STATISTICAL ANALYSIS PLAN

PROTOCOL: REP0220

A phase 3, double-blind, randomized, placebo-controlled, multicenter study on the efficacy and safety of Reparixin in the treatment of hospitalized patients with severe COVID-19 pneumonia.

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APPROVAL PAGE

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The Statistical Analysis Plan has been completed and reviewed and the contents are approved for use for the analysis.

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Table of Contents

Index of Tables

1. Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BDRM	Blind Data Review Meeting
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
DMC	Data Monitoring Committee
eGFR	Epidermal growth factor receptor
ENR	Enrolled set
FAS	Full Analysis set
FiO2	Fraction of inspired oxygen
ICH	International Council for Harmonization
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
IMV	Invasive Mechanical Ventilation
IRS	Interactive Response System
ITT	Intent to Treat
KM	Kaplan-Meier
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing not at random
NCI-CTCAE	National Cancer Institute- Common Terminology Criteria for Adverse Events
PaO2	Partial arteriolar oxygen pressure
PCR	Polymerase chain reaction
P/F	Partial arteriolar oxygen pressure (PaO2) to fraction of inspiration O2 (FiO2) ratio
PP	Per Protocol set
PT	Preferred Term

RND	Randomized set
Rt-PCR	Reverse transcriptase Polymerase Chain Reaction
RTF	Rich Text Format
SAE	Serious Adverse Event
SAF	Safety set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus 2
SAS	Statistical Analysis Systems
SD	Standard Deviation
SE(M)	Standard Error (of the Mean)
SI	Standard International
SOC	System Organ Class
SPO2	Peripheral arterial oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TID	Ter in die - three times a day
TLF(s)	Tables, Listings and Figures
VAS	Visual Analog Scale
WHO DD	World Health Organization Drug Dictionary
WHO-OS	7-point WHO Ordinal Scale of clinical improvement

2. Revision History

Document Version	Changes Made	Document Date
Final 1.0	Final version	PPD
Final 2.0	Primary endpoint sensitivity analysis added, (excluding patients who were already in the ICU at baseline) Analysis visit definition changed and, in particular, extended to cover End of Treatment, End of Study and Hospital Discharge Analyses of number of ICU admissions up to Day 28, number of invasive mechanical ventilation use, or ECMO up to Day 28, and number of ICU admission, invasive mechanical ventilation use, or ECMO or death up to Day 28 added.	PPD
Final 3.0	The SAP version 2.0 has been reviewed after the Blind Data review Meeting. The previous version is confirmed except for the following items reported in Table 4: - Total number of tablets scheduled during the treatment period - PaO2/FiO2 ratio (when data is not available in the eCRF but PaO2 and FiO2 are available separately.	PPD

3. Introduction

This document outlines the statistical methods to be implemented in the analysis of the data of REP0220 Clinical Trial. The purpose of this plan is to provide general guidelines from which the analysis will proceed, containing a more technical and detailed elaboration of the principal features of the analysis described in the protocol. Any changes to the protocol or Case Report Form (CRF) may necessitate updates to the Statistical Analysis Plan (SAP). In case of deviations from this updated SAP, explanations will be provided in the clinical study report.

This SAP is based on study protocol Version 3.0 final – 09 April 2021[1], Case Report Form Version 2.2 – 21 April 2021[2].

4. Study Objectives

The objective of this clinical trial is to assess efficacy and safety of Reparixin treatment as compared to placebo (both on top of standard treatment) in adult patients with severe COVID-19 pneumonia.

5. Study Design

5.1 General design and plan

This is a phase 3 clinical trial designed as a randomized, placebo-controlled, multicenter study to evaluate the efficacy and safety of Reparixin in hospitalized adult patients with severe COVID-19 pneumonia.

Patients will be screened for the participation in the study and eventually randomized based on an unbalanced randomization scheme (2:1) to Reparixin oral tablets (2 x 600 mg TID) for up to 21 days or to placebo. The investigational treatment is not foreseen to be continued at home after discharge from hospital. CCI [redacted] The placebo control arm is justified by the unavailability of a well-defined "standard of care" for subjects with COVID-19 pneumonia who are candidates for this study. All patients will receive the standard supportive care based on the patient's clinical need. Follow-up information on the patient's clinical condition (new hospitalization, need of supplemental oxygen, adverse events) and survival will be collected until Day 90.

An interim analysis for efficacy and futility is planned when half of the planned patients has reached the primary endpoint.

DMC meetings will be performed during the trial, in order to monitor the safety of the patients and to protect study subjects from undue harm.

5.2 Visit Schedule and Visit Windows

Assessments and study visits will be performed as listed in Paragraph no. 7 “Assessments and procedures” of the Study Protocol containing additional details about scheduled visits and time windows.

Baseline is defined as the last visit prior to and including date of the randomization visit. Unless otherwise specified, baseline values are defined as the measurements taken during this visit.

In case of multiple measurements during baseline visit, the last assessment will be considered as baseline evaluation before start of treatment.

In general, for efficacy and safety endpoints, data will be evaluated according to the Visit at which they have been collected, also if performed out-of-window (in case visit has been performed out of predefined window, available information at the actual effective day will be considered).

For example, for the primary efficacy endpoint, the analysis will be performed using data collected in Day 28 visit (corresponding to 28±2 days); if assessment is out-of-window, the available information at 28 days post randomization will be used. In case the day of “Day 28” visit is after 30 days, we can use that collected information. In case the day of “Day 28” visit is before 26 days, we have to evaluate the next assessment (i.e.: “Day 60” visit or an unscheduled visit). This approach will be implemented for primary and key-secondary efficacy endpoints with a defined “Day”.

For convenience, Day 3, Day 7, Day 14, Day 21, Day 28, Day 60 and Day 90 will be used throughout the document.

Table 1: Study Flow Chart

Study procedures	**Screening**	**Baseline Day 1**	**Day 3**	**Day 7** (±1)	**Day 14** (±2)	**Day 21** (±2) **or EoT** [1]	**Day 28** (±2) **or discharge or EoS** [1]	**Day 60** (±2) **or discharge or EoS** [1]	**Day 90** (±2) **or EoS**[1]
Informed Consent	X								
Inclusion/Exclusion Criteria	X	X							
Pregnancy Test	X								
Randomization		X							
Demographics	X								
Medical History	X								
Child Pugh score	X	X	X	X	X	X	X		
Previous and concomitant medications	<---------- X								
Preventive off-label use of other anti-COVID-19 medications	X	X	X	X	X	X	X	X	
Timing until start of investigational treatment [2]		X							
Clinical severity score (7-point WHO-OS)	X	X	X	X	X	X	X	X	X
CCI	X	X	X	X	X	X	X	X	
Dyspnea Liker scale			X	X	X	X	X		
Dyspnea VAS scale	X	X	X	X	X	X	X		
Supplemental Oxygen	X	X	<---------- X 3						
Non-invasive mechanical ventilation	X	X	<---------- X 3						
Invasive mechanical ventilation / ECMO			<---------- X 3						
Total days of hospitalization			<---------- X 3						
ICU admission			<---------- X 3						
Chest imaging	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	
SpO_2, PaO_2, FiO_2, P/F (PaO_2/FiO_2)	X	X	X	X	X	X	X	X	
[redacted] CCI	CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted] CCI	CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted] CCI		CCI				CCI			
[redacted] CCI		CCI	[redacted]	[redacted]					
samples for Reparixin concentration [8]			X						
CCI		CCI				[redacted]			
SARS-CoV-2 virology (rt-PCR)	<---------- X						X		
Study drug administration		<---------- X ---------->							
Record AEs / SAEs	<---------- X ---------->								

[1] EoT: End of Treatment. EoS: End of Study

EoT is the last day of treatment administration. The investigational treatment will last up to 21 days. Reasons for earlier treatment termination are: Investigator's decision based on clinical judgment of improvement, even if the patient is still hospitalized but no longer requiring supplemental oxygen or significant medical care; occurrence of adverse events; patient's withdrawal of consent to the treatment. After EoT, laboratory and clinical examinations shall be collected on the day of patient's discharge from hospital, or on Day 28. The collection of follow-up information should be continued after EoT until EoS (Day 90), unless the patient also withdraws the consent to the follow-up. For subjects discharged home before the completion of the 21-day treatment period, follow-up (preferably in person at the Center, or via a telephone call) at days 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) - 60 (±2) and/or 90 (±2) depending on the discharge time point.

EoS is defined as the last day the last patient completes the last study assessment (including the follow-up assessments), or withdraws the consent to participate in the study, including follow-wp. Subjects with EoS before Day 28 should undergo a full evaluation (as required on Day 28). Subjects with EoS after Day 28 but earlier than Day 90 should undergo evaluation as required on Day 90.

[2] CCI [redacted]

[3] to be recorded over the whole duration of the hospitalization (total number of days to be reported). For supplemental oxygen, please record daily (average) delivery as < 6 L/min, 6 - 10 L/min, >10 L/min

[4] When deemed appropriate by the investigators

[redacted]

[redacted]

[redacted]

[8] Samples for the determination of Reparixin concentrations collected immediately before and one hour (± 15 min) after first dosing at day 3

5.3 Remapping visit

As specified in the section 0, in general, the following analysis timepoints will be presented:

- Baseline Day 1
- Day 3
- Day 7 (+/- 1)
- Day 14 (+/- 2)
- Day 21 (+/- 2)
- Day 28 (+/- 2)
- Day 60 (+/- 2)
- Day 90 (+/- 7)

In addition, the following analysis time points will generally be presented:

- End of Treatment (EoT)
- Hospital discharge
- End of Study (EoS)

Data collected directly in the eCRF in the visits named “Baseline Day 1”, “Day 3”, “Day 7 (+/- 1)”, “Day 14 (+/- 2)”, “Day 21 (+/- 2) or EoT” (with visit type specified as “Visit as per study protocol schedule”), and “Day 28 (+/- 2) or discharge or EoS” (with visit type specified as “Visit as per study protocol schedule”),” will be used in the analysis, whenever present. In these cases, no visits remapping will be performed.

The Day 60 (+/-2), Day 90 (+/-7), End of Treatment, Hospital discharge and End of Study analysis visits are defined as follows:

Day 60 (+/-2):

- Data collected at “Day 60 (+/-2) or discharge or EoS” with visit type specified as “Visit as per protocol schedule” or
- Data collected at “Day 60 (+/2) or discharge or EoS” with missing information on visit type (only for patients who did not re-consent to protocol amendment v3.0 or had this visit performed prior to re-consent) and between day 58 and day 62 of study

Day 90 (+/-7):

- Data collected at “Day 90 (+/2) or EoS” and between day 83 and day 97 of study (somewhat extending the per-protocol window).

End of Treatment:

- Data collected at “Day 21 (+/2) or End of Treatment” (irrespective of visit type)

End of Study:

- Data collected at “Day 90 (+/-2) or EoS” or data collected at “Day 28 (+/2) or discharge or EoS” with visit type specified as “End of study evaluation” or data collected at “Day 60 (+/2) or discharge or EoS” with visit type specified as “End of study evaluation”
- Data collected at “Day 60 (+/2) or discharge or EoS” with missing information on visit type, in case that the patient either did not re-consent to protocol amendment v3.0 or in case that the patient is known to have completed/prematurely discontinued the study without a “Day 90 (+/-2) or EoS” visit performed.

Hospital discharge:

- Data collected at “Day 28 (+/-2) or hospital discharge or EoS” with visit type specified as “Hospital discharge” or data collected at “Day 60 (+/-2) or hospital discharge or EoS” with visit type specified as “Hospital discharge”

5.3.1 Remapping Follow-up visits

In case data was not collected at the above defined visits for Day 7 (+/-1), Day 14 (+/- 2), Day 21 (+/-2), Day 28 (+/-2) or Day 60 (+/-2), data collected at the follow-up visits will be remapped and used in the analysis:

- Follow-up Visit/Phone Call Day 7 (+/- 1) remapped as Day 7 (+/- 1)
- Follow-up Visit/Phone Call Day 14 (+/- 2) remapped as Day 14 (+/- 2)
- Follow-up Visit/Phone Call Day 21 (+/- 2) remapped as Day 21 (+/- 2)
- Follow-up Visit/Phone Call Day 28 (+/- 2) remapped as Day 28 (+/- 2)
- Follow-up Visit/Phone Call Day 60 (+/- 2) remapped as Day 60 (+/- 2)

In case data was not collected at an analysis visit of “Hospital discharge” (see section 5.3 above), data collected at the visit “Follow-up Visit/Phone Call Discharge” will be remapped as “Hospital discharge” visit.

5.3.2 Remapping of other visits

Additionally, at the eCRF, data can be collected at the following study moments (that may or may not coincide with the analysis timepoints defined above):

- End of Treatment (EoT)
- Hospital Discharge
- End of Study (EoS)

After remapping of follow-up visits and in case data are still missing at a Day 3, Day 7 (+/-1), Day 14 (+/- 2), Day 21 (+/-2), Day 28 (+/-2), Day 60 (+/-2) or Day 90 (+/-7) analysis visit , data collected in any of these additional moments will be remapped if the date of collection is within the analysis

timepoint window ("date of collection" defined as the specific assessment date, or the visit date in case the specific assessment date is not collected or is empty).

