Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS200569-0026
Title	A Phase II, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of M5049 in Hospitalized Participants with COVID-19 Pneumonia
Study Phase	II
Investigational Medicinal Product(s)	M5049
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Integrated Analysis Plan Reviewers	

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Approval Page

Integrated Analysis Plan: MS200569-0026

A Phase II, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of M5049 in Hospitalized Participants with COVID-19 Pneumonia

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within ELDORADO via eSignature. With the approval, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

By using eSignature, the signature will appear at the end of the document.

1 Table of Contents

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2 List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical classification
AVT	Anti-Viral Therapy
BLQ	Below lower limit of quantification
CI	Confidence Interval
C_{max}	Maximum observed concentration
COVID-19	Coronavirus disease 2019
C_{trough}	Concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing)
CV	Coefficient of Variation
eCRF	electronic Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
ECMO	Extra Corporeal Membrane Oxygenation
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FiO_2	Fractional Inspired Oxygen
GeoCV	Geometric Coefficient of Variation
GeoMean	Geometric Mean
HR	Hazard Ratio
IDMC	Independent Data Monitoring Committee
IAP	Integrated Analysis Plan
ICU	Intensive care unit
ITT	Intention to treat
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events

OR	Odds Ratio
PaO_2	Arterial Oxygen Partial Pressure
CCI	[redacted]
PT	Preferred Term
PK	Pharmacokinetic(s)
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SpO_2	Peripheral Capillary Oxygen Saturation
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time to Maximum Concentration
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	08-AUG-2020	PPD	Not applicable, as first version.
2.0	29-APR-2021	PPD	Primary efficacy endpoint was changed. Intent-To-Treat Analysis Set and Safety Analysis Set definitions were updated. Subgroup selection and analysis per subgroups were updated. Additional imputation rules for missing data were added. Analysis visits were described. Subject disposition analysis was updated. Censoring rules for time-to-event analysis were updated. Inclusion of stratification factors to the models was updated. Time to hospital discharge analysis was added. Sensitivity analysis was kept only for the primary efficacy endpoint. Randomization date/time was replaced with first dose date/time for all duration and time-to calculations. Appendix 2 was removed.

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the analysis of data collected for protocol MS200569-0026 (ANEMONE). Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). CCI [redacted] Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon Section 10 (Statistical Considerations) of the study protocol and is prepared in compliance with ICH E9. Details of the IDMC analyses of the participants' safety and PK are also described. The first version of this IAP was finalized before the first IDMC data review meeting, scheduled once the first 15 patients complete their 14-day treatment period. The current version of the IAP incorporates changes resulting from protocol amendments as described in protocol version 4.0 dated 01 March 2021, notably the change of primary endpoint.

5 Objectives and Endpoints

5.1 Part A Objectives

Part A objectives will be separately described only in case of early termination of the study for safety reasons before the start of Part B, otherwise all data from all study participants from Part A and Part B will be combined.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)	IAP SECTIONS
Primary		
To assess the safety of M5049 compared to placebo.	• Incidence of TEAEs, AESIs, TEAEs leading to treatment discontinuation, and SAEs from Day 1 through Day 60. • Clinically significant changes in laboratory parameters and ECGs from Day 1 through Day 28.	• 15.1 • 15.3 and 15.5
Secondary		
To evaluate clinical deterioration with M5049 compared to placebo.	• Time to ICU (Day 1 through Day 28). • Time to invasive mechanical ventilation (Day 1 through Day 28).	• 14.2.5 • 14.2.7
To evaluate the change in clinical status with M5049 compared to placebo.	Clinical status from Day 1 through Day 60 (on a 9-point ordinal scale): **0.** Uninfected: no clinical or virological evidence of infection. **1.** Ambulatory: no limitation of activities.	14.2.2

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)	IAP SECTIONS
	2. Ambulatory: limitation of activities. **3.** Hospitalized, mild disease: hospitalized, no oxygen therapy. **4.** Hospitalized, mild disease: oxygen by mask or nasal prongs. **5.** Hospitalized, severe disease: noninvasive ventilation or high flow-oxygen. **6.** Hospitalized, severe disease: intubation and mechanical ventilation. **7.** Hospitalized, severe disease: ventilation + additional organ support – e.g., pressors, RRT, ECMO. **8.** Death.	
To assess the PK of M5049.	Pharmacokinetic parameters: C_{max}, t_{max}, λ_z, $t_{1/2}$, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}12h}$, $AUC_{0\text{-}\infty}$, CL/F, V_z/F, C_{max}/D, $AUC_{0\text{-}tlast}$/D, $AUC_{0\text{-}12h}$/D, $AUC_{0\text{-}\infty}$/D, $R_{acc}(AUC_{0\text{-}12h})$, $R_{acc}(C_{max})$ on Day 1 and Day 7..	16.1

AESI = adverse event of special interest; CL/F = apparent total body clearance of study intervention following extravascular administration; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; IAP = Integrated Analysis Plan; ICU = intensive care unit; λz = elimination rate constant; PK = pharmacokinetic; RRT = rapid response team; SAE = serious adverse event; TEAE = treatment-emergent adverse event; V_z/F = apparent volume of distribution.

5.2 Part B Objectives

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)	IAP SECTIONS
Primary Efficacy		
To evaluate the time to recovery in participants hospitalized due to COVID-19 pneumonia with M5049 compared to placebo.	Time to recovery from Day 1 through Day 28, defined as time from Day 1 to first occurrence of WHO 9-point ordinal scale 3 or less.	14.1
Primary Safety		
To assess the safety of M5049 compared to placebo.	• Incidence of TEAEs, AESIs, TEAEs leading to treatment discontinuation, and SAEs from Day 1 through Day 60. • Clinically significant changes in laboratory parameters and ECGs from Day 1 through Day 28.	• 15.1 • 15.3 and 15.5
Secondary		
To assess the proportion of participants free of respiratory support with M5049 compared to placebo.	Alive and not requiring supplemental oxygenation (including any supplemental oxygen, noninvasive or mechanical ventilation and ECMO) through Day 28.	14.2.1
To evaluate the change in clinical status with M5049 compared to placebo.	Clinical status from Day 1 through Day 60 (on a 9-point ordinal scale): **0.** Uninfected: no clinical or virological evidence of infection. **1.** Ambulatory: no limitation of activities. **2.** Ambulatory: limitation of activities. **3.** Hospitalized, mild disease: hospitalized, no oxygen therapy. **4.** Hospitalized, mild disease: oxygen by mask or nasal prongs. **5.** Hospitalized, severe disease: noninvasive ventilation or high flow-oxygen. **6.** Hospitalized, severe disease: intubation and mechanical ventilation. **7.** Hospitalized, severe disease: ventilation + additional organ support – e.g., pressors, RRT, ECMO. **8.** Death.	14.2.2
To assess normalization of oxygenation status with M5049 compared to placebo in participants who are alive and not on mechanical ventilation.	Time to SpO_2 of ≥ 94% sustained for at least 24 hours in room air from Day 1 through Day 28. Further referred as "time to SpO_2 improvement"	14.2.3

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)	IAP SECTIONS
To evaluate the numbers of deaths with M5049 compared to placebo.	All-cause mortality (Day 1 through Day 60).	14.2.4
To evaluate clinical deterioration with M5049 compared to placebo.	• Time to ICU (Day 1 through Day 28). • Time to invasive mechanical ventilation (Day 1 through Day 28). • Time to noninvasive mechanical ventilation (Day 1 through Day 28).	• 14.2.5 • 14.2.7 • 14.2.6
To assess the length of stay in the ICU with M5049 compared to placebo.	Total days in ICU from Day 1 through Day 60.	14.2.8
To assess the length of hospital, stay with M5049 compared to placebo.	• Total days in the hospital from Day 1 through Day 60. • Time to hospital discharge from Day 1 to Day 28	14.2.9
To evaluate modulation of biomarkers of COVID-19 inflammation with M5049 compared to placebo.	Inflammatory biomarkers (CRP, d-dimer, and ferritin) during study period (Day 1 through Day 28).	14.2.10
To evaluate modulation of select biomarkers with M5049 compared to placebo.	Biomarkers (IL-6, TNF alpha, IL-8) during study period (Day 1 through Day 28).	14.2.11
To evaluate occurrence of relapse with M5049 compared to placebo.	Occurrence of relapse in participants during the study period (if first discharged within the 60-day study period). Relapse refers to worsening oxygenation, with either a positive result of any respiratory pathogenic nucleic acid test, or worsening lesions on chest imaging with re-hospitalization.	14.2.12
To assess occurrence of re-hospitalizations due to COVID-19 disease complications.	Occurrence of re-hospitalization in participants during the study period (if first discharged within the 60-day study period) due to COVID-19 disease complications (Day 5 through Day 60)	14.2.13

[redacted]

AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; C_{trough} = predose observed concentration; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; IAP = Integrated Analysis Plan; ICU = intensive care unit; IFN = interferon; CCI ; PK = pharmacokinetic; CCI RRT = rapid response team; SAE = serious adverse event; SARS-CoV = severe acute respiratory syndrome coronavirus; SpO_2 = peripheral capillary oxygen saturation; TEAE = treatment-emergent adverse event; CCI

6 Overview of Planned Analyses

All statistical analyses, with the exception of listings provided for internal Independent Data Monitoring Committee (IDMC) meeting 1, will be performed on the basis of CDISC SDTM data, used as source for CDISC ADaM data creation. These SDTM data contain as clean as possible eCRF data as well as external data including pharmacokinetics (PK) data CCI CCI

6.1 Analyses for IDMC meeting 1

The IDMC meeting 1 was held to assess the safety of the investigational treatment, to safeguard the interests of study participants and to monitor the overall conduct of the clinical study.

Once all Part A participants completed the 14 days treatment period or discontinued from study prematurely, a data snapshot of as clean as possible eCRF data was taken for provision of IDMC outputs. The data cut-off was the date of data snapshot.

