Statistical Analysis Plan

A Phase II/III Study of Sargramostim in Patients with Coronavirus Infection (COVID-19)

Sponsor: Nobelpharma Co., Ltd

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Version history

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1.0	2021/8/12	[redacted]	Preparation of the first version
1.1	2021/12/16	[redacted]	2.1.2.10.2.1 Changes in alveolar-arterial oxygen difference (A-aDO_2) from baseline to each time point 2.1.2.10.2.6 Changes in arterial blood-gas values (PaO_2, $PaCO_2$) from baseline to each time point Handling of the data was added, and it was added that the model estimation will be also carried out on the measurement value. And, the analysis method was reviewed. 2.1.2.10.2.5 Changes from baseline in pulmonary inflammatory findings at each time point In association with establishment of the evaluation procedure of the thorax HRCT images, the analysis method was added and modified, and the details were described. 2.1.2.10.2.10 Other items specified as exploratory Analysis of time to improvement by at least 2-rank on a 7-point ordinal scale reflecting the end of treatment during tapering of steroid treatment, time from baseline to Category 5 on a 7-point ordinal scale, and time to improvement at least 1-rank on a 7-point ordinal scale were added. 2.1.2.14 Handling of missing data, unspecified observations and other inappropriate data Handling of the values of arterial blood gas analysis was added. 2.1.2.15 Subgroup analysis Class of steroid used and category on a 7-points ordinal scale at baseline were added as factors in subgroup analysis. In addition to above, description was generally modified, in reflecting the decision at the Case Review Committee.

TABLE OF CONTENTS

1 Introduction

This statistical analysis plan provides details of the statistical analysis specified in the protocol and is structured to meet Sections 9.7, 9.8 and 16.1.9 of the Clinical Study Report.

2 Protocol-designed statistical methods and sample size determination (Section 9.7 of Clinical Study Report)

2.1 Statistical and analytical plan

Statistical analysis of this clinical study will be performed according to "Statistical Principles for Clinical Trials" (Evaluation and Licensing Division, PMSB 1047 dated November 30, 1998).

2.1.1 Analysis set

The analysis sets are defined as follows. In addition, if judgement of inclusion/exclusion of a patient such as a deviated patient is difficult, inclusion/exclusion of the case in the analysis set will be determined at the Case Review Committee.

2.1.1.1 Safety population

All the patients who received the assigned study drug will be included in the Safety Population (SP).

2.1.1.2 Efficacy analysis set

Of any assigned patients, any patients excluding those who did not receive the study drug or those from whom no information on efficacy was available after allocation are defined as the Full Analysis Set (FAS). In this study, an analysis will be performed in the FAS. In addition, any patients in the FAS excluding those with major protocol violations after start of treatment and for whom the efficacy is evaluable are defined as the Per Protocol Set (PPS). Analysis of the primary endpoint will be performed in the PPS.

2.1.1.3 Randomized patients

Patients assigned with an allocation code are regarded as Randomized Patients.

2.1.2 Analysis item and analytical method

2.1.2.1 Breakdown of patients

(1) Analysis set : Randomized Patients

(2) Analytical method :

1) The number of patients who were treated, completed, or discontinued and the proportion will be summarized by treatment group (number of patients, %).
2) The number of discontinued patients and the proportion in each reason for discontinuation will be summarized by treatment group (number of patients, %).
3) A list of discontinued patients will be prepared.

2.1.2.2 Breakdown of analysis set

(1) Analysis set : Randomized Patients

(2) Analytical method :

1) The number of patients who were included in or excluded from each analysis set and the proportion will be summarized by treatment group (number of patients, %).

2) A list of the patients who were excluded from the analysis set will be prepared.

2.1.2.3 **Background factors of the patients**

(1) Analysis set : SP, FAS

(2) Analysis item :

< Continuous variable >

Age, height, body weight, BMI, oxygen-saturation (SpO_2) at screening

< Categorical variables >

Sex, age (<40, 40≤ to <65, 65≤ to 75<, 75≤), BMI(<30, 30≤), oxygen saturation (SpO_2) at screening (≤90%, >90%), history of alcohol intake, smoking history, with or without concomitant use of antiviral drugs for COVID-19, with or without concomitant use of steroids and their classes (dexamethasone, methylprednisolone or prednisolone, others[mixture of dexamethasone and methylprednisolone or prednisolone]), with or without concomitant use of JAK (Janus kinase) inhibitors, category on a 7-point ordinal scale at baseline, presence or absence of comorbidity (heart disease [myocardial infarction, congestive heart failure], cerebrovascular disease, dyslipidemia, hypertension, diabetes, and bronchial asthma), time since onset (<10 days, 10 days≤)

(3) time point : at screening, Day 0

(4) Analytical method

BMI will be derived.

<BMI>BMI is calculated using height and body weight.

Height at the screening will be used for calculation of BMI.

•BMI = Body weight(kg) / Height(m)^2

1) Continuous variables : Summary statistics (number of patients, arithmetic mean, standard deviation, median, minimum, maximum) will be calculated by treatment group. In addition, the p-value (two-sample t-test) will be calculated.