Example: "End of Treatment" happens at day 13 of study and there is no data collected at visit "Day 14 (+/- 2)" for that subject, then the data collected in the "End of Treatment" moment will be remapped to "Day 14 (+/- 2)" and it will be used in the analysis for that timepoint.

All End of Treatment, Hospital Discharge and End of Study visits will also be analyzed "as such", irrespective of whether they were also remapped to another study visit as per above (see section 5.3).

5.3.3 Additional notes for remapping

The following additional rules will be applied when performing visit remapping:

- If more than one of additional visit (End of Treatment, Hospital Discharge, or End of Study) can be remapped to a specific analysis visit, then the one closer to the exact visit day of the "Day xx" visit will be used. If both are at the same time distance, then the latest one will be used. If there are two visits on the same day (e.g. End of treatment and Hospital Discharge performed at the same date but recorded twice in the CRF on the forms for "Day 21 (+/2) or EoT" and "Day 28 (+/2) or discharge or EoS"), then the information from the End of Study will be used, when available. Otherwise, the information from the Hospital Discharge will be used.
- Visit remapping is done in each form independently of data collected in other forms.
- Visit remapping performed at parameter-level (each parameter within the form will be considered independently):
    - Applies to: Clinical Severity Score, Dyspnea VAS Scale, Dyspnea Likert Scale, CCI [redacted] Chest Imaging, Lung Function, CCI [redacted].
        - CCI [redacted]
- Visit remapping performed at form-level (all data parameters must be remapped within the form or none is) for the following forms:
    - Child Pugh Score will be fully remapped if the "Total Score" is missing due to missing data in one or more parameters.
        - Example: "Ascites" is missing in the Child Pugh Score at "Day 14 (+/- 2)" and because of that the total score and class are also missing. The subject has an "End of Treatment" at study day 15 (within window) in which the "Child Pugh Score" was fully collected. In this case, the full "Child Pugh Score" collected in the "End of Treatment" will be remapped and that will be the score used in the analysis for "Day 14 (+/- 2)".
    - "Additional Information" form will only be remapped if the form is fully missing at the analysis timepoint.
        - Example: "Does the patient need invasive mechanical ventilation / ECMO?" is missing in the form at "Day 14 (+/- 2)" but the subject has an "End of Treatment" at study day 15 (within window) in which the "Additional

Information" was fully collected. In this case, the full "Additional Information" form on "End of Treatment" will not be remapped.

- Visits that cannot be mapped to any analysis visit will only be shown in subject data listings with the visit name as recorded in the CRF.

- Forms that will not be remapped:
  - CCI will not be remapped as it is planned to be collected only at "Baseline Day 1" and "Day 21 or EoT".
  - "SARS-CoV-2 virology (rt-PCR)" will not be remapped as it is planned to be collected only at "Baseline Day 1" and "Day 28 or Discharge or EoS".
  - "Covid-19 Medication" will not be remapped as it is not needed for the analysis.

5.4 Sample size justification

The sample size of the study is calculated based on results from the phase II, open label REPAVID-19 study.

Considering a randomization ratio 2:1 (Reparixin:placebo) and a one-sided alpha of 0.025, a total of 264 evaluable patients will allow to achieve an overall power of 90% to detect a group difference ≥20% in proportion of patients alive and free of respiratory failure at Day 28 in favor of Reparixin, assuming that the proportion of patients alive and free of respiratory failure in the placebo group will be approximately 60%.

The sample size has been adjusted in order to take into consideration an interim analysis during the study. Details on interim analysis are provided in section 6.5 of this document. No additional multiplicity correction of alpha is required.

Assuming that 15% of subjects will not be evaluable for the primary analysis, a total of approximately 312 subjects is expected to be enrolled.

5.5 Randomization and blinding

Eligible Patient will be randomized in a 2:1 fashion to either Reparixin or placebo.

Randomization will be performed through an Interactive Response System (IRS). Specific procedures for randomization through the IRT are contained in the study procedures manual.

Each Patient's treatment pack/Kit number will be randomly associated with a treatment group. The randomization list will be provided to the facility responsible for IMP packaging/labelling for the purpose of IMP preparation. Each randomized patient will be allocated with randomization number according to the stratified randomization list. Dropouts after randomization will not be replaced.

Randomization will be stratified by site, gender and age class (<65 yrs. vs ≥ 65 yrs.) to ensure balanced assignment across treatment groups. The stratified permuted block randomization list will be generated with a computer procedure by an independent statistician not involved in the conduct of the study.

For each randomized subject, individual code breaks will be accessible in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. Only the responsible investigator, or authorized delegates, can break the code via the IRT or by opening the sealed envelopes with indication of the actual treatment.

The DMC will have access to fully unblinded DMC reports.

The randomization code will be broken when the last enrolled patient has completed therapy, and once the database has been locked.

5.6 Overview of planned statistical analyses

The study plans for the following statistical analyses:

- Interim analysis for efficacy or futility: this analysis will be conducted by an independent statistician when half of the planned evaluable patients has reached the primary endpoints at Day 28 (details in section 6.5);
- Key first efficacy analysis: this analysis will be conducted by an independent statistician when all enrolled patients are evaluable for the primary analysis at 28 days (details in section 6.6);
- Final analysis: this analysis will be conducted when all enrolled subjects have completed the study and the study database has been unblinded and locked;
- Analyses for the Data Monitoring Committee: these analyses will be produced periodically according to the DMC Charter.

5.7 Efficacy endpoints

5.7.1 Primary endpoints

The primary efficacy endpoint is the proportion of patients alive and free of respiratory failure at Day 28, i.e., with no need of invasive mechanical ventilation or ECMO or admission to ICU linked to worsening of respiratory parameters compared to baseline.

Admissions to ICU has to be considered only in presence of significant worsening of respiratory status. This condition will be objectively identified by means of a decrease of PaO2/FiO2 ratio of at least 40% from the baseline value or by a worsening of Investigator's Interpretation.

5.7.2 Key secondary endpoints

The key secondary endpoints are the following:

- Proportion of patients alive and free of respiratory failure (as described for the primary endpoint) at Day 60,
- Mortality rates up to Day 28,
- Incidence of ICU admission until Day 28,
- Time to recovery (category 1 - 2 - 3 of the 7-point WHO Ordinal Scale of clinical improvement (WHO-OS) until Day 28.

5.7.3 Additional secondary endpoints

The additional secondary efficacy endpoints are the following:

- Proportion of patients alive and free of respiratory failure (as described for the primary endpoint) at fixed time-points: days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) -60(±2) after randomization (randomization = day 1),
- Mean changes in clinical severity score based on the 7-point WHO-OS,
- Time to clinical improvement 1 (decline of 1 category in the 7-point WHO-OS) up to Day 28,
- Time to clinical improvement 2 (decline of 2 categories in the 7-point WHO-OS) up to Day 28,
- Time to discharge from hospital (up to day 28),
- Clinical status at days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) - 60 (±2) - 90 (±2) either in hospital or at home (7-point WHO-OS). When patient is at home, his/her clinical status can be assessed by phone,
- Dyspnea severity (Likert scale and VAS scale) at days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge,
- Duration of supplemental oxygen treatment (days) up to Day 28,
- Incidence of invasive mechanical ventilation use, or ECMO up to Day 60,
- Duration of invasive mechanical ventilation, or ECMO (days) up to Day 60,
- Duration of non-invasive mechanical ventilation (days) up to Day 60,
- Duration of ICU admission (days) up to Day 60,
- Duration of hospitalization since randomization (days) up to Day 60,
- Partial pressure of oxygen (PaO2): change from baseline to the firstly available daily value at days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge,
- Pulse oximetry by measurement of peripheral arterial oxygen saturation (SpO2) at days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge,
- P/F ratio [partial arteriolar oxygen pressure (PaO2) to fraction of inspiration O2 (FiO2) ratio] from baseline to days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge,
- Hs-CRP: change from baseline to days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge (alternatively, CRP),
- Mortality rates up to Day 60 and Day 90,
- Freedom from (time to) death or respiratory failure (as described for the primary end-point).

CCI :

- CCI

- CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

5.8 Safety endpoints

The safety endpoints are the following:

- Incidence of Adverse Events (AEs),
- Incidence of Serious Adverse Events (SAEs),
- CCI

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) toxicity grading scale will be used to capture the severity of adverse events.

6. Statistical Analysis

6.1 General

Appropriate descriptive statistics will be produced by treatment arms according to the nature of the variable. For continuous data, number of observations, mean, standard deviation, median, upper and lower quartiles, minimum, and maximum will be presented. For qualitative data, frequency distributions and percentages per category will be presented. If appropriate, confidence intervals around the mean or the proportions will be presented.

For time-to-event variables, cumulative freedom from event will be evaluated using the Kaplan-Meier method. The degree of uncertainty will be expressed with 95% confidence limits (calculated per the method proposed by Greenwood[3]). Comparison of curves among arms will be performed with the log-rank test. Kaplan-Meier graphs will be presented along with the number of patient-at-risk at exact time points. Subjects who are free from event will be censored at the study termination for the final analysis and will be censored at clinical cut-off date for the interim analysis. Reasons

for discontinuation will be incorporated into the analysis for determining censoring and failure status. Specifically, study discontinuation for Adverse Event, Death, Loss to follow-up or other negative outcomes (assessed during the Blinded Data Review Meeting (BDRM)) will be considered as failure events. Subjects who have discontinued for other reasons without an event will be censored at the date of discontinuation.

Unless otherwise specified, the significance level used for statistical testing will be 0.05 and two-sided tests will be used.

Additional post-hoc analysis may be produced to further allow comparison between treatment and control, according to the results obtained. Any deviations from the original statistical plan (including unplanned analyses) will be documented in the Clinical Study Report.

All the data collected and derived in the study will be presented in subject data listings. All patient data collected on the CRF will be listed by patient and center.

6.2 Analysis sets

6.2.1 Enrolled set

The Enrolled set (ENR) will consist of all patients with signed written informed consent and undergoing to study evaluations/procedures.

6.2.2 Randomized set

The Randomized set (RND) will consist of all patients in the ENR set who are randomized to the study, regardless of whether they receive the Investigational Medicinal Product (IMP) or not.

6.2.3 Safety set

The Safety set (SAF) will consist of all randomized patients who receive at least one dose of the IMP. SAF population will be analyzed according to the actual treatment received and will be used to present results on safety data.

6.2.4 Full Analysis set

The Full Analysis Set (FAS) will consist of all randomized patients who receive at least one dose of the IMP (either Reparixin or placebo). FAS population will be analyzed according to ITT principle, i.e. by treatment allocation regardless of intercurrent events (treatment policy strategy). The FAS population will be used for the primary analyses of the study and to present results on efficacy data.

6.2.5 Per Protocol set

The Per Protocol set (PP) will consist of all patients from the FAS without any Major Protocol Deviations. The PP set will be used for sensitivity analyses.

All the protocol deviations will be discussed case by case by the clinical team during the BDRM before the DB lock and described in the BDRM Report.

6.3 Usage of analysis sets

The usage of the analysis sets (see previous section) for the creation of tables and figures are illustrated in

Table 2.

Unless otherwise specified, all listings will be done for RND set. All listings will report:

- planned and actual treatment names included,
- the flag(s) of the analysis set(s) used to analyze the information of the listing (according to
- Table 2).

Table 2: Usage of analysis set

Analysis	ENR	RND	FAS	SAF	PP
Subject enrolment and disposition	☒	☐	☐	☐	☐
Protocol deviations	☐	☒	☐	☐	☐
Study discontinuations	☐	☒	☐	☐	☐
Demographics and baseline characteristics	☐	☐	☒	☐	☐
Medical or surgical history and/or Concomitant Diseases	☐	☐	☒	☒	☐
Prior and concomitant medications	☐	☐	☒	☐	☐
Other baseline characteristics	☐	☐	☒	☐	☐
Compliance to IMP	☐	☐	☐	☒	☐
Exposure to IMP	☐	☐	☐	☒	☐
Analysis of primary efficacy endpoints	☐	☐	☒	☐	☐
Sensitivity analysis	☐	☐	☒	☐	☒
Analysis of secondary efficacy endpoints	☐	☐	☒	☐	☐
CCI [redacted]	☐	☐	☒	☐	☐
Adverse events	☐	☐	☐	☒	☐
CCI [redacted]	☐	☐	☐	☒	☐
CCI [redacted]	☐	☐	☐	☒	☐
CCI [redacted]	☐	☐	☐	☒	☐
Child Pugh Score	☐	☐	☐	☒	☐

6.4 Sub-group analyses

Statistical tests for interaction (between subgroup and treatment arm) will be performed to decide about the need to further investigate subgroups of the trial population. The consistency of the treatment effect will be assessed using a logistic regression model including treatment, subgroup variable and their interaction as covariate.

The following subgroups will be defined based on demographic or baseline characteristics:

- age group (<65 yrs vs ≥ 65 yrs),

- Gender (Male, Female),
- presence of concomitant disease (Yes, No).

Subgroup analyses will be performed if interaction tests are statistically significant at 15% nominal level. In this case all primary and secondary efficacy endpoints will be analyzed in the same way as described in sections 9.1.2 and 9.2.2.

