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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

CMAS825

CMAS825F12201 / NCT04382651

MAS825: A Phase 2, randomized, placebo-controlled, participant and investigator blinded, multi-center study to assess efficacy and safety of MAS825 for the treatment of SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function

Statistical Analysis Plan (SAP)

Author(s): Personal Protected Data

Document type: SAP Documentation – NIBR

Document status: Final

Release date: 20-May-2021

Number of pages: 51

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CMAS825F12201".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol to be reported in the CSR as well as any potential IA. The data presentation and analyses for the DMC are not part of this analysis plan.

1.2 Study reference documentation

This SAP is based on the protocol amendment v01 for study CMAS825F12201 dated 03-Jul-2020.

1.3 Study objectives

Table 1-1 Objectives

Objective(s)	Endpoint(s)
Primary Objective(s) • To evaluate the effect of MAS825, compared with placebo, on the Acute Physiology and Chronic Health Evaluation II (APACHE II) score	Endpoint(s) for primary objective(s) • APACHE II severity of disease score on Day 15 or on day of discharge (whichever is earlier) with worst case imputation for death
Secondary Objective(s) • To evaluate the effect of MAS825, compared with placebo on inflammatory status	Endpoint(s) for secondary objective(s) • Serum C-reactive protein (CRP) levels and ferritin
• To evaluate the effect of MAS825, compared with placebo, on clinical status	Endpoints based on the 9-point ordinal scale: • Survival without the need for invasive mechanical ventilation at Days 15 and 29 • At least one level improvement in clinical status at Days 15 and 29 • Clinical status over time
• To evaluate the safety of MAS825, compared with placebo	• Number of participants with Adverse Events (AE), Serious Adverse Events (SAE), clinically significant changes in laboratory measures, and vital signs

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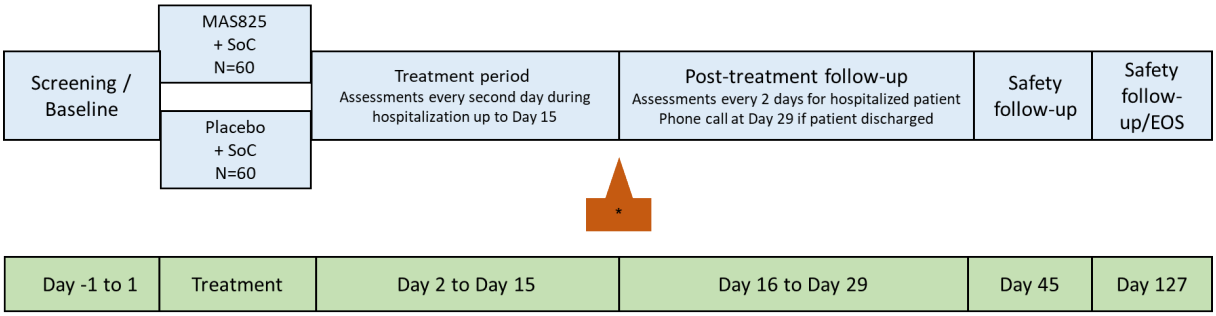
1.4 Study design and treatment

This is a Phase 2, randomized, placebo -controlled, participant and investigator blinded, multi-center study to assess the efficacy and safety of MAS825 for the treatment of SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function (Figure 1-1).

Figure 1-1 Study design



* End points calculated on day of discharge in patients discharged prior to Day 15

The study consists of five parts:

1. **Screening / Baseline** / **Treatment** (Day -1 to 1): lasts up to a maximum of 24 hours and comprises a screening / baseline assessment. This visit will be used to confirm that the study inclusion and exclusion criteria are met and serves as baseline assessment prior to randomization. Baseline blood tests will be performed in all patients; those who screen fail because of study inclusion / exclusion criteria (e.g., serum CRP, liver function tests), will not undergo randomization.

   Eligible patients will receive a single i.v. infusion of CCI MAS825 or placebo on Day -1 to 1 and will be observed until Day 15. Patients will be randomized as soon as possible, but within a maximum of 24 hours after screening in a 1:1 ratio to receive either treatment with MAS825 or placebo in addition to SoC. Randomization will be stratified according to the following, all of which may influence outcome in COVID-19:

   - age (≤65years, >65years)
   - administration of any anti-viral therapy (e.g., hydroxychloroquine, chloroquine, convalescent plasma, remdesivir, faripivavir, ritonavir, lopinavir) as SoC (yes / no)
   - presence of ≥1 of the following comorbidities: diabetes, hypertension, cardiovascular disease, chronic lung disease (yes / no)
2. **Treatment period** (Day 2-15): Study assessments to be conducted every 2 days for hospitalized patients. If patients are discharged from the hospital prior to Day 15, assessments on the day of discharge should be performed according to the schedule listed under Day 15 and patient should return to the site for the Day 15 assessment (all other visits between discharge and Day 15 can be omitted). If a hospital visit is not possible at Day 15, then home nursing services may be used to support this last visit where these are available in accordance with local guidelines and should include all possible assessments (e.g. oxygen saturation with portable monitors). In case home nursing is not possible, patients will be contacted by phone on day 15.
3. **Follow-up** (Day 16-29): After completion of the treatment period, patients will be observed until Day 29 or discharged from hospital, whichever is sooner. Study assessments to be conducted every 2 days for domiciled patients.
   If patients are discharged from hospital prior to Day 29, a study visit conducted by telephone will occur on Day 29 (all other visits between discharge and Day 29 can be omitted).
4. **Safety follow-up visit assessment** (Day 45): A follow-up visit will be conducted at Day 45 if the patient is hospitalized. If patients are discharged from hospital prior to Day 45, a study visit will be conducted by telephone on Day 45.
5. **End of Study/Safety follow-up visit assessment** (Day 127): A follow-up visit for safety will be conducted at Day 127 if the patient is hospitalized. If patients are discharged from hospital prior to Day 127, a study visit will be conducted by telephone on Day 127.

