quantitative RT-PCR for SARS associate coronavirus will be summarized by geometric mean at baseline, at discharge for those who are discharged on or before Day 29, at Day 29 for those who are not discharged on or before Day 29. The summary will also be provided by the day interval between Day 1 to discharge from hospital: Discharge on Day 1 to Day 7, discharge on Day 8 to Day 14, Discharge on Day 15-Day 21, Discharge on Day 21 to Day 29.

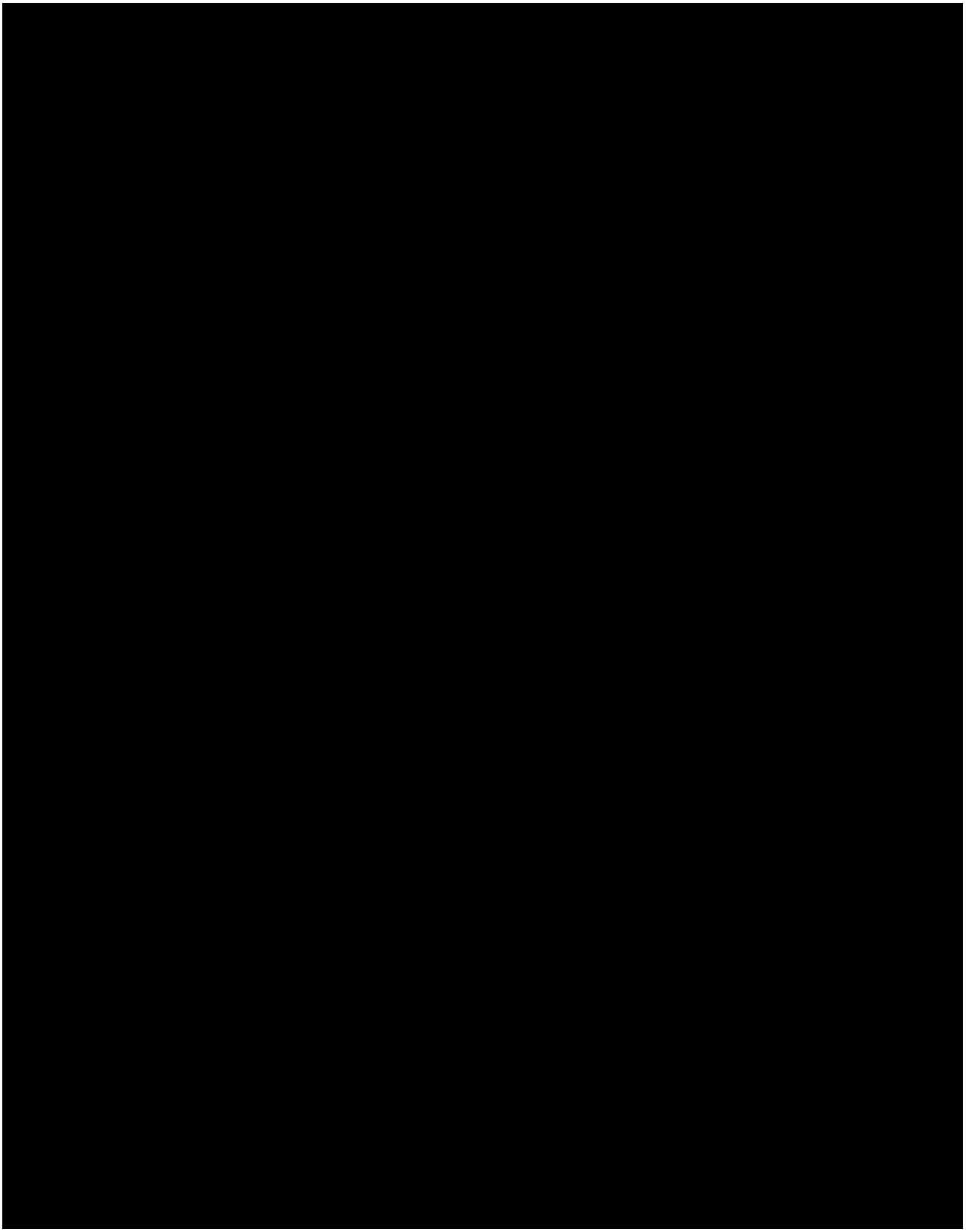
In addition, a summary on number (%) of patients with positive (a reading ≥LLOQ) or negative (<LLOQ) test results will be provided at baseline, at discharge for those who are discharged on or before Day 29, at Day 29 for those who are not discharged on or before Day 29, and by the discharge day interval.