The IDMC was provided with a subset of partially unblinded safety data using group-level masking. The data included demographics, adverse events, deaths, ICU admission, use of mechanical ventilation.

Pooled dose-normalized PK summary statistics across dose groups was provided to the IDMC CCI .

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Further details on the full membership, mandate, and processes, analyses and data handling for IDMC are presented in the documents listed below:

- IDMC Charter and appendices
- Listings for IDMC1 meeting (shells)
- Unblinding Plan

6.2 Analyses for subsequent IDMC Meetings

Additional IDMC meetings were held to review accumulating safety data as defined in the Clinical Study Protocol (CSP) and to monitor the overall conduct of the clinical study. Blinded and partially blinded outputs were created to support IDMC safety review based on the list reported in the "MS200569_0026_TOC_Section15" Excel document.

6.3 Final Analysis

This analysis will be the main analysis. All planned analyses identified in the study protocol and in this IAP will be performed only after the last participant has completed the safety follow up period with all study data in-house, and the database will be locked for the analysis.

A data review meeting will be held prior to any database lock.

7 Changes to the Planned Analyses in the Clinical Study Protocol

The inclusion of all stratification factors is identified as a potential source of problems in the implementation and interpretation of statistical models used to analyze efficacy. For this, use of corticosteroids before randomization and country will only be included, as deemed the most relevant factors, while presence of obstructive lung disease and use of antiviral therapy before randomization will be analyzed as subgroups.

8 Analysis Populations and Subgroups

8.1 Definition of Analysis Populations

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock and unblinding.

Enrolled Analysis Set

The Enrolled Analysis Set includes all participants who sign informed consent and will be used to report disposition data.

Intent-To-Treat Analysis Set (ITT)

The ITT consists of all treated participants and it will be used for the primary efficacy analysis.

Participants will be analyzed according to the actual treatment received, which will be determined based on the treatment taken just after randomization, as collected in the electronic Case Report Form (eCRF). Occurrences of mistreatment (i.e. a different treatment from the one assigned via randomization) will be evaluated on a case by case basis.

Safety Analysis Set (SAF)

The SAF consists of all participants who received at least one dose of study intervention and is used for evaluation of safety endpoints.

Participants will be analyzed according to the actual treatment received, which will be determined based on the treatment taken just after randomization, as collected in the eCRF. Occurrences of mistreatment will be evaluated on a case by case basis.

Therefore, the ITT and the SAF are the same population and can be used interchangeably.

Pharmacokinetics Analysis Set (PKAS)

The PKAS will include all participants who received at least one dose of active treatment, for whom at least one quantifiable post dose plasma concentration of M5049 is obtained, and without any relevant protocol deviations and absence of factor that may have an influence on PK. It will be used for the evaluation of PK endpoints.

Participants will be analyzed according to the actual treatment received, which will be determined based on the treatment taken just after randomization, as collected in the eCRF. Occurrences of mistreatment will be evaluated on a case by case basis.

Pharmacodynamics Analysis Set (PDAS)

The PDAS will include all participants who received at least one dose of study intervention, for whom at least one post-baseline biomarker result is obtained and without any relevant protocol deviations or events that may have an influence on pharmacodynamics. It will be used for the evaluation of endpoints related to inflammatory and CCI biomarkers.

Participants will be analyzed according to the actual treatment received, which will be determined based on the treatment taken just after randomization, as collected in the eCRF. Occurrences of mistreatment will be evaluated on a case by case basis.

Analyses per Analysis Sets

The following table summarizes the use of the analysis sets in the different analyses.

	Analysis Sets		
Analyses	**ITT/SAF**	**PKAS**	**PDAS**
Baseline Characteristics	✓		
Previous and Concomitant Therapies	✓		
Compliance and Exposure	✓		
Efficacy: Primary	✓		
Other Efficacy	✓		
Inflammatory CCI Biomarkers			✓
Pharmacokinetics		✓	
Safety	✓		

8.2 Subgroup Definition and Parameterization

The following factors, based on data collected on the eCRF, will be used as cofactors for all the stratified analyses:

- Treatment with corticosteroids therapy within 48 hours from randomization (as collected in the 'Randomization' eCRF page)
    - Corticosteroids dose ≤ 15 mg of prednisone-equivalent (reference level)
    - Corticosteroids dose > 15 mg of prednisone-equivalent

- Country
    - United States of America (reference level)
    - Philippines
    - Brazil

The following subgroups then, including the two stratification factors defined above and based on information collected at baseline, will be defined:

Comorbidities:

- Presence of obstructive lung disease (as collected in the 'Medical History' eCRF page)
    - No (reference level)
    - Yes
- Obesity based on BMI
    - No: Body Mass Index (BMI - derivation described at Section 11.1) < 30 kg/m^2 (reference level)
    - Yes: BMI ≥ 30 kg/m^2
- Diabetes co-morbidity at study entry (as collected in the 'Medical History' eCRF page)
    - No (reference level)
    - Yes
- Heart diseases co-morbidity at study entry (as collected in the 'Medical History' eCRF page)
    - No (reference level)
    - Yes
- Hypertension co-morbidity at study entry (as collected in the 'Medical History' eCRF page)
    - No (reference level)
    - Yes

- Number of relevant comorbidities (derived for each participant counting the number of comorbidities among the ones listed above, including obesity based on BMI):
    - No (reference level)
    - Yes: 1 or 2
    - Yes: more than 2

Use of Relevant Therapies at baseline:

- Treatment with corticosteroids therapy within 48 hours from randomization (as collected in the 'Randomization' eCRF page)
    - Corticosteroids dose $\leq$ 15 mg of prednisone-equivalent (reference level)
    - Corticosteroids dose > 15 mg of prednisone-equivalent
- Treatment with antiviral therapy (AVT) including convalescent serum within 48 hours from randomization (as collected in the 'Randomization' eCRF page)
    - No (reference level)
    - Yes

Demographic characteristics:

- Age (derivation described at Section 11.1)
    - Age < 60 (reference level)
    - Age $\geq$ 60
- Gender
    - Male (reference level)
    - Female
- Ethnicity
    - Hispanic or Latino
    - Not Hispanic nor Latino (reference level)

Other characteristics:

- Country
    - United States of America (reference level)
    - Philippines
    - Brazil
- Site
- Smoking status at study entry (as collected in the 'Substance Usage' eCRF page)
    - Smoker (former, or regular tobacco use)
    - Non-Smoker (never used tobacco, reference level)

Subgroup analyses will be performed on primary and selected secondary efficacy endpoint as defined below. CCI

For the definition of subgroup level, data as documented in the eCRF will be taken. The category "missing" will not be included in any subgroup analysis.

For subgroups with two categories only, in case of less than 9 participants within each category the subgroup will not be considered for the analysis.

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9 General Specifications for Data Analyses

This section describes any general specifications not included in subsequent sections.

Part A objectives will be separately described only in case of early termination of the study for safety reasons, otherwise all data from all study participants from Part A and Part B will be combined.

Study treatment groups are defined and labeled as Placebo, M5049 50 mg BID, and M5049 100 mg BID. Unless otherwise indicated, all tables will be presented by study treatment groups. For demographics, baseline and safety data a total column is also presented.

The "start date" for this study is the first dose date (Day 1).

Unless otherwise specified, comparisons will be presented for each dose of M5049 versus placebo.

In this study there will be no hypothesis testing: therefore, all statistical tests mentioned in this IAP are to be regarded as exploratory. Exploratory statistical tests comparing study treatment groups will be performed two-sided and confidence intervals (CI) will be two-sided with a confidence probability of 95%, unless otherwise specified in this IAP.

All analyses will be performed using SAS® Software Version 9.2 or higher, with the exception of M5049 PK parameters which will be derived using noncompartmental methods with the validated computer program PPD or higher PPD

9.1 Presentation of continuous and qualitative variables

Continuous variables other than PK will be summarized using the following descriptive statistics, i.e.

- number of subjects with non-missing values (n)
- mean, standard deviation

- median, 25th Percentile - 75th Percentile (Q1-Q3)
- minimum (Min) and maximum (Max)

Missing statistics, e.g. when they cannot be calculated, should be presented as "nd". For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as "nd".

Qualitative variables will be summarized by counts and percentages.

Mean, median, Q1, Q3, Min, and Max will have the same precision as collected in SDTM datasets for non-derived data. Standard deviation will be presented with 1 digit more than the mean. Percentage and percent change from baseline will be reported using 1 decimal digit, if not specified otherwise.

Unless otherwise stated, the calculation of proportions will be based on the number of subjects in the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

For variables where a subject may have more than one category due to multiple responses per subject (i.e. not mutually exclusive categories), the number of subjects included in each category will be summarized as a percentage from all subjects. Therefore, the total frequency across categories may not equal the total number of all subjects in the population.

9.2 Presentation of Pharmacokinetic Results

9.2.1 Presentation of Pharmacokinetic Concentration Data

M5049 concentration data will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), SD, coefficient of variation (CV%), minimum (Min), median (Median), and maximum (Max). In cases with $n \leq 2$, only n, Min, and Max will be reported.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data and rounded for reporting purposes only. The following conventions will be applied when reporting descriptive statistics of PK concentration data:

Mean, Min, Median, Max:	3 significant digits
SD:	4 significant digits
CV%:	1 decimal place

9.2.2 Presentation of Pharmacokinetic Parameter Data

Pharmacokinetic parameter data will be descriptively summarized using: n, Mean, SD, CV%, Min, Median, Max, geometric mean (GeoMean), the geometric coefficient of variation (GeoCV), and the 95% CI for the GeoMean (LCI 95% GM, UCI 95% GM). For time to reach maximum observed

concentration (t_{max}), only n, Min, Median, and Max will be reported. In cases with n ≤ 2, only n, Min, and Max will be reported. The PK parameter maximum observed plasma concentration (C_{max}) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. In export datasets, as well as in the SDTM PP domain, PK parameters will be provided with full precision, and will not be rounded. Descriptive statistics of PK parameter data will be calculated using full precision values, and rounded for reporting purposes only.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

Mean, Min, Median, Max, GeoMean, 95% CI:	3 Significant digits
SD:	4 Significant digits
CV%, GeoCV%:	1 decimal place

9.3 Definition of Baseline and Change from Baseline

In general, the last non-missing measurement prior to first dose will serve as baseline measurement.