2 First interpretable results (FIR)

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3 Interim analyses

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4 Statistical methods: Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment(s) randomized.

The Safety analysis set will include all randomized participants that have received any study drug.

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The PD analysis set will include all randomized participants with no protocol deviations with relevant impact on PD data.

The PD analysis set 2 will include all randomized participants with no protocol deviations with relevant impact on PD data. The participants that did not meet all the eligibility criteria mentioned in study protocol section 5 will be excluded from this set programmatically. Exclude participants with APACHE II score less than 10 at baseline programmatically.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from safety analysis in case of these PDs:		Exclude subject from safety analysis set
INCL02	Informed consent form not obtained	Yes

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Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from safety analysis in case of these PDs:		Exclude subject from safety analysis set
INCL02	Informed consent form not obtained	Yes
Subjects are excluded from PD analysis set in case of these PDs:		Exclude subject from PD analysis set
INCL06	Patient enrolled but APACHE II score is less than 10 at Screening Visit	Yes
INCL03	Patient randomized but no confirmed coronavirus (SARS-CoV)-2 infection	Yes
INCL02	Informed consent form not obtained	Yes
Subjects are excluded from PD analysis set 2 in case any of the inclusion/exclusion criteria related PDs occur		Exclude subject from PD analysis set 2
INCLxx, EXCLxx		Yes

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

4.1 Baseline

The baseline value is defined as the last assessment performed prior to randomization.

4.2 Unscheduled visits

Data collected at unscheduled visits will not be used for analysis by visit, but will used to replace missing values if a Last observation carried forward (LOCF) approach is applied (i.e. for the mortality scores APACHE II, SAPS II and SOFA as described below).

6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

The primary aim of the study is to evaluate the effect of MAS825 compared with placebo on the APACHE II score. A decrease in the score is considered a favourable outcome.

6.1.1 Variable

The primary clinical question of interest is: What is the effect of MAS825 compared with placebo in SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function on APACHE-II severity of disease score taking into account early discharge from hospital or death but regardless of investigational treatment discontinuation?

The justification for the primary estimand is that it will capture the combined effect of investigational treatment in participants who remain in hospital for 14 days, the effect on early discharge within 14 days and the effect on death rate within 14 days, in a manner than reflects clinical practice. In this document the primary estimand will be referred to as the "**combined APACHE II score**".

The primary estimand is described by the following attributes:

- **Population:** SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function.
- **Endpoint**: APACHE II severity of disease score on Day 15 or on day of discharge (whichever is earlier) with worst case imputation for death. Participants who die on Day 15 or earlier will be assigned the highest observed APACHE II score of any of the participants at any time during the trial. Note this imputation for death takes precedence over the APACHE II score on day of discharge.
- **Treatment of interest:** the randomized treatment (the investigational treatment MAS825 or placebo).
- **Handling of remaining intercurrent events:** Treatment discontinuation for any reason will be ignored and thus follow a treatment policy strategy i.e. participants who discontinue treatment will be treated in the same manner as those that continue the treatment as planned.
- **Summary measure:** The difference in variable means between treatments.

APACHE II scores are on a range between 0 and 71 points, however, in practice it is rare for any patient to accumulate more than 55 points. A decrease in the APACHE II score is considered a favorable outcome.

The APACHE II scores are derived from a number of different clinical endpoints according to the scoring table as outlined in (Knaus et al., 1985) and listed in the Appendix. The handling of missing data is described in Section 6.1.7.

6.1.2 Descriptive analyses

To assess the impact of the replacement with score values at early discharge and the worst case imputation for death on the combined APACHE II score the following summary statistics will be provided:

- only for the participants with an early discharge (i.e. prior to day 15): if APACHE II score values at the early discharge visit and the actual Day 15 visit are available these will be summarized separately by visit ("early discharge", "Day 15").
- In addition the frequency of worst case imputation for deaths per treatment group will be provided.

Panels of individual spaghetti plots over time for APACHE II scores and their change from baseline will be provided by treatment group. The profiles of all participants in the respective treatment group will be included in these graphs as grey lines in the background and the respective individual participants profile will be plotted with darker color in the foreground. It will be indicated by a symbol when a patient was discharged or died (see data handling rules below in Section 6.1.8).

The sub-scores contributing to APACHE II scores derivation would be summarized.

6.1.3 Statistical model, assumptions and hypotheses

The combined APACHE II endpoint as described in the estimand above is assumed to follow a normal distribution.

The primary endpoint will be analyzed by an analysis of covariance model including treatment group and the three stratification factors as factors and baseline APACHE-II score as a covariate. The analysis will be performed on the safety analysis set. The mean differences of MAS825 vs placebo will be reported with 90% confidence intervals (CIs). The 1-sided p-value for the overall treatment factor will be reported.

The primary objective will be achieved if the null hypothesis that MAS825 is not different to placebo is rejected using a one side alpha of 10%.

6.1.4 Sensitivity analysis for primary objective

The combined APACHE II endpoint as described in the estimand above is assumed to follow a normal distribution.

The primary endpoint will be analyzed by an analysis of covariance model including treatment group and the three stratification factors as factors and baseline APACHE-II score as a covariate. The analysis will be performed on the PD analysis set 2. The mean differences of MAS825 vs placebo will be reported with 90% confidence intervals (CIs). The 1-sided p-value for the overall treatment factor will be reported.