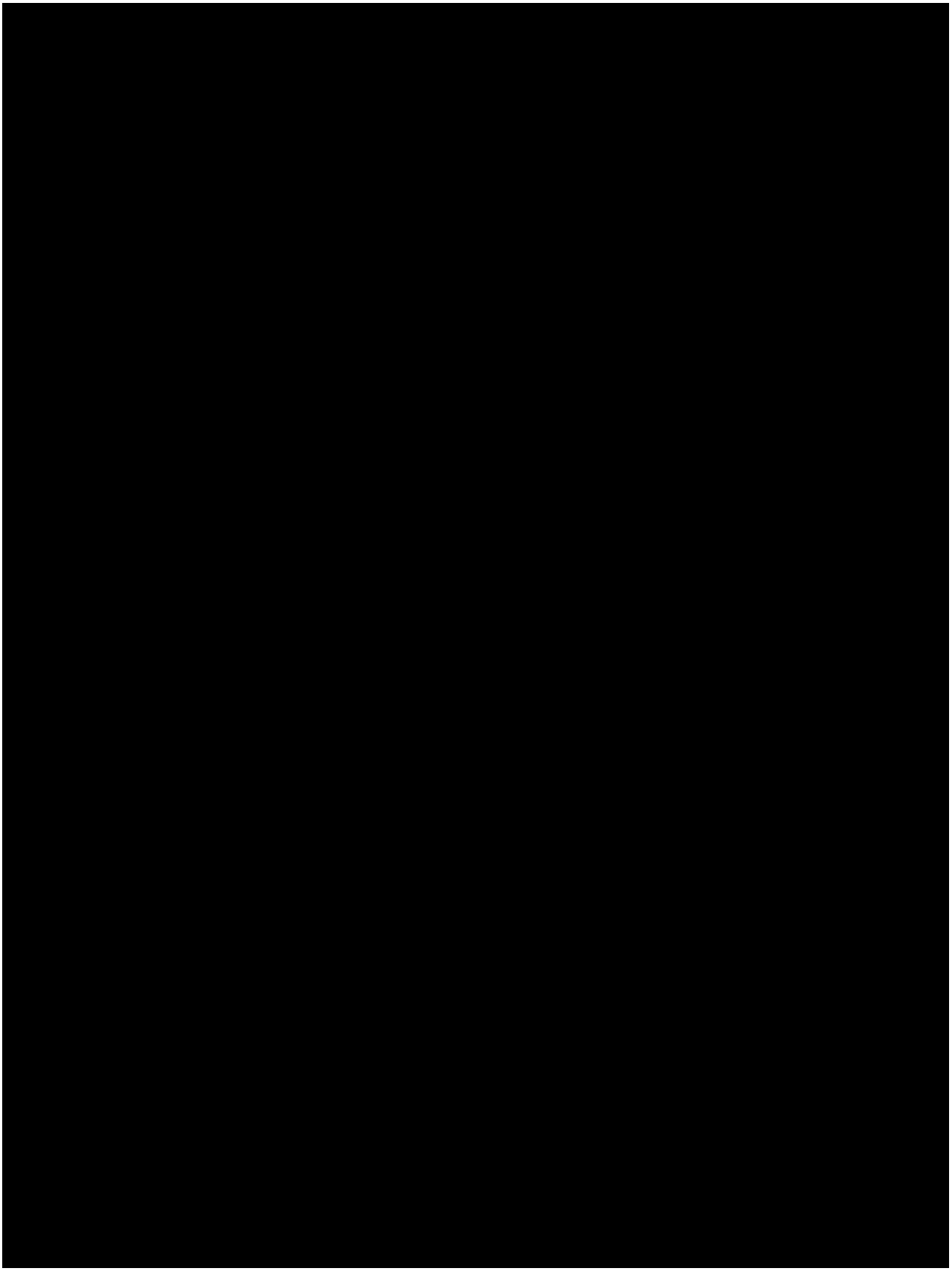
2.8.3.2 Vital signs

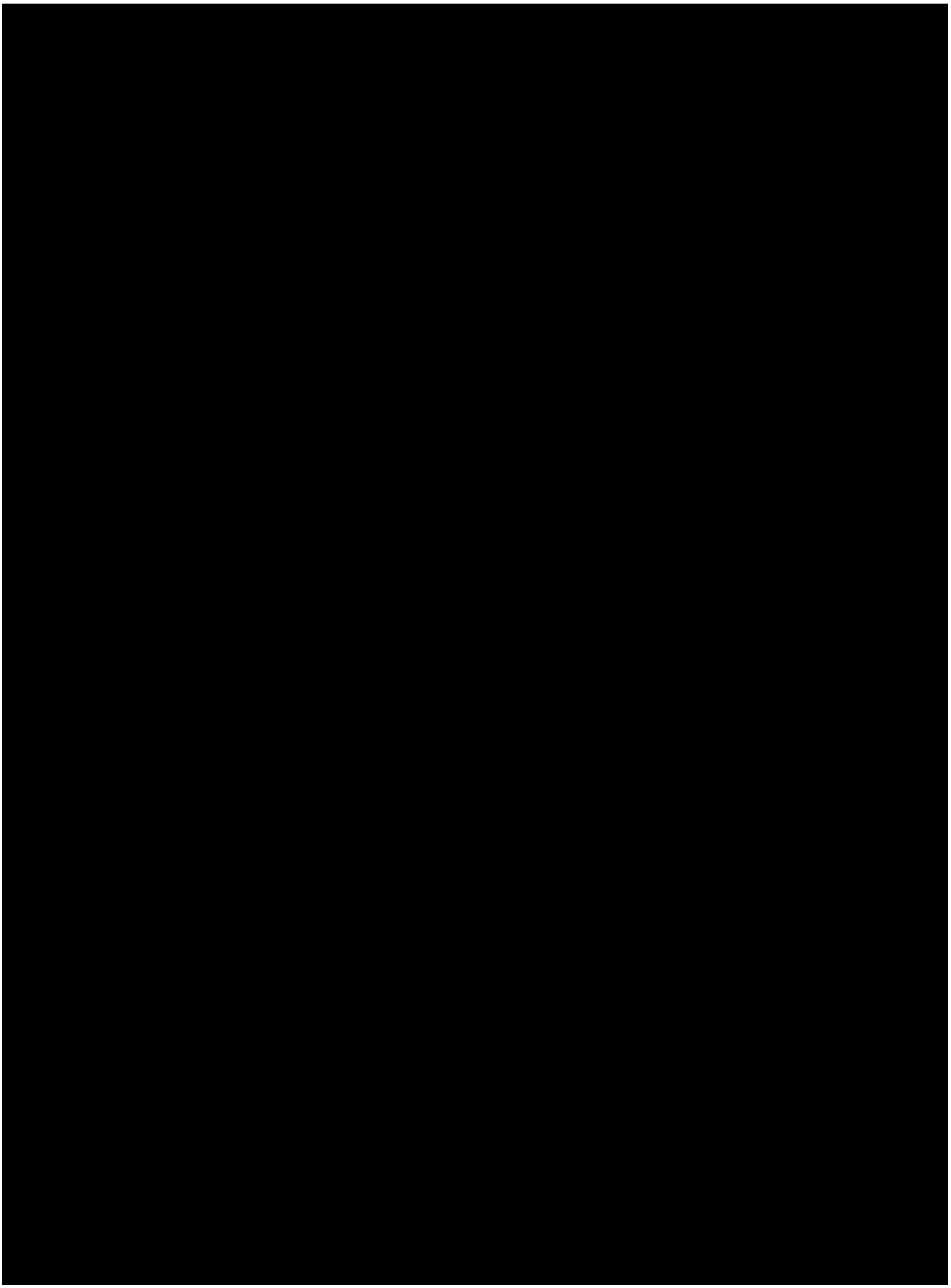
Vital sign measurements include respiratory rate, pulse rate, systolic and diastolic blood pressure, and body temperature. Absolute values and change from baseline will be summarized for each of the aforementioned vital sign parameters by treatment group, visit and time point including the minimum and maximum Post-baseline value.