Therefore, the steps to be performed are the following (for example age group):

1. Perform logistic regression model including treatment, age group and their interaction as covariates,
2. Evaluate interaction test "treatment*age group",
3. If this test is statistically significant at 15% nominal level (i.e., p-value < 0.15), then all primary and secondary efficacy endpoints will be analyzed in the same way as described in in sections 9.1.2 and 9.2.2 divided by age group, otherwise
4. If the test is not statistically significant at 15% nominal level (i.e., p-value >= 0.15), all primary and secondary analyses will not be analyzed by age group.

All points from 1 to 4 will be repeated for all subgroup variables.

6.5 Interim analysis

An interim analysis is planned when half of the planned evaluable patients have reached the primary endpoints at Day 28 (i.e., first 132 patients, ordering by randomization date and afterwards by random number, who met the FAS definition; if the primary endpoint at Day 28 is missing, multiple imputation described in the section 9.1.2 will be used) for identification of early superiority of Reparixin (efficacy) or for early stopping of the trial for futility.

O'Brien-Fleming spending functions will be used to control the type I and II errors for analyses of primary endpoints. P-values boundaries for efficacy and futility at interim and key first efficacy analyses are reported in Table 3.

Table 3: O'Brien-Fleming spending functions boundaries for primary endpoints

Analysis	Sample Size (evaluable patients)	Boundaries for primary endpoint	
		Efficacy	Futility
Interim	132	p-value <0.00258	p-value ≥0.32561
Key first efficacy analysis	264	p-value <0.02400	p-value ≥0.02400

The interim analysis will be conducted by an independent statistician who will share the results on primary endpoint with the DMC. On the basis of the interim results, DMC will communicate to the Sponsor the decision on the continuation of the study. The following scenarios may emerge:

- Scenario 1: The communication will be "Not enough evidence for demonstrate superiority of Reparixin". In this case, since results are not considered enough to draw conclusions on primary endpoints, the enrolment will continue up to the final analysis step, and treatments and follow-ups will proceed without modifications. Key first efficacy analysis and final analysis will be performed according to the rules described in section 5.6.
- Scenario 2: The communication will be "Superiority of Reparixin is shown". In this case, enrolment of subjects is stopped and considered completed. Already-enrolled subjects continue their residual treatment and follow-up as planned. Key first efficacy analysis and final analysis will be performed according to the rules described in section 5.6.
- Scenario 3: The communication will be "Superiority of Reparixin is excluded". In this case, the enrolment (if still ongoing) will be stopped and all subjects will discontinue the treatment and will be followed-up until the next scheduled visit where they will be notified of the termination of the study. When database is closed, final analysis will be performed and the clinical study report will be written and released.

The level of data cleaning requested for the interim analysis is the following:

- Primary efficacy endpoint and variables for the definition of FAS population: all data must be checked in term of missingness and inconsistencies, and all queries resolved up to the Day 28,
- The following forms will be cleaned: Eligibility, Inclusion Criteria, Exclusion Criteria, Randomization and IMP assignment (also for all visits post randomization), Additional Information on Invasive Mechanical Ventilation and ICU (it has to be aligned with the corresponding forms), Invasive Mechanical Ventilation / ECMO, ICU admission summary, Lung Function, Death report and Visit date,
- Data not related to the interim analysis: no specific cleaning activities are required at this point.

6.6 Key first efficacy analysis

The aim of this key first analysis is to provide efficacy results on primary endpoint to populate an intermediate clinical study report. It will be performed when all patients are evaluable for the primary analysis at Day 28. This analysis will be conducted by an independent statistician.

To maintain the blinding, results will be disclosed to the Sponsor in an aggregate way. The entire study personnel will remain blinded to patient-level information.

The level of data cleaning requested for the key first efficacy analysis is the same as described in the interim analysis section 6.5.

6.7 Data Monitoring Committee (DMC)

DMC meetings will be performed during the trial, in order to monitor the safety of the patients and to protect study subjects from undue harm.

The following information will be analyzed for safety reason at each meeting:

- Major protocol changes,
- Information on subject screening,
- Study accrual,
- Eligibility violations,
- Demographics,
- Length of follow-up data available,
- Analyses of adverse events,
- CCI [redacted],
- CCI [redacted] lyses,
- Discontinuation of medications.

Further details will be provided in the DMC Charter, where all roles and responsibilities will be defined.

Access to unblinded information on the efficacy analyses is allowed on DMC request in order to balance patient safety risk against a possible gain in efficacy.

The DMC will give careful consideration to the appropriateness of trial continuation if there is emerging evidence that reparixin is harmful. Since the DMC does not monitor primary endpoints for early efficacy termination (except for the Interim Analysis), no Type I error adjustment is necessary.

The DMC will be involved in the evaluation of the interim analysis results and in the consequent decision on the continuation of the study.

6.8 Handling of missing and incomplete data

The number of patients with missing data will be presented under the "Missing" category, if present. Missing values will not be included in the denominator count when computing percentages. Similarly, only the non-missing values will be evaluated for computing summary statistics for continuous endpoint. Any exception will be clarified as a note.

Critical missing data will be discussed prior to treatment unblinding, if any. Decisions will be taken during the BDRM and will be fully documented in the BDRM Report.

6.9 Changes in the planned analysis

Duration of non-invasive mechanical ventilation and duration of hospitalization since randomization (additional secondary endpoints) will be analyzed up to Day 60, instead of Day 28 as specified in the Protocol Version 3.0.

6.10 Blinded Data Review Meeting

A BDRM will be held before the DB lock and the unblinding of the data. Any other details will be provided in the BDRM Report.

6.11 Software

All statistical analyses and data processing will be performed using Statistical Analysis Systems (SAS®) Software (release 9.4 or later).

7. Evaluation of Demographic and Baseline Characteristics

7.1 Subject enrolment and disposition

All presentations of subject disposition will be by treatment group, and overall.

For describing the subject disposition, the following populations will be summarized:

- Subjects enrolled (overall);
- Subjects enrolled but not randomized and reasons for non-allocation (overall);
- Subjects randomized;
- Subjects randomized but not treated;
- Subjects in each analysis set (FAS, SAF, PP) and reasons for exclusion;

For the overall report, the percentage denominator will be the number of ENR subjects. For the "by treatment group" calculations, the percentage denominator will be the number of randomized subjects within each arm.

Listings will be provided based on ENR set.

7.2 Protocol deviations

All the protocol deviations will be discussed case by case before unblinding of the treatment code with the clinical team during the BDRM and described in the BDRM Report. Number of occurrences and of subjects with at least one major and minor protocol deviation will be summarized for each treatment.

7.3 Study discontinuations

The following information will be summarized for the randomized patients by treatment and overall:

- Trial completers;
- Subjects who discontinued the trial prematurely (and reasons);
- Number of subjects who completed each planned visit;
- Subjects who discontinued the IMP (and reasons): Subjects who discontinued the IMP are defined as subjects without clinical judgement of improvement (as noted on the end of treatment page) and with a primary reason for end of treatment different from "reached Day 21". Correspondingly, subjects with clinical judgement of improvement or the primary reason for end of treatment given as "reached Day 21" are evaluated as having completed the treatment;
- Primary reason for ending the treatment: overall and in subjects with clinical judgment of improvement
- Subjects who discontinued the IMP but completed the study;

- Subjects who discontinued the IMP and discontinued the trial prematurely;
- Broken randomization code (and reasons).

If more than 30% of randomized subjects discontinue the study prematurely, the distribution of the time from randomization to discontinuation will be summarized using time-to-event method. Subjects who have not prematurely discontinued the trial will be censored at study termination for final analysis and will be censored at clinical cut-off date for interim analysis and key first results.

7.4 Demographics and baseline characteristics

The baseline demographic characteristics will be summarized by treatment and overall, by means of descriptive statistics. No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and baseline characteristics will be reported for this study:

- Geographic region of the site (Italy, US, Other)
- Demographics:
  - Age (years);
  - Age group (<65 years, ≥65 years);
  - Gender (Male, Female);
    - If female, potential childbearing (Yes, No);
  - Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander , Other);
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Pregnancy test result (Positive or Negative), if appropriate;
- Reasons for no pregnancy test;
- Height (cm), weight (Kg) and BMI (BMI≤25kg/m2 vs 25kg/m2<BMI≤30kg/m2 vs BMI>30kg/m2);
- Has the patient ever consumed alcohol? (Never, Former or Current) ;
  - If former or current, Amount of alcohol consumed daily (<1 Liter of wine (or equivalent) or (≥1 Liter of wine (or equivalent));
- Has the patient ever consumed tobacco? (Never, Former or Current) ;
  - If former or current, Amount of cigarettes consumed daily (<10 cigarettes or ≥10 cigarettes);
- Influenza test result (Positive or Negative);
- SARS-CoV-2 RT-PCR test result (Positive, Negative or Not evaluable);
- RT-PCR output.

7.5 Medical or Surgical History and/or Concomitant Diseases

A disease is considered as medical/surgical history if it has ended before screening visit date.

A disease is considered as concomitant disease if it is ongoing at screening visit.

Medical history and concomitant diseases will be coded using the Medical Dictionary for regulatory activities (MedDRA) dictionary and frequency distributions and percentages will be summarized by treatment, by System Organ Class (SOC), and Preferred Term (PT).

Medical history and concomitant diseases will be analyzed separately. Frequency distributions and percentages by treatment will be given for both SOC and PT by subject. Subjects experiencing more than one past/concomitant disease event will be counted only once within each SOC and PT.

7.6 Prior and concomitant medications

Medications will be coded using World Health Organization Drug Dictionary (WHO DD).

Prior medications are those which stopped prior to the date of informed consent. Concomitant medications are those which:

- start prior to, on or after the date of informed consent and start no later than date of study completion or discontinuation, and
- end on or after the date of informed consent or are ongoing at the study completion or discontinuation.

In case of missing or incomplete dates/times not directly allowing allocation to either of the two categories of medications, a worst-case allocation will be done according to the available parts of the start and the end dates (see Table 6). The medication will be allocated to the first category allowed by the available data, according to the following order:

- concomitant medication;
- prior medication.

Prior and concomitant medications will be summarized separately. Frequency distributions and percentages by treatment will be given by Anatomical Main Group (1st level of the Anatomical Therapeutic Chemical (ATC) classification), Chemical Subgroup (4th level of the ATC classification) and Preferred Name.

Subjects taking more than one medication classified in the same category (prior medications or concomitant medications) within the same anatomical main group, chemical subgroup and preferred name will be counted only once.

Preventive off-label use of anti-COVID-19 medication and Standard care for COVID-19 medications (CCI [redacted] and **Error! Reference source not found.**) will be evaluated separately in the same way as described in this section. These medications will be collected in the CRF in the same form of the prior and concomitant medications and will be clearly identifiable via a corresponding tick-box.

7.7 Other baseline characteristics

7.7.1 Clinical severity score (7-point WHO-OS)

Frequency distributions and percentages by treatment of Clinical severity score (7-point WHO-OS) at baseline will be provided.

7.7.2 Dyspnea VAS Scale

Dyspnea VAS Scale (from 0 to 100, where number "0" equals the worst breathing the patient has ever felt and the number "100" equals the best the patient has ever felt) results will be descriptively summarized by treatment.

7.7.3 Respiratory parameters

Summary statistics by treatment of respiratory parameters at baseline will be provided.

The following information will be summarized:

- FiO2 (0.21 to 1)
- SpO2 (%)
- PaO2 (mmHg)
- PaO2/FiO2 (Ratio)
- Investigator's interpretation (Normal, Abnormal NCS, Abnormal CS, No Result) for each parameter.

7.7.4 Chest imaging

Frequency distributions and percentages by treatment of clinical evaluation of Chest imaging at baseline will be provided.

8. Evaluation of Treatment Compliance and Exposure

8.1 Compliance to IMP

Descriptive analyses of the following parameters will be presented by treatment group at each available time point and during the entire treatment period:

- Total number of tablets administered
- Volume administered
- Total number of treatment days

On a per patient basis, the evaluation of the compliance by visit and during the overall treatment period will be done using the following formula:

$$Compliance\ (\%) = \frac{total\ number\ of\ tablets\ taken\ during\ the\ treatment\ period}{total\ number\ of\ tablets\ scheduled\ during\ the\ treatment\ period} \times 100$$

where "*total number of tablets taken during the treatment period*" is the sum of number of tables taken during each day, while the "*total number of tablets scheduled during the treatment period*" is given by the number of total scheduled tablets, considering that each patient takes 2 tablets three times daily (6 tablets daily) for up to 21 days or until decision of premature interruption (for improvement or, in any case, for the physician's decision).

Further details are reported in Table 4.

Compliance will be summarized by treatment by means of summary statistics. In addition, compliance to IMP will also be presented for the following categories: <80%, ≥80%.

8.2 Exposure to IMP

The extent of exposure to IMP in days will be summarized overall with descriptive statistics by treatment group. The extent of exposure (days) will be calculated using the formula reported in Table 4.

9. Evaluation of Efficacy

9.1 Analysis of primary efficacy endpoint

9.1.1 Testing strategy and multiplicity adjustment

The following null hypothesis is defined: the proportion of patients alive and free of respiratory failure at Day 28 (See section 5.7.1 for details) in Reparixin ($T_{REPARIXIN}$) is lower or equal control ($T_{CONTROL}$):

H_0: $T_{REPARIXIN} \leq T_{CONTROL}$

H_1: $T_{REPARIXIN} > T_{CONTROL}$

where $T_{REPARIXIN}$ and $T_{CONTROL}$ are the proportions of patients alive and free of respiratory failure at Day 28 for Reparixin and control groups, respectively. The null hypothesis H_0 will be rejected, and superiority of Reparixin is declared if primary analysis p-value will be lower than pre-specified threshold, depending at which analysis (interim or key first efficacy) the test is performed. Thresholds are calculated according to O'Brien-Fleming spending function boundaries and are reported in Table 3.