6.1.5 Model checking procedures

The appropriateness of the normality assumption of the combined APACHE II score will be assessed by graphical means e.g. residual plots.

6.1.6 Intercurrent events

As described in the primary estimand discontinuation of study treatment for any reason will be ignored.

6.1.7 Missing data

Missing data for the APACHE II score will be handled as follows:

- Missing values for age at screening will be replaced by using the stratification information assigning 3 points to participants up to 65 years (<=65 years) and 5 points to participants above 65 years.
- Missing information on acute renal failure status: use Serum Creatinine values without renal status information.
- Subscores of the Glasgow Coma Score (i.e. responses to Best Eye Response, Motor Response, Verbal Response) scored as “untestable”, “unknown” or missing will be replaced by the last available actual score. The response “untestable” is selected if the patient is unconcious (e.g. through sedation in case of mechanical ventilation).
- Missing values in any of the other parameters required for the derivation of the APACHE II score will be replaced by the last available assessment, as long as data is not carried forward by more than 4 days.

For a given visit, these missing data rules will only be applied if for at least one of the parameters contributing to the APACHE II score a value at this visit was reported.

6.1.8 Handling of discharge and death

For the APACHE II score,

- in case a participant is discharged before Day 29 it will not be derived for any visits after the discharge visit (i.e. the last APACHE II score will be derived on the day of discharge).
- In case a participant dies no APACHE II score will be derived starting from the day of death.

6.1.9 Derivation of the primary estimand

The primary estimand, referred to as the “**combined APACHE II score**”, will be derived as follows from the APACHE II scores after application of the missing data as well as discharge and death handling approaches described above:

- For participants hospitalized at Day 15: APACHE II score at Day 15
- For participants discharged prior to Day 15: APACHE II score at the discharge visit is used

- For participants that died on Day 15 or earlier: highest observed APACHE II score of any of the participants at any time during the trial.
- Imputation for death takes precedence over the imputation of the APACHE II score on day of early discharge.

6.1.10 Supportive analysis

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Variable and analysis set

For analysis 1 the combined APACHE II score as for the primary analysis will be used. This analysis will be run on the PD analysis set.

For analyses 2-4 mentioned above all available APACHE II scores at all scheduled visits (excluding discharge or early discharge visits) up to Day 29 after applying the rules for missing data and handling of discharge and death. These analyses will be based on the safety analysis set.

For the subgroup analyses the “PD analysis set” is used. In addition only participants in the high baseline CRP group are considered. The high baseline CRP group is defined as any subject with a baseline CRP value > median baseline CRP value of all participants in this study.

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Model checking procedures

The appropriateness of the normality assumption of the APACHE II scores will be assessed by graphical mean e.g. residual plots.

Graphical presentation of results

Estimated mean APACHE II scores +/- SE will be plotted over time by treatment group.

6.2 Secondary objectives

6.2.1 Variables

The following variables and corresponding objectives are classified as secondary pharmacodynamic endpoints and will be evaluate for their effect of MAS825 compared with placebo,

- On inflammatory status: Serum C-reactive protein (CRP) levels and ferritin
- On clinical status: Endpoints based on the 9-point ordinal scale:
- Survival without the need for invasive mechanical ventilation at Days 15 and 29 defined by a 9-point ordinal scale score of < 6 points at all time points
- At least one level improvement in clinical status at Days 15 and 29: defined as difference of ≥1 in the 9-point ordinal scale score of the screening value – Day 15 or Day 29 respectively.
- Clinical status over time

Missing data

For the clinical status 9-point ordinal scale missing values will be handled as follows:

- For participants who died prior to Day 29: The score for death will be imputed for all visits following the death up to and including Day 29.

For all other participants: LOCF will be applied up to and including Day 127. Following discharge or early discharge LOCF will be applied to all intermediate visits.

6.2.2 Descriptive analyses

CRP and ferritin

Panels of individual spaghetti plots over time for CRP and ferritin will be provided using a logscale. The profiles of all participants in the respective treatment group will be included in these graphs as grey lines in the background and the respective individual participants profile will be plotted with darker color in the foreground. The respective applicable normal ranges will be added and it will be indicated by a symbol if a patient died.

Survival without the need for invasive mechanical ventilation

The numbers and percentages of responders will be calculated up to Day 15 and up to Day 29 respectively. It will be presented by treatment group together with the difference in response rates.

Improvement in clinical status

The numbers and percentages of responders will be calculated up to Day 15 and up to Day 29 respectively. It will be presented by treatment group together with the difference in response rates and a two-sided 90% CI based on Fishers exact test.

In addition a shift table of changes in response status will be provided with weekly time intervals (e.g. baseline, week 1, week 2, week 3 and week 4). For this the following response categories will be included:

- improvement of at least 1 step from baseline,
- no change from baseline
- worsening from baseline.

Also a stacked barchart illustrating the percentage of participants in each response categories as outlined above will be provided. Treatment groups will be presented next to each other. This will be provided for weeks 1, 2, 3 and 4.

For the subgroup analysis a shift table and stacked barchart for subgroup of participants with high baseline CRP by high and low corticosteroid dose during week 1 will be provided.

Clinical status over time

The 9-point ordinal scale will be summarized (mean, median, standard deviation, minimum, maximum, frequencies and percentages in each category) will be summarized by visit (including a time point for data from early discharge) and treatment group.
A stacked barchart illustrating the percentage of participants for each category of the 9-point ordinal scale with one bar will be provided. Treatment groups will be presented next to each other within one category. This will be provided for Day 8, Day 15, Day 21 and Day 29 (labeled as weeks 1, 2, 3 and 4).