2.10 Interim analysis

Summaries of safety data will be produced for DMC safety monitoring when needed.

3 Sample size calculation

3.1.1 Primary endpoint

Approximately 450 patients will be randomized to canakinumab + SOC or placebo + SOC in a 1:1 ratio.

Patients infected with COVID-19 exhibit a wide range of clinical severity. With recent initial outbreak and evolving pandemic situations, limited data is available to precisely estimate the rate of disease progression after hospital admission for the population of interest under SOC. The CDC reported 31.4% hospitalizations and 11.5% ICU admissions (among patients with known hospitalization and ICU admission status) in the United States between February 12 and March 16, 2020 (CDC COVID Response Team 2020). An earlier summary (Wu and McGoogan 2020) of 72314 diagnosed cases in China estimated about 81% mild cases, 14% severe cases, 5% critical case and an overall case-fatality rate of 2.3%. A worldwide tally by WHO as of March 12th, 2020 estimated a mortality rate of 3.7% with 125,048 confirmed cases. A study by Zhou et al (2020) based on complete follow-up of 191 in-hospital patients during the early outbreak of COVID-19 in China reported an in-hospital CFR as high as 28%, while other studies

reported much smaller CFR with incomplete follow-up data. Detailed summaries of disease progression time course during hospitalization or by disease status based on large samples, however, were not found.

With this study enrolling only hospitalized patients with COVID-19 induced pneumonia and CRS, and assuming that more than half of this patient population will likely require invasive mechanical ventilation, the true response rate for the control arm of this study is considered most likely in the range from 20% - 50%, while the CFR is not likely to be more than 25%.

Invasive mechanical ventilation is a radical departure from the physiology of breathing spontaneously, which put patients under risks of various immediate and long-term complications (Soni and Williams 2008) regardless of the survival outcome. The benefits of canakinumab for COVID-19 patients is considered clinically meaningful if it leads to an absolute increase of 15% patients who survived without ever requiring invasive mechanical ventilation. A 4-week CFR reduction by half (i.e. relative risk=0.5) is also considered meaningful clinical benefit outweighing the known risks of canakinumab.

Assuming the true response rate for the control arm lies within the range of 20% - 50%, a total sample size of 450 and 1:1 randomization ratio will provide at least 89% power to detect the minimum clinically meaningful benefit of interest.

Table 3-1 Power for primary analysis under varying assumptions (sample size = 450)

Response Rate (%)		Clinically meaningful benefits			Power (2-side α=0.05)
Control	ACZ885	difference	OR	RR	
50	65	15	1.86	1.3	89%
40	55	15	1.83	1.38	89%
30	45	15	1.91	1.5	90%
20	35	15	2.15	1.75	94%

Early discontinuation from study before patient recovery is considered unlikely in this study, hence the sample size is not adjusted for attrition. Blinded sample size reevaluation may be performed to confirm the assumptions for the sample size calculation, based on which the sample size may be updated without inflation of type I error.

3.1.2 Key secondary endpoint

Using a hierarchical testing procedure for familywise 2-sided type I error control at 0.05, the hypothesis test in key secondary analysis on 4-week CFR will be performed if and only if null hypothesis in primary analysis is rejected. The conditional power for detecting a 50% drop of 4-week CFR are evaluated under different assumptions on control arm 4-week CFR.

Table 3-2 Power for key secondary analysis (sample size = 450)

CFR (%)		Clinically meaningful benefits			Power (2-side α=0.05)
Control	ACZ885	Difference	OR	RR	
25	12.5	-12.5	0.43	0.5	92%
20	10	-10	0.44	0.5	83%

15	7.5	-7.5	0.46	0.5	70%

Cases of lost to follow up before patient's recovery (clinical status = 0 or 1 on the 9-point ordinal scale) and before Day 29 is expected to be minimal. Sample size adjustment for key secondary analysis is not planned.