2) Categorical variables : The number of patients and the proportion will be summarized by treatment group (number of patients, %). In addition, the p-value (chi-square test) will be calculated.

2.1.2.4 **Medical history/current medical condition**

(1) Analysis set : SP

(2) Analysis item: medical history, current medical condition

(3) Time point : at screening

(4) Analytical method

Diagnostic names described in the Case Report Form will be read using the specified version of the MedDRA.

1) The number of patients and the proportion will be summarized by SOC and PT in each treatment group (number of patients, %).

2) A list of medical history and current medical conditions of the patients will be prepared. Analysis set : Randomized Patients

2.1.2.5 **Concomitant medication**

(1) Analysis set : SP

(2) Analysis item : concomitant drug

(3) Time point : at screening to Day 14

(4) Analytical method :

The drug name described in the Case Report Form will be changed to the generic name using WHO-DD.

1) The number of patients who are taking concomitant drugs and the proportion will be summarized by drug name (generic name) in each treatment group (number of patients, %).

2) A list of concomitant drugs taken by the patients will be prepared. Analysis set : Randomized Patients

2.1.2.6 **Standard medication**

(1) Analysis set : SP

(2) Analysis item : standard drug

(3) Time point : at screening to Day14

(4) Analytical method :

The drug name described in the Case Report Form will be changed to the generic name using WHO-DD.

1) The number of patients who are taking standard drugs and the proportion will be summarized by drug name (generic name) in each treatment group (number of patients, %).

2) A list of standard drugs taken by the patients will be prepared. Analysis set : Randomized Patients

2.1.2.7 **Concomitant therapy**

(1) Analysis set : SP

(2) Analysis item : combination therapy

(3) Time point : at screening to Day 14

(4) Analytical method :

1) The number of patients who are receiving concomitant therapies and the proportion will be summarized by therapy in each treatment group (number of patients, %).

2) A list of concomitant therapies received by the patients will be prepared. Analysis set : Randomized Patients

2.1.2.8 **Standard therapy**

(1) Analysis set : SP

(2) Analysis item : standard therapy

(3) Time point : at screening to Day 14

(4) Analytical method :

1) The number of patients who are receiving standard therapies and the proportion will be summarized by therapy in each treatment group (number of patients, %).

2) A list of standard therapies received by the patients will be prepared. Analysis set : Randomized Patients

2.1.2.9 **Treatment compliance of study drug**

(1) Analysis set : SP, FAS

(2) Analysis item : number of doses

(3) Time point : Day 1 to Day 10

(4) Analytical method :

1) Summary statistics (number of patients, arithmetic mean, standard deviation, median, minimum, and maximum) for the number of doses will be calculated by treatment group. In addition, the number of patients and the proportion will be summarized by the number of doses in each treatment group (number of patients, %).

2) The number of patients and the proportion will be summarized by the reasons for discontinuation in each treatment group (N, %).

3) A list of the treatment compliance and the reasons for discontinuation of the study drug will be prepared. Analysis set : Randomized Patients

2.1.2.10 **Efficacy Evaluation**

2.1.2.10.1 **Primary endpoint**

(1) Analysis set : FAS, PPS

(2) Analysis item : period to the first improvement by at least 2-rank between baseline and Day 28 on a 7-point ordinal scale.

(3) Time point : Day 0 to Day 28

(4) Analytical method : The following analysis will be performed.

1) As the main analysis, the improvement rate will be estimated by treatment group using Kaplan-Meier method, and the comparison between groups using the log-rank test with a significance level of 5% will be performed as well. In addition, assessment using Cox's proportional hazards model with the presence or absence of concomitant antiviral drugs for COVID-19 as a covariate will be performed. Definitions of the events and censoring are presented in Table 2.3.

Table 2.1 7-Point ordinal scale

Category	ordinal scale
1	Have died
2	Use an invasive ventilator or ECMO
3	Use a noninvasive ventilator or high-flow oxygen supply device
4	Require oxygen supply
5	Do not require oxygen supply but require continuous therapy (related to COVID-19 or others)
6	Do not require both oxygen supply and continuous therapy
7	Have been discharged from hospital

2.1.2.10.2 **Secondary endpoints**

2.1.2.10.2.1 Changes in alveolar-arterial oxygen difference (A-aDO_2) from baseline to each time point

(1) Analysis set : FAS

(2) Analysis item : measured values and changes in A-aDO_2 (values at each time point- those at Day1)

(3) Time point : Day 1, Day 3, Day 5, Day 10, at discontinuation/completion of treatment

(4) Analytical method :