The 9-point ordinal scale will also be plotted using a heat map with one row representing one patient and the score from baseline up to Day 29 visit will be shown by time using one unique color for each level of scale. The heat map will be plotted for each treatment group, within which patients will be sorted by the 9-point ordinal scale from high to low and by visit. The time when discharged from hospital will also be flagged on the plot. Values imputed by LOCF will be indicated by a different pattern (e.g. stripes) but the same color.

In addition a shift table and stacked barchart of changes between the categories of the 9-point scale will be provided with weekly time intervals (e.g. baseline, week 1, week 2, week 3 and week 4).

For the subgroup analysis a shift table and stacked barchart for subgroup of participants with high baseline CRP by high and low corticosteroid dose during week 1 will be provided.

6.2.3 Statistical model, assumptions and hypotheses

CRP and ferritin

CRP levels are assumed to follow a log-normal distribution. Thus the log-transformed CRP data will be analyzed by fitting an MMRM model. Treatment, visit and their interaction as well as the three stratification factors will be included as fixed factors and baseline CRP as a covariate. Interactions between visit and each of the terms in the model will also be included. To model the dependency of observations an unstructured variance-covariance matrix will be fitted.

The analysis will be performed on the PD analysis set. The back-transformed geometric means for both treatment groups as well as the geometric mean ratios (MAS825 vs placebo) will be reported together with 90% confidence intervals (CIs) for each visit. The 1-sided p-value for the overall treatment factor will be reported. Ferritin levels will also be analyzed in the same manner.

For the subgroup analysis the same model as for the original MMRM analysis including in addition a factor for high vs. low corticosteroid use during week 1 (see Section 7.2.2 for details) and its 3-way interaction with treatment and visit. The geometric means (+/-SE) per corticosteroid category and treatment group as well as the ratio of geometric mean (90% CI) per corticosteroid group are reported for each visit.

6.2.4 Model checking procedures

CRP and ferritin

The appropriateness of the log-normality assumption of CRP and ferritin values will be assessed by graphical mean e.g. residual plots.

6.2.5 Graphical presentation of results

CRP and ferritin

Estimated mean CRP +/- SE will be plotted over time by treatment group. The estimated geometric mean ratio to baseline in CRP +/- SE will also be presented. Ferritin levels will also be presented in the same manner.

For the subgroup analyses the following graphs will be provided:

- A line plot of the geometric means (+/-SE) are provided by corticosteroid dose category and treatment group together with the estimated values of the primary analyses by treatment group over time.

Side-by-side a second line plot on the treatment ratios (90% CI) per by corticosteroid dose category together with the estimated treatment difference (90% CI) of the primary analyses over time is given.

Survival without the need for invasive mechanical ventilation

Kaplan-Meier graphs with separate lines by treatment group will be provided for a graphical presentation. Participants will be censored discontinuating from the study or not experiencing an event.

6.3 Exploratory objectives

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7 Statistical methods for safety and tolerability data

All safety presentations and analyses will be based on the Safety Analysis Set.

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, respiratory rate, body temperature, peripheral oxygen saturation, oxygen flow rate and/or FiO2), ECG intervals, safety laboratory measurements, as well as subject demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data, which will also be summarized where appropriate (e.g. change from baseline summaries).

The on-treatment period lasts from the date of administration of study treatment to Day 127.

7.2.1 Subject demographics and other baseline characteristics

Screen failures with SAEs

For screen failed participants in case the participant experienced a serious adverse event during the screening phase the following information is captured and listed: demographic information, informed consent, as well as information on SAEs. Inclusion/Exclusion criteria will be summarized.

Disposition

The following disposition status will be summarized as the number and percentage of participants

- who were screened but not randomized (percentage based on all screened participants)
- who were randomized (percentage based on all screened participants)
- who were randomized but not treated (overall and by reason)
- who were discharged prior to day 15 and day 29
- who completed the study until day 15, day 29, day 45 as well as day 127
- who discontinued treatment prior to day 15,
- who discontinued from study (overall and by the primary reason for discontinuation).

The number and percentage of participants included in each analysis set will be tabulated by treatment group. Participants excluded from an analysis sets will be listed with reasons for exclusion (i.e. including both protocol and non-protocol deviations).

Unless otherwise stated any percentages are based on the respective number of randomized participants.

Demographic and Baseline characteristics

Demographic characteristics, including gender, race, ethnicity, age, age categories (<65 and ≥ 65 years), height, body weight at screening, body categories (40 to <60 kg, 60 to <80 kg, 80 kg to <100 kg, 100 kg to <120 kg, >=120 kg), body mass index (BMI), BMI categories (< 30.0 kg/m^2 and 30.0 kg/m^2 to 40 kg/m^2 , >=40 kg/m^2) will be summarized with descriptive statistics by treatment and overall.

A stacked barchart illustrating gender, race and ethnicity will be done. Boxplots will be done for all continuous variables in demographics and baseline characteristics.

Body weight and BMI will be also summarized by time point.

Body mass index (BMI) will be calculated using the following formula:

- BMI = Body weight (kg) / $[\text{Height (m)}]^2$

The Screening visit height measurement will be used for BMI calculations throughout the study.

The number of days between the onset of symptoms to start of treatment will be listed.