Unless otherwise specified, if a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be analyzed similar to an unscheduled post-dose measurement.

Absolute and percent changes from baseline are defined as:

absolute change = analysis visit value – baseline value

percent change = 100 * (analysis visit value – baseline value) / baseline value

9.4 Study Treatment Day

Day 1 is the day of first study drug administration, the day before is Day -1 (no Day 0 is defined). Study day is defined relative to Day 1.

9.5 Definition of Duration and 'time since' Variables

Durations in days will be calculated by the difference of start and stop date/time (e.g. survival time (days) = date/time of death – date/time of first dose) if not otherwise specified.

The time since an event (e.g. time since diagnosis) will be calculated as reference date/time minus date/time of event, when available.

9.6 Conversion Factors

The following conversion factors will be used to convert days into months or years:

1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

If height is recorded in inches, height (cm) = height (in) × 2.54.

If weight is recorded in pounds, weight (kg) = weight (lbs) ÷ 2.2046.

9.7 Definition of On-treatment Period

The on-treatment period is defined as any time on or after the first dose of study treatment.

The on-treatment period ends with the date of last contact or death, whichever occurs first.

9.8 Imputation of Missing Data

Unless otherwise specified all data will be evaluated as observed, and no imputation method for missing values will be used, with the exception of:

- Handling of missing data for PK parameter calculations is discussed under Section 16.1;
- Handling of the following data, for which imputed values will be presented in all participant data listings and imputed information will be flagged:

Adverse events	Incomplete AE-related dates will be imputed as follows: • If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment. If the end date or resolution date indicates that the AE has stopped before start of treatment, this date will be used for imputation instead of start of treatment date. • If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015. If the end date or resolution date indicates that the AE has stopped before start of treatment, this date will be used for imputation instead of start of treatment date. • If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014. If the end date or resolution date indicates that the AE has stopped before start of

	treatment, this date will be used for imputation instead of start of treatment date. • In all other cases the missing onset day and/or missing onset month will be replaced by 1. • Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case the date of death will be used to impute the incomplete stop date. • In all other cases the incomplete stop date will not be imputed. If stop date of AE is after date of cut-off this date will be kept. Incomplete AE-related times will be imputed as follows: • If the AE onset time is missing, but the date is equal to the start of study treatment, then the AE onset time will be replaced by the start time of study treatment. • In all the other cases missing start time will not be imputed. • Incomplete stop times will not be imputed.
Concomitant Medications	For identification of previous or concomitant medications/procedures, no formal imputation will be performed on missing or incomplete dates. Rules presented in Table 2 will be used to define if a medication/procedure is considered as a previous, concomitant or both previous and concomitant medication/procedure.
Exposure	Incomplete exposure times will be imputed as follows: • If the first dose time is missing, then: o if the first dose date is equal to date of randomization then the first dose time will be imputed as the time of randomization. o if the first dose date is after the date of randomization then the first dose time will be imputed: ▪ as 08:00 if timing = "Morning" or unknown ▪ as 20:00 if timing = "Evening" • If the last dose time is missing, then, it will be imputed: o as 08:00 if timing = "Morning" or unknown o as 20:00 if timing = "Evening".
ICU admission and discharge	Incomplete ICU admission dates will be imputed as follows: • If the ICU admission day is missing, it will be imputed as the latest between 1st day of the month and the date of hospital admission. • In all other cases ICU admission date will not be imputed

	Incomplete ICU times will be imputed as follows: • If the ICU admission time is missing, but the date is equal to the start of study treatment, then the ICU admission time will be replaced by the start time of study treatment. • In all the other cases, ICU admission time will be imputed as 00:00. • Incomplete discharge times will be imputed as 23:59, if not resulting in a date and time later than the date and time of participant's death. In the latter case the time of death will be used to impute the incomplete discharge time.
Hospital discharge	Incomplete hospital discharge dates will be imputed as follows: • If the hospital discharge day is missing, it will be imputed as the last day of the month. • In all other cases hospital discharge date will not be imputed

Table 1 Stopping rules for medication/procedure end dates

End date of medication/procedure			Rules to derive medication/procedure stop
Day	Month	Year	
UNK	UNK	UNK	After treatment start (ongoing)
UNK	UNK	< Treatment start (year)	Before treatment start
UNK	UNK	>= Treatment start (year)	After treatment start
UNK	< Treatment start (month and year)		Before treatment start
UNK	>= Treatment start (month and year)		After treatment start
< Treatment start (complete date)			Before treatment start
>= Treatment start (complete date)			After treatment start

UNK = Unknown

Table 2 Rules to define previous and/or concomitant medication

Start date of medication/procedure			Stopping rule (see Table 1)	Medication/procedure
Day	Month	Year		
UNK	UNK	UNK	Before treatment start	Previous
UNK	UNK	UNK	After treatment start	Previous and concomitant
UNK	UNK	<= Treatment start (year)	Before treatment start	Previous
UNK	UNK	<= Treatment start (year)	After treatment start	Previous and concomitant
UNK	UNK	> Treatment start (year)	After treatment start	Concomitant
UNK	<= Treatment start (month and year)		Before treatment start	Previous
UNK	<= Treatment start (month and year)		After treatment start	Previous and concomitant
UNK	> Treatment start (month and year)		After treatment start	Concomitant
<= Treatment start (date)			Before treatment start	Previous
<= Treatment start (date)			After treatment start	Previous and concomitant
> Treatment start (date)			After treatment start	Concomitant

UNK = Unknown

9.9 Analysis visit windows

For endpoints to be reported by visit, the following analysis visit windows will be defined:

- Baseline (see Section 9.3 for definition)
- Analysis Day 2
- Analysis Day 3
- Analysis Day 4
- Analysis Day 5: Day 5 and 6
- Analysis Day 7: Day 7 and 8
- Analysis Day 10: from Day 9 to Day 11
- Analysis Day 14: from Day 12 to Day 17
- Analysis Day 21: from Day 18 to Day 24
- Analysis Day 28: from Day 25 to Day 35
- Analysis Day 44: from Day 36 to Day 52
- Analysis Day 60: from Day 53 onwards

In case of multiple assessments collected within the same window, the one closest to the target date will be used for summary statistics. All the assessments will be used for worst case analyses.

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study treatment/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Participants and Discontinuations

Disposition information will be collected in the 'Demography', 'Exposure', 'End of Study Treatment' and 'Disposition' eCRF pages.

The number and percentage of participants in each of the below disposition categories will be presented by actual treatment group for the enrolled analysis set. Percentages will be presented with respect to the number of treated participants

- Total number of participants enrolled (i.e. participants who gave informed consent)
- Number of participants who discontinued from the study prior to randomization overall and grouped by the main reason (e.g. the failed specific inclusion or exclusion criteria, withdrawal of consent)

- Number of randomized participants.

The treatment status will be summarized as follows:

- Number and percentage of participants who did not receive any dose of study treatment
- Number and percentage of participants who took at least one dose of study treatment.

The end of treatment status will be summarized by:

- Number and percentage of treated participants who completed study treatment (defined as participants which completed the full course of the study as per 'End of Study Treatment' eCRF page).
- Number and percentage of treated participants who discontinued the study treatment, overall and by primary reason.

The end of study status will be summarized by number and percentage of treated participants who completed or prematurely discontinued the study after randomization, grouped by main reason.

Additionally, the number of participants enrolled, and treated in each analysis set will be provided overall, by country and by site.

The results of the randomization algorithm (according to IWRS) will be summarized as follows:

- Cross tabulation: participants randomized (Placebo / M5049 50 mg BID / M5049 100 mg BID) vs. treated (Placebo / M5049 50 mg BID / M5049 100 mg BID)
- Cross tabulation: participants randomized to each stratum according to the IWRS vs. stratum according to the eCRF

The following listings will be created to report disposition information:

- Subject disposition: presenting information related to informed consent signature, protocol version, randomization and screen failure status for the enrolled analysis set
- Discontinued subjects: presenting information of treatment and study discontinuation for the ITT/SAF analysis set
- Randomization scheme: presenting information on randomization and analysis strata for all the subjects randomized or treated.

10.2 Protocol Deviations / Exclusion from Analysis Populations

10.2.1 Important Protocol Deviations

Important protocol deviations (IPDs) are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

They will be identified for all participants by either site monitoring, medical review processes or programming and confirmed prior to or at the Data Review Meeting at the latest.

All important protocol deviations are documented in SDTM datasets whether identified through site monitoring, medical review or programming.

A full list of potential protocol deviations including definition and categorization is maintained in the most recent study protocol deviation guide.

Important protocol deviations will be summarized by category.

A listing of important protocol deviations will be provided based on the ITT/SAF.

10.2.2 Reasons Leading to the Exclusion from an Analysis Population

A listing presenting reasons of exclusion from PK/PD analysis sets will be provided.

11 Demographics and Other Baseline Characteristics

If not stated otherwise, the following analyses will be performed based on the ITT/SAF, by treatment groups and overall.

11.1 Demographics

Demographic characteristics and physical measurements will be summarized descriptively using the following information from the 'Demography' and 'Screening Vital Signs' eCRF pages.