9.1.2 Analysis details

Primary endpoint will be analyzed by means of logistic regression adjusting by pre-defined baseline factors (treatment, gender, age class and presence of concomitant disease as fixed effect and site as random effect) and a one-sided test will be used to test for differences between treatment groups.

Missing data on the primary endpoint will be handled by means of Multiple Imputation using retrieve dropouts (MI-RD) under MNAR assumption. Specifically, MI will be performed based on the subjects' allocated treatment arm and observed values as covariates in a regression model using data from subjects that discontinued the treatment but have the primary endpoint measurement with gender, age class and presence of concomitant disease as covariates. Please see section 7.3 for definition of treatment discontinuation.

If there are no enough retrieved dropouts for convergence of MI regression model, MI will be performed using data from completers from the placebo arm (i.e., subjects in the placebo arm with assessment of primary endpoint). The final decision will be done at the time of the analysis and reported in the CSR. Measurements for patients on the placebo arm with missing primary endpoint will be imputed using a monotone regression model based on observed data of placebo completers with gender, age class and presence of concomitant disease as covariates. For patients on the reparixin arm who had missing primary endpoint data, the imputation model with subject's gender, age class and presence of concomitant disease as covariates will be used based on data from completers from the placebo arm.

One thousand data sets will be generated. The random seed number will be 200582. Each of 1000 imputed dataset will be analyzed by means of the logistic regression model specified above. Rubin's rule will be used for combining results to draw inference. The adjusted estimated treatment odds ratio between reparixin and placebo at Day 28 will be displayed together with the corresponding 95% confidence interval and p-value. This p-value will be compared to the thresholds in Table 3 in order to demonstrate the superiority of reparixin.

9.1.3 Sensitivity analysis

The primary analyses will be assessed in sensitivity analyses using different assumptions and populations, as detailed below.

- The analysis of the primary endpoint will be repeated on the PP set instead of FAS, as well as on the FAS excluding patients who were already in the ICU at baseline, using the same methodology described in section 9.1.2. These analyses will assess the robustness of results to protocol deviations.
- The comparison between treatment and control will be performed in the FAS population considering complete cases only (i.e. without considering patients with missing primary endpoints at Day 28) instead of MI under MNAR. This analysis will assess the robustness of results to the method of handling missing data. Comparison between treatment will be performed according to the logistic regression model described in section 9.1.2.
- The comparison between treatment and control will be performed in the FAS population by means of MI under missing at random (MAR) assumption instead of MNAR. MI will be implemented in this way:
    - Imputation assuming MAR will be carried out to impute missing data based on logistic regressions. A separate imputation model will be used for each treatment arm. The imputation models will include the gender, age class and presence of concomitant disease. In case of non-convergence or non-estimability issues, a single model will be considered with treatment arm added as an explanatory variable in the model.
    - Rounding restrictions will be applied to imputed binary values due to type of primary endpoint variable (endpoint = 0 if value <0.5, endpoint = 1 if value ≥0.5).
    - Imputed data will consist of 200 imputed datasets. The random seed number for imputation with the MCMC method will be 40110.
    - Each of the 200 imputed datasets will be analyzed using observed and imputed data using regression logistic models as described in section 9.1.2. Rubin's rule will be used for combining results to draw inference. The adjusted estimated treatment odds ratio between Reparixin and placebo at Day 28 will be displayed together with the corresponding 95% confidence intervals and p-value.
- A tipping point strategy will be used as a sensitivity analysis for missing data for assessment of superiority (if shown) of Reparixin. Tipping point analysis will assess how departures from MI under MNAR assumptions must be in order to overturn conclusions from the primary superiority analysis. Tipping point will be based on iterative application of MI. In the first iteration, MI-RD method is assumed as described in section 9.1.2. In successive iterations, the imputed values for the Reparixin arm are shifted by a constant to represent a worse effect in each iteration. This can be achieved by using the N completed data-sets obtained under

MI-RD and shift the imputed values. The tipping point is the shift at which the p-value becomes non-significant. Outline of tipping point:

- Use MI-RD to impute missing values;
- Assuming that the tipping point is between -3 and 3, the following actions will be performed for $\Delta = 3, 2.9, 2.8, \ldots, 0, -0.1, -0.2, -0.3, \ldots, -3$:
  - Add Δ to the imputed values at the Reparixin arm;
  - Analyze the completed data sets using the same method outlined in section 9.1.2;
- the plot of all p-values for Δ between -3 and 3 will be created;
- based on the plot, the approximate value of the tipping point Tp_{approx} is identified considering a threshold for the p-values of 0.02400;
- after identification of Tp_{approx}, a finest research of the tipping point will be performed in the range $Tp_{approx} \pm 1$ by incrementing Δ of 0.01 and following the usual steps:
  - Add Δ to the imputed values at the Reparixin arm;
  - Analyze the completed data sets using the same method outlined in section 9.1.2;
- The tipping point is the smallest Δ at which p-value ≥ 0.02400.

- The comparison between treatment and control will be performed in the FAS population using the Win Ratio (R_{WIN}) calculated by Pocock et al method[4] with the unmatched approach. The outcomes used in calculating the win ratio ordered by their clinical importance (from high to low) will be:
  - death,
  - Invasive Mechanical Ventilation or ECMO, and
  - admission to ICU linked to worsening of respiratory parameters compared to baseline

within Day 28.

The steps needed to follow for the calculation of R_{WIN}:

1. Let N_R= total patients on Reparixin, and let N_P= total patients on Placebo;
2. Compare the timing of death, IMV and ICU for each patient on Reparixin to each patient on Placebo (N_R x N_P comparisons) for the shortest time duration that exists between each pair of patients (this determination would happen if event dates are available for both patients, or if one patient was censored at a later time than the event time for the other);
3. Classify each patient into one of 7 exclusive categories:
   a. Reparixin patient died prior to Placebo patient,
   b. Placebo patient died prior to Reparixin patient,
   c. Reparixin patient had IMV prior to Placebo patient,
   d. Placebo patient had IMV prior to Reparixin patient,
   e. Reparixin patient had ICU admission prior to Placebo patient,
   f. Placebo patient had ICU admission prior to Reparixin patient,
   g. None of the above;
4. Calculate R_{WIN}:
   - Since groups b, d and f are in favor of Reparixin, $N_b + N_d + N_f = N_{WIN}$,
   - Since groups a, c and e are not in favor of Placebo, $N_a + N_c + N_e = N_{LOSS}$,
   - $R_{WIN} = Nwin/N_{LOSS}$.

The significance test and the method for determining the p-value for the unmatched approach is based on the Finkelstein and Schoenfeld[5] approach:

1. If patient *i* is known to have a better condition than patient *j* (point b., d., and f. according to the above criteria), then u_{ij} = 1; else, if patient *j* is known to have a better condition than patient *i*, then u_{ij} = -1, otherwise u_{ij} = 0. In all cases, $u_{ij} = -u_{ji}$.
2. The final test statistic is based on the sum of the scores for patients in the Reparixin group:

$$T = \sum_{i=1}^{N} U_i D_i$$

where:

- N is the total of patients ($N_R + N_P$),
- $U_i = \sum_{i \neq j} u_{ij}$, and
- D_i = 1 for patients in the Reparixin group and let D_i = 0 for patients in the Placebo group.

Values for T greater than zero indicate superiority of the Reparixin arm as the mean of the test statistic is 0 under the null hypothesis of no difference between treatment and control. Finkelstein and Schoenfeld[5] derive the variance for this statistic according to the following rule:

$$V = \frac{N_R * N_P}{N(N-1)} \sum_{i=1}^{N} U_i^2$$

Superiority of the Reparixin group will be tested by comparing $T / V^{1/2}$ to the percentiles of the standard normal distribution.

Finally, the confidence interval of R_{WIN} will be calculated by the bootstrap method: data will be sampled with replacement 1000 times and from each bootstrap sample the win ratio will be calculated in order to determine the empirical distribution of the win ratio. The random seed number will be 31598. The 95% confidence interval will be created by calculating the 2.5th and 97.5th percentiles of the empirical distribution. The bootstrap method will proceed as follows:

1. a random sample S_P of size N_P is drawn from the original Placebo group;
2. The unmatched analysis is performed on the samples S_R and S_P, and the win ratio is calculated;
3. Steps 1 and 2 are repeated M times (M=1000);
4. the empirical bootstrap distribution of the win ratio is determined from the M bootstrap values;
5. the 2.5th and 97.5th percentiles of the bootstrap distribution are obtained: these are the estimated limits of the 95% confidence interval for the win ratio.

9.2 Analysis of secondary efficacy endpoints

9.2.1 Testing strategy and multiplicity adjustment

In case the analysis of the primary endpoints leads to rejection of null hypothesis (section 9.1.1), the following key secondary endpoints will be tested in a conditional sequential manner to show superiority of Reparixin versus control according to the following ranking:

1. Proportion of patients alive and free of respiratory failure (as described for the primary endpoint) at Day 60,
2. Mortality rates up to Day 28,
3. Incidence of ICU admission until Day 28,
4. Time to recovery (category 1 – 2 – 3 of the 7-point WHO-OS of clinical improvement) until Day 28.

This hierarchical test strategy protects the family-wise false positive error rate at the overall one-sided 0.025 level. In case of futility at interim analysis (scenario 3, see section 6.5) or in case of not rejection of null hypothesis, the above test strategy will not be performed.

9.2.2 Analysis details

Analysis of key secondary endpoints are detailed below in sections 9.2.2.1, 9.2.2.2, 9.2.2.3, and 9.2.2.4, and p-values to be evaluated for comparison between treatments in a sequential order are the following:

1. P-value of treatment variable from logistic regression model,
2. P-value of treatment variable from logistic regression model,
3. P-value of treatment variable from logistic regression model,
4. P-value from Gray's test.

Independently of results on primary and key secondary endpoints, descriptive in nature analyses will be performed on all secondary endpoints (section 5.7.2 and 5.7.3) at each available timepoints by means of descriptive statistics (section 6.1). In case of continuous measures, analyses will be provided for:

- baseline visit,
- each post-baseline visit, and
- the change from baseline measurements to each visit.

In case of categorical variables, shift tables showing difference as to the respective classifications at baseline will be provided.

In addition to the above summary statistics, comparisons between treatments will be performed as detailed in the next sub-sections. Parametric tests (i.e. two-sample t-test (assuming unequal variances) for continuous variables, Chi-square test for categorical) will be adopted as a first choice. In case the required assumptions are not met, the corresponding non-parametric counterparts will be used (i.e. the two-sample Mann–Whitney U test for continuous variables (using the normal approximation with continuity correction), and the Fisher's Exact test for the categorical variables). Assumption of normal distribution of endpoints for continuous data will be assessed by a visual inspection of distribution. If required, data transformation will be applied and specified in the notes.

Comparison will be performed at each available time point, where applicable. Any exception will be declared.

9.2.2.1 Proportion of patients alive and free of respiratory failure at Day 60

Number and proportion along with the 95% confidence interval (Clopper-Pearson's formula) of patients alive and free of respiratory failure will be calculated.

Proportion of patients alive and free of respiratory failure at Day 60 will be compared between treatments group using the same logistic regression model used for primary endpoint and detailed in section 9.1.2.

9.2.2.2 Mortality rates up to Day 28

Number and proportion along with the 95% confidence interval (Clopper-Pearson's formula) of subjects who die will be calculated up to Day 28.

Mortality rates up to Day 28 will be compared between treatments group using a logistic regression model, with treatment group, age group, gender and presence of concomitant disease at baseline as covariates.

9.2.2.3 Incidence of ICU admission until Day 28

Number and proportion along with the 95% confidence interval (Clopper-Pearson's formula) of subjects requiring post-randomization ICU admission will be calculated up to Day 28. All deaths until Day 28 will be counted as failures.

Similarly, number and proportion along the 95% confidence interval (Clopper-Pearson's formula) of patients requiring post-randomization ICU admission up to Day 28 which has been followed by invasive mechanical ventilation (or ECMO) or death will be calculated by treatment group.

In both cases, incidences of ICU admission until Day 28 will be compared between treatments group using a logistic regression model, with treatment group, age group, gender and presence of concomitant disease at baseline as covariates.

9.2.2.4 Time to recovery (category 1 - 2 - 3 of the 7-point WHO-OS of clinical improvement)

Time to recovery up to Day 28 will be analyzed according to survival analysis methodology detailed in section 9.1.2 with the following modifications:

- the common representation of survival curves using the Kaplan-Meier estimator will be replaced by the cumulative incidence function,
- death, discontinuation for Adverse Events and patient transferred to another institution will be considered as competing risks.
- the comparison between treatment and control will be performed by means of a Gray's test[6] instead of the standard log-rank test.

An event (recovery) will be considered as such, if patient has scored category 1, 2 or 3 from the 7-point WHO Ordinal Scale of clinical improvement (WHO-OS), otherwise it will be considered free of event.