1) Summary statistics (number of patients, arithmetic mean, standard deviation, median, minimum, maximum) for measured values and changes will be calculated by treatment group and by time point. In addition, a chart for the mean ± standard deviation over time and box-and-whisker plot will be prepared by treatment group.
2) Estimated values of the differences between groups, 95% confidence intervals, and p-values (Day 3, Day 5, Day 10) will be calculated using mixed effect model for repeated measures (cLDA method) by time point with the measured values as the response variable, time point, treatment group, and treatment group * time point as the fixed effects, and patients as the random effect, setting that both groups have the common mean value on Day 1. In addition, estimated values and 95% confidence intervals over time will be prepared by treatment group.
3) Estimated values of the differences between groups, 95% confidence intervals, and p-values (Day 5, at discontinuation/completion of treatment) will be calculated using mixed effect model for repeated measures with the measured values and changes as the response variable, baseline values as the covariate, time point (Day 1, Day 5, at discontinuation/completion of treatment), treatment group, treatment group * time point as the fixed effects, and patients as the random effect. In addition, a chart for the estimated values and 95% confidence intervals over time will be prepared by treatment group.
4) The number of patients of whom changes from baseline (Day 1) decreased (improved) by 33% or more and the proportion will be calculated by treatment group and by time point (number of patients, %), and the p-values (Fisher's exact test) will be calculated.

2.1.2.10.2.2 Period from baseline to the day of discharge (days until shifting to Category 7 on a 7-point ordinal scale)

(1) Analysis set : FAS
(2) Analysis item : period from baseline to the day of discharge (time point - Day 0)
(3) Time point : Day 0 to Day 28
(4) Analytical method :

1) Period from baseline to the day of discharge will be estimated by treatment group using the Kaplan-Meier method, and comparison between groups will be performed as well using the log-rank test with a significance level of 5%. Definitions of events and censoring are presented in Table 2.3.

2.1.2.10.2.3 Period from baseline to shifting to Category 6 or 7 on a 7-point ordinal scale

(1) Analysis set : FAS
(2) Analysis item : period to shifting to Category 6 or 7 on a 7-point ordinal scale from baseline (time point - Day 0)
(3) Time point : Day 0 to Day 28
(4) Analytical method :

1) Period from baseline to shifting to Category 6 or 7 on a 7-point ordinal scale will be estimated by treatment group using the Kaplan-Meier method, and comparison between groups will be performed as well using the log-rank test with a significance level of 5%. Definitions of events and censoring are presented in Table 2.3.

2.1.2.10.2.4 Rate of shifting to Category 1 or 2 on a 7-point ordinal scale during the period from baseline to Day 10 or Day 28

(1) Analysis set : FAS

(2) Analysis item : rate of shifting to Category 1 or 2 on a 7-point ordinal scale from baseline (time point - Day 0)

(3) Time point : Day 0 to Day 28

(4) Analytical method :

1) The number of patients of whom the category has shifted to Category 1 or 2 on a 7-point ordinal scale and the proportion during the period from baseline to Day 10 or Day 28 will be summarized by treatment group and by time point (number of patients, %).

2) The p-values (Fisher's exact test) on Day 10 or Day 28 will be calculated for the rate of shifting to Category 1 or 2 on a 7-point ordinal scale during the period from baseline to Day 10 or Day 28.

3) Period from baseline to shifting to Category 1 or 2 on a 7-point ordinal scale will be estimated by treatment group using the Kaplan-Meier method, and comparison between groups will be performed as well using the log-rank test with a significance level of 5%. Definitions of events and censoring are presented in Table 2.3.

2.1.2.10.2.5 Changes from baseline in pulmonary inflammatory findings at each time point

(1) Analysis set : FAS

(2) Analysis item : changes from baseline in pulmonary inflammatory findings (each time point - Day 0)

(3) Time point : Day 0, Day 5, at discontinuation/completion of treatment

(4) Analytical method :

1) Pulmonary inflammatory findings will be examined according to Section 13.11 “High Resolution Chest CT (HRCT) or Plain Chest CT or Chest X-ray” at the time point specified in Section 2 "Observation/Examination Schedule" of the protocol and the finding results will be classified into 3 categories by the investigator. Then, the number of patients and the proportion in each category will be summarized by treatment group and by time point (number of patients, %).

2) Regarding the number of cross sections for which Crazy-paving appearance, Bronchial wall thickening, Subpleural curvilinear shadow, Vascular thickening, Airspace consolidation, Small nodule opacity, Reticular shadow, Plate atelectasis、or AIP/ARDS pattern（DAD pattern）has been found in the specified 9 cross sections each in the left and right side (18 cross sections in total) on chest HRCT, summary statistics (number of patients, arithmetic mean, standard deviation, median, minimum, maximum) for each finding will be calculated by treatment group and by time point. In addition, a chart for mean ± standard deviation over time will be prepared by treatment group. Moreover, estimated values of the differences between groups, 95% confidence intervals, and p-values (Day 5, at discontinuation/completion of treatment) will be calculated using mixed effect model for repeated measures with the changes from baseline to each time point as the response variable, baseline values as the covariate, time point, treatment group, and treatment group * time point as the fixed effects. A chart for changes in the estimated values and 95% confidence intervals over time will be also prepared by treatment group.