The following demographic characteristics will be included:

- Sex: male, female
- Race: white, black or African American, Asian/ Pacific Islander, American Indian or Alaska Native, more than one race, other, unknown
- Ethnic origin: Hispanic or Latino/Not Hispanic or Latino
- Age (years)
- Age categories:
  - < 60 years,
  - ≥ 60 years
- Country: Brazil, Philippines, United States of America
- Site
- Height (cm) at Baseline

- Weight (kg) at Baseline
- BMI (kg/m^2) at Baseline
    - < 30 kg/m^2,
    - ≥ 30 kg/m^2

Specifications for computation:

- Age [years]
    - (date of given informed consent - date of birth + 1) / 365.25
    - In case of missing day for at least one date, but month and year available for both dates: For the derivation of age, the day of informed consent and the day of birth will be set to 1 and the formula above will be used
    - In case of missing month for at least one date, but year available for both dates: For the derivation of age, the day and the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used

  The integer part of the calculated age will be used for reporting purposes.
- BMI [kg/m²] = $\frac{\text{weight [kg]}}{\text{height[cm]}^2} \times 10000$

All demographic data will be reported in listings.

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using MedDRA version 23.0 or higher, preferred term (PT) as event category and system organ class (SOC) body term as Body System category. Each participant will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables, ordered by primary SOC and PT in alphabetical order, and listed.

11.3 Other Baseline Characteristics

Tobacco consumption will be collected in the 'Substance Usage' eCRF page. The following information will be summarized together with demographic characteristics:

- Tobacco Status;

The following disease history characteristics will be summarized overall and by treatment group:

- Based on data from 'Medical History" eCRF page
    - Time since COVID-19 symptoms onset (days)
    - Time since diagnosis (days)

- Presence of the following co-morbidities:
  - Diabetes
  - Heart disease
  - Obstructive lung disease
  - Other lung disease
  - Chronic liver disease
  - HIV
  - Tuberculosis
  - Central nervous system disease
  - Hypertension

- Based on data from 'COVID Symptom Assessment" eCRF page
  - Presence of each of the following COVID-19 symptoms at study entry
    - Cough
    - Fever
    - Myalgia
    - Diarrhea
    - Dyspnea
    - Fatigue/malaise
    - Loss of appetite
    - Loss of smell
    - Loss of taste

'Time since' disease history characteristics, in days, will be calculated as follows:

- Time since symptoms onset (days) = (Date of first administration of study treatment - Date of symptoms onset)
- Time since diagnosis (days) = (Date of first administration of study treatment - Date of diagnosis)

The following listings will be created:

- Tobacco use
- Co-morbidities

- COVID symptoms.

Baseline characteristics with respect to vital signs, and hematology/biochemistry will be part of Section 15 (Safety Analysis).

12 Previous or Concomitant Medications/Procedures

The following analyses will be performed based on the ITT/SAF analysis set by study treatment group.

Concomitant treatments are medications, other than study treatment, which are taken by participants any time during the on-treatment period, see Section 9.7.

Previous medications are medications, other than study treatment, which started before first administration of study treatments.

A medication may be classified as both concomitant and previous. The respective flags will be derived based on start and end date.

Partially or completely missing medication start and stop dates will be handled as described in Section 9.8.

Previous and concomitant treatments will be summarized separately by number and percentage of participants from the "Concomitant medications" eCRF page. Anatomical Therapeutic Chemical classification (ATC) 2nd level and preferred term will be tabulated as given from the WHO-DD dictionary most current version. If any medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted by decreasing frequency of drug class and decreasing frequency of drug name in a given drug class in the total column. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have an ATC classification level 2 coded term, it will be summarized under "UNCODED ATC classification" category. Each participant will only be counted once per medication, even if he/she received the same medication at different times.

All medications (prior, and concomitant) will be listed.

All **concurrent procedures**, collected in the "Related Procedures" eCRF page, will be coded using MedDRA version 23.0 or higher and reported in listings.

13 Study Treatment: Compliance and Exposure

The following analyses will be performed based on the ITT/SAF analysis set by treatment group.

All dosing calculations and summaries will be based on "Exposure" eCRF page. Each participant is expected to be treated with the drug assigned by the randomization system for 14 consecutive days, twice per day.

In case of discharge from the hospital before the end of treatment period, the participant will be instructed to take the study treatment at home and a diary card will be handled to collect daily dosing information.

In case the start date is missing or incomplete, it is assumed that the first dose of study treatment is given at the randomization date.

Duration of exposure to study drug (days) = (end date/time – date/time of first dose of study drug), where end date/time is the date/time of last dose of study drug.

Dose administered at each administration will be derived as follows:

- Participants randomized to M5049 50 mg = number of tablets administered * 12.5 mg
- Participants randomized to M5049 100 mg = number of tablets administered * 25 mg

Cumulative dose is the sum of all doses administered.

Compliance will be derived using information from 'Drug accountability' eCRF page.

Compliance (%) = 100× (Number of tablets taken / Number of planned tablets to be taken)

where:

- Number of tablets taken = (total number of tablets dispensed – total number of tablets returned)
- Number of planned tablets = Planned duration of exposure (i.e. 14 days) × Number of planned tablets per day (i.e. 8 tablets/day) = 112 tablets

In case of study drug not returned and amount returned missing, it will be assumed that all tablets have been taken for compliance calculation. Considering that 120 tablets are dispensed to ensure the subject has sufficient stock, compliance for subjects not returning any tablet will be 107% = 120/112*100).

The summary of treatment exposure will include the following information:

- Exposure duration (days)
- Cumulative dose (mg)
- Compliance (%)

A separate listing will be presented for:

- Treatment exposure
- Drug accountability
- Exposure and compliance parameters
- Subjects receiving investigational product(s) from specific kits.

14 Efficacy Analyses

The following analyses will be performed based on the ITT by treatment group except when otherwise stated.

For the time to event analysis, failure will be defined as follows:

Definition	eCRF page	Value
Invasive or Non-Invasive Mechanical Ventilation	Ordinal Scale on Clinical Severity	Ordinal Scale on Clinical Severity >= 5
ICU admission leading to treatment discontinuation (both the following conditions)	End of study treatment AND Hospitalization	Did the subject complete the full course of study treatment? = NO AND Date of treatment completion/discontinuation occurring during ICU/HDU stay
Relapse	Date of Visit	Reason for Relapse completed

14.1 Primary Endpoint: Time to Recovery

14.1.1 Primary Objective: Derivation and Analysis of the Primary Endpoint Time to Recovery

The primary efficacy variable is the time to recovery, defined as the time from first dose (Day 1) through Day 28 to first occurrence of WHO 9-point ordinal scale 3 or less, in days:

- Time to recovery (days) = (Date/time of first ordinal scale for clinical severity <= 3 – Date/time of first dose)

The rules for the different types of censoring/event below will be followed:

#	Description	Date of Response or Censoring	Outcome
1	Death from Day 1 up to D60/Study completion	D28	Censored
2	Failure at any point and time during the study from D1 up to D28, defined as: * ICU admission leading to treatment discontinuation * use of mechanical ventilation * relapse	D28	Censored
3	Participant not confirmed to be eligible based on inclusion criterion 6 (PDEV05 code)	Date of first dose of study drug	Censored
4	No post-baseline clinical status data	Date of first dose of study drug	Censored
5	Clinical status <= 3 before Day 28	Date of clinical status <=3	Event
6	Clinical status > 3 through Day 28 without death or failure	D28	Censored
7	Early discontinuation before or on Day 28 without improvement, failure or death	Date/time of last available result of clinical status from Day 1 through Day 28	Censored

Number and percentage of participants with and without recovery will be presented.

The hypotheses that will be tested for each dose level using a one-sided stratified log-rank test of distribution of time to recovery with use of corticosteroids at a prednisone equivalent daily dosage of ≤ 15 mg or > 15 mg within 48 hours prior to randomization, and country as stratification factors, are:

- H_{0i}: $HR_i \leq 1$

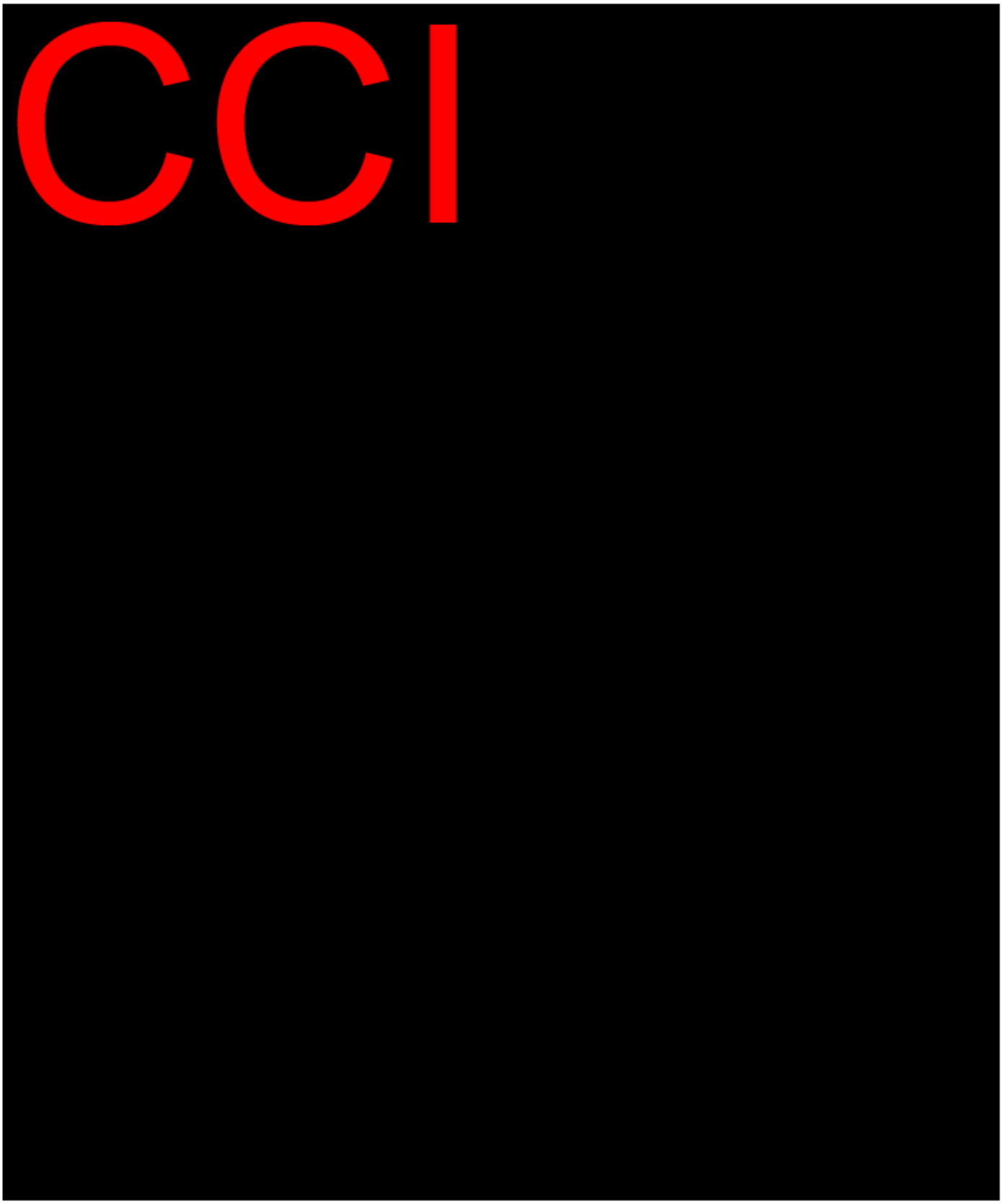
- H_{1i}: $HR_i > 1$

where

- HR_i denotes the Hazard Ratio of M5049 dose i versus placebo
- i denotes M5049 50 mg BID or M5049 100 mg BID
- $HR_i > 1$ denotes an improvement compared to placebo.

Estimation of the effect of each treatment dose (and 95% two-sided CI) separately compared to placebo will be based on hazard ratio from stratified Cox-model of recovery hazard rate, with terms for treatment group (each active treatment separately against placebo), use of corticosteroids at a prednisone equivalent daily dosage of ≤ 15 mg or > 15 mg within 48 hours prior to randomization, and country. Ties will be handled using the discrete method.

Cumulative distribution function for time to recovery will be estimated via Kaplan-Meier (product limit) method by treatment group and presented together with associated statistics (median time to recovery, recovery rates at Day 7, Day 14, Day 21 and Day 28) including the corresponding two-sided 95% CI. The estimates of the standard error (SE) will be computed using Greenwood's formula.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14.2 Secondary Endpoints

14.2.1 Proportion of Subjects Alive and Not Requiring Supplemental Oxygenation

The proportion of responders is defined as participants who are alive and do not require supplemental oxygenation or ventilatory support (including noninvasive or mechanical ventilation and Extra Corporeal Membrane Oxygenation [ECMO]).

The difference in proportion of each dose to placebo will be derived with two-sided 95% CIs based on the Miettinen-Nurminen method and presented in a tabular and graphical format at the following analysis visits: Day 7, Day 14, Day 21, Day 28, Day 44 and Day 60.

The derivation of response at Day 14 will be based on the Ordinal Scale for Clinical Severity presented in Section 14.2.2 and the same logic will be applied for all the other time points, data collected on the 'Ordinal Scale for Clinical Severity' eCRF page, using the following derivation algorithm:

- If clinical status score < 4 on analysis Day 14 then the participant will be considered a responder on Day 14;

- If clinical status ≥ 4 on analysis Day 14 then the participant will be considered a non-responder on that day.

The rules below to define responder status in special cases will be followed:

#	**Situation**	**Outcome**
1	Death on or before Day 28	Non-responder
2	Missing on analysis Day 14	Missing

Number and percentage of subjects with response at each analysis visit and the corresponding two-sided Wilson 95% CI will be presented.

In addition, summary score estimates of the common difference in proportion, stratified for corticosteroids use in the 48h prior to randomization and country will be presented with 95% CIs based on stratified Newcombe confidence limits for the differences in proportions (Kim, 2013).

14.2.2 Clinical Status

Clinical status will be based on data collected on the 'Ordinal Scale for Clinical Status' eCRF page and is assessed with the following ordinal scale:

0. Uninfected: no clinical or virological evidence of infection.
1. Ambulatory: no limitation of activities.
2. Ambulatory: limitation of activities.
3. Hospitalized, mild disease: hospitalized, no oxygen therapy.
4. Hospitalized, mild disease: oxygen by mask or nasal prongs.
5. Hospitalized, severe disease: noninvasive ventilation or high-flow oxygen.
6. Hospitalized, severe disease: intubation and mechanical ventilation.
7. Hospitalized, severe disease: ventilation + additional organ support – e.g., pressors, RRT, ECMO
8. Death.

In case of death, the participant will be counted with the clinical status =8 (death) for any scheduled timepoint after death date. There will be no imputation of missing data.

Clinical status is expected every day during hospitalization and then at every scheduled visit after discharge. Day 1 assessment will serve as baseline measurement. If missing, the last non-missing measurement prior to randomization will be used.

The number and percentage of participants in each clinical status category as well as summary statistics for absolute and change from baseline status will be presented by treatment group, in a tabular and graphical form, using a stacked bar chart.

A cumulative logit model will be used to compare the clinical status results of each M5049 group versus placebo at the following analysis visits: Day 7, Day 14, Day 21, Day 28, Day 44 and Day 60 according to the ordinal scale described above. Under the assumption of proportional odds, the odds ratio (OR) and its 95% Wald CI will be estimated for each M5049 group versus placebo. A score test for the proportional odds assumptions will be reported.

Should the model fail, due to an insufficient number of observations per category of the dependent variable, then relevant categories may be collapsed.

In addition, the following dichotomized versions of the clinical status will be derived, only if at least 6 participants in each level are present:

- Death (clinical status = 8) versus any other category (clinical status ≠ 8)
- Worsening (clinical status ≥ 5) versus stable/improvement (clinical status < 5)
- In-hospital (clinical status ≥ 3) versus hospital discharged (clinical status < 3).

A logistic regression model will be used to compare the dichotomized version of the clinical status at each time point of interest, with terms for treatment arm and strata defined by randomization strata. The OR and its 95% Wald CI will be estimated for each M5049 group versus placebo.

The same logistic regression model will be used to analyze the clinical status deterioration (change from baseline > 0) versus stable/improvement (change from baseline ≤ 0) compared to baseline.

No multiplicity correction will be applied.

14.2.3 Time to $SpO_2 \geq 94\%$ sustained for at least 24 hours in room air from Day 1 through Day 28

Time to $SpO_2 \geq 94\%$ sustained for at least 24 hours in room air will be based on data collected on the 'Pulse Oximetry' and 'Respiratory Status' eCRF pages from Day 1 through Day 28.

The time to SpO_2 improvement, defined as the time from first dose (Day 1) to the date of first $SpO_2 \geq 94\%$ sustained in room air, in days:

- Time to SpO_2 improvement (days) = (Date/time of first $SpO_2 \geq 94\%$ sustained in room air – Date/time of first dose)

The rules for the different types of censoring below will be followed:

#	Description	Date of Event or Censoring	Outcome
1	Death from Day 1 up to D60/Study completion	D28	Censored
2	Failure at any point and time during the study from D1 up to D28, defined as: * ICU admission leading to treatment discontinuation * use of mechanical ventilation * relapse	D28	Censored

3	Participant not confirmed to be eligible based on inclusion criterion 6 (PDEV05 code)	Date of first dose of study drug	Censored
4	No post-baseline SpO2 data	Date of first dose of study drug	Censored
5	Sustained SpO2 >= 94% at room air before Day 28	Date of first SpO2 >= 94% sustained at room air	Event
6	SpO2 < 94% at room air through Day 28 without death or failure	D28	Censored
7	Early discontinuation before or on Day 28 without improvement, failure or death	Date/time of last available result of clinical status from Day 1 through Day 28	Censored

Of note, the endpoint will not be considered met if the assessment is not done at room air, irrespective from the actual SpO2 value.

Number and percentage of subjects with and without improvement will be presented.

The hypotheses that will be tested for each dose level using a one-sided stratified log-rank test of distribution of time to improvement with use of corticosteroids at a prednisone equivalent daily dosage of ≤ 15 mg or > 15 mg within 48 hours prior to randomization, and country as stratification factors, are:

- H_{0i}: $HR_i \leq 1$
- H_{1i}: $HR_i > 1$

where

- HR_i denotes the Hazard Ratio of M5049 dose i versus placebo
- i denotes M5049 50 mg BID or M5049 100 mg BID
- $HR_i > 1$ denotes an improvement compared to placebo.

Estimation of the effect of each treatment dose (and 95% two-sided CI) separately compared to placebo will be based on hazard ratio from stratified Cox-model of improvement hazard rate, with terms for treatment group (each active treatment separately against placebo), use of corticosteroids

at a prednisone equivalent daily dosage of ≤ 15 mg or > 15 mg within 48 hours prior to randomization, and country. Ties will be handled using the discrete method.

Cumulative distribution function for time to improvement will be estimated via Kaplan-Meier (product limit) method by treatment group and presented together with associated statistics (median time to improvement, improvement rates at Day 7, Day 14, Day 21 and Day 28) including the corresponding two-sided 95% CI. The estimates of the standard error (SE) will be computed using Greenwood's formula.

14.2.4 All-cause Mortality

All-cause mortality analysis will be based on data collected on the 'Death' eCRF page.

All-cause mortality is defined as the proportion of subjects who died during the study, regardless of the cause of death.

Number and proportion of subjects dying through Day 60 and the corresponding two-sided Wilson 95% CI will be provided by treatment groups based on the ITT analysis set.

In case more than 6 deaths are observed, the difference in proportion of each dose to placebo will be presented with two-sided 95% CIs based on the Miettinen-Nurminen method. In addition, summary score estimates of the common difference in proportion, stratified for use of corticosteroids at a prednisone equivalent daily dosage of ≤ 15 mg or > 15 mg within 48 hours prior to randomization, AVT use in the 48h prior to randomization and country will be presented with 95% CIs based on stratified Newcombe confidence limits.