4 Change to protocol specified analyses

No changes on the primary analyses for the primary and key secondary endpoints that are pre-specified on the protocol.

The following analyses are not specified on the protocol but added and specified on the SAP to address comments from various health authority comments on the protocol:

- Sensitivity analysis comparing the rate difference between treatment arms using the marginal standardization method has been added to both the primary and key secondary endpoints.
- A supplementary analysis considering any patients who discontinued from study or lost to of follow-up as non-survivors is added for the key secondary endpoint.

[redacted]

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Missing or partial dates are not allowed, therefore, no imputation will be made to the study treatment date.

5.1.2 AE date imputation

For the start and end dates of the adverse event records, when incomplete or missing, dates will be imputed according to Novartis standards as described below.

5.1.2.1 AE end date imputation

Incomplete or missing AE end date will be dealt with in the following way:

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

4. If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

5.1.2.2 AE start date imputation

The following table explains the notation used in the logic matrix. Please note that completely missing start dates will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Date	(2.b) Before Treatment Date	(2.b) Before Treatment Date	(2.b) Before Treatment Date
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Date	(4.c) Uncertain	(4.c) After Treatment Date
YYYY > TRTY	(3.a) After Treatment Date	(3.b) After Treatment Date	(3.b) After Treatment Date	(3.b) After Treatment Date

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment date then AE start reference date = min (informed consent date, earliest visit date).
2. Else AE start reference date = treatment date

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.

2. If the AE start date year value is less than the treatment date year value, the AE started before treatment. Therefore:

   a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).

   b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

3. If the AE start date year value is greater than the treatment date year value, the AE started after treatment date. Therefore:

   a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).

   b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the treatment date year value:
   a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
   b. Else if the AE month is less than the treatment month, the imputed AE start date is set to the mid-month point (15MONYYYY).
   c. Else if the AE month is equal to the treatment date month or greater than the treatment date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

For the start and end dates of the concomitant medication records, when incomplete or missing, dates will be imputed according to Novartis standards as described below. The same data imputation rules will be applied for therapies and procedures.

5.1.3.1 Concomitant medication end date imputation

Incomplete or missing end date for prior therapies will be dealt with in the following way
1. If the CM end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the CM end year value is missing or ongoing, the imputed CM end date is set to NULL.
2. Else, if the CM end date month is missing, the imputed end date should be set to the earliest of the (study end date, 31DECYYYY, date of death).
3. If the CM end date day is missing, the imputed end date should be set to the earliest of the (study end date, last day of the month, date of death).

If the imputed CM end date is less than the existing CM start date, use the CM start date as the imputed CM end date.

5.1.3.2 Concomitant medication start date imputation

In order to classify a medication as prior and prior/concomitant, it may be necessary to impute the start date.

Completely missing start dates will be set to one day prior to treatment date. As a conservative approach, such treatments will be classified as prior and concomitant (and summarized for each output).

Concomitant treatments with partial start dates will have the date or dates imputed.

The following table explains the notation used in the logic matrix

	Day	**Month**	**Year**
Partial CMD Start Date	Not used	MON	YYYY
Treatment Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a) Before Treatment Date	(2.b) Before Treatment Date	(2.b) Before Treatment Date	(2.b) Before Treatment Date
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Date	(4.a) Uncertain	(4.c) After Treatment Date
YYYY > TRTY	(3.a) After Treatment Date	(3.b) After Treatment Date	(3.b) After Treatment Date	(3.b) After Treatment Date

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to Treatment date.
2. If the CM start date year value is less than the Treatment date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).

3. If the CM start date year value is greater than the Treatment date year value, the CM started after treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the Treatment date year value:
    a. And the CM month is missing or the CM month is equal to the Treatment date month, then the imputed CM start date is set to one day prior to Treatment date.
    b. Else if the CM month is less than the Treatment date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
    c. Else if the CM month is greater than the treatment date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.4 Concomitant therapies and procedures date imputation

The missing dates will be imputed using the same rule as for the concomitant medication.