Separately from the above assessment, presence or absence of findings of Lymph node enlargement, Pleural effusion, Pericardial effusion, Pneumothorax, or Pneumomediastinum will be checked in the entire lungs, and the number of patients who have such findings and the proportion will be summarized for each finding by treatment group and by time point (number of patients, %).

3) Assuming normal lung, GGO, or consolidation, summary statistics (number of patients, arithmetic mean, standard deviation, median, minimum, maximum) for the percentage of each volume on chest HRCT against the total lung volume will be calculated. In addition, a chart for mean values ± standard deviation over time will be prepared by treatment group. Moreover, estimated values of the differences between groups, 95% confidence intervals, and p-values (Day 5, at discontinuation/completion of treatment) will be calculated using mixed effect model for repeated measures with the changes from baseline to each time point as the response variable, baseline values as the covariate, time point, treatment group, and treatment group* time point as the fixed effects. A chart for changes in estimated values and 95% confidence intervals over time will be also prepared by treatment group.

Total lung volume	Bilateral lung volume from hilum to periphery excluding trachea and main bronchus (mL)
Normal	CT Value: Volume of the region approximately at -801 HU or lower. *Assuming normal lung
High-density area 1	CT Value: Volume of the region approximately between -800 and -551 HU. *Assuming GGO
High-density area 2	CT Value: Volume of the region approximately at -550 HU or higher *Assuming consolidation

The volume of the following five regions in the entire lungs excluding the trachea and main bronchus will be calculated, and the percentages of those volumes against total lung volume will be calculated. The ranges of CT values for calculation of the volume are as follows.

- Volume_1 : [-801] HU or lower
- Volume_2 : [-800 to -601] HU
- Volume_3 : [-600 to -401] HU
- Volume_4 : [-400 to -201] HU
- Volume_5 : [-200] HU or higher

Summary statistics (number of patients, arithmetic mean, standard deviation, median, minimum, maximum) for the changes from baseline in the percentage of above mentioned each Volume will be calculated by treatment group and by time point. In addition, box-and-whisker plots for the changes from baseline to Day 5 will be prepared in each Volume by treatment group. Estimated values of the differences between groups, 95% confidence intervals, and the p-values will be calculated using generalized estimating equations with the changes in percentages of any Volumes from baseline to Day 5 as the response variable, treatment group, categories of Volume and treatment group * categories of Volume as the fixed effects, and patients as the repeatedly measured correlation group.

2.1.2.10.2.6 Changes from baseline in arterial blood gas values (PaO_2, $PaCO_2$, pH) to each time point.

(1) Analysis set : FAS

(2) Analysis item : measured values and changes in arterial blood gas (each time point - Day 1)

(3) Time point : Day 1, Day 3, Day 5, Day10, at discontinuation/completion of treatment

(4) Analytical method :

1) Summary statistics (number of patients, arithmetic mean, standard deviation, median, minimum, maximum) for measured values of arterial blood gas and changes from baseline to each time point will be calculated by treatment group and by time point. In addition, a chart for changes in the mean ± standard deviation over time will be prepared by treatment group.

2) Estimated values of the differences between groups, 95% confidence intervals, and the p-values (Day 3, Day 5, Day 10) will be calculated using mixed effect model for repeated measures (cLDA method) with the measured values as the response variable, time point, treatment group, and treatment group * time point as the fixed effects, and the patients as the random effect , setting that both groups have the common mean value on Day 1. In addition, a chart for changes in the estimated values and 95% confidence intervals over time will be prepared by treatment group.

3) Estimated values of the differences between groups, 95% confidence intervals, and the p-values (Day5, at discontinuation/completion) will be calculated using mixed effect model for repeated measures with the measured values of arterial blood gas and the changes from baseline to each time point as the response variables, baseline values as the covariate, time point, treatment group, and treatment group * time point as the fixed effects. In addition, a chart for estimated values and 95% confidence intervals over time will be prepared by treatment group.

4) The number of patients and the proportion according to implementation status of arterial blood gas analysis (implemented, implemented while supplementing oxygen because supplementing oxygen could not be suspended, not implemented, not implemented because supplementing oxygen could not be suspended) will be summarizes by treatment group (number of patients, %).

5) A list of outliers in PaO_2 values on Smirnov-Globus test (significance level of 0.1) in any of the treatment groups will be prepared by time point.

2.1.2.10.2.7 Changes from baseline in the inflammatory marker (CRP) and cytokines to each time point.

(1) Analysis set : FAS

(2) Analysis item : changes from baseline in the inflammatory marker (CRP) and cytokines (each time point - Day 1)

(3) Time point : Day 1, Day 3, Day 5, at discontinuation/completion of treatment

(4) Analytical method :

1) Summary statistics (number of patients, arithmetic mean, standard deviation, median, minimum, maximum) for measured values and changes from baseline in inflammatory marker (CRP), cytokine markers (measured values and log2 log-transformed values of IL-6, IL-1β, TNF-α, IL-10, CCL17, CXCL9, MMP-12) and CXCL9/CCL17 ratios to each time point will be calculated by treatment group and by time point. In addition, a chart for the mean ± standard deviation over time will be prepared by treatment group.