9.2.2.5 Proportion of patients alive and free of respiratory failure at fixed time-points

Number and proportion along the 95% confidence interval (Clopper-Pearson's formula) of patients alive and free of respiratory failure (as described for the primary endpoint – Section 5.7.1) will be calculated for each time point. The comparison between the two study treatment arms will be performed by means of a Chi-square test or, if more appropriate, a Fisher's Exact test at each time point.

9.2.2.6 Mean changes in clinical severity score based on the 7-point WHO-OS

Changes from baseline in clinical severity score based on the 7-point WHO-OS will be analyzed at each available time points by means of descriptive statistics (Section 6.1). Comparison between treatments will be performed by means of two-sample Mann-Whitney U test.

Along with this analysis, absolute values at baseline and post-baseline will be analyzed at each available time points by means of descriptive statistics (Section 6.1).

9.2.2.7 Time to clinical improvement 1 (decline of 1 category in the 7-point WHO-OS)

Time to clinical improvement 1 up to Day 28 will be analyzed as described in section 9.2.2.4.

An event will be considered as such, if patient declines of at least 1 category in the 7-point WHO Ordinal Scale of clinical improvement (WHO-OS) respect to the baseline, otherwise it will be considered free of event.

9.2.2.8 Time to clinical improvement 2 (decline of 2 categories in the 7-point WHO-OS)

Time to clinical improvement 2 up to Day 28 will be analyzed as described in section 9.2.2.4.

An event will be considered as such, if patient declines of at least 2 categories in the 7-point WHO Ordinal Scale of clinical improvement (WHO-OS) respect to the baseline, otherwise it will be considered free of event.

9.2.2.9 Time to discharge from hospital (up to Day 28)

Time to discharge from hospital up to Day 28 will be analyzed as described in section 9.2.2.4.

9.2.2.10 Clinical status (7-point WHO-OS)

Number and proportion along with the 95% confidence interval (Clopper-Pearson's formula) of patients with clinical status (7-point WHO-OS) by category and treatment group will be calculated for each time point. The comparison between the two study treatment arms will be performed by means of a Chi-square test or, if more appropriate, a Fisher's Exact test at each time point.

When patient is at home, his/her clinical status can be assessed by phone.

9.2.2.11 Dyspnea severity (Likert scale and VAS scale)

Number and proportion along with the 95% confidence interval (Clopper-Pearson's formula) of patients with Dyspnea severity Likert scale by score and treatment group will be calculated for each time point. The comparison of the Liker scale between the two study treatment arms will be performed by means of a Chi-square test or, if more appropriate, a Fisher's Exact test at each time point.

VAS scale will be analyzed at each available time points by means of descriptive statistics (Section 6.1). Specifically, analyses will be provided for baseline visit, each post-baseline visit and the change from baseline measurements to each visit. Comparison between treatments for change from baseline will be performed by means of two-sample t-test or, if assumptions of normality is not confirmed (by a visual inspection of distribution), two-sample Mann-Whitney U test.

9.2.2.12 Duration of supplemental oxygen treatment (days) up to Day 28

Number and proportion along with the 95% confidence interval (Clopper-Pearson's formula) of patients using supplemental oxygen treatment by treatment group will be calculated.

Cumulative duration of supplemental oxygen treatment (days) will be analyzed by means of descriptive statistics (Section 6.1) by treatment and overall. Comparison between treatments will be performed by means of two-sample t-test or, if assumptions of normality is not confirmed (by a visual inspection of distribution), two-sample Mann-Whitney U test.

9.2.2.13 Incidence of invasive mechanical ventilation use, or ECMO up to Day 60

Number and proportion along the 95% confidence interval (Clopper-Pearson's formula) of patients requiring invasive mechanical ventilation or ECMO up to Day 60 by treatment group will be calculated.

Similarly, number and proportion along the 95% confidence interval (Clopper-Pearson's formula) of patients requiring invasive mechanical ventilation or ECMO up to Day 60 which has been followed by death will be calculated by treatment group.

In both cases, the comparison between the two study treatment arms will be performed by means of a Chi-square test or, if more appropriate, a Fisher's Exact test.

9.2.2.14 Duration of invasive mechanical ventilation, or ECMO (days) up to Day 60

Cumulative duration of invasive mechanical ventilation or ECMO (days) up to Day 60 will be analyzed by means of descriptive statistics (Section 6.1) by treatment and overall. Comparison between treatments will be performed by means of two-sample t-test or, if assumptions of normality is not confirmed (by a visual inspection of distribution), two-sample Mann-Whitney U test.

9.2.2.15 Duration of non-invasive mechanical ventilation (days) up to Day 60

Cumulative duration of non-invasive mechanical ventilation (days) up to Day 60 will be analyzed by means of descriptive statistics (Section 6.1) by treatment and overall. Comparison between treatments will be performed by means of two-sample t-test or, if assumptions of normality is not confirmed (by a visual inspection of distribution), two-sample Mann-Whitney U test.

9.2.2.16 Duration of ICU admission (days) up to Day 60

Cumulative duration of ICU admission (days) up to Day 60 will be analyzed by means of descriptive statistics (Section 6.1) by treatment and overall. Comparison between treatments will be performed by means of two-sample t-test or, if assumptions of normality is not confirmed (by a visual inspection of distribution), two-sample Mann-Whitney U test.

9.2.2.17 Duration of hospitalization since randomization (days) up to Day 60

Duration of hospitalization (days) up to Day 60 will be analyzed by means of descriptive statistics (Section 6.1) by treatment and overall. Comparison between treatments will be performed by means of two-sample t-test or, if assumptions of normality is not confirmed (by a visual inspection of distribution), two-sample Mann-Whitney U test.

9.2.2.18 Partial pressure of oxygen (PaO2): change from baseline to the firstly available daily value

Partial pressure of oxygen (PaO2) will be analyzed at each available time points by means of descriptive statistics (Section 6.1). Specifically, analyses will be provided for baseline visit, each post-baseline visit and the change from baseline measurements to each visit. Comparison between treatments will be performed by means of two-sample t-test or, if assumptions of normality is not confirmed (by a visual inspection of distribution), two-sample Mann-Whitney U test.

Summary statistics of Investigator's interpretation (Normal, Abnormal NCS, Abnormal CS) will be provided by treatment arm at each timepoint. The comparison between the two study treatment arms will be performed by means of a Chi-square test or, if more appropriate, a Fisher's Exact test at each time point.

9.2.2.19 Pulse oximetry by measurement of peripheral arterial oxygen saturation (SpO2)

Pulse oximetry by measurement of peripheral arterial oxygen saturation (SpO2) will be analyzed at each available time points by means of descriptive statistics (Section 6.1). Specifically, analyses will be provided for baseline visit, each post-baseline visit and the change from baseline measurements to each visit. Comparison between treatments will be performed by means of two-sample t-test or, if assumptions of normality is not confirmed (by a visual inspection of distribution), two-sample Mann-Whitney U test.

Summary statistics of Investigator's interpretation (Normal, Abnormal NCS, Abnormal CS) will be provided by treatment arm at each timepoint. The comparison between the two study treatment arms will be performed by means of a Chi-square test or, if more appropriate, a Fisher's Exact test at each time point.

9.2.2.20 P/F ratio [partial arteriolar oxygen pressure (PaO2) to fraction of inspiration O2 (FiO2) ratio] from baseline

PaO2/FiO2 ratio will be analyzed at each available time points by means of descriptive statistics (Section 6.1). Specifically, analyses will be provided for baseline visit, each post-baseline visit and the change from baseline measurements to each visit. Comparison between treatments will be performed by means of two-sample t-test or, if assumptions of normality is not confirmed (by a visual inspection of distribution), two-sample Mann-Whitney U test.

In addition, number and proportion of patients with a decrease of PaO2/FiO2 ratio of at least 40% or a worsening of Investigator's Interpretation (from "Normal" to "Abnormal" or from "Abnormal, not clinically significant" to "Abnormal, clinically significant") from the baseline value will be provided to each visit.

The number and proportion of patients with a decrease of PaO2/FiO2 ratio of at least 40% or a worsening of Investigator's Interpretation from the baseline value which has been followed by:

- an ICU admission, and/or
- IMV or ECMO, and/or
- death

will be provided to each visit by treatment group.

Summary statistics of Investigator's interpretation (Normal, Abnormal NCS, Abnormal CS) will be provided by treatment arm at each timepoint. The comparison between the two study treatment arms will be performed by means of a Chi-square test or, if more appropriate, a Fisher's Exact test at each time point.

9.2.2.21 Hs-CRP: change from baseline

Hs-CRP (alternatively CRP) will be analyzed at each available time points by means of descriptive statistics (Section 6.1). Specifically, analyses will be provided for baseline visit, each post-baseline visit and the change from baseline measurements to each visit. Comparison between treatments will be performed by means of two-sample t-test or, if assumptions of normality is not confirmed (by a visual inspection of distribution), two-sample Mann-Whitney U test.

Summary statistics of Investigator's interpretation (Normal, Abnormal NCS, Abnormal CS, No Result) will be provided by treatment arm at each timepoint. The comparison between the two study treatment arms will be performed by means of a Chi-square test or, if more appropriate, a Fisher's Exact test at each time point.

9.2.2.22 Mortality rates up to Day 60 and Day 90

Number and proportion along with the 95% confidence interval (Clopper-Pearson's formula) of subjects who die will be calculated up to Day 60 and Day 90.

Mortality rates up to Day 60 and Day 90 will be compared between treatments group using a logistic regression model, with treatment group, age group, gender and presence of concomitant disease at baseline as covariates.

9.2.2.23 Freedom from (time to) death or respiratory failure

Freedom from (time to) death or respiratory failure (need of invasive mechanical ventilation or ECMO or admission to ICU linked to worsening of respiratory parameters compared to baseline) up to Day 90 will be performed using the same Kaplan-Meier analysis and the one-sided log-rank test will be used to test for differences between treatment groups.

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9.3.1 Analysis details

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10. Evaluation of Safety

10.1 Adverse events

Any AE which starts at or after the first administration of study treatment will be considered a Treatment Emergent Adverse Event (TEAE). Pre-treatment AEs and TEAEs will be presented separately. Pre-treatment AEs will be presented in the listings only. In case of missing or incomplete dates not allowing a direct allocation to any of the two categories of AEs, a worst-case allocation will be done according to the available parts of the onset and the end dates (see Table 5). The AE will be allocated to the first category allowed by the available data, according to the following order:

- TEAE;
- Pre-treatment AE.

In case of TEAE, the event can be classified as:

- On Treatment Period, or
- On Follow-up period

according to the available parts of the onset and the end dates (see Table 5).

All AEs will be assigned to a Preferred Term (PT) and will be classified by primary System Organ Class (SOC) according to the MedDRA thesaurus. In addition, each AE will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) toxicity grading scale (version 5.0) to capture the severity, as per definition in the table below:

Grading scale of the Adverse Event

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

*Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

TEAEs will be reported on a per-patient basis, i.e. if a patient reported the same event repeatedly (i.e. events mapped to the preferred term) the event will be counted only once.

For summaries, the drug-event relationship will be assessed as “None”, “Unlikely”, “Possible” “Probable” or “Highly probable” by the investigator. Any TEAE reported in the study having a possible, probable or highly probable relationship to IMP will be defined as “Adverse Drug Reaction” (ADR).

The following tables and listings will be presented by treatment group:

- An overview of TEAEs including the number of patients who exhibited at least one TEAE, at least one severe TEAE, at least one serious TEAE, at least one non-serious TEAE, at least one ADR, at least one serious ADR, at least one TEAE leading to discontinuation of IMP, at least one TEAE leading to discontinuation of study, at least one TEAE leading to death, number of TEAEs, number of non-serious TEAEs, number of TESAEs, number of ADRs, number of serious ADRs, number of severe TEAEs, number of TEAEs leading to discontinuation of IMP, number of TEAEs leading to discontinuation of study, number of TEAEs leading to deaths.;
- Summary of TEAEs by primary System Organ Class and Preferred Term and by study period (on treatment/follow-up and overall);
- Summary of TEAEs by primary System Organ Class, Preferred Term and Severity;
- Summary of Serious TEAEs by Primary System Organ Class and Preferred Term and by study period (on treatment/follow-up and overall);
- Summary of ADRs by Primary System Organ Class and Preferred Term and by study period (on treatment/follow-up and overall);
- Summary of ADRs by Primary System Organ Class and Preferred Term and Severity;
- Summary of TEAEs leading to IMP Discontinuation by Primary System Organ Class and Preferred Term and by study period (on treatment/follow-up and overall);

- Summary of TEAEs leading to study Discontinuation by Primary System Organ Class and Preferred Term and by study period (on treatment/follow-up and overall);
- Summary of TEAEs leading to Death by Primary System Organ Class and Preferred Term;
- Listing of all AEs by Patient;
- Listing of all AEs leading to IMP discontinuation;
- Listing of all AEs leading to study discontinuation;
- Listing of SAEs by Patient;
- Listing of ADR by Patient;
- Listing of Deaths.

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10.5 Child Pugh Score

Summary statistics by treatment of the Child Pugh Score will be provided along with summary of the change from baseline at each available timepoint. Comparison between treatments for change from baseline will be performed by means of two-sample t-test or, if assumptions of normality is not confirmed (by a visual inspection of distribution), two-sample Mann-Whitney U test. In addition, summary statistics of the number and frequency of patients for all other categorical parameters will be provided by treatment arm and overall at each available timepoint.