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

- Days from the onset of symptom to randomization
- Days from the onset of symptoms to treatment
- Days from diagnosis to randomization
- Number of days from hospital admission to randomization
- Chest X-ray or CT scan interpretation (Normal/Abnormal/not available)
- Clinical status based on the 9-point ordinal scale (Score=0, 1, ...8)
- Use of corticosteroid at the time of randomization (based on prednisone equivalent dose see Section 10.7)
- Use of anti-coagulants at the time of randomization
- Use of anti-infectives at the time of randomization
- Use of anti-viral treatment at the time of randomization (Yes, No) and by type of anti-viral treatment (e.g. hydroxychloroquine, chloroquine, convalescent plasma, remdesivir, faripivavir, ritonavir, lopinavir)
- Number and presence of the following comorbidities: diabetes, hypertension, cardiovascular disease (i.e. chronic heart disease), chronic lung disease (e.g. COPD, asthma)Baseline Oxygen use based on the type of pulmonary/ventilatory support (defined in Table 6-1)
- Marker for inflammation as continuous variables: CRP, Serum Ferritin, D-Dimer, LDH, neutrophil counts, BNP and troponin.
- A stacked barchart illustrating the percentage of participants by treatment with the number of comorbidities at baseline (0, 1, 2, 3, 4, 5, 6 or more)
- A barchart illustrating the number and presence of the following comorbidities: diabetes, hypertension, cardiovascular disease (i.e. chronic heart disease), chronic lung disease (e.g. COPD, asthma)

The distribution of the three stratification parameters will be summarized separately by treatment group.

For oxygen requirement at baseline the type of support required prior but closest to the day of randomization will be reported.

Protocol deviations will be listed and summarized by treatment group.

All medical history including the comorbidities will be listed.

Randomization information will be listed and summarized by treatment group.

7.2.2 Treatment

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by treatment group. For corticosteroids ATC-Subclasses will be added. Convalescent plasma treatment will included in the anti-viral treatment presentations.

For any of the below mentioned three treatment categories, if it started prior to treatment and continued during the study, it will be reported under baseline as well as part of SoC during study participation.

A graphical presentation of the cumulative use of different concomitant medications at baseline over the course of the study by treatment group will be provided. For this the cumulative average percentage use will be plotted on the y-axis over the cumulative number of enrolled participants on the x-axis. This presentation will be provided for the following medications:

- Dexamethasone
- Remdesivir
- Hydroxchloroquine or Chloroquine
- Anti-coagulants (using ATC class as provided)

Corticosteroids use

The number and percentage of patients will be summarized by treatment group for the following parameters:

- receiving any corticosteroids after randomization
- receiving Dexamethasone after randomization reporting the highest total daily dose observed during the study using the following ranges:
  <6 mg, 6-<12 mg, >= 12 mg

The following presentations will be based on the prednisone equivalent dose (see Appendix for details):

- with a change in their corticosteroids dose after randomization (increased/reduced/stable dose)
- receiving corticosteroids after randomization reporting the highest total daily dose observed during the study using the following ranges:
  <7.5 mg, 7.5-<20 mg, >= 20 mg

For subgroup analyses the participants with a high vs. a low corticosteroid dose during the first week following randomization were identified. This was defined as follows:

- Considering any corticosteroid mediation selected by ATC class administered between randomization and the following 7 days (i.e. start date < day 8 and end date > 0).
- Only medication reported with a unit of "mg" was included
- Doses are converted into prednisone equivalent doses applying Table 10-2.
- The total daily dose is derived based in the administration frequency reported in the CRF:

1. "ONCE", "QD", "QID", "Q24H" – factor 1
2. "BID" – factor 2
3. "TID", "Q8H" – factor 3
4. "Q6H" – factor 4

- The total dose administered during the first week is derived based on the actual number of days the drug was administered in this period. This is done on a "day" scale, i.e. additional details on administration times are not considered.
- The sum of the total daily doses during the first week in the study is calculated
- The average total daily dose is derived by dividing the sum of the total daily doses by 7.
- A dose of zero is added for any participants not receiving corticosteroids during the first week.
- The average daily prednisone equivalent doses during the first week (dailydose1wk) in mg are categorized as follows:
  - dailydose1wk = 0: "none"
  - dailydose1wk <= 10 (including zero): "<=10"
  - 10< dailydose1wk <= 20: ">10-20"
  - 20< dailydose1wk <= 50: ">20-50"
  - 50< dailydose1wk <= 100: ">50-100"
  - 100< dailydose1wk <= 200: ">100-200"
  - 200< dailydose1wk: ">200"

A stacked barchart is provided showing the distribution in these dose categories by treatment group.

- For further subgroup analyses the categories "<=10 mg (Low)" and ">10 mg (High)" are used.

For the medications listed below barcharts on the "counts" use of corticosteroids at baseline by treatment group will be given.

- Dexamethasone
- Methylprednisolone
- Prednisone
- Other

- None

Anti-viral medication use

The number and percentage of patients will be summarized by treatment group for the following parameters:

- receiving any anti-viral medication after randomization
- receiving hydroxychloroquine/chloroquine/remdesivir/faripivavir/ritonavir/lopinavir/ convalescent plasma after randomization receiving a combination of the above anti-viral medications after randomization tabulated by all combinations actually occurring.

For the medications listed below barcharts on the "counts" use of anti-virals at baseline by treatment group will be given.

- Azithromycin
- Hydroxychloroquine
- Remdesivir
- Convalescent plasma
- Immunoglobulin G human
- Other
- None

For convalescent plasma and immunoglobulin G human, also consider them as baseline records if any participant had them administered before screening/baseline visit.

Anti-coagulation therapy

The number and percentage of patients will be summarized by treatment group for the following parameters:

- receiving any anti-coagulation medication after randomization

The "counts" at baseline will be displayed in a barchart.