2) Estimated values of differences between groups, 95% confidence intervals and the p-values (Day 3, Day 5, at discontinuation/completion of treatment) will be calculated using mixed effect model for repeated measures with and changes from baseline in inflammatory marker (CRP) and cytokine markers (measured values and log2 log-transformed values of IL-6, IL-1β, TNF-α, IL-10, CCL17, CXCL9, MMP-12) and CXCL9/CCL17 ratio to each time point as response variables, baseline values as the covariate, time point, treatment group, and time point * treatment group as the fixed

effects. In addition, a chart for the changes in estimated values and 95% confidence intervals over time will be prepared by treatment group.

2.1.2.10.2.8 Distribution and proportion of patients in each category on a 7-point ordinal scale from Day 0 until Day 28

(1) Analysis set : FAS

(2) Analysis item : 7-point ordinal scale

(3) Time point : Day 0 to Day 28

(4) Analytical method :

1) The number of patients and the proportion in each category on the 7-point ordinal scale shown in Table 2.1 from Day 0 until Day 28 will be summarize by treatment group and by time point (number of patients, %). In addition, a bar chart showing the percentage of each category will be prepared by treatment group and by time point.

2) For patients who were categorized in each category on a 7-point ordinal scale on Day 14 (or at the last observation the point) and Day 28 (or at the last observation time point between Day 15 and Day 27), the p-values (Wilcoxon's rank sum test) of the differences between groups will be calculated.

2.1.2.10.2.9 Distribution and proportion of patients in each category of oxygen requirement until Day14

(1) Analysis set : FAS

(2) Analysis item : oxygen requirement

(3) Time point : Day 0 to Day 14

(4) Analytical method :

1) The number of patients and the proportion in each category on the oxygen requirement shown in Table 2.2 until Day 14 will be summarize by treatment group and by time point (number of patients, %). In addition, a bar chart showing the percentage of each category will be prepared by treatment group and by time point.

2) For patients who were categorized in each category on the oxygen requirement on Day 5 and Day 14, the p-values (Wilcoxon's rank sum test) of the differences between groups will be calculated.

Table 2.2 Oxygen requirement

Category	Ordinal scale
1	Require oxygen supply of 4 L/min or more using oxygen mask
2	Require oxygen supply of 2 L/min or more using nasal cannulas
3	Require oxygen supply of less than 2 L/min using nasal cannulas
4	Do not require oxygen supply but feel shortness of breath during walking or moving
5	Do not require oxygen supply and do not feel shortness of breath during walking or moving

Table 2.3 Definition of event/censoring in Time to event analysis

Analysis item	Event/ Censoring	Definition of event/censoring	Period
・Period to the first improvement by at least 2-rank between baseline and Day 28 on a 7-point ordinal scale ・Period from baseline to the day of discharge ・Period from baseline to shifting to Category 6 or 7 on a 7-point ordinal scale ・Period from baseline to shifting to Category 5 on a 7-point ordinal scale ・Period to from baseline to improvement by 1 rank or more on a 7-point ordinal scale	Event	A patient who developed an event	Period until the onset of the first event
	Censoring	A patient who completed the study without any event	Period until the last observation day
		A patient who discontinued or died	Censored after complementing 29 days*
Period from baseline to shifting to Category 1 or 2 (worsening) on a 7-point ordinal scale	Event	A patient who developed an event	Period from baseline to shifting to Category 1 or 2 (worsening) on a 7-point ordinal scale
	Censoring	A patient who completed the study without any event	Period until the last observation day
		A patient who discontinued or discharged from the hospital	Period until discontinuation or discharge

*Reasons for setting: In the event of early discontinuation due to worsening, the improvement rate may be overestimated due to the drop out of the patient who developed the event from the denominator. This was set in order to conservatively assess the improvement rate.

2.1.2.10.2.10 Other items specified as exploratory

(1) Regarding "No longer required ongoing medical care" defined in Category 6 on the 7- point ordinal scale, period to improvement by at least 2-rank on a 7-point ordinal scale will be recalculated in the case that the end of treatment during tapering of steroid therapy according to the patient's condition has been defined. And similar analysis to the primary endpoint will be performed. The analysis will be performed only in the FAS. The end of treatment is defined as "use of dexamethasone 4 mg (equivalent to prednisolone 25 mg or methylprednisolone 20 mg) or less."

(2) Similar analysis to that in Section 2.1.2.10.2.2 will be performed for the period from baseline to shifting to Category 5 on a 7-point ordinal scale. Patients who are in Category 3 or 4 at baseline on a 7-point ordinal scale will be included in the analysis. Definitions of event/censoring are presented in Table 2.3.

(3) Similar analysis to that in Section 2.1.2.10.2.2 will be performed for the period from baseline to improvement by at least 1 rank on a 7-point ordinal scale. Definitions of events/censoring are presented in Table 2.3.