11. Derivations and date conventions

11.1 Variable derivation

Table 4: Variable derivation rules

Parameter	Calculation
Need of invasive mechanical ventilation or ECMO at Day 28 (or Day 60)	From INVASIVE MECHANICAL VENTILATION / ECMO form or ADDITIONAL INFORMATION form: Event derivation: The subject will be considered as having an "IMV/ECMO" event (“Yes”) at Day 28 (or Day 60), if one of the following criteria is met: • At least one observation in the "INVASIVE MECHANICAL VENTILATION / ECMO" form with start date after randomization date and up to Day 28 (or Day 60); • At least one observation in the "ADDITIONAL INFORMATION" form performed in a visit after "Baseline Day 1" and up to Day 28 (or Day 60) with answer to question "Does the patient need invasive mechanical ventilation / ECMO?" = "Yes". The subject will be considered as not having an "IMV/ECMO" event (“No”) at Day 28 (or Day 60) if the following criteria are met: • He/she has completed the Day 28 (or Day 60) assessment, or subsequent; • He/she has no observations in “INVASIVE MECHANICAL VENTILATION / ECMO” form up to Day 28 (or Day 60). Event date derivation: If the subject has the event ("Yes") then the event date will be the minimum date among the following: • Start date of IMV/ECMO in the "INVASIVE MECHANICAL VENTILATION / ECMO" form (after randomization date) • Date of the visit in which the "ADDITIONAL INFORMATION" form performed after "Baseline Day 1" visit has the answer to the question "Does the patient need invasive mechanical ventilation / ECMO?" = "Yes".

Parameter	Calculation
Admission to ICU at Day 28 (or Day 60)	From ICU ADMISSION SUMMARY form or ADDITIONAL INFORMATION form: Event derivation: The subject will be considered as having an "ICU" event (“Yes”) at Day 28 (or Day 60) if one of the following criteria is met: • At least one observation in the "ICU ADMISSION SUMMARY" form with start date after randomization date and up to Day 28 (or Day 60); • At least one observation in the "ADDITIONAL INFORMATION" form performed in a visit after "Baseline Day 1" and up to Day 28 (or Day 60) with answer to question "Does the patient need to be admitted to the ICU?" = "Yes". The subject will be considered as not having an "ICU" event (“No”) at Day 28 (or Day 60) if the following criteria is met: • He/she has completed the Day 28 (or Day 60) assessment, or subsequent; • He/she has no observations in “ICU ADMISSION SUMMARY” form up to Day 28 (or Day 60). Event date derivation: If the subject has the event ("Yes") then the event date will be the minimum date among the following: • Start date of ICU in the "ICU ADMISSION SUMMARY" form (after randomization date) • Date of the first visit in which the "ADDITIONAL INFORMATION" form performed after "Baseline Day 1" visit has the answer to the question "Does the patient need to be admitted to the ICU?" = "Yes".
PaO2/FiO2 ratio	When the PaO2/FiO2 ratio is not reported in the eCRF (i.e. the value is missing) but the two values for PaO2 and FiO2 are available separately, the PaO2/FiO2 ratio will be derived as ratio between the two values.

Parameter	Calculation
Worsening of respiratory parameters (decrease of PaO2/FiO2 ratio of at least 40% or a worsening of Investigator's Interpretation from the baseline value) at Day 28 (or Day 60)	From LUNG FUNCTION form: Event derivation: The subject will be considered as having a "Respiratory worsening" event ("Yes") at Day 28 (or Day 60) in case of: • a decrease of PaO2/FiO2 ratio of at least 40% from the baseline value and up to Day 28 (or Day 60), or • a worsening of Investigator's Interpretation (from "Normal" to "Abnormal" or from "Abnormal, not clinically significant" to "Abnormal, clinically significant") from the baseline value and up to Day 28 (or Day 60). The subject will be considered as not having a "Respiratory worsening" event ("No") at Day 28 (or Day 60) if the following criteria are met: • He/she has completed the Day 28 (or Day 60) assessment, or subsequent; • He/she has no decrease of PaO2/FiO2 ratio (or case of a decrease lower than 40%) and no worsening of Investigator's Interpretation from baseline and up to Day 28 (or Day 60) . Event date derivation: If the subject has the event ("Yes") then the event date will be the date of assessment or PaO2/FiO2 ratio If baseline PaO2/FiO2 ratio is missing, the change from baseline cannot be computed and it will be set as missing.
Need of admission to ICU related to a worsening of the respiratory parameters at Day 28 (or Day 60)	From Admission to ICU (see above derivation rule) and Worsening of respiratory parameters (see above derivation rule): Event derivation: The subject will be considered as having a "Need of an admission to ICU related to a worsening of respiratory parameters" event ("Yes") at Day 28 (or Day 60) if the following criteria are met: • Admission to ICU at Day 28 (or Day 60) ="Yes" with an non-missing event date • Respiratory worsening at Day 28 (or Day 60) ="Yes" with an non-missing event date • The Admission to ICU has happened within 7 days after Respiratory worsening. The subject will be considered as not having an " Need of an admission to ICU related to a worsening of respiratory parameters " event ("No") at Day 28 (or Day 60) if the following criteria is met: • He/she has no Admission to ICU happening within 7 days after Respiratory worsening up to Day 28 (or Day 60). In case of admission to ICU and missing change from baseline of PaO2/FiO2 ratio, information from queries might be used in order to determine if ICU is linked to worsening of respiratory parameters.

Parameter	Calculation
Primary endpoint (patients alive and free of respiratory failure at Day 28)	The primary endpoint is equal to "No" if at least one of the following criteria is met before Day 28: • The patient died within Day 28 date; • The patient had need of invasive mechanical ventilation or ECMO at Day 28 (see derivation rule); • The patient had need of admission to ICU related to a worsening of the respiratory parameters at Day 28 (see derivation rule); Otherwise, the primary endpoint is equal to "Yes" if all the following criteria are met up to Day 28 (i.e. there are no missing assessment for "Need of Invasive Mechanical Ventilation or ECMO" and for "Admission to ICU related to a worsening of the respiratory parameters" up to Day 28): • The patient is alive at Day 28; • The patient had no need of invasive mechanical ventilation or ECMO at Day 28 (see derivation rule); • The patient had no need of admission to ICU related to a worsening of the respiratory parameters at Day 28 (see derivation rule). In case of the last available assessment of endpoint is before Day 28, the primary endpoint at Day 28 will be set as missing.
Secondary endpoint (patients alive and free of respiratory failure at Day 60)	The primary endpoint is equal to "No" if at least one of the following criteria is met before Day 60: • The patient died within Day 60 date; • The patient had need of invasive mechanical ventilation or ECMO at Day 60 (see derivation rule); • The patient had need of admission to ICU related to a worsening of the respiratory parameters at Day 60 (see derivation rule); Otherwise, the primary endpoint is equal to "Yes" if all the following criteria are met up to Day 60 (i.e. there are no missing assessment for "Need of Invasive Mechanical Ventilation or ECMO" and for "Admission to ICU related to a worsening of the respiratory parameters" up to Day 60): • The patient is alive at Day 60; • The patient had no need of invasive mechanical ventilation or ECMO at Day 60 (see derivation rule); • The patient had no need of admission to ICU related to a worsening of the respiratory parameters at Day 60 (see derivation rule). In case of the last available assessment of endpoint is before Day 60, the primary endpoint at Day 60 will be set as missing.
Time to death (days)	Time to death (days) = Date of death - Date of randomization + 1

Parameter	Calculation
Time to recovery (days)	Recovery = any of these answers from 7-point WHO Ordinal Scale: • 1 = not hospitalized, with resumption of normal activities • 2 = not hospitalized, but unable to resume normal activities • 3 = hospitalized, not requiring supplemental oxygen Time to recovery (days) = First recovery date – Date of randomization + 1 Subjects who are free from event will be censored at the study termination for the final analysis and will be censored at clinical cut-off date for interim analysis. Subjects who have discontinued without an event will be censored at the date of discontinuation.
Time to clinical improvement 1 (days)	Improvement 1 = decline of at least 1 category in the 7-point WHO Ordinal Scale respect to the baseline Time to improvement 1 (days) = Date of visit when there is an improvement – Date of randomization + 1
Time to clinical improvement 2 (days)	Improvement 2 = decline of at least 2 categories in the 7-point WHO Ordinal Scale respect to the baseline Time to improvement 2 (days) = Date of visit when there is an improvement – Date of randomization + 1
Time to discharge from hospital (days)	Time to discharge from hospital (days) = Date of discharge - Date of randomization + 1
Cumulative duration (days) of supplemental oxygen treatment	Cumulative duration of supplemental oxygen treatment (days) = Sum of duration of supplemental oxygen administration (days) in DAILY SUPPLEMENTAL OXYGEN form, from randomization up to Day 28. Duration of supplemental oxygen administration (days) = count how many time patients require any supplement oxygen administration, counting number of rows from DAILY SUPPLEMENTAL OXYGEN form.
Cumulative duration (days) of invasive mechanical ventilation or ECMO	Cumulative duration of invasive mechanical ventilation or ECMO (days) = Sum of duration of invasive mechanical ventilation or ECMO (days) in INVASIVE MECHANICAL VENTILATION / ECMO form, from randomization to Day 28. Duration of invasive mechanical ventilation or ECMO (days) = End date – Start date + 1. Only post-randomization events will be considered.

Parameter	Calculation
Cumulative duration (days) of non-invasive mechanical ventilation	Cumulative duration of non-invasive mechanical ventilation (days) = Sum of duration of non-invasive mechanical ventilation (days) in NON-INVASIVE MECHANICAL VENTILATION form, from randomization to Day 28. Duration of non-invasive mechanical ventilation (days) = End date – Start date + 1 Only post-randomization events will be considered.
Duration (days) of ICU admission	Duration of ICU admission (days) = Discharge date – Admission date + 1 Only post-randomization events will be considered.
Duration (days) of hospitalization since randomization up to Day 28	Duration of hospitalization (days) = Discharge date – Hospital admission date + 1 Only post-randomization events will be considered.
Number of ICU admissions up to Day 28	Number of non-adjacent entries (defined as number of entries with ≥ 2 days of difference between end date of previous entry and start date of next entry, when soring all entries by start date) of ICU admission in the ICU admission summary form, from randomization to Day 28. Only post-randomization events will be considered.
Number of use of invasive mechanical ventilation or ECMO up to Day 28	Number of non-adjacent entries (defined as number of entries with ≥ 2 days of difference between end date of previous entry and start date of next entry, when soring all entries by start date) of invasive mechanical ventilation or ECMO in INVASIVE MECHANICAL VENTILATION / ECMO form, from randomization to Day 28. Only post-randomization events will be considered.
Number of ICU admissions use of invasive mechanical ventilation or ECMO and death up to Day 28	For patients who died up to Day 28: Sum of number of ICU admissions and number of use of invasive mechanical ventilation or ECMO up to Day 28 +1 Otherwise: Sum of number of ICU admissions and number of use of invasive mechanical ventilation or ECMO up to Day 28
Follow-up time until Day 28 (in 4 weeks)	For patients who discontinued the study prior to Day 28: (date of discontinuation – date of randomization +1)/28 Otherwise: 1
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Parameter	Calculation
Total number of tablets taken during the treatment period	The total number of tablets taken will be calculated considering the period from the first date and time of IMP intake at Day 1 and the date and time of the next day of the interested visit. For example: if a subject takes the first dose (Day 1) at 01JAN2021 08:00 we will consider all doses up to 02JAN2021 07:59 as being part of "Day 1" of administration. If for example the subject takes the first dose (Day 1) at 01JAN2021 22:00, to derive the number of tablets taken up to "Day 7 (+/- 1)" all the tablets up to 08JAN2021 21:59 will be considered.
Total number of tablets scheduled during the treatment period	Total number of tablets scheduled = 6* Extent of exposure where extent of exposure is expressed in days.
Extent of exposure (days)	Extent of exposure (days) = Date / time of last IMP intake – Date / time of first IMP intake + 1 day.
Time from randomization to study discontinuation (days)	Time from randomization to study discontinuation (days) = Date of study discontinuation - Date of randomization +1.
Change from baseline	For changes from baseline the baseline value will constitute the subtrahend and the later value the minuend.
Conversion of Time Intervals	If a time interval was calculated in minutes, hours or days and needs to be converted into months or year the following conversion factors will be used: • 1 hour = 60 minutes • 1 day = 24 hours • 1 week = 7 days • 1 month = 30.4375 days • 1 year = 365.25 days
General rule	For calculation of difference between dates, in case time is available, it is considered in the formula.