- **Anti-infectives therapy**

The number and percentage of patients will be summarized by treatment group for the following parameters:

- receiving any anti-infectives medication after randomization

The "counts" at baseline will be displayed in a barchart.

Combination of SoC medications

The number and percentage of patients receiving any combination of steroids, anti-viral, anti-infectives and/or anti-coagulants treatments after randomization will be summarized by treatment group.

7.2.3 Vital signs

Vital sign measurements include respiratory rate, pulse rate (PR), systolic and diastolic blood pressure, mean arterial pressure body temperature, weight and BMI. Peripheral oxygen saturation on room air should also be measured at the same time as the vitals. For participants requiring supplemental oxygen, the oxygen flow rate (L/min) and/or FiO2 is also recorded.

Summary statistics will be provided by treatment group and visit/time.

The following exploratory MMRM analyses were conducted for body temperature:

1. Including all participants using the safety analysis set.
2. on the high baseline CRP subgroup and by corticosteriod dose during the first week following randomization using the "PD analysis set" is used.

In addition only participants in the high baseline CRP group are considered. The high baseline CRP group is defined as any subject with a baseline CRP value > median baseline CRP value of all participants in this study.

For analysis 1. the MMRM model is including treatment, visit and their interaction as well as the three stratification factors and their interaction with visit as fixed factors and baseline body temperature as a covariate. Interactions between visit and each of the terms in the model will also be included. To model the dependency of observations an unstructured variance-covariance matrix will be fitted.

The means per treatment group as well as the mean difference (MAS825 vs. Placebo) will be reported together with 90% confidence intervals (CIs) for each visit. In addition the 1-sided p-values for the overall treatment factor will be reported.

Estimated mean body temperatures +/- SE will be plotted over time by treatment group.

For analysis 2. the same model as for the original MMRM analysis including in addition a factor for high vs. low corticosteroid use during week 1 (see Section 7.2.2 for details) and its 3-way interaction with treatment and visit.

The means (+/-SE) per corticosteroid category and treatment group as well as the mean differences (90% CI) per corticosteroid group are reported for each visit.

A line plot of the means (+/-SE) are provided by corticosteroid dose category and treatment group together with the estimated values of the primary analyses by treatment group over time. Side-by-side a second line plot on the treatment differences (90% CI) per by corticosteroid dose category together with the estimated treatment difference (90% CI) of the primary analyses over time is given.

7.2.4 ECG evaluations

Heart rate, PR, QRS, QT, QTcF, and RR intervals will be obtained from ECGs (12-lead or 5-lead) for each participant during the study. ECG data will be read and interpreted locally.

Categorical analysis of QT/QTcF interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTcF intervals or changes from baseline will be presented.

Summary statistics will be provided by treatment group and visit/time.

7.2.5 Clinical laboratory evaluations

Summary statistics will be provided by treatment group and visit/time.

In case for one parameter multiple types of assessments were reported for the same visit/assessment the following rules are applied for any analysis e.g. summarizing the results:

- In case both absolute counts and percentages (e.g. “bands” or ratios) are provided, absolute counts are used.
- In case both Urea and BUN parameters are provided, Urea is used.
- In case for troponin multiple versions are provided (e.g. troponin T, I and/or C), troponin T is used; if not available troponin I is used.

In addition to the parameters collected the ratio of Urea/creatinine will be reported, where both parameters are converted to the same unit e.g. mg/dL (see Section 10.3 for conversion details for Urea).

Estimated mean values +/- SE will be plotted over time by treatment group for each of the following lab parameters.

- Leukocytes, Neutrophils, Eosinophils, and Platelets.

To ensure that lab parameters only have numerical values, censored values will be imputed as follows

- Values like <xx.x are replaced by xx.x/2.
- Values like >xx.x are replaced by xx.x.

7.2.6 Adverse events

All information obtained on adverse events will be listed by treatment and subject.

Summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. Separate summaries will be provided for study medication related adverse events and other significant adverse events leading to discontinuation.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT until day 29 and after day 29.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by PT until day 29 and after day 29.

A subject with multiple adverse events within a body system is only counted once towards the total of this body system and treatment.

For the legal requirements of ClinicalTrials.gov and EudraCT, two tables are required:

on treatment emergent adverse events which are not serious adverse events and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety analysis set.

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

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

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

The SAEs and deaths by State will be graphically presented in a barchart. Refer to Section 10.8 for details on the state.

7.2.7 Graphical presentation

For all vital signs, ECGs and laboratory parameters the following graphical presentations will be provided:

Panels of individual spaghetti plots over time for each parameter and their change from baseline will be drawn. The profiles of all participants in the respective treatment group will be included in these graphs as grey lines in the background and the respective individual participants profile will be plotted with darker color in the foreground. The respective applicable normal ranges will be added and it will be indicated by a symbol if a patient died.

Means (+/- SE) will be plotted over time by treatment group

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9 Reference list

Knaus WA, Draper EA, Wagner DP, et al (1985) APACHE II: a severity of disease classification system. Crit Care Med; 13(10):818-29.

10 Appendix

10.1 Units and conversions

Special care must be taken with respect to converting lab parameters prior to applying the scoring described below to avoid propagation of rounding errors. The following principles will be applied:

- If the unit of the original lab assessment from the local lab is equal to the unit used in the scoring table, this original value is used.
- In case the SI unit which is available within the SDTM data sets is equal to the unit used in the scoring table, the value converted to SI units is used.