2.1.2.11 **Safety Evaluation**

2.1.2.11.1 **Adverse Event (AE)**

The names of adverse events (AEs) described in the Case Report Form will be read using the specified version of MedDRA. AEs will be tabulated in SOC and PTs unless otherwise specified. When the causality of an AE with the study drug is considered "related", the event is considered as an adverse drug reaction (ADR).

2.1.2.11.1.1 AE and ADR

(1) Analysis set : SP

(2) Analysis item : AE and ADR

(3) Time point : start of treatment to Day 28

(4) Analytical method :

1) Regarding AEs, serious AEs (SAEs), AEs leading to death, AEs leading to dose reduction of the study drug, AEs leading to discontinuation of the study, and significant AEs, the number of events, the number of patients who developed such events and the proportion will be calculated by treatment group. ADRs will be calculated in the same way.

2) Regarding AEs and ADRs, the number of events, number of patients who developed such events and the proportion will be summarized by treatment group and by SOC and PT (number of patients, number of events, %). Similarly, the data will be summarized by time period.

3) A list of AEs will be prepared Analysis set : Randomized Patients

2.1.2.11.1.2 AE and ADR by severity

The number of events, the number of patients who developed AEs or ADRs and the proportion will be summarized by treatment group, by SOC and PT, and by severity. If the same event occurred more than once in the same patient, the number of patient will be counted only once for the most severe event.

2.1.2.11.1.3 Death, SAEs

A list of deaths and SAEs will be prepared.

2.1.2.11.1.4 Significant AEs

A significant AE includes a non-serious AE leading to discontinuation of the study drug and regarded as a non-SAE that is considered to be of special interest due to its clinical significance. A list of significant AEs will be prepared.

2.1.2.11.2 **Laboratory test**

(1) Analysis set : SP

(2) Analysis item : measured values and changes (each time point - Day 0).

Test item :

< Hematology >

Red blood cell count, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count, hemoglobin, hematocrit

< Blood chemistry >

Total protein, albumin, AST (GOT), ALT (GPT), γ-GTP, ALP, LDH, CK (CPK), total bilirubin,

total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (TGs), BUN, creatinine, blood glucose, Ca, Na, K, P, Cl

< Urinalysis >

Qualitative analysis (occult blood, protein, sugar, urobilinogen)

< Pregnancy test >

Qualitative analysis (urinary hCG or serum hCGs)

(3) Time point: Day 0, Day 5, at discontinuation/completion of treatment

*If more than one test value prior to administration including the value at Unscheduled visit are obtained, the value immediately prior to administration will be used as that on Day 0 (baseline).

(4) Analytical method : :

1) Summary statistics (number of patients, mean, standard deviation, minimum, median, maximum) for the measurement values and changes in each parameter of the blood test will be calculated by treatment group and by time point.

2) A chart for the measurement values of each parameter of each blood test over time in each patient will be prepared by treatment group. Box-and-whisker plots for summary statistics will be also prepared.

3) The number of patients and the proportion based on the qualitative data of each parameter in urinalysis will be summarized by treatment group and by time point (number of subjects, %)

4) A list of measured values outside the reference range of the institution will be prepared.

5) A list of laboratory test data will be prepared. Analysis set : Randomized Patients

6) A list of laboratory reference values of the institution will be prepared. Analysis set : Randomized Patients

2.1.2.11.3 **Vital signs**

(1) Analysis set : SP

(2) Analysis item : measured values and changes (each time point - Day 0)

Test parameter : blood pressure (systolic, diastolic), pulse rate, temperature, respiratory rate

(3) Time point : Day 0, Day 5, at discontinuation/completion of treatment

(4) Analytical method :

1) Summary statistics (number of patients, mean, standard deviation, minimum, median, maximum) for each measured values and changes will be calculated by treatment group and by time point.

2) A chart for measured values of each parameter over time in each patient will be prepared by treatment group.

3) A list of measured values outside the reference range in each institution will be prepared.

4) A list of data on vital signs will be prepared. Analysis set : Randomized Patients

2.1.2.11.4 **Resting 12-lead electrocardiogram (ECG)**

(1) Analysis set : SP

(2) Analysis item : measured values

Test parameter : heart rate

(3) Time point : Day 0, Day 5, at discontinuation/completion of treatment

(4) Analytical method :

1) A chart for measured heart rates of each patient over time will be prepared by treatment group.

2) The number of patients and the proportion based on presence or absence of ECG abnormality will be summarized by treatment group and by time point (number of patients, %).
3) A list of resting12-lead ECG findings will be prepared. Analysis set : Randomized Patients

2.1.2.12 **Interval estimation and level of significance**

As a general rule, the significance level of 5% two-sided will be applied, and a two-sided 95% confidence coefficient (1-α) will be applied for the interval estimation.