14.2.5 Time to ICU Admission (Day 1 Through Day 28)

Time to ICU admission will be based on data collected on the 'Hospitalization' eCRF page.

Time to ICU admission is defined as the time from first dose (Day 1) to the date/time of ICU admission, or death, whichever occurs first, in days:

- Time to ICU admission (days) = (Date/time of ICU admission – Date/time of first dose)

The rules below to define censoring/event dates will be followed:

#	Description	Date of Event or Censoring	Outcome
1	Subject with first dose administered while in ICU	Date of first dose of study drug	Censored

2	ICU admission or Death from Day 1 up to D28	Earliest between date of ICU admission and date of death (in case of death)	Event
3	For subjects never admitted to ICU and not died	Earliest between D28 and date of discontinuation	Censored

Number and percentage of subjects with and without the event will be summarized.

The hypotheses that will be tested for each dose level using a one-sided stratified log-rank test of time to ICU admission with use of corticosteroids at a prednisone equivalent daily dosage of ≤ 15 mg or > 15 mg within 48 hours prior to randomization, and country as stratification factors, are:

- H_{0i}: $HR_i \geq 1$
- H_{1i}: $HR_i < 1$

where

- HR_i denotes the Hazard Ratio of M5049 dose i versus placebo
- i denotes M5049 50 mg BID or M5049 100 mg BID
- $HR_i < 1$ denotes an improvement compared to placebo.

Estimation of effect each treatment dose (and 95% two-sided CI) separately compared to placebo will be based on hazard ratio from stratified Cox-model of event hazard rate, with terms for treatment arm (each active treatment separately against placebo), use of corticosteroids at a prednisone equivalent daily dosage of ≤ 15 mg or > 15 mg within 48 hours prior to randomization, and country. Ties will be handled using the discrete method.

Event-free survival function for time to event will be estimated via Kaplan-Meier (product-limit) method by treatment group and presented in a tabular and graphical format together with associated statistics (median time to event, event rates at Day 7, Day 14, Day 21 and Day 28) including the corresponding two-sided 95% CI. The estimates of the standard error (SE) will be computed using Greenwood's formula.

14.2.6 Time to Non-Invasive Mechanical Ventilation (Day 1 Through Day 28)

Time to non-invasive mechanical ventilation will be based on data collected on the 'Ordinal Scale for Clinical Severity' eCRF page.

Time to non-invasive mechanical ventilation is defined as the time from first dose (Day 1) to the date/time of clinical status >= 5, in days:

- Time to non-invasive mechanical ventilation (days) = (Date/time of clinical status >= 5 – Date/time of first dose)

The rules below to define censoring/event dates will be followed:

#	Description	Date of Event or Censoring	Outcome
1	Clinical status >= 5 or Death from Day 1 up to D28	Earliest between date of clinical status >= 5 and date of death (as applicable)	Event
2	For subjects which never started mechanical ventilation and not died	Earliest between D28 and date of discontinuation	Censored

Analyses will be performed as specified in Section 14.2.5.

14.2.7 Time to Invasive Mechanical Ventilation

Time to invasive mechanical ventilation will be based on data collected on the 'Ordinal Scale for Clinical Severity' eCRF page.

Time to invasive mechanical ventilation is defined as the time from first dose (Day 1) to the date/time of clinical status >= 6, in days:

- Time to invasive mechanical ventilation (days) = (Date/time of clinical status >= 6 – Date/time of first dose)

The rules below to define censoring/event dates will be followed:

#	Description	Date of Event or Censoring	Outcome
1	Clinical status >= 6 or Death from Day 1 up to D28	Earliest between date of clinical status >= 6 and date of death (in case of death)	Event
2	For subjects which never invasive started mechanical ventilation and not died	Earliest between D28 and date of discontinuation	Censored

Analyses will be performed as specified in Section 14.2.5.

14.2.8 Total Days in ICU

Total days in ICU will be based on data collected on the 'Hospitalization' eCRF page.

Total days in the ICU are defined as the sum, for all ICU admissions, of the time from ICU admission to the date of ICU discharge, in days:

Total days in the ICU (days) = $\sum_h$ (Date/*Time* of ICU discharge – Date/*Time* of ICU admission)

where h = number of ICU admissions during the study.

In case of ICU admission and discharge prior to first dose, the occurrence will not be considered for derivation of total days in ICU. In case ICU admission prior to and discharge after first dose, date and time of first dose will be used in place of date and time of ICU admission for calculation of total days in ICU.

The following information will be presented:

- Number and percentage of participants admitted in ICU
- Number and percentage of participants with more than one ICU admission
- Number and percentage of participants in the following discharge categories: death in ICU, discontinuation in ICU, discharged from ICU.
- Summary statistics of duration of ICU stay.

Participants never admitted to ICU will not be considered for descriptive statistics derivation.

14.2.9 Total Days in the Hospital and Time to Hospital Discharge

Total days in the hospital will be based on data collected on the 'Hospitalization' eCRF page.

Total days in the hospital are defined as the sum, for all hospitalization events, of the time from first dose to the date of hospital discharge, in days:

- Total days in the hospital (days) =
  First hospitalization: *Date of hospital discharge – Day 1 + 1*
  +
  Subsequent hospitalization: Date of discharge – date of admission + 1

In other words, in case of hospital admission prior to and discharge after first dose, date of first dose will be used in place of date of hospital admission for calculation of total days in the hospital. In case of multiple hospitalizations, the total number of days of each event will be added up.

The following information will be presented:

- Number and percentage of participants with more than one hospital admission (only non-consecutive hospitalization will be included in the count)
- Number and percentage of participants in the following discharge categories: death in hospital, discontinuation in hospital, discharged from hospital.
- Summary statistics of duration of hospital stay.

In addition, time to hospital discharge will be based on data collected on the 'Hospitalization' eCRF page from Day 1 through Day 28.

The time to hospital discharge, defined as the time from first dose (Day 1) to the date of first hospitalization discharge, in days:

- Time to hospital discharge (days) = (Date of first hospitalization discharge – Date of first dose)

The rules for the different types of censoring/event below will be followed:

#	Description	Date of Event or Censoring	Outcome

1	Death from Day 1 up to D60/Study completion	D28	Censored
2	Failure at any point and time during the study from D1 up to D28, defined as: * ICU admission leading to treatment discontinuation * use of mechanical ventilation * relapse	D28	Censored
3	Hospital discharge before Day 28	Date of hospital discharge	Event
4	No hospital discharge before Day 28/discontinuation without death or failure	Earliest between D28 and date of discontinuation	Censored

Analyses will be performed as specified in Section 14.2.3.

14.2.10 Inflammatory Biomarkers

Inflammatory biomarker analysis will be based on data collected on the 'Inflammatory biomarkers' eCRF page and will be performed based on the PDAS.

The following inflammatory biomarkers will be collected for this study and analyzed by a local laboratory as per the schedule of events reported in the protocol:

- C-Reactive Protein, D-dimer, Ferritin

The following summaries will be provided by treatment group and total based on the PDAS for each inflammatory biomarker:

- Observed, change and percent change from baseline by analysis visit;
- Box and whisker plots over time for observed, change and percent change from baseline by treatment group;
- Spaghetti plots of change and percent change from baseline by treatment group


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14.2.12 Occurrence of Relapse

Occurrence of relapse analysis will be based on data collected on the 'Date of Visit' eCRF page.

Relapse is defined as a participant who has been discharged from the hospital with an SpO_2 of $\geq$ 94% sustained for at least 24 hours in room air, but who must be readmitted before or on Day 60, due to either or both the following conditions:

1. Worsening oxygenation (an $SpO_2 < 94\%$ in room air), with a positive result of respiratory pathogenic nucleic acid test;

2. Worsening oxygenation (an $SpO_2 < 94\%$ in room air), with a worsening lesion on chest imaging (i.e., compared to the participant's chest X-ray or computed tomography at discharge)

Number and proportion of subjects with relapse during the study period (if first discharged) and the corresponding two-sided Wilson 95% CI will be provided by treatment group based on the ITT analysis set.

In case more than 6 events of relapse are observed, the difference in proportion of each dose to placebo will be presented with two-sided 95% CIs based on the Miettinen-Nurminen method. In addition, summary score estimates of the common difference in proportion, stratified for use of corticosteroids at a prednisone equivalent daily dosage of $\leq$ 15 mg or > 15 mg within 48 hours prior to randomization, AVT use in the 48h prior to randomization and country will be presented with 95% CIs based on stratified Newcombe confidence limits for the differences in proportions.

14.2.13 Occurrence of Re-hospitalization due to COVID-19 Complications

The analysis of occurrence of re-hospitalization due to COVID-19 complications will be based on data collected on the 'Hospitalization' eCRF page.

Re-hospitalization is defined as a participant who has been discharged from the hospital with an SpO_2 of $\geq$ 94% sustained for at least 24 hours in room air, but who must be readmitted before or on Day 60, for COVID-19 related complications.

Number and proportion of subjects with re-hospitalization due to COVID-19 during the study period (if first discharged) and the corresponding two-sided Wilson 95% CI will be provided by treatment group based on the ITT analysis set.

In case more than 6 events of re-hospitalization are observed, the difference in proportion of each dose to placebo will be presented with two-sided 95% CIs based on the Miettinen-Nurminen method. In addition, summary score estimates of the common difference in proportion, stratified for use of corticosteroids at a prednisone equivalent daily dosage of $\leq$ 15 mg or > 15 mg within 48 hours prior to randomization, AVT use in the 48h prior to randomization and country will be presented with 95% CIs based on stratified Newcombe confidence limits for the differences in proportions.

15 Safety analysis

Safety analyses will be done on the SAF analysis set and according to the actual treatment received (see Section 8.1).

15.1 Adverse Events

Adverse events information is collected in the 'Adverse Event' eCRF page.

Treatment-emergent adverse events (TEAE) are those events with onset or worsening dates occurring within the on-treatment period as defined in Section 9.7.