- If neither the original nor the SI unit are matching the unit used in the scoring table then convert the original value from the local lab to the unit required by the scoring table. Note that for some parameters there are scoring tables available for different units.
- Do convert the value in SI units further.
- Do apply rounding to the precision required in the scoring table only after conversion to the unit used in the scoring table has been done.

10.1.1 Conversion for absolute neutrophil counts

If not reported the absolute neutrophil counts can be derived if

- % of neutrophils
- Total WBC

is available via the following formula:

absolute neutrophil count = total WBC * neutrophil percentage.

10.2 APACHE II

The APACHE II score is derived from a number of different clinical endpoints according to the scoring table as outlined in (Knaus et al., 1985):

1. Body temperature (°C)

   Depending on the collection method selected apply the following correction factors before scoring:

   - Core: no correction needed
   - Axillary: + 1.0 °C
   - Oral: + 0.5 °C
   - No method selected: no correction.

2. Mean Arterial Pressure (mmHg)

   In case the "method" is reported as "calculated" confirm the calculation by applying the following formula: MAP = [SBP + (2x DBP)] / 3. If the reported and recalculated numbers differ by more than 10% use the recalculated value (i.e. if reported value < 0.9* recalculated value or reported value >1.1* recalculated value)

3. Heart Rate (beats per minute)

   If the participant has a pacemaker any HR <= 109 bpm will be scored to 0.

4. Respiratory Rate (breaths per minute)

5. Oxygenation: depending on the Fraction of inspired Oxygen (FiO2, where FiO2 is a value between 0 and 1 (i.e. not on % scale)):

   a. If FiO2 < 0.5: use PaO2 (mmHg)

   b. If FiO2 >= 0.5: use A-aDO2 (mmHg): where A-aDO2 is calculated as A-aDO2 = (FiO2 × 713 - PaCO2/0.8) – PaO2)

In case PaO2 is not available for a certain visit it can be derived from SPO2 if available instead using the following conversion table:

Table 10-1Conversion of SpO2 to PaO2

SpO2 (%)	PaO2 (mmHg)
80	44
81	45
82	46
83	47
84	49
85	50
86	52
87	53
88	55
89	57
90	60
91	62
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145

In case PaCO2 is not available for a certain visit it can be derived from HCO3 if available instead using the following conversion:

PaCO2 (mmHg) = HCO3(mEq/L)*1.5 + 8

6. Arterial pH: if Arterial pH is not available use Serum HCO3 (venous mMol/L) instead
7. Serum Sodium (mmol/L)
8. Serum Potassium (mmol/L)
9. Serum Creatinine (mg/dL=mg/100mL)
10. Hematocrit (%)

11. White Blood Count (10^9/L = 1000/mm^3 = 10^3/mm^3)
12. Age at screening (years)
13. Chronic Health Points at Screening:

Points are assigned only if for this patient "Did the subject experience Severe organ system insufficiency or is immunocompromised ?" is selected as "yes".

- If "Did the subject experience Severe organ system insufficiency or is immunocompromised ?" = "no", no points are assigned and a record should not be created for this question in the SDTM data set.

- If "Did the subject experience Severe organ system insufficiency or is immunocompromised ?" is selected as "yes" Chronic Health points will be derived from "Admission Classification":
  - Medical(non-operative)
  - Emergency post-operative
  - Elective post-operative

If in this scenario none of these conditions is selected the Chronic Health points will be set to 0.

14. Glasgow Coma Score: First each sub-score is scored according to the socring table below
    - Best Eye Response
    - Motor Response
    - Verbal Response

Then these three subscores are added up to obtain the scoring of the "Total Glasgow Coma Score". The value included in the APACHE II for Glasgow-Coma-Score is then = 15 – "Total Glasgow Coma Score".

SDTM Mapping strategy

APACHE II specific mapping strategy: It provides guidance on how the result variables (RSORRES, RSSTRESC, and RSSTRESN) should be populated for the measure. All original results are represented with preferred terminology in RSORRES. This result is then transformed into a standard numeric score in RSSTRESN and a character representation of the standard numeric score in RSSTRESC.

To obtain the total APACHE II score all 14 derived values of RSSTRESN are then added up. If one item is missing the APACHE II score at STDM level for this visit is missing. Missing data imputation will be implemented at ADAM level.

10.2.1 APACHE II Scoring

Temperature (°C)

RSORRES	RSSTRESC	RSSTRESN
>=41	4	4
39-40.9	3	3
38.5-38.9	1	1
36-38.4	0	0
34-35.9	1	1
32-33.9	2	2
30-31.9	3	3
≤29.9	4	4

Mean Arterial Pressure (mmHg)

RSORRES	RSSTRESC	RSSTRESN
>=160	4	4
130-159	3	3
110-129	2	2
70-109	0	0
50-69	2	2
<=49	4	4

Heart rate (BEATS/MIN)

Does the participant have a pacemaker?	RSORRES	RSSTRESC	RSSTRESN
Irrespective	>=180	4	4
Irrespective	140-179	3	3
Irrespective	110-139	2	2
No/unknown	70-109	0	0
No/unknown	55-69	2	2
No/unknown	40-54	3	3
No/unknown	<=39	4	4
Yes	<=109	0	0

Respiratory rate (BREATHS/MIN)
Note: Ventilated or non-ventilated patient scores will be the same as per table below

RSORRES	RSSTRESC	RSSTRESN
>=50	4	4
35-49	3	3
25-34	1	1
12-24	0	0
10-11	1	1

6-9	2	2
<=5	4	4

Impute the unit for respiratory rate as breaths/min in case it is missing.Oxygenation:

- If FiO2 >= 0.5 then use A-aDO2 (mmHg)

RSORRES	RSSTRESC	RSSTRESN
>=500	4	4
350-499	3	3
200-349	2	2
<200	0	0

- If FiO2 < 0.5 then use PaO2 (mmHg)

RSORRES	RSSTRESC	RSSTRESN
>70	0	0
61-70	1	1
55-60	3	3
<55	4	4

If any value for <X, impute the value X in that case.