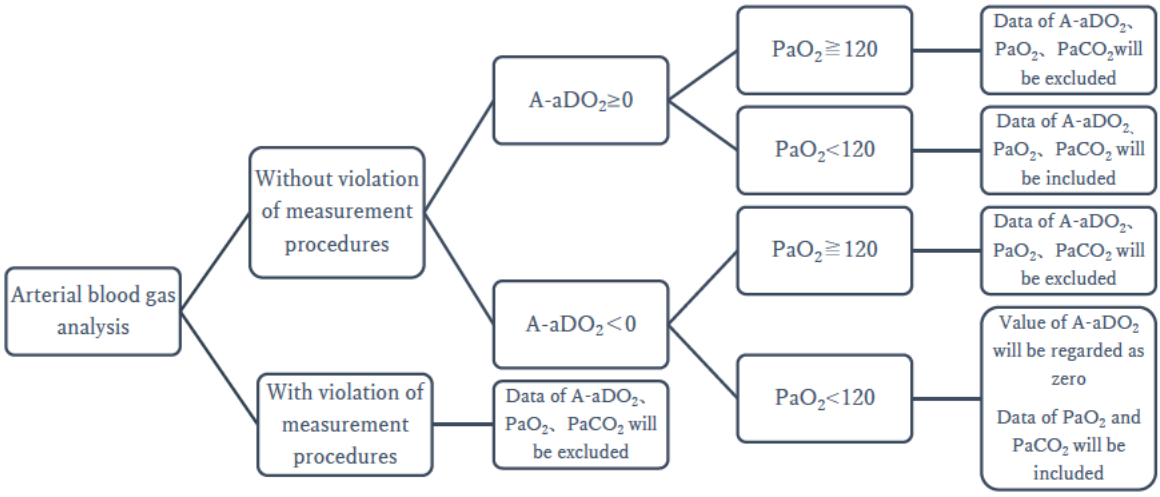
2.1.2.13 **Multiple comparison and multiplicity**

Multiplicity will not be considered.

2.1.2.14 **Handling of missing data, unspecified observations and other inappropriate data**

(1) If a measurement error or another artificial error in the laboratory measurement has been scientifically proven, the re-measurement result will be adopted.
(2) If the cause of an abnormal data is not clear, the data will be used for evaluation.
(3) If any missing data not specified above are found, consultation with the medical expert will be conducted as necessary, and handling of those data will be discussed at the Case Review Committee before data fixation.
(4) If any categorical variables in the efficacy endpoint are missing until the date of completion or discontinuation of the study, the missing category will be set and the data will be summarized after the values have been included in the denominator.
(5) Handling of data on arterial blood-gas analysis (A-aDO_2, PaO_2, $PaCO_2$, pH) at discontinuation/completion of treatment
If the actual date of discontinuation/completion of treatment is Day 1, Day 3, Day 5, or Day 10 from the start of treatment, then the data on the day will be regarded as the data at the time in the analysis.

(6) Arterial blood gas analysis will be handled as shown below



2.1.2.15 **Subgroup analysis**

A subgroup analysis for the analysis defined in Section "2.1.2.10.1 primary endpoint" will be performed (only in the FAS). The factors for subgroup are as follows.

- Sex
- Age (<65 years, ≧65 years)
- With or without concomitant use of antiviral drugs for COVID-19 (excluding Cox's proportional hazards model)
- Class of steroid used (dexamethasone, methylprednisolone or prednisolone, other [mixture of dexamethasone and methylprednisolone or prednisolone])
- Baseline category on a 7-point ordinal scale (3/4/5)

A subgroup analysis for the analysis defined in 2) of Section "2.1.2.11.1.1 AE and ADR" will be performed. The factors for subgroup are as follows.

- Sex
- Age (<65 years, ≧65 years)
- With or without concomitant use of antivirals drugs for COVID-19

2.1.2.16 **Exploratory analysis**

Refer to Section 2.1.2.10.2.10

2.1.2.17 **Interim analysis**

Not applicable.

3 **Changes to conduct of the study or planned analysis (Section 9.8 of Clinical Study Report)**

Not applicable.

4 **Technical details contained in the analysis methodology document (Section 16.1.9 of the Clinical Study Report)**

4.1 **Handling of dating**

(1) Handling of incomplete dating and calculation of the period
Relevant data will be reviewed in the Case Review Committee.

(2) Handling of "discontinuation" and "unspecified examination"
If an examination has been conducted as an examination on the specified Visit, the data will be included in the analysis as the data on the specified Visit. Otherwise, they will not be included in the analysis. Handling of those data will be examined in the Case Review Committee. All the data including those at discontinuation or unspecified examinations will be outputted in the listing.

4.2 **Unit and detection limit**

The unit and reference values for the laboratory test and vital signs will be used as those in the institution, and not be converted.
If any BLQ (Below the lower limit of quantification) or ALQ (Above the upper limit of quantification) values are included in the measured values for cytokine markers, the following lower limit and upper limit will be complemented.
IL-6：4.07 pg/mL - 990.00 pg/mL
IL-1β：16.42 pg/mL - 3990.00 pg/mL
TNF-α：7.33 pg/mL - 1780.00 pg/mL
IL-10：12.72 pg/mL - 1030.00 pg/mL
CCL17：104.40 pg/mL - 25370.00 pg/mL
CXCL9：709.14 pg/mL - 172320.00 pg/mL
MMP-12：47.61 pg/mL - 11570.00 pg/mL
*Based on the final report of the “Validation study of concentration measurement method of cytokines in human serum (M20-0182-02)”.