Adverse events related to study treatment are those events with relationship missing, or yes.

All analyses described in this section will be based on TEAEs if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not).

Unless otherwise specified, TEAEs will be summarized by number and percentage of participants with the specific TEAE of interest, by treatment group, primary SOC and PT in alphabetical order.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

15.1.1 All Adverse Events

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 5.0), in alphabetical order by MedDRA PT as event category and MedDRA primary system organ class (SOC) body term as Body System category, using MedDRA version 23.0 or later.

In case a participant has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

Incomplete AE-related dates will be handled as specified in Section 9.8.

The following tables will be created, by treatment group:

- Overall summary of AEs: it will include the frequency (number and percentage) of participants with each of the following:
    - TEAEs
    - TEAEs with NCI-CTCAE Grade ≥ 3, Grade ≥ 4
    - Related TEAEs
    - Related TEAEs with NCI-CTCAE Grade ≥ 3, Grade ≥ 4
    - TEAEs leading to permanent treatment discontinuation
    - Related TEAEs leading to permanent treatment discontinuation
    - Serious TEAEs
    - Related Serious TEAEs
    - TEAEs leading to death
    - Related TEAEs leading to death

- TEAEs by SOC and PT
- TEAEs by SOC and PT and worst grade
- Treatment related TEAEs by SOC and PT
- Treatment related TEAEs by SOC and PT and worst grade
- TEAEs leading to death by SOC and PT
- Related TEAEs leading to death by SOC and PT
- TEAEs excluding SAEs, with frequency ≥ 5% in any treatment arm by SOC and PT
- TEAEs by age subgroup, as defined in Section 8.2, by SOC and PT
- TEAEs by gender subgroup, as defined in Section 8.2, by SOC and PT.

15.1.2 Adverse Events Leading to Discontinuation of Study Treatment

TEAEs leading to permanent discontinuation of study drug are those events recorded as "Drug withdrawal" on the AE pages of the eCRF.

The frequency (number and percentage) of participants with each of the following will be presented for TEAEs leading to permanent discontinuation of each study drug by treatment group:

- TEAEs leading to study treatment discontinuation by SOC and PT
- Related TEAEs leading to study treatment discontinuation by SOC and PT

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

All deaths will be tabulated based on information from the "Death" eCRF page, summarizing the following information:

- Number of Deaths
- Number of Deaths within 30 days after last dose of study treatment
- Primary Reason of Death, among:
  - Progressive disease and/or other disease related condition
  - Event unrelated to study treatment
  - Unknown

In addition, date and cause of death will be provided in individual participant data listing together with selected dosing information (date of first and last administration and number of doses).

This listing will include:

- AEs with fatal outcome (list preferred terms of AEs with outcome=fatal)
- Flag for death within 30 days of last study treatment

15.2.2 Serious Adverse Events

The following overall frequency tables will be prepared for serious treatment-emergent adverse events (SAEs):

- Incidence of serious TEAEs by SOC and PT
- Incidence of related serious TEAEs by SOC and PT

The listings of treatment - emergent SAEs will also be provided with the relevant information.

15.2.3 Other Significant Adverse Events

Adverse events of special interest will be identified on the 'Adverse Event' eCRF page and using Standardized MedDRA queries.

The frequency (number and percentage) of participants with each of the following treatment emergent adverse event of special interest (AESI) will be presented by treatment group:

- Infections, defined as any Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3 or serious adverse events (SAEs) of infection and opportunistic infection;
- Seizure, defined as any type of seizures/epilepsy of any grade or its consequences;
- Serotonin syndrome and its spectrum of symptoms;
- Clinically significant arrythmias.

All AESIs will be flagged in adverse event listing.

15.3 Clinical Laboratory Evaluation

Clinical laboratory evaluation will be collected on the 'Local Laboratory Results: Hematology' and 'Local Laboratory Results: Chemistry' eCRF pages.

Laboratory values (including corresponding normal ranges) from the local labs will be used for summary statistics and shift tables.

Quantitative laboratory parameters reported as "< X", below the lower limit of quantification (BLQ), "> X" or above the upper limit of quantification (ULQ), will be converted to X/lower

limit/upper limit for the purpose of quantitative summaries (with the exception of eGFR), but will be presented as recorded, i.e. as "< X", BLQ, "> X" or ULQ in listings.

The full list of parameters with NCI-CTCAE grades available and not available and relevant directions of abnormalities of interest are listed in Appendix 1 at section 18.1.

Laboratory results will be classified according to the NCI-CTCAE criteria version 5.0. Some of the toxicity gradings are based on laboratory measurements in conjunction with clinical findings. Non-numerical qualifiers will not be taken into consideration in the derivation of CTCAE criteria (e.g., hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived).

Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

For estimated glomerular filtration rate (mL/min/1.73 m^2) the value collected in CRF will be used when reported. When missing or reported as ">/<X", it will be calculated using the Modification of Diet in Renal Disease equation:

$$eGFR = 175 \times (\text{serum creatinine in mg/dL})^{-1.154} \times (\text{age in years})^{-0.203} \times 0.742 \text{ (if female)} \times 1.212 \text{ (if race is black)}$$

The following summaries will be provided by treatment group for each of chemistry and

hematology laboratory:

All parameters:

- Summary results based on normal ranges by time points will include number and percentage of participants below normal limit, within normal limits and above normal limit.

Non-gradable parameters according to NCI-CTCAE:

- Shift from baseline to the worst on-treatment value according to normal range criteria

Gradable parameters according to NCI-CTCAE:

- Shift from baseline to the worst on-treatment value for each relevant directionality (minimum and/or maximum value) according to the CTCAE toxicity grades; the highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary

- Summary results based on CTCAE grade by time point will include number and percentage of participants with Grade 1, 2, 3, 4, 3/4, and any grade (1 to 4).

For those parameters which are graded with two directions of toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (e.g., hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g., hyperkalemia), and vice versa.

Spaghetti plots for Aspartate Aminotransferase, Alanine Aminotransferase and Total Bilirubin, will be presented by treatment group, including only those participants with any NCI CTCAE grade 2 or higher at any point in time during the study.

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by actual treatment, then subject ID, parameters and assessment dates for each participant. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges and CTCAE grades. A listing for laboratory normal ranges will also be provided.

15.4 Vital Signs

Vital signs will be collected on the ‘Screening Vital Signs’ and ‘Vital Signs’ eCRF pages.

The following vital sign parameters will be collected for this study as per the schedule of events:

- Systolic blood pressure (SBP) (mmHg)

- Diastolic blood pressure (DBP) (mmHg)

- Pulse rate (beats per minute [bpm])
- Respiratory rate (breaths/min)
- Body temperature (ºC)
- Weight (kg) at baseline
- Height (cm) at baseline

The following summaries will be provided by treatment group based on the SAF analysis set for each vital sign parameter:

- Descriptive statistics and changes from baseline over time by treatment group;

All vital sign data will be listed.

15.5 Other Safety or Tolerability Evaluations

ECG data will be collected on the 'ECG' eCRF page.

ECG summaries will include all ECG assessments from the on-treatment period.

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis we will use some of those methods of correction, as described below. The QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds, and can be estimated as 60/Heart Rate.

QTcF values collected in the eCRF will be used for the analysis. In case those are missing, this parameter will be derived based on RR and QT.

The following analyses will be performed for each of the applicable ECG parameters (ventricular rate, denoted as HR in what follows, PR, RR, QRS, QT, QTc and QTcF) by treatment group, during the on-treatment period. Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes.

- For each of the ECG parameters (HR, PR, RR, QRS, QT, QTc and QTcF), descriptive statistics of absolute and changes from baseline values at scheduled time points will be reported.
- Shift to worst post-baseline investigator interpretation.
- Shift to worst post-baseline value according to the notable ECG categories presented below. Maximum post-baseline value will be used.
    - QTcF increase from baseline >30 ms, >60 ms
    - QTcF > 450 ms, > 480 ms, > 500 ms

Complete ECG profiles will be listed, and notable ECG interval value or change will be flagged.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

Population: PK Analysis Set

Non-compartmental computation of M5049 PK parameters will be performed using the computer program PPD or higher PPD. The statistical software SAS® PPD, Version 9.2, or higher, will be used to produce tables, listings, and figures. Figures will be prepared with SAS Version 9.2, or higher.

M5049 tables, listings, and figures will be generated using SAS.

Pharmacokinetic parameters will be calculated using standard non-compartmental methods, the actual administered dose, and actual elapsed time from dosing.

Further exploratory analyses of M5049 PK and exposure-response relationships with respect to biomarkers/clinical endpoints will be described using modeling and simulation. Full details of the relevant (integrated) population modeling and simulation activities (including objectives, relevant endpoints, methodology, software, etc.) will be defined in a separate Pharmacometry analysis plan and presented separately from the main clinical study report.

Blood will be collected for M5049 determination according to the following schedules:

Table 3: Pharmacokinetic Sampling Times for Part A

Day	Time (h)	Time from Scheduled Sampling Allowed
Day 1	Predose	Within 60 minutes prior to dose administration
	1	± 20 minutes
	2	± 20 minutes

Day	Time (h)	Time from Scheduled Sampling Allowed
	6	± 30 minutes
	12	± 120 minutes
Day 7	Predose	Within 60 minutes prior to dose administration
	1	± 20 minutes
	2	± 20 minutes
	6	± 30 minutes

Note: Samples collected by site when possible.

Table 4: Pharmacokinetic Sampling Times for Part B

Day	Time (h)	Time from Scheduled Sampling Allowed
Day 1	Predose	Within 60 minutes prior to dose administration
	1 to 2 hours	N/A
	4 to 6 hours	N/A
	8 to 12 hours	N/A
Day 3 and 7	Predose	Within 60 minutes prior to dose administration
	1 to 2 hours	N/A
	4 to 6 hours	N/A

Part A samples that are collected outside the specified time windows will be included in the PK parameter estimation (NCA) but will be excluded from the concentration summary and mean concentration plots. Part B samples that are collected outside the specified time windows will be included in the PK parameter estimation, flagged in the concentration listing, and excluded from the concentration summary and mean concentration plots.