11.3 Partial date conventions

Table 5: Algorithm for Treatment Emergence of Adverse Events

AE START DATE	AE STOP DATE	RULE for TEAE definition	RULE for "Treatment"/"Follow-up" study period definition for TEAE summaries
Known	Known, Partial or Missing	If AE start date < IMP start date, then not TEAE If AE start date >= IMP start date, then TEAE	*In case of Treatment Discontinuation (for definition, see section 7.3):* If start date > Date of last IMP intake, then Follow-up study period for TEAE occurrence. Otherwise, Treatment study period for TEAE occurrence. *In case of NO Treatment Discontinuation:* If start date ≥ Date of "Day 21" visit, then Follow-up study period for TEAE occurrence. Otherwise, Treatment study period for TEAE occurrence.
Partial, but known components show that it cannot be on or after IMP start date	Known, Partial or Missing	Not TEAE	Not applicable
Partial, could be on or after IMP start date	Known	If AE stop date < IMP start date, then not TEAE If AE stop date >= IMP start date, then TEAE	If TEAE, then Treatment study period for TEAE occurrence.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If AE stop date < IMP start date, then not TEAE If AE stop date >= IMP start date, then TEAE	
	Missing	Assumed TEAE	

AE START DATE	AE STOP DATE	RULE for TEAE definition	RULE for "Treatment"/"Follow-up" study period definition for TEAE summaries
Missing	Known	If AE stop date < IMP start date, then not TEAE If AE stop date >= IMP start date, then TEAE	If TEAE, then Treatment study period for TEAE occurrence.
	Partial	Impute AE stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If AE stop date < IMP start date, then not TEAE If AE stop date >= IMP start date, then TEAE	
	Missing	Assumed TEAE	

NOTE: Assignment to "Treatment" or "Follow-up" study period is applicable only for TEAEs.

Table 6: Algorithm for Prior/Concomitant medications

MEDICATION START DATE	MEDICATION STOP DATE	RULE for prior or concomitant categorization
Known	Known	If medication stop date < date of informed consent, assign as prior If medication stop date >= date of informed consent, assign as concomitant
	Partial	Impute medication stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If medication stop date < date of informed consent, assign as prior If medication stop date >= date of informed consent, assign as concomitant
	Missing	Assign as concomitant
Partial or Missing	Known	If medication stop date < date of informed consent, assign as prior If medication stop date >= date of informed consent, assign as concomitant
	Partial	Impute medication stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If medication stop date < date of informed consent, assign as prior If medication stop date >= date of informed consent, assign as concomitant
	Missing	Assign as concomitant

12. Tables, Figures and Listings

12.1 Output conventions

- Each Table, Listing and Figure (TLF) should be numbered, following the ICH E3 Guideline.
- All titles have to be sufficiently explanatory, i.e. the content of the outputs should be clear even when consulted independently from the SAP.
- For numeric variables, units will be presented enclosed in square brackets ([ ])., when appropriate.
- Each table and each figure should provide reference to the listing where the data on which the table/figure is based are shown.
- Listings should include raw data, i.e. data collected in CRF or other data collection tool, as well as derived data, i.e. data of variables that have been generated for statistical analysis. The derived data must be clearly identified.
- Every TLF should report the following information on the upper side of the output:
    - Left aligned:
        - Protocol number
    - Centered aligned:
        - "Confidential"
    - Right aligned:
        - Dompé Farmaceutici SpA
        - Draft/Final Run <date>
- Every TLF should report the following information on the bottom side of the output:
    - Left aligned:
        - the name of the SAS program which will generate the output
    - Centered aligned:
        - Draft/Final Version - Date <date>
    - Right aligned:
        - "Page n of N", where n is the page number and N is the total number of pages of the document.

12.2 Format requirements:

- All TLFs will be produced in landscape format on A4 paper size, unless otherwise specified.
- The titles are centered. The analysis sets are identified on the line following the title.
- it is preferable to use "Courier New" with minimal font size of 8, which is the smallest acceptable point size for the Regulatory Authorities.
- Output files will be delivered in Rich Text Format (RTF) that can be manipulated in Word.

12.3 Table Conventions

- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table even in case of frequency equal to 0.
- If the categories are not ordered (e.g., Medical History), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and SDs.
- Missing descriptive statistics or p-values which cannot be estimated are reported as “-”.

12.4 Listing Conventions

- Listings will be sorted for presentation in order of treatment groups, subject number, and visit.
- Dates are printed in SAS DATE9.format (“ddMMMyyyy”: 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000).
- In case listings will not fit the page, it will be splitted in two different parts.

13. Reference

1. Study protocol, A phase 3, double-blind, randomized, placebo-controlled, multicenter study on the efficacy and safety of Reparixin in the treatment of hospitalized patients with severe COVID-19 pneumonia, Protocol Version - Date: Version 3.0 final – 09 April 2021.
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14. Appendices

14.1 TABLES

Number	Title	Population	DMC	Interim	Key First Efficacy Results	Final
Table 14.1.1	Subject enrolment and disposition	Enrolled Set	X	X	X	X
Table 14.1.2	Analysis Sets	Randomized Set				X
Table 14.1.3.1	Study discontinuations	Randomized Set	X	X	X	X
Table 14.1.3.2	Time to discontinuation	Randomized Set				X
Table 14.1.4.1	Major protocol violations	Randomized Set				X
Table 14.1.4.2	Minor protocol violations	Randomized Set				X
Table 14.1.5.1	Demographics and baseline characteristics – part 1	Full Analysis Set	X	X	X	X
Table 14.1.5.2	Demographics and baseline characteristics – part 2	Full Analysis Set	X	X	X	X
Table 14.1.6.1	Medical or surgical history	Full Analysis Set	X			X
Table 14.1.6.2	Concomitant Diseases	Full Analysis Set	X			X
Table 14.1.7.1	Prior medications	Full Analysis Set				X
Table 14.1.7.2	Concomitant medications	Full Analysis Set	X			X
Table 14.1.7.3	Standard care for COVID-19 medications	Full Analysis Set				X
Table 14.1.8	Other baseline characteristics	Full Analysis Set	X	X	X	X
Table 14.2.1.1	Compliance to IMP – by visit	Safety Set				X
Table 14.2.1.2	Compliance to IMP - overall treatment period	Safety Set	X	X	X	X
Table 14.2.2.1	Proportion of patients alive and free of respiratory failure at Day 28 – Logistic regression model with Multiple Imputation under missing not at random	Full Analysis Set		X	X	X
Table 14.2.2.2.1	Sensitivity Analysis: Proportion of patients alive and free of respiratory failure at Day 28 – Logistic regression model with Multiple Imputation under missing not at random	Per Protocol Set				X
Table 14.2.2.2.2	Sensitivity Analysis: Proportion of patients alive and free of respiratory failure at Day 28 – Logistic regression model with Multiple Imputation under missing not at random	Full Analysis Set, excluding pts in the ICU at baseline				X
Table 14.2.2.3	Sensitivity Analysis: Proportion of patients alive and free of respiratory failure at Day 28 – Logistic regression model considering complete cases only	Full Analysis Set				X

Number	Title	Population	DMC	Interim	Key First Efficacy Results	Final
Table 14.2.2.4	Sensitivity Analysis: Proportion of patients alive and free of respiratory failure at Day 28 – Logistic regression model with Multiple Imputation under missing at random	Full Analysis Set				X
Table 14.2.2.5	Sensitivity Analysis: Proportion of patients alive and free of respiratory failure at Day 28 – Tipping point analysis	Full Analysis Set				X
Table 14.2.2.6	Sensitivity Analysis: Win-ratio analysis	Full Analysis Set		X	X	X
Table 14.2.3.1.1	Proportion of patients alive and free of respiratory failure at Day 60 – Logistic regression model	Full Analysis Set		X	X	X
Table 14.2.3.1.2	Mortality rates up to Day 28 – Logistic regression model	Full Analysis Set		X	X	X
Table 14.2.3.1.3	Incidence of ICU admission until Day 28 – logistic regression model	Full Analysis Set		X	X	X
Table 14.2.3.1.4.1	Time to recovery until Day 28 – Cumulative incidence function	Full Analysis Set		X	X	X
Table 14.2.3.2	Proportion of patients alive and free of respiratory failures at fixed time points	Full Analysis Set		X	X	X
Table 14.2.3.3	Mortality rates up to fixed time points	Full Analysis Set		X	X	X
Table 14.2.3.4.1	Proportion of incidence of ICU admission until Day 28	Full Analysis Set		X	X	X
Table 14.2.3.4.2	Proportion of incidence of ICU admission until Day 28 followed by invasive mechanical ventilation (or ECMO) or death	Full Analysis Set		X	X	X
Table 14.2.3.4.3	Incidence of ICU admission until Day 28 followed by invasive mechanical ventilation (or ECMO) or death – logistic regression model	Full Analysis Set		X	X	X
Table 14.2.3.5	Summary of clinical severity score based on the 7-point WHO-OS as measured at fixed time points and change from baseline	Full Analysis Set			X	X
Table 14.2.3.6.1	Time to clinical improvement 1 up to Day 28 – Kaplan-Meier methodology	Full Analysis Set			X	X
Table 14.2.3.7.1	Time to clinical improvement 2 up to Day 28 – Kaplan-Meier methodology	Full Analysis Set			X	X
Table 14.2.3.8.1	Time to discharge from hospital up to Day 28 – Kaplan-Meier methodology	Full Analysis Set			X	X
Table 14.2.3.9	Clinical status at fixed time points either in hospital or at home	Full Analysis Set			X	X
Table 14.2.3.10.1	Dyspnea severity (Likert scale) at fixed time points	Full Analysis Set			X	X
Table 14.2.3.10.2	Summary of Dyspnea severity (VAS scale) at fixed time points and change from baseline	Full Analysis Set			X	X
Table 14.2.3.11	Duration of supplemental oxygen treatment (Days) up to Day 28	Full Analysis Set				X
Table 14.2.3.12.1	Incidence of invasive mechanical ventilation use, or ECMO up to Day 60	Full Analysis Set		X	X	X
Table 14.2.3.12.2	Incidence of invasive mechanical ventilation use, or ECMO up to Day 60 followed by death	Full Analysis Set		X	X	X
Table 14.2.3.13	Duration of invasive mechanical ventilation, or ECMO (days) up to Day 60	Full Analysis Set				X
Table 14.2.3.14	Duration of non-invasive mechanical ventilation (days) up to Day 60	Full Analysis Set				X
Table 14.2.3.15	Duration of ICU admission (days) up to Day 60	Full Analysis Set				X
Table 14.2.3.16	Duration of hospitalization since randomization (days) up to Day 60	Full Analysis Set				X
Table 14.2.3.17.1	Summary of partial pressure of oxygen (PaO2) and change from baseline	Full Analysis Set			X	X
Table 14.2.3.17.2	Summary of partial pressure of oxygen (PaO2) – Investigator's interpretation	Full Analysis Set			X	X

Number	Title	Population	DMC	Interim	Key First Efficacy Results	Final
Table 14.2.3.18.1	Summary of pulse oximetry by measurement of peripheral arterial oxygen saturation (SpO2) and change from baseline	Full Analysis Set			X	X
Table 14.2.3.18.2	Summary of pulse oximetry by measurement of peripheral arterial oxygen saturation (SpO2) – Investigator's interpretation	Full Analysis Set			X	X
Table 14.2.3.19.1	Summary of PaO2/FiO2 ratio and change from baseline	Full Analysis Set		X	X	X
Table 14.2.3.19.2.1	Proportion of patients with a decrease of PaO2/FiO2 ratio from the baseline value	Full Analysis Set		X	X	X
Table 14.2.3.19.2.2	Proportion of patients with a decrease of PaO2/FiO2 ratio from the baseline value followed by ICU admission or IMV or ECMO or death	Full Analysis Set		X	X	X
Table 14.2.3.19.3	Summary of PaO2/FiO2 ratio – Investigator's interpretation	Full Analysis Set		X	X	X
Table 14.2.3.20.1	Summary of Hs-CRP and change from baseline	Full Analysis Set			X	X
Table 14.2.3.20.2	Summary of Hs-CRP – Investigator's interpretation	Full Analysis Set			X	X
Table 14.2.3.21	Mortality rates up to Day 60 and Day 90 – Logistic regression model	Full Analysis Set				X
Table 14.2.3.22.1	Freedom from (time to) death or respiratory failure – Kaplan Meier methodology	Full Analysis Set		X	X	X
Table 14.2.4.1	CCI [redacted]	Full Analysis Set				X
Table 14.2.4.2	CCI [redacted]	Full Analysis Set				X
Table 14.2.4.3	CCI [redacted] nts	Full Analysis Set	X		X	X
Table 14.2.4.4	CCI [redacted]	Full Analysis Set				X
Table 14.2.4.5	Summary of concentration of Reparixin in serum measured immediately before and one hour (± 15 min) after first dosing at Day 3	Full Analysis Set				X
Table 14.2.4.6.1	Summary of SARS-CoV-2 viral burden (quantitative rt-PCR)	Full Analysis Set				X
Table 14.2.4.6.2	Summary of SARS-CoV-2 viral burden – categorical result	Full Analysis Set				X
Table 14.2.5.1	Subgroups evaluation: Proportion of patients alive and free of respiratory failure at Day 28 – Logistic regression model	Full Analysis Set				X
Table 14.2.5.2.1	Proportion of patients alive and free of respiratory failure at Day 28 by Age group – Logistic regression model	Full Analysis Set				X
Table 14.2.5.2.2	Proportion of patients alive and free of respiratory failure at Day 60 by Age group – Logistic regression model	Full Analysis Set				X
Table 14.2.5.2.3	Mortality rates up to Day 28 by Age group – Logistic regression model	Full Analysis Set				X
Table 14.2.5.2.4	Incidence of ICU admission until Day 28 by Age group – Logistic regression model	Full Analysis Set				X
Table 14.2.5.2.5	Time to recovery up to Day 28 by Age group – Cumulative incidence function	Full Analysis Set				X
Table 14.2.5.2.6	Proportion of patients alive and free of respiratory failure at fixed timepoints by Age group	Full Analysis Set				X
Table 14.2.5.2.7	Mortality rates up to fixed timepoints	Full Analysis Set				X
Table 14.2.5.2.8	Proportion of incidence of ICU admission until Day 28 by Age group	Full Analysis Set				X