4.3 **Digits displayed for the statistics**

Item		Digits displayed
Measured value		Same digits as significant digits
Number of cases		Integer
Percentage, ratio		one decimal place
BMI		two decimal places
Summary statistics	Number of patients	Integer
	Mean, median	Rounded off to one significant digit
	Standard deviation, Standard error	Rounded off to two significant digits
	Minimum, maximum	Same digits as significant digits
	95% confidence interval	Rounded off to one significant digit
Testing/estimation	P value	If the value is less than 0.001, then <0.001. If the value is 0.001 or higher, then rounded off to three decimal places

Significant digits: The standard number of digits after the decimal point of the data value. If the data value is not standardized, the maximum number of digits will be adopted.

4.4 **Significant protocol deviation**

Significant protocol deviations are out of the scope of this document.

4.5 **Definition of clinically significant abnormal changes in laboratory data**

Not applicable.

4.6 **Software used for analysis**

Refer to Section "4. Statistical Analysis Environment" of "Statistical Analysis Procedures Ver. 1.0" (February 5, 2021), separately.

4.7 **SAS Code**

- SAS Code for implementing Cox regression model is shown below.

```
ods output ParameterEstimates = [OUTPUT];
proc phreg data = [DATASET];
  class [GROUP] [THERAPY];
  model [TARGET] * [CENSOR FLG](0) = [GROUP] [THERAPY] / rl alpha = 0.05;
run;
```

- SAS Code for implementing MMRM model is shown below.

```
proc mixed data = [DATASET];
  class [SUBJECT] [VISIT] [GROUP];
  model CHG = BASE [VISIT] [GROUP] [VISIT] * [GROUP] /ddfm = KR;
  lsmeans [GROUP]* [VISIT];
  repeated [VISIT]/ subject = [SUBJECT] type = UN;
```

```
run;
```

・SAS Code for implementing analysis using generalized estimating equation is shown below.

```
proc genmod data = [DATASET];
  class [SUBJECT] [VOLUME] [GROUP];
  model CHG = [GROUP] [VOLUME] [GROUP]* [VOLUME] ;
  lsmeans [GROUP]* [VOLUME];
  repeated subject = [SUBJECT] type = UN or CS;
run;
```

・SAS Code for implementing analysis using MMRM model (cLDA method) is shown below.

```
* The coefficient of Estimate must be changed to suit the data.
*The vaslue of DIF3, DIF5, and DIF10 in the active group is 1 at each time point, otherwise 0.
  proc mixed data = [DATASET] order = internal;
    class AVISITN(ref = "1") USUBJID;
    model AVAL_ = AVISITN DIF3 DIF5 DIF10/noint s ddfm = kr;
    random USUBJID;
    /* difference between groups in each time point*/
    estimate "Diff (NPC-26 - Placebo) Day3" DIF3 1    /cl;
    estimate "Diff (NPC-26 - Placebo) Day5" DIF5 1 /cl;
    estimate "Diff (NPC-26 - Placebo) Day10" DIF10 1 /cl;
    /* Mean CHG in each time point in each group */
    estimate "LSMean of Change from BL (Placebo) Day3"      AVISITN 1 0 0 -1 /cl;
    estimate "LSMean of Change from BL (Placebo) Day5"      AVISITN 0 1 0 -1 /cl;
    estimate "LSMean of Change from BL (Placebo) Day10" AVISITN 0 0 1 -1 /cl;
    estimate "LSMean of Change from BL (NPC-26) Day3"      AVISITN 1 0 0 -1 DIF3 1 /cl;
    estimate "LSMean of Change from BL (NPC-26) Day5"      AVISITN 0 1 0 -1 DIF5 1 /cl;
    estimate "LSMean of Change from BL (NPC-26) Day10" AVISITN 0 0 1 -1 DIF10 1 /cl;
    /*Mean AVAL in each time point in each group */
    estimate "LSMean    (Placebo) Day1"      AVISITN 0 0 0 1 /cl;
    estimate "LSMean    (Placebo) Day3"      AVISITN 1 0 0 0 /cl;
    estimate "LSMean    (Placebo) Day5"      AVISITN 0 1 0 0 /cl;
    estimate "LSMean    (Placebo) Day10" AVISITN 0 0 1 0 /cl;
    estimate "LSMean    (NPC-26) Day1"      AVISITN 0 0 0 1 /cl;*This is same as in common with
Placebo;
    estimate "LSMean    (NPC-26) Day3"      AVISITN 1 0 0 0 DIF3 1 /cl;
    estimate "LSMean    (NPC-26) Day5"      AVISITN 0 1 0 0 DIF5 1 /cl;
    estimate "LSMean    (NPC-26) Day10" AVISITN 0 0 1 0 DIF10 1 /cl;
  run;
```