Pharmacokinetic concentrations which are erroneous due to a protocol violation (as defined in the CSP), sampling processing or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed by the Sponsor. In this case the rationale for exclusion must be provided in the CSR. Any other PK concentrations that appear implausible to the Clinical Pharmacologist/Clinical PK/PD Scientist will not be excluded from the analysis. Any implausible data will be documented in the CSR.

Any PK concentrations or PK parameters excluded from summary statistics will be included in subject listings and flagged; a reason for exclusion will be detailed in the CSR (e.g. a footnote or a table of exclusions). Any flags should be included in the study specific SDTM and ADaM data sets**.**

IDMC 1 PK analysis will be based on Part A concentrations (Day 1 and Day 7-predose only) and parameters (Day 1 only), as listed below. The PK outputs for IDMC 1 are presented in Section 6.1.

The following PK parameters will be reported for M5049 on Day 1 and Day 7 in Part A only except where noted, where data permit.

$AUC_{0\text{-}tlast}$ Area under the concentration-time curve (AUC) from time of dosing to the time of the last quantifiable observation.

$AUC_{0\text{-}tlast}$/Dose The dose-normalized $AUC_{0\text{-}tlast}$. Normalized using the actual dose, using the formula $AUC_{0\text{-}tlast}$/Dose.

$AUC_{0\text{-}12h}$ AUC from time of dosing to time 12 hours post dose. $AUC_{0\text{-}12h}$ (Day 1) will be based on the estimated concentration at 12 hours after dosing. $AUC_{0\text{-}12h}$ (Day 7) will be based on predose Day 7 concentration used for estimated concentration at 12 hours.

$AUC_{0\text{-}12h}$/Dose The dose-normalized $AUC_{0\text{-}12h}$. Normalized using the actual dose, using the formula $AUC_{0\text{-}12h}$/Dose.

$AUC_{0\text{-}\infty}$ AUC from time of dosing extrapolated to infinity on Day 1 only, based on the predicted value for the concentration at t_{last}, as estimated using the linear regression from λ_z determination. $AUC_{0\text{-}\infty}=AUC_{0\text{-}tlast}+C_{last\ pred}/\lambda_z$.

$AUC_{0\text{-}\infty}$/Dose The dose-normalized $AUC_{0\text{-}\infty}$. Normalized using the actual dose, using the formula $AUC_{0\text{-}\infty}$/Dose on Day 1 only.

CL/F The apparent total body clearance of study intervention following extravascular administration on Day 1 only, CL/F = Dose/$AUC_{0\text{-}\infty}$.

C_{max} Maximum observed concentration.

C_{max}/Dose The dose-normalized maximum observed concentration. Normalized using the actual dose, and the formula C_{max} /Dose.

C_{trough} The concentration observed immediately before next dosing on Day 7 only.

λ_z Terminal first order elimination rate constant.

$R_{acc}(AUC_{0\text{-}12h})$ The accumulation ratio of $AUC_{0\text{-}12h}$ from Day 1 to Day 7. $R_{acc}(AUC_{0\text{-}12h})= AUC_{0\text{-}12h12}$ (Day 7)/$AUC_{0\text{-}12h}$ (Day 1)

$R_{acc}(C_{max})$ The accumulation ratio of C_{max} from Day 1 to Day 7. $R_{acc}(C_{max}) = C_{max}$ (Day 7)/ C_{max} (Day 1)

t_{max} Time to reach the maximum observed concentration C_{max}.

$t_{1/2}$ Apparent terminal half-life, $t_{1/2} = \ln 2/\lambda_z$.

V_z/F The apparent volume of distribution during the terminal phase following extravascular administration on Day 1 only, $V_z/F = Dose/(AUC_{0\text{-}\infty} \times \lambda_z)$.

The following PK parameters will be calculated for M5049 for diagnostic purposes and listed, but will not be summarized:

- First ($\lambda_{z\ low}$) and last ($\lambda_{z\ up}$) time point of the time of the log-linear regression to determine λ_z.
- Number of data points included in the log-linear regression analysis to determine λ_z.
- Goodness of fit statistic (Rsq,adj) for calculation of λ_z.
- AUC_{extra}: The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. AUC_{extra} = (extrapolated area/$AUC_{0-\infty}$)*100.

The following PK parameters will be reported for M5049 on Day 1, Day 3, and Day 7 in Part B only except where noted, where data permit.

C_{max}	Maximum observed concentration.
C_{trough}	The concentration observed immediately before next dosing on Day 3 and 7 only.
t_{max}	Time to reach the maximum observed concentration C_{max}.

The calculation of the AUC will be performed using the mixed linear-log trapezoidal method. The actual time of blood sampling (14 significant digits or the SAS format Best12) will be used for PK parameter calculation. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time.

Values below the lower limit of quantification of the assay (LLOQ) will be taken as zero for summary statistics of PK concentration data, PK parameter estimation, and for graphical presentations. In case BLQ concentrations occur at the end of the dosing interval (12 h), these concentrations will be excluded from the calculation of the AUC_{0-12}.

The regression analysis should contain data from at least 3 different time points in the terminal phase consistent with the assessment of a straight line on the log-transformed scale. PPD "best fit" methodology will be used as standard. However, in some cases, further adjustment may be made by the pharmacokineticist, if warranted, after agreement with the Sponsor. The last quantifiable concentration should always be included in the regression analysis, while the concentration at t_{max} and any concentrations <LLOQ which occur after the last quantifiable data point should not be used.

The coefficient of correlation (Rsq,adj) should be ≥0.8000, AUC_{extra} should not be greater than 20%, and the observation period over which the regression line is estimated should be at least twofold the resulting $t_{1/2}$ itself. If these criteria are not met, then the rate constant and all derived parameters (CL/F, V_z/F, $t_{1/2}$, $AUC_{0-\infty}$, and $AUC_{0-\infty}$/D) will be included in the parameter listings and descriptive statistics but will be flagged in listings and discussed appropriately.

The following listings and summary statistics of M5049 PK concentration and parameter data will be provided, where data permit:

- Listing of individual PK concentration data by part, dose, day, and scheduled time point

- Listing of individual single dose PK parameters by part and dose
- Listing of individual multiple dose PK parameters by part and dose
- Descriptive summary table of PK concentration data by dose, day, and scheduled time point (Part A) or time window (Part B)
- Descriptive summary table of PK parameter data by part, dose, and day
- Individual concentration-time profiles (linear and semi-logarithmic scales) will be plotted by part, dose level, and day as spaghetti plots, using actual time points (where available).
- Arithmetic mean concentrations will be plotted on both linear (±SD) and semi-logarithmic scales using scheduled time points – with all dose levels overlaid by part and day. Part B will use the midpoint of the allowed sampling window for the time value when plotting.
- Scatter plots of dose-normalized C_{max}, dose-normalized $AUC_{0\text{-}12h}$, dose-normalized $AUC_{0\text{-}tlast}$, and dose-normalized $AUC_{0\text{-}\infty}$ (as applicable) against dose for each corresponding day, where applicable. (Part A only)
- Scatter plot of C_{max} against dose for each corresponding day, where applicable. (Part B only)

All descriptive summaries of PK data will be performed using the PKAS. Individual PK data will be listed using the ITT Analysis Set. The mean concentration-time profiles and PK parameter plots will be plotted using the PKAS and the individual subject concentration-time profiles will use the ITT Analysis Set.

Exploratory dose proportionality analysis for Part A will be performed by visual inspection of the scatter plots of C_{max}/dose, $AUC_{0\text{-}12h}$/dose, $AUC_{0\text{-}tlast}$/dose, and $AUC_{0\text{-}\infty}$/dose versus dose (where available).

PPD NCA Core Output will be provided in a separate listing.

17 References

Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26

Yeonhee Kim and Seunghyun Won. “Adjusted proportion difference and confidence interval in stratified randomized trials.” PharmaSUG 2013 - Paper SP04

18 Appendices

18.1 Appendix 1 - NCI-CTC Gradable and Non-Gradable Safety Laboratory Test Parameters and Direction(s) of Abnormality

NCI-CTC gradable parameters

Laboratory Assessment	Parameters	Name in NCI-CTC	Direction(s) of abnormality
Hematology	Hemoglobin	Anemia / Hemoglobin increased	Low/High
	Leukocytes (WBC)	White blood cell decreased / Leukocytosis	Low/High
	Neutrophils	Neutrophil count decreased	Low
	Eosinophils	Eosinophilia	High
	Lymphocytes	Lymphocyte count decreased / increased	Low/High
	Platelets	Platelet count decreased	Low
Biochemistry	Albumin	Hypoalbuminemia	Low
	Alanine Aminotransferase (ALT)	Alanine Aminotransferase increased	High
	Aspartate Aminotransferase (AST)	Aspartate Aminotransferase increased	High
	Alkaline Phosphatase (ALP)	Alkaline Phosphatase increased	High
	Bicarbonate	Blood Bicarbonate decreased	Low
	Total Bilirubin	Blood bilirubin increased	High
	Creatinine	Creatinine increased	High
	Creatine Kinase (CK)	CPK increased	High
	Sodium	Hyponatremia / Hypernatremia	Low / High
	Potassium	Hypokalemia / Hyperkalemia	Low / High
	Glucose	Hypoglycemia	Low

Note: parameters with both Low and High directions of abnormality are going to be split. For example, Calcium is going to be split in Calcium Low and Calcium High.

NCI-CTC non-gradable parameters

Laboratory Assessment	Parameters	Direction of interest
Hematology	Hematocrit	

Laboratory Assessment	Parameters	Direction of interest
	Mean corpuscular volume (MCV)	High
	Basophils	
	Monocytes	High
Biochemistry	Total Protein	Low
	Chloride	High
	Urea Nitrogen (BUN)	High
	Estimated Glomerular Filtration Rate (eGFR)	Low