Arterial pH

- Use arterial pH if reported

RSORRES	RSSTRESC	RSSTRESN
>=7.7	4	4
7.6-7.69	3	3
7.5-7.59	1	1
7.33-7.49	0	0
7.25-7.32	2	2
7.15-7.24	3	3
<7.15	4	4

- Alternatively use Serum HCO3 (mmol/L)

RSORRES	RSSTRESC	RSSTRESN
>=52	4	4
41-51.9	3	3
32-40.9	1	1
22-31.9	0	0
18-21.9	2	2
15-17.9	3	3
<15	4	4

Serum sodium (mmol/L)

RSORRES	RSSTRESC	RSSTRESN
>=180	4	4
160-179	3	3
155-159	2	2
150-154	1	1
130-149	0	0
120-129	2	2
111-119	3	3
<=110	4	4

Serum potassium (mmol/L)

RSORRES	RSSTRESC	RSSTRESN
>=7	4	4
6-6.9	3	3
5.5-5.9	1	1
3.5-5.4	0	0
3-3.4	1	1
2.5-2.9	2	2
<2.5	4	4

Serum creatinine (mg/dL)

RSORRES	RSSTRESC	RSSTRESN
>=3.5 and acute renal failure =”yes”	8	8
2-3.4 and acute renal failure =”yes”	6	6
1.5-1.9 and acute renal failure=”yes”	4	4
0.6-1.4 and acute renal failure =”yes”	0	0
<0.6 and acute renal failure =”yes”	4	4
>=3.5	4	4
2-3.4	3	3
1.5-1.9	2	2
0.6-1.4	0	0
<0.6	2	2

Hematocrit (%)

RSORRES	RSSTRESC	RSSTRESN
>=60	4	4
50-59.9	2	2

46-49.9	1	1
30-45.9	0	0
20-29.9	2	2
<20	4	4

White Blood Count (10^9/L)

RSORRES	RSSTRESC	RSSTRESN
>=40	4	4
20-39.9	2	2
15-19.9	1	1
3-14.9	0	0
1-2.9	2	2
<1	4	4

Age points (years)

RSORRES	RSSTRESC	RSSTRESN
<=44	0	0
45-54	2	2
55-64	3	3
65-74	5	5
>=75	6	6

Chronic health points

RSORRES	RSSTRESC	RSSTRESN
For non-operative or emergency post-operative patients	5	5
For elective post-operative patients	2	2
None selected	0	0

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10.5 Glasgow Coma Score

10.5.1 Glasgow Coma Scoring

- Best eye response

Result	Score (Char)	Score (Num)
No eye opening	1	1
Eye opening to pain	2	2
Eye opening to verbal command	3	3
Eyes open spontaneously	4	4
Untestable	Untestable	
Unknown	Unknown	

- Motor response

Result	Score (Char)	Score (Num)
No motor response	1	1
Abnormal extension	2	2
Abnormal flexion	3	3
Flexion withdrawal	4	4
Localizes pain	5	5
Obeys command	6	6
Untestable	Untestable	
Unknown	Unknown	

- Verbal response

Result	Score (Char)	Score (Num)
No verbal response	1	1
Incomprehensible sound	2	2
Inappropriate words	3	3
Confused	4	4
Oriented	5	5
Untestable	Untestable	
Unknown	Unknown	

10.6 9-point ordinal scale

Patient State	Descriptor	Score	Abbreviated description
Uninfected	No Clinical or virological evidence of infection	0	Uninfected
Ambulatory	No limitation of activities	1	Amb: No limitations
	Limitation of activities	2	Amb: Limitations
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3	Hosp: No Oxygen
	Oxygen by mask or nasal prongs	4	Hosp: Oxy Mask/ Nasal prongs
Hospitalized Severe disease	Non-invasive ventilation or high-flow oxygen	5	Hosp: Non-Inv Vent/ High flow oxy
	Intubation and mechanical ventilation	6	Hosp: Intub + Mech Vent
	Ventilation + additional organ support - pressors, RRT, ECMO	7	Hosp: Vent + pressors
Dead	Death	8	Dead

10.7 Steroid conversion factors

Steroids will be displayed using prednisone equivalent doses. The doses displayed in the following table are considered equivalent. To determine prednisone equivalent doses, doses (in unit mg) will be multiplied by the conversion factor shown in Table 10-2. In case multiple corticosteriods are used at a certain visit the prednisone equivalent doses will be added up to obtain the total prednisone equivalent dose.

Table 10-2 Steroids conversion factors

WHO drug code	Preferred Term Corticosteroid	Equivalent Dose [mg]	Conversion Factor
000447xx	Prednisone	5	1
000162xx	Prednisolone	5	1
000496xx	Methylprednisolone	4	1.25
012428xx	Meprednisone	4	1.25
001867xx	Prednylidene	5 5/7	0.875
000319xx	Triamcinolone	4	1.25
000146xx	Cortisone	25	0.2
000286xx	Hydrocortisone	20	0.25
002131xx	Fludrocortisone	2	2.5
000085xx	Betamethasone	0.75	20/3
000664xx	Paramethasone	2	2.5
000160xx	Dexamethasone	0.75	20/3
008827xx	Deflazacort	6	5/6

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