5.2 AEs coding/grading

AEs are coded using the MedDRA terminology. The latest version of MedDRA will be used and will be specified on the footnote of relevant output.

AEs grade are assessed by investigators and captured on the AE CRF based on three levels: mild, moderate, and severe.

5.3 Statistical models

5.3.1 Primary analysis

[redacted]

5.3.1.1 Sensitivity analysis of the primary endpoint

[redacted]

[redacted]

5.3.2 Key secondary analysis

The null hypothesis for the key secondary analysis is that there is no difference in the COVID-19 related death rate (i.e. CFR) in patients treated with canakinumab compared to placebo. The alternative hypothesis is that there is a difference between the two treatment groups.

The statistical superiority test based on odds ratio will be performed to compare the CFR between canakinumab and placebo arms and the same logistic regression model as described for the primary analysis will be used.

Same sensitivity analysis using the marginal standardization method as for the primary endpoint will also be provided for the key secondary endpoint.

5.4 Rule of exclusion criteria of analysis sets

Table 5-1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL01	Informed consent not obtained	Excluded from FAS, Safety set

Table 5-2 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
Enrolled	INCL01	
FAS	INCL01	Not Randomized
Safety set	INCL01	No double-blind study drug taken

5.5 Clinical status (9-point ordinal scale)

Assessment of clinical status using a 9-point ordinal scale (WHO 2020) will be recorded at baseline on Day 1 and then again once daily every morning till discharge from the hospital or Day 29. Each day, the worse score for the previous day will be recorded (i.e. on Day 3, Day 2 score is obtained and recorded as Day 2). The description for each score level is specified in Table 5-3.

There are cases that site may report two 9-point status assessments on early discharge visit or early discontinuation visit:

- one assessment is captured as the worst assessment on the day of early discharge/discontinuation visit and entered under the visit of Day X (X=early discharge/discontinuation date-Day 1+1)
- one assessment is captured as the status by the time of early discharge/discontinuation and entered under the visit of early discharge/discontinuation

In summary by visit, the worse score will be used for the summary on Day X and the score reported for early discharge/discontinuation will be used for data imputation with LOCF and other analyses based on the latest status by early discharge/discontinuation.

Table 5-3 Clinical status (9-point ordinal scale)

Patient State	Descriptor	Score
Uninfected	No Clinical or virological evidence of infection	0
Ambulatory not in hospital or in hospital and ready for discharge)	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy (defined as $SpO_2 \geq$ 94% on room air)	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support - pressors, RRT, (renal replacement therapy), ECMO (extracorporeal membrane oxygenation)	7
Dead	Death	8

5.6 Type of pulmonary/ventilatory support

The level of Oxygen requirement is assessed based on the type of support specified in the table below.

Table 5-4 Type of pulmonary/Ventilatory support based on the level of oxygen requirement from low to high

Type of support	Require supplemental oxygen	Require mechanical ventilation
Low flow nasal oxygen	Yes	No
High flow nasal oxygen	Yes	No
Oxygen via face mask	Yes	No
Non-invasive ventilation	Yes	No
Mechanical ventilation	Yes	Yes
Intubation	Yes	Yes
Tracheostomy	Yes	Yes

Type of support	Require supplemental oxygen	Require mechanical ventilation
ECMO	Yes	Yes

The baseline use of pulmonary ventilatory support is the latest type of Oxygen supply that started before the study treatment. There are records with an oxygen supply starting from Day 1 but there is no time information provided, in which case, it is not possible to tell if such procedure started pre-/post-treatment. Here is the summary on how to define baseline when time information is missing from a procedure that starts/ends on Day 1:

- If a patient is on type A oxygen supply from a pre-treatment date and end on Day 1 then changed from type A to type B on the same date, type A will be considered as the baseline type of oxygen supply.
- If a patient has one record on oxygen supply that ends on Day 1 but with one record starting on Day 1, the perspective oxygen supply type will be considered as the baseline.

6 Reference

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