Number	Title	Population	DMC	Interim	Key First Efficacy Results	Final
Table 14.2.5.2.9	Summary of clinical severity score based on the 7-point WHO-OS as measured fixed time points and change from baseline by Age group	Full Analysis Set				X
Table 14.2.5.2.10	Time to clinical improvement 1 up to Day 28 by Age group – Cumulative incidence function	Full Analysis Set				X
Table 14.2.5.2.11	Time to clinical improvement 2 up to Day 28 by Age group – Cumulative incidence function	Full Analysis Set				X
Table 14.2.5.2.12	Time to discharge from hospital up to Day 28 by Age group – Cumulative incidence function	Full Analysis Set				X
Table 14.2.5.2.13	Clinical status at fixed time points either in hospital or at home by Age group	Full Analysis Set				X
Table 14.2.5.2.14	Dyspnea severity (Likert scale) at fixed time points by Age group	Full Analysis Set				X
Table 14.2.5.2.15	Summary of Dyspnea severity (VAS scale) at fixed time points and change from baseline by Age group	Full Analysis Set				X
Table 14.2.5.2.16	Duration of supplemental oxygen treatment (Days) up to Day 28 by Age group	Full Analysis Set				X
Table 14.2.5.2.17	Incidence of invasive mechanical ventilation use, or ECMO up to Day 60 by Age group	Full Analysis Set				X
Table 14.2.5.2.18	Duration of invasive mechanical ventilation, or ECMO (days) up to Day 60 by Age group	Full Analysis Set				X
Table 14.2.5.2.19	Duration of non-invasive mechanical ventilation (days) up to Day 60 by Age group	Full Analysis Set				X
Table 14.2.5.2.20	Duration of ICU admission (days) up to Day 60 by Age group	Full Analysis Set				X
Table 14.2.5.2.21	Duration of hospitalization since randomization (days) up to Day 60 by Age group	Full Analysis Set				X
Table 14.2.5.2.22	Summary of partial pressure of oxygen (PaO2) and change from baseline by Age group	Full Analysis Set				X
Table 14.2.5.2.23	Summary of pulse oximetry by measurement of peripheral arterial oxygen saturation (SpO2) and change from baseline by Age group	Full Analysis Set				X
Table 14.2.5.2.24	Summary of PaO2/FiO2 ratio and change from baseline by Age group	Full Analysis Set				X
Table 14.2.5.2.25	Proportion of patients with a decrease of PaO2/FiO2 ratio from the baseline value by Age group	Full Analysis Set				X
Table 14.2.5.2.26	Summary of Hs-CRP and change from baseline by Age group	Full Analysis Set				X
Table 14.2.5.2.27	Mortality rates up to Day 60 and Day 90 by Age group – Logistic regression model	Full Analysis Set				X
Table 14.2.5.2.28	Freedom from (time to) death or respiratory failure by Age group – Kaplan Meier methodology	Full Analysis Set				X
Table 14.2.5.X.1-28 (X can vary from 3 to 4, based on how many subgroups will be used)	Repeat set of tables from 14.2.5.2.1 to 14.2.5.2.28 for all subgroups defined in the SAP (section 6.4), in case the interaction is statistically significant in the logistic regression model specified before (i.e. 14.2.5.1)	Full Analysis Set				X
Table 14.2.5.29	Number of ICU admissions until Day 28 – Poisson regression model	Full Analysis Set				X
Table 14.2.5.30	Number of invasive mechanical ventilation or ECMO until Day 28 – Poisson regression model	Full Analysis Set				X
Table 14.2.5.31	Number of IC admission, invasive mechanical ventilation or ECMO or Death until Day 28 – Poisson regression model	Full Analysis Set				X

Number	Title	Population	DMC	Interim	Key First Efficacy Results	Final
Table 14.3.1	Exposure to IMP	Safety Set				X
Table 14.3.2.1	Overview of Treatment Emergent Adverse Events	Safety Set	X	X	X	X
Table 14.3.2.2	Summary of Treatment Emergent Adverse Events by primary System Organ Class and Preferred Term and by study period	Safety Set	X	X	X	X
Table 14.3.2.3	Summary of Treatment Emergent Adverse Events by primary System Organ Class, Preferred Term and Severity	Safety Set				X
Table 14.3.2.4	Summary of Serious Treatment Emergent Adverse Events by primary System Organ Class and Preferred Term and by study period	Safety Set	X		X	X
Table 14.3.2.5	Summary of ADRs by primary System Organ Class and Preferred Term and by study period	Safety Set	X		X	X
Table 14.3.2.6	Summary of ADRs by Primary System Organ Class and Preferred Term and Severity	Safety Set				X
Table 14.3.2.7	Summary of TEAEs leading to IMP Discontinuation by Primary System Organ Class and Preferred Term and by study period	Safety Set	X		X	X
Table 14.3.2.8	Summary of TEAEs leading to study Discontinuation by Primary System Organ Class and Preferred Term and by study period	Safety Set	X			X
Table 14.3.2.9	Summary of TEAEs leading to Death by Primary System Organ Class and Preferred Term	Safety Set				X
Listing 14.3.3	Deaths	Safety Set	X	X	X	X
Table 14.3.5.1.1.1	CCI [redacted]	Safety Set	X		X	X
Table 14.3.5.1.2	CCI [redacted]	Safety Set				X
Table 14.3.5.1.3	CCI [redacted]	Safety Set				X
Table 14.3.5.2.1.1	CCI [redacted]	Safety Set	X		X	X
Table 14.3.5.2.2	CCI [redacted]	Safety Set				X
Table 14.3.5.2.3	CCI [redacted]	Safety Set				X
Table 14.3.6.1.1	CCI [redacted]	Safety Set	X		X	X
Table 14.3.6.2.1.1	CCI [redacted]	Safety Set	X		X	X
Table 14.3.6.2.2	CCI [redacted]	Safety Set				X
Table 14.3.6.2.3	CCI [redacted]	Safety Set				X
Table 14.3.6.3.1	Summary of Child Pugh Score and change from baseline	Safety Set				X
Table 14.3.6.3.2	Child Pugh Score: proportion of patients for all categorical parameters	Safety Set				X

14.2 LISTINGS

Number	Title	Population	DMC	Interim	Key First Efficacy Results	Final
Listing 16.1.7	Randomization schedule	Randomized Set				X
Listing 16.2.1.1	Disposition of subjects	Enrolled Set	X			X
Listing 16.2.1.2.1	Subjects enrolled but not randomized	Enrolled Set				X
Listing 16.2.1.2.2	Study termination	Randomized Set				X
Listing 16.2.1.2.3	Treatment termination	Randomized Set				X
Listing 16.2.2.1	Inclusion criteria	Randomized Set				X
Listing 16.2.2.2	Exclusion criteria	Randomized Set				X
Listing 16.2.2.3.1	Major protocol deviations	Randomized Set	X*			X
Listing 16.2.2.3.2	Minor protocol deviations	Randomized Set				X
Listing 16.2.3.1	Analysis Sets	Enrolled Set				X
Listing 16.2.3.2	Subjects excluded from Full Analysis Set	Enrolled Set				X
Listing 16.2.4.1.1	Demographic and baseline characteristics – part 1	Randomized Set				X
Listing 16.2.4.1.2	Demographic and baseline characteristics – part 2	Randomized Set				X
Listing 16.2.4.2	Medical or Surgical History	Randomized Set				X
Listing 16.2.4.3	Concomitant Diseases	Randomized Set	X			X
Listing 16.2.4.4	Prior Medications	Randomized Set				X
Listing 16.2.4.5	Concomitant Medications	Randomized Set	X			X
Listing 16.2.4.6	Other baseline characteristics	Randomized Set				X
Listing 16.2.5.1	Compliance to study medication	Randomized Set				X
Listing 16.2.6.1.1	Primary endpoint and mortality rates	Randomized Set				X
Listing 16.2.6.1.2	ICU admission	Randomized Set				X
Listing 16.2.6.1.3	Clinical severity score based on the 7-point WHO-OS	Randomized Set				X
Listing 16.2.6.1.4	Dyspnea severity (Likert scale and VAS scale)	Randomized Set				X
Listing 16.2.6.1.5	Daily Supplemental Oxygen	Randomized Set				X
Listing 16.2.6.1.6	Invasive mechanical ventilation / ECMO	Randomized Set				X
Listing 16.2.6.1.7	Non-Invasive mechanical ventilation	Randomized Set				X
Listing 16.2.6.1.8	Lung function	Randomized Set				X
Listing 16.2.6.1.9	CCI [redacted]	Randomized Set				X
Listing 16.2.6.2	Exposure to study medication	Randomized Set				X
Listing 16.2.7.1	Pre-treatment Adverse Events	Randomized Set				X
Listing 16.2.7.2	Treatment emergent adverse events	Randomized Set	X			X
Listing 16.2.7.3	Serious treatment emergent adverse events	Randomized Set				X

Number	Title	Population	DMC	Interim	Key First Efficacy Results	Final
Listing 16.2.7.4	Treatment emergent adverse drug reactions	Randomized Set				X
Listing 16.2.7.5	Serious treatment emergent adverse drug reactions	Randomized Set				X
Listing 16.2.7.6	Severe treatment emergent adverse events	Randomized Set				X
Listing 16.2.7.7	Treatment emergent adverse events leading to IMP discontinuation	Randomized Set				X
Listing 16.2.7.8	Treatment emergent adverse events leading to study discontinuation	Randomized Set				X
Listing 16.2.7.9	Treatment emergent adverse events leading to death	Randomized Set				X
Listing 16.2.8.1	CCI [redacted]	Randomized Set	X			X
Listing 16.2.8.2	CCI [redacted]	Randomized Set	X			X
Listing 16.2.8.3	CCI [redacted]	Randomized Set				X
Listing 16.2.8.4	CCI [redacted]	Randomized Set				X
Listing 16.2.8.5	Child Pugh Score	Randomized Set				X

**All deviations will be reported for DMC meetings*

14.3 FIGURES

Number	Title	Population	DMC	Interim	Key First Efficacy Results	Final
Figure 14.1.3.3	Time from randomization to discontinuation (Kaplan-Meier)	Randomized Set				X
Figure 14.2.2.5.2	Tipping point analysis	Full Analysis Set				X
Figure 14.2.3.1.4.2	Time to recovery (Cumulative Incidence Function)	Full Analysis Set		X	X	X
Figure 14.2.3.6.2	Time to clinical improvement 1 (Cumulative Incidence Function)	Full Analysis Set				X
Figure 14.2.3.7.2	Time to clinical improvement 2 (Cumulative Incidence Function)	Full Analysis Set				X
Figure 14.2.3.8.2	Time to discharge from hospital (Cumulative Incidence Function)	Full Analysis Set				X
Figure 14.2.3.22.2	Time to death or respiratory failure up to Day 90 (Kaplan Meier)	Full Analysis Set				X
Figure 14.3.5.1.1.2	CCI [redacted]	Full Analysis Set	X			X
Figure 14.3.5.1.1.3	CCI [redacted]	Full Analysis Set	X			X
Figure 14.3.5.1.1.4	CCI [redacted]	Full Analysis Set	X			X
Figure 14.3.5.1.1.5	CCI [redacted]	Full Analysis Set	X			X
Figure 14.3.5.2.1.2	CCI [redacted]	Full Analysis Set	X			X
Figure 14.3.5.2.1.3	CCI [redacted]	Full Analysis Set	X			X
Figure 14.3.5.2.1.4	CCI [redacted]	Full Analysis Set	X			X
Figure 14.3.5.2.1.5	CCI [redacted]	Full Analysis Set	X			X
Figure 14.3.6.1.2	CCI [redacted]	Full Analysis Set	X			X
Figure 14.3.6.1.3	CCI [redacted]	Full Analysis Set	X			X
Figure 14.3.6.1.4	CCI [redacted]	Full Analysis Set	X			X
Figure 14.3.6.1.5	CCI [redacted]	Full Analysis Set	X			X
Figure 14.3.6.2.1.2	CCI [redacted]	Full Analysis Set	X			X

14.4 SAS Code for the primary analysis

First Step: Multiple imputation MNAR, using data from subjects that discontinued treatment (EOTSTT=”NOT COMPLETED”) but have the primary endpoint measurement (i.e. whether the patient was alive and free of respiratory failure at Day 28 or not (AVALC = “Y” or “N”)), to impute missing information on the primary endpoint with the following covariates: planned treatment group (TRT01P), sex (SEX), presence of concomitant disease (CONDISBL), and age class (AGEGR1).

CCI [redacted]

CCI [redacted]

Second Step: Fit the primary analysis logistic regression model with the same fixed effects as above and site (SITEID) as random effect in each of the imputed datasets.

CCI [redacted]

Third Step: Combine the results across the imputed datasets using Rubin's rule.